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Glomerulonephritis

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Editors

Glomerulonephritis

With 163 Figures and 113 Tables

Springer

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Dedication – from Dr. Edgar V. Lerma

To all my mentors and friends at the University of Santo Tomas Faculty of Medicine and Surgery in Manila, Philippines, and Northwestern University Feinberg School of Medicine in Chicago, IL, who have, in one way or another, influenced and guided me to become the physician that I am.
To all the medical students, interns, and residents at Advocate Christ Medical Center and MacNeal Hospital, whom I have taught or learned from, especially those who eventually decided to pursue nephrology as a career.
To my parents and my brothers, without whose unwavering love and support through the good and bad times I would not have persevered and reached my goals in life.
Most specially, to my two lovely and precious daughters Anastasia Zofia and Isabella Ann, whose smiles and laughter constantly provide me unparalleled joy and happiness, and my very loving and understanding wife Michelle, who has always been supportive of my endeavors, both personally and professionally, and who sacrificed a lot of time and exhibited unwavering patience as I devoted a significant amount of time and effort to this project. Truly, they provide me with motivation and inspiration.

Foreword

Many contemporary textbooks of nephrology devote multiple chapters to the topic of glomerulonephritis, but until now, a single-volume, multi-author treatise that deals comprehensively with this subject in both adults and children has been notably absent. While glomerulonephritis is an old subject (first recognized by Richard Bright in 1827), its evolution has been quickened by the application of percutaneous renal biopsy, the advent of sophisticated immunopathology and serology, and the description of many new and unique forms of the generic disease. In the modern era, glomerulonephritis is an immensely diverse and challenging field of inquiry and a common clinical problem in clinical practice. It continues to evolve at a rapid pace, particularly impacted by the burgeoning fields of molecular genetics, proteomics, experimental pathology, and immuno-serology. Summarizing the cogent and current information available on this subject is a daunting task.

The coeditors of *Glomerulonephritis* have taken on this exercise with rigor, inclusiveness, and zeal, ably supported by a cast consisting of a multitude of internationally recognized expert authors. Together, they have melded a truly remarkable tome. It is full of pearls of wisdom and practical advice, leavened with careful attention to the extant evidence. In a series of chapters equal to a deck of cards, they have laid out, in a comprehensive but readable fashion, the broad panorama of contemporary glomerulonephritis. The details will satisfy the curiosity of students, trainees, investigators, and clinicians alike. Mechanisms, etiologies, diagnostic approaches, pathology, prognosis, and treatment all receive an appropriate level of attention. Any such effort can only capture what is known at the moment the text is finalized – the field will continue to advance, and new discoveries will undoubtedly alter the portraits of the glomerulonephritis family painted here in lucid and selected images – but such is progress.

My heartiest congratulations to the coeditors, authors, and the publisher for filling a gap in textual material dealing with a complex array of glomerular diseases affecting adults and children. Their combined efforts have been highly rewarding, and they have produced a real gem.

David Geffen School of Medicine
at UCLA
January 31, 2019

Richard J. Glassock, M.D., MACP
Emeritus Professor

Preface

The glomerulus has always been the signature structure within the kidney, a beautiful object of fascination from the moment doctors could examine kidney tissue under the microscope. There is no denying the importance of glomerular diseases because they are a major cause of end-stage kidney disease globally throughout the life-span. However, approaches to the scientific study of glomerular disease lagged behind other structures in the kidney and other organs. As a consequence, there has been little progress in the treatment of these disorders.

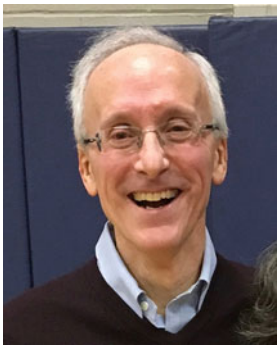
But to quote a Nobel laureate, "the times they are a-changin'." With advances in genetics, molecular profiling, and drug development and testing, we stand poised on the threshold of significant advances in the diagnosis and management of glomerular disease. This is paralleled by substantial changes in medical education and teaching tools used by medical students, house officers, trainees in nephrology, and attending physicians.

This book represents an effort to incorporate state-of-the-art knowledge about disease pathogenesis, epidemiology, and clinical management in a format that is responsive to how physicians learn and practice medicine at the present time. The content is geared to students and clinicians who are ready to enter the era of precision medicine. The book is heavy but will also be portable. It is a blend of printed text and online material that should be accessible to nephrologists of all ages and learning styles. It juxtaposes pediatric and medicine discussions and includes high-quality pathology material. Moreover, the book will be a living text that each contributing author will be able to update when new knowledge about etiology or treatment emerges for any clinical disease. As such, we hope that this textbook will have a long shelf life but never gather dust.

We want to thank all the authors who contributed to this book and ensured the high quality of the final product. We welcome feedback and suggestions from readers to improve the book. We wish our readers many years of productive activity in nephrology and hope our book will become a useful resource, one that will have broad acceptance in the community of health-care professionals engaged in the care of patients, young and old, with glomerular disease.

Contents

About the Editors



Howard Trachtman, **M.D.**, is professor of pediatrics at NYU School of Medicine. He is the director of the Division of Pediatric Nephrology, NYU Langone Health. Dr. Trachtman has authored numerous peer-reviewed articles, reviews, and book chapters focusing on glomerular disease and hypertension. He has been the principal investigator for a wide range of NIH- and industry-sponsored clinical trials in glomerular disease and a co-investigator in the NEPTUNE and CureGN observational cohort studies.

Leal C. Herlitz, **M.D.**, is the director of the Renal Pathology Division at the Cleveland Clinic. She is an experienced academic renal pathologist and has published numerous original articles and book chapters in the field of renal pathology, primarily focused on glomerular disease.

Edgar V. Lerma is clinical professor of medicine at the University of Illinois at Chicago College of Medicine. He is educational coordinator for the Section of Nephrology at UIC/Advocate Christ Medical Center in Oak Lawn, IL. He has authored more than 100 publications and presentations; notable publications which he edited include *Current Diagnosis & Treatment: Nephrology & Hypertension*, *Nephrology Secrets*, and *Henrich's Principles and Practice of Dialysis*. He has peer-reviewed and served on editorial boards for numerous journals and currently serves as associate editor for *Clinical Reviews in Bone and Mineral Metabolism*, *Reviews in Endocrine and Metabolic Disorders*, and *Journal of Clinical Lipidology*. He serves as visual abstract editor for the *Clinical Journal of the American Society of Nephrology* (CJASN) and section editor for *Geriatric Nephrology for International Urology and Nephrology* medical journal. Dr. Lerma's clinical and research interests include CKD, hypertension, bone and mineral disorders, and dyslipidemias in CKD. He is also actively involved with nephrology-related social media projects such as #Nephpearls, #NephJC (online journal club), and #Nephmadness.

Jonathan J. Hogan, **M.D.**, attended medical school at the University of Pennsylvania in Philadelphia. He completed his residency training in internal medicine at the Hospital of the University of Pennsylvania and his fellowship in nephrology at Columbia University Medical Center in New York. Following fellowship, Dr. Hogan completed a fellowship in glomerular diseases at

Columbia under the mentorship of Dr. Gerald Appel. In 2014, Dr. Hogan returned to Philadelphia as an assistant professor of medicine at the Perelman School of Medicine, University of Pennsylvania. He is also the clinical director of the Penn Glomerular Disease Center. Dr. Hogan has authored numerous peer-reviewed articles and book chapters and has spoken at multiple invited lectures nationwide, with a focus on glomerular disease and onco-nephrology. He is also site principal investigator or co-investigator for multiple NIH- and industry-sponsored studies in glomerular disease.

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Approach to Renal Biopsy

1

Timothy Yau

Contents

Abstract

The percutaneous kidney biopsy has transformed both the fields of nephrology and pathology. Prior to its introduction in the 1950s, analysis of kidney tissue was available only from deceased autopsy specimens. Advances in technology, technique, and imaging have led to both an improvement in tissue yield in addition to lower morbidity from complications. The kidney biopsy is currently the diagnostic gold standard for nearly all kidney diseases. Although a thorough history and physical in addition to basic serum and urine studies can aid the clinician, the biopsy is oftentimes the next necessary

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step to confirm a specific diagnosis. Direct sampling of kidney tissue also adds significant prognostic value and can guide management strategies for a variety of disease states. This chapter will outline the history of the kidney biopsy, review tissue adequacy and staining, provide an overview of techniques for native and transplant kidneys along with the associated complications, and discuss future directions and possibilities with this procedure.

Keywords

Kidney biopsy · Renal biopsy · Medical history · Nephrology · Nephropathology · Renal pathology · Bleeding complications · Proteomics

Historical Perspective

The earliest reports of diseased human kidneys were gross findings on postmortem examination, which date back to the mid-nineteenth century, and the first reports of open kidney biopsies are from the 1890s. Physicians in this era were performing "nephropexy" to surgically fix mobile kidneys in patients who suffered from Bright's disease (now an obsolete term referring to nonspecific glomerulonephritis). In 1901, surgeons in New York performed renal decapsulation in a 43-year-old female with chronic Bright's disease followed by kidney tissue sampling which revealed advanced chronic interstitial nephritis (Edebohls 1904). Interestingly, these surgeries were meant to cure the patients of their kidney disease, as decapsulation of the swollen organs was hypothesized to relieve the inflammation and promote healing.

The next several decades saw similar publications where renal sampling was performed via the open approach. An interesting surgical approach to hypertension in the 1940s was splanchnicectomy and sympathectomy, which were performed to mechanically vasodilate the splanchnic capillary beds to allow for a decrease in blood pressure. As this was an open procedure that exposed the kidneys, open renal tissue sampling was often performed secondarily. Many of the fathers of renal pathology (e.g., Robert Heptinstall from Great Britain) examined tissue from open biopsies and published the first reports on renal vascular histologic changes associated with hypertension (Heptinstall 1953).

The percutaneous kidney biopsy was first described in 1951 by Iversen and Brun in Copenhagen, Denmark (Iversen and Brun 1951). The initial technique utilized an aspiration liver biopsy needle in conjunction with intravenous pyelography imaging. The patient was positioned in the sitting position and a 1.9 mm serrated needle was used to cut the tissue, followed by applied suction to the needle to secure the sample. Minor complications of gross hematuria and pain were noted, but no major complications developed. However, tissue yield was only adequate for diagnosis in 50% of cases.

The technique was modified in 1952 by Kark and Muehrcke at Presbyterian Hospital in Chicago (Kark and Muehrcke 1954). Their technique improved sampling by placing the patient in the prone position and avoided suction aspiration of the tissue. In their published description, a 4 in. sandbag was placed under the prone patient's lower abdomen to displace the kidney more posteriorly. The procedures were performed using anatomic landmarks and palpation of the kidney with respiration. A 20 gauge exploring needle was inserted, and the patient inhaled and exhaled deeply. If the needle tip was in the kidney, the hub of the needle would swing up and down in an arc during inspiration/expiration as the kidney was pushed by the diaphragm. Once the depth and location were confirmed, the physicians would anesthetize and insert a modified Vim-Silverman needle. Rather than aspiration of tissue described by Iversen and Brun, the modified needle used a cutting edge and longitudinal groove which retained a 1–2 cm core of tissue when the needle was withdrawn. In their own words, the tissue was "punched and bitten from the kidney." Their publication demonstrated adequate tissue for diagnosis in 96% (48/50) of biopsies. Complications included gross hematuria in 8%, pain in

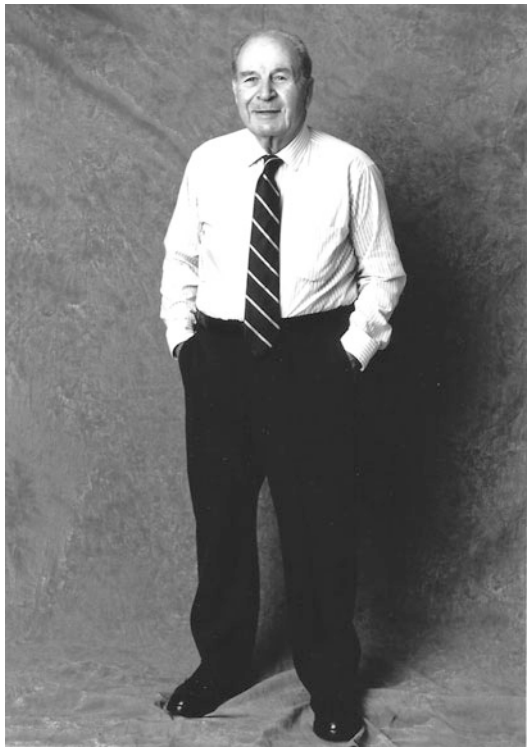

Fig. 1 Dr. Robert Kark, the pioneer of the percutaneous kidney biopsy in Chicago, Illinois. (Image courtesy of Dr. Stephen Korbet and Dr. Roger Rodby at Rush Presbyterian Hospital, Chicago, Illinois)

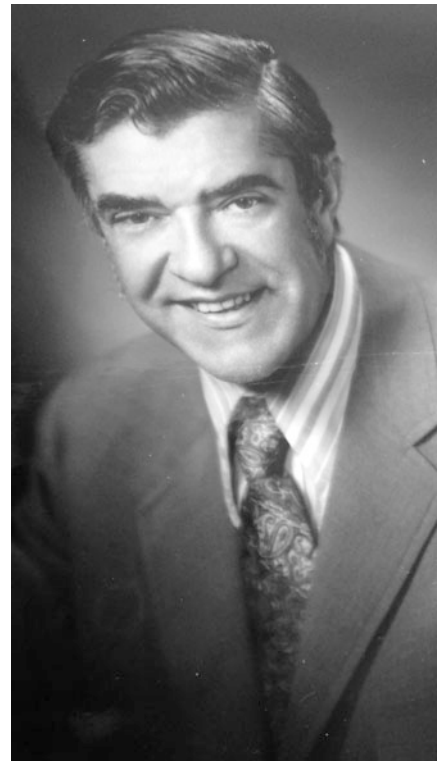

Fig. 2 Dr. Robert Muehrcke, who worked with Dr. Kark (Figure 1) in Chicago, Illinois. (Image courtesy of Dr. Stephen Korbet and Dr. Roger Rodby at Rush Presbyterian Hospital, Chicago, Illinois)

10%, and one patient (2%) required a transfusion. Remarkably, the clinical diagnosis changed based on the histologic findings in half (25/50) of the patients. The physician pairing of Drs. Kark and Muehrcke were joined by Dr. Conrad Pirani, a pathologist at the University of Illinois in Chicago. Pirani applied systematic semiquantitative scores of activity and chronicity in his evaluation of their renal tissue that are still utilized today (Figs. 1, 2, and 3).

Around this same time, pioneers were pushing the boundaries of pathology by coupling fluorescent probes to antibody to detect immunoglobulin in frozen sections. Drs. Robert McCluskey and Gloria Gallo at New York University first published the application of immunofluorescence in human kidney biopsy samples in 1966 (D'Agati et al. 2013, McCluskey et al. 1966). Similarly, electron microscopy (which had been developed in the 1930s) was being utilized to examine kidney biopsy specimens. In addition to showing fine resolution of glomerular structures such as the podocyte foot processes and fenestrated endothelium, a host of new diseases were discovered. Diffuse foot process effacement was identified as the hallmark finding of minimal change disease. "Zebra" inclusion bodies of lipid storage diseases such as Fabry's disease were reported. To this day, nephropathology is one of the few subspecialties in pathology where electron microscopy remains a standard of care (Figs. 4, 5, and 6).

Newer technology pertaining to the kidney biopsy over the past 60 years has mostly included advances in the use of real-time ultrasound or CT guidance and the quality of automated biopsy needles. The spring-loaded biopsy gun was developed in 1982, with a modified Tru-Cut needle.

Fig. 3 Franklin modified Vim Silverman needle. The upper needle is the outer trocar. Once the tip of this needle is in the renal capsule, the lower needle is punched into the kidney. When retrieved, the end splits to allow the operator to retrieve the tissue core

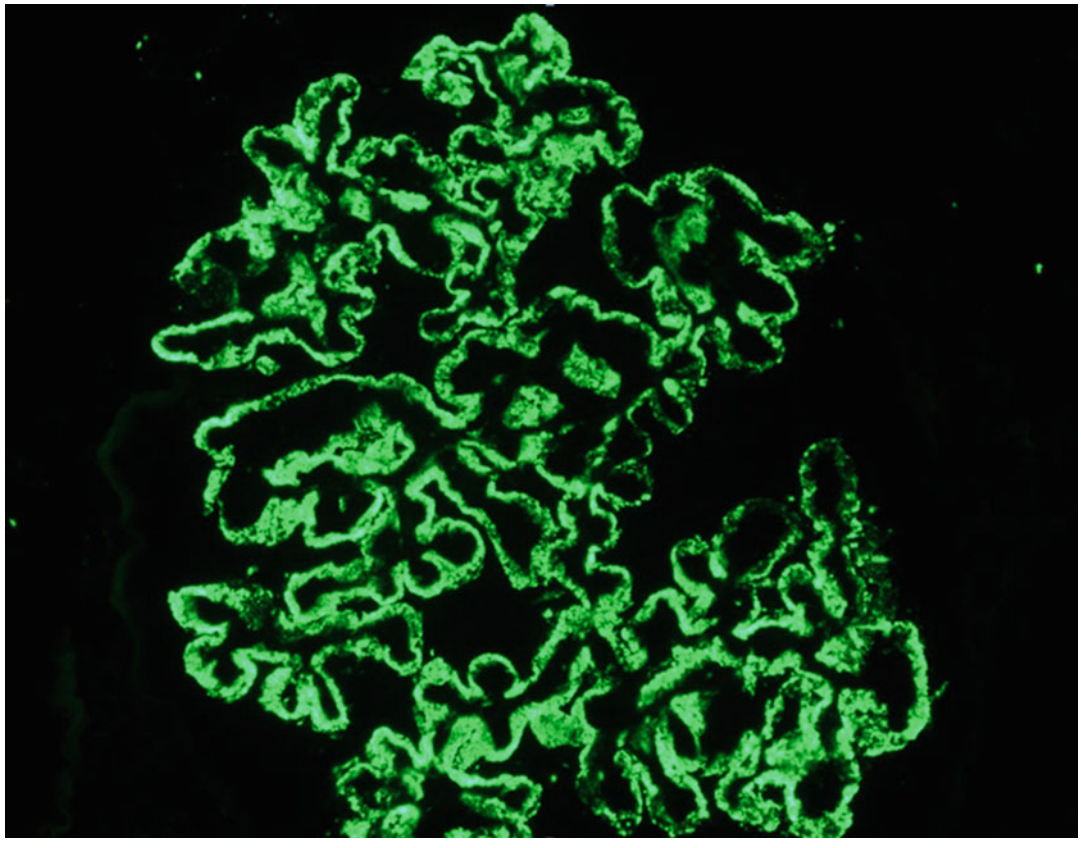

Fig. 4 Image of the IgG immunofluorescence, showing the granular capillary loop staining in a case of membranous nephropathy

When the tip of this biopsy needle is in place, the spring is released. The inner trocar is thrust forward first, followed quickly by a forward thrust of the outer cutting cannula. This delayed movement traps the tissue in the notch of the trocar when the cutting sheath is advanced (Fig. 7).

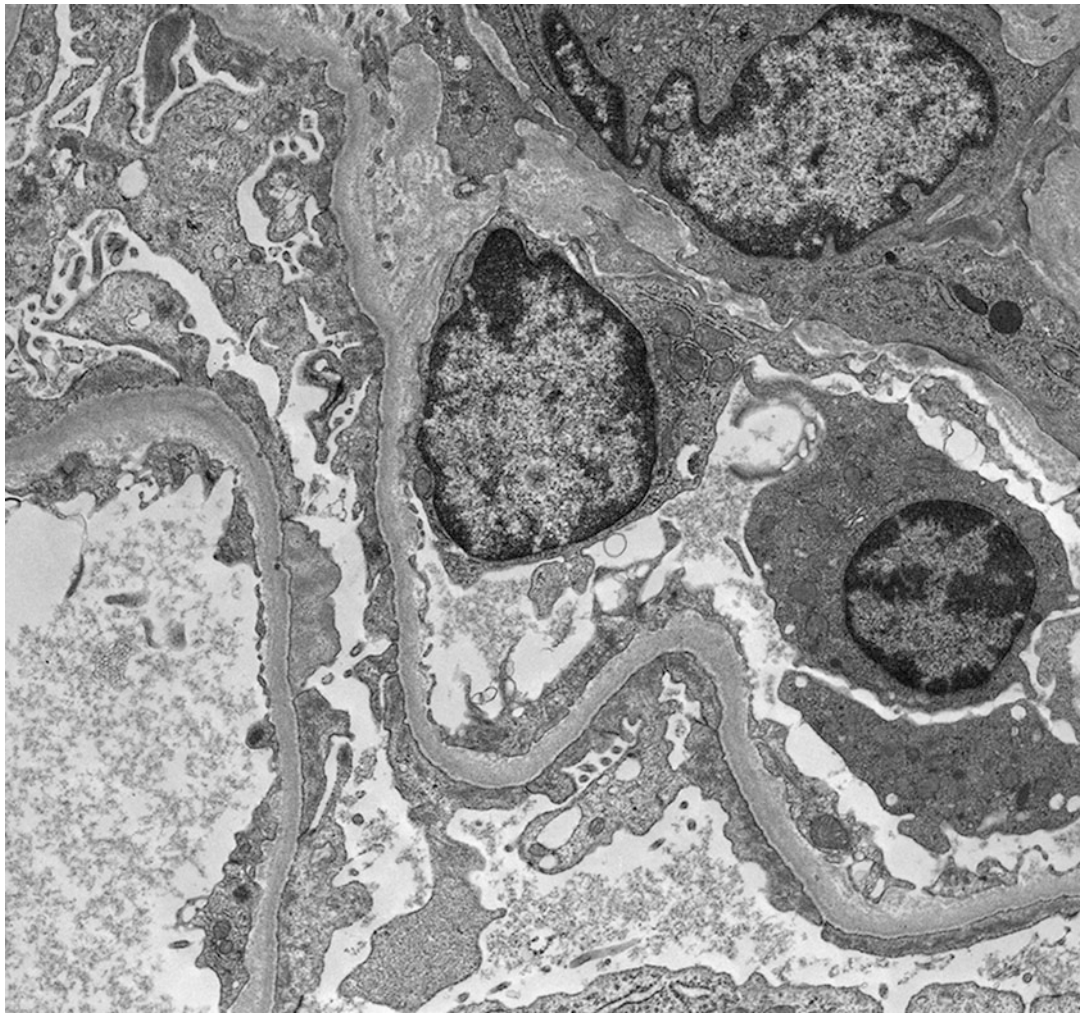

Fig. 5 Image of the diffuse foot process effacement seen in minimal change disease (×7000)

Another advance in the field during this time included alternative approaches to the kidney itself. This includes a transvenous approach, which was modified in the 1990s from transjugular liver biopsy technicians (Lindgren 1982). With this procedure, the kidney is accessed via the venous system into a medullary interlobular vessel. The needle is passed through the vein into kidney cortex for sampling. Theoretically, this approach has the benefit of minimizing bleeding into the renal capsule, as any bleeding would drain directly into the vein whose wall was breached. Glomerular yield can also be a concern with this approach, as this technique accesses the kidney from the inside out, with most glomeruli in the outer cortex of the organ. Open or laparoscopic surgical biopsies can still be performed in certain circumstances (e.g., severe bleeding diatheses) or if a patient is already undergoing an open surgical procedure. The yield of surgical biopsies is excellent as there is direct visualization of the kidney with sampling, but these procedures carry the additional morbidity and mortality of general anesthesia.

Despite these alternative approaches, the percutaneous renal biopsy remains the standard of

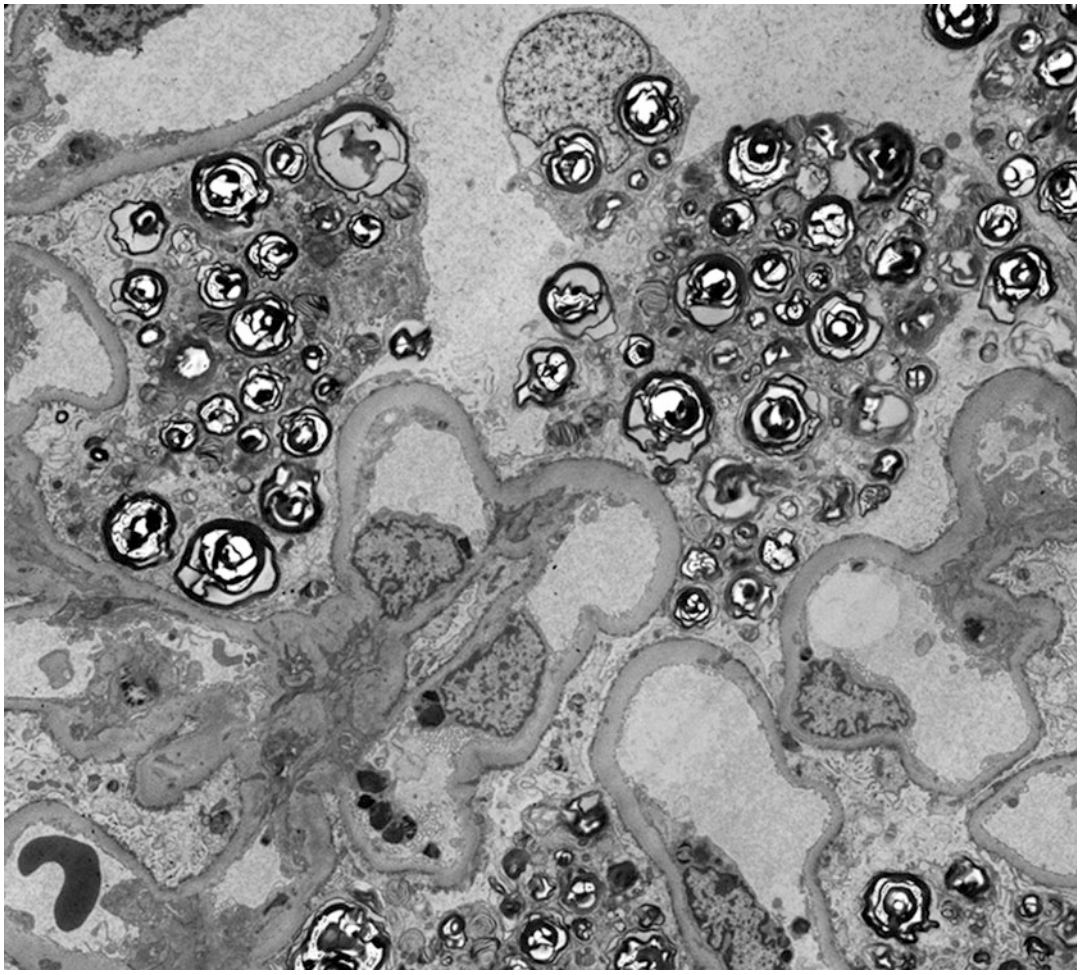

Fig. 6 Image of the "zebra body" inclusions seen in Fabry's disease (×2000)

care. The modifications of real time imaging and spring-loaded biopsy guns have established the procedure as a safe and effective method of obtaining kidney parenchyma.

Tissue Adequacy

The earliest case series from Iversen and Brun reported adequate tissue for diagnosis in less than half of their patients. The uses of spring-loaded automated biopsy guns and imaging advances have certainly improved tissue sampling, but there is still no absolute quantifiable metric to gauge adequacy. Oftentimes, sampling 10 glomeruli will not be diagnostic if there is a very focal lesion. Other times, even one glomerulus can provide the clinician enough information to make a diagnosis.

In modern practice, the number of cores required for an adequate sample depends on the length of the needle. Needles that take shorter cores may require three or more samples to ensure adequate sampling, whereas longer devices may take cores that are several centimeters long, and one pass may be all that is required. Kidney tissue can be viewed under a light or dissecting microscope directly as a wet mount to ensure that the core is kidney tissue rather than skeletal muscle, adipose tissue, or nonrenal organs. Immediate

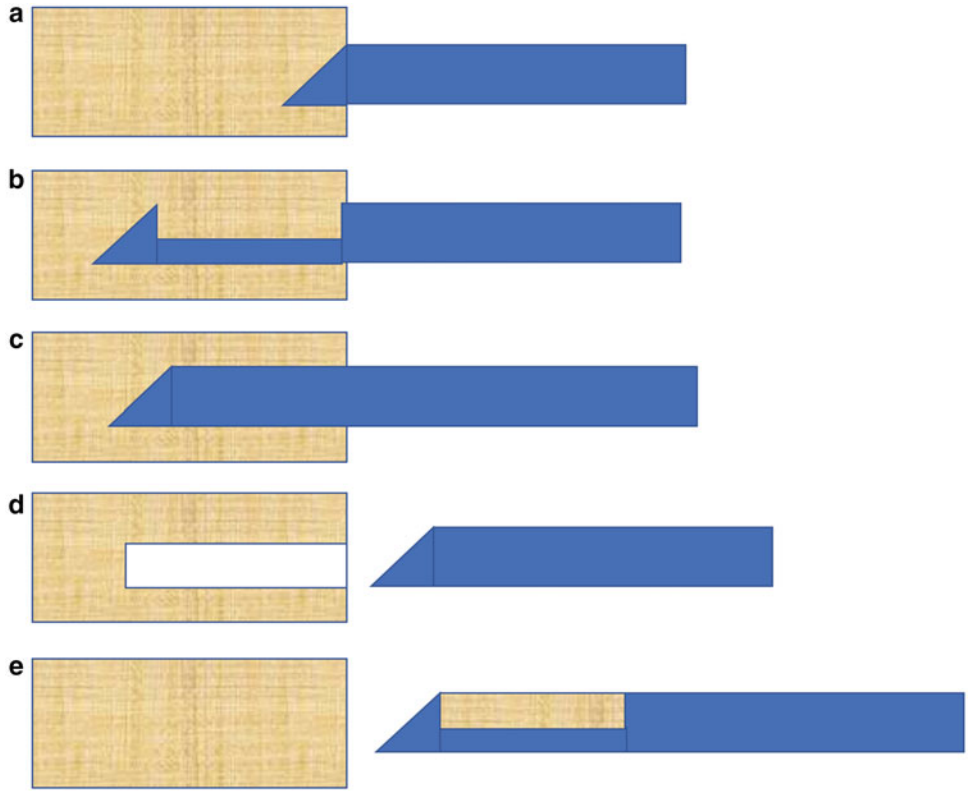

Fig. 7 Schematic of the cutting action of the spring-loaded biopsy gun. (**a**) Needle (in blue) introduced into kidney (brown). (**b**) When the gun is fired, the inner trocar is advanced, followed quickly by (**c**). (**c**) Outer cutting cannula is advanced. (**d**) Closed needle is retracted. (**e**) Tissue wedge obtained when outer cannula is retracted

direct visualization with a well-trained eye can also ascertain how much of the sample is cortex, medulla, or a mixture of both.

There is no absolute number of glomeruli that makes an individual biopsy diagnostic. The greater the number of glomeruli in the sample, the lower the likelihood of missing a focal lesion (e.g., segmental scar in FSGS, crescent in ANCA-related disease). For example, biopsy of a patient with nephrotic syndrome secondary to FSGS has a 35% chance of missing a segmental scar on light microscopy if only 10 glomeruli are sampled, and segmental scars are present in 10% of glomeruli. However, if 20 glomeruli are sampled, the statistical likelihood of missing a segmental lesion drops to 12% (Corwin et al. 1988). Based on these statistical analyses, it is ideal to have a sample taken that has at least 10 or more glomeruli for evaluation. Biopsies with smaller numbers of glomeruli can and should still be interpreted, but awareness of the possibility of a sampling error should be noted (Fig. 8).

Tissue Staining

Once a biopsy sample is deemed adequate by the proceduralist, the tissue is fixed and stained. Complete evaluation of kidney tissue obtained by renal biopsy typically entails three components:

- Light microscopy (LM)
- Immunofluoresence (IF)
- Electron microscopy (EM)

The standard approach is to remove the ends of cores for EM and place them in a suitable fixative such as formalin or glutaraldehyde. If the sample

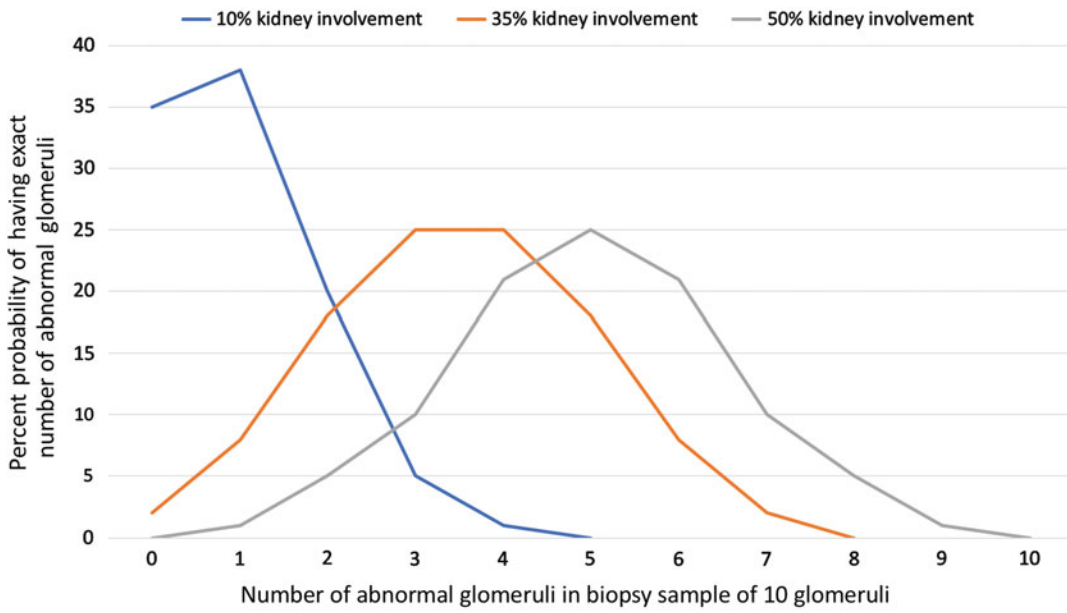

Fig. 8 The graph represents a binomial distribution of the number of abnormal glomeruli, which would be found in biopsy samples obtained from kidneys with an actual percentage of abnormal glomeruli of 10%, 35%, and 50% (represented by the blue, red, and green lines, respectively). As you can see, if a focal lesion is only affecting 10% of the glomeruli, there is a 35% chance of missing the lesion if only 10 glomeruli are sampled. (Data adapted from Corwin et al. 1988)

is mostly kidney cortex, the remaining core can then be divided for IF and LM, and additional passes may need to be made if adequacy is a concern. LM tissue is most commonly fixed with formalin, although various laboratories may use other solutions. IF is best performed on unfixed sections, so the sample reserved for IF should be set aside for separate transport to the laboratory (Walker et al. 2004). In situations where tissue might be limited, the clinician can make a decision to reserve larger cores for different purposes. This decision would be guided by determining which stain will provide the greatest clinical relevance for that individual scenario.

When examining tissue under the microscope, the pathologist and clinician should evaluate the four discrete compartments of the kidney (Fig. 9).

1. Glomeruli
2. Tubules
3. Interstitium
4. Vessels

Further details of kidney histopathologic interpretation and classification of glomerular diseases will be reviewed in future chapters.

Indications for Kidney Biopsy and Patient Preparation

The indications for kidney biopsy vary greatly from patient to patient. When a thorough history, physical, and ancillary blood and urine testing do not bring the clinician to a specific diagnosis, a kidney biopsy usually offers the highest diagnostic sensitivity. Other times, a kidney biopsy may be performed to ascertain the degree of activity versus chronicity to determine if the disease might be reversible. For example, a patient with systemic lupus erythematosus and a serum creatinine of 4.0 mg/dL may not be treated with aggressive immunosuppression for lupus nephritis if the biopsy revealed chronic fibrotic changes. The indications for kidney biopsy include, but are not limited to:

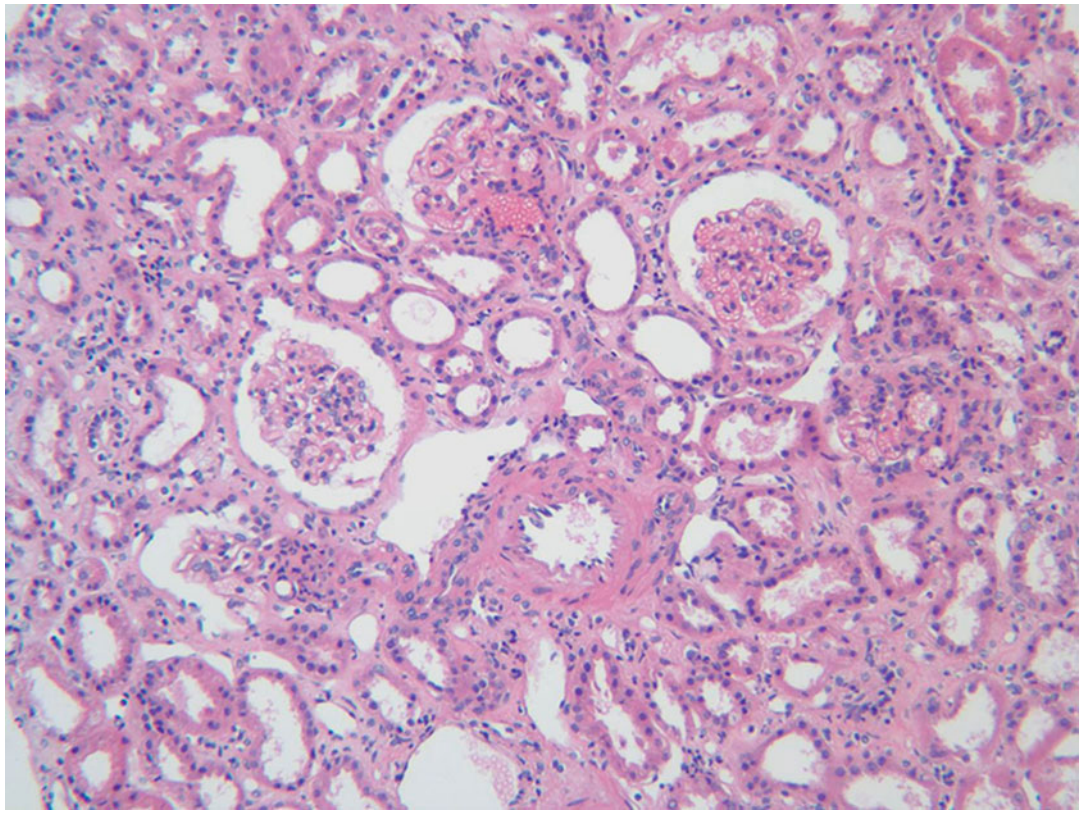

Fig. 9 Hematoxylin and Eosin stain demonstrating the four compartments of the kidney that are evaluated histologically

1. Unexplained decrease in glomerular filtration rate
2. Nephrotic or nephritic syndrome
3. Unexplained proteinuria
4. Isolated glomerular hematuria

The procedure is typically under performed under ultrasonographic or CT guidance by a nephrologist or interventional radiologists. Institutions or individuals may have differing prebiopsy protocols. However, most providers agree that the patient should have the following labs prior to the procedure:

1. Complete blood count
2. Prothrombin time/international normalized ratio
3. Activated partial thromboplastin time
4. Type and Screen

For nonemergent biopsies, antiplatelet or antithrombotic agents and nonsteroidal anti-inflammatory drugs should be discontinued at least 1 week in advance of a scheduled biopsy. For hospitalized inpatients that require heparin, this medication should be held approximately 6–12 h in advance to allow the aPTT to normalize. Blood pressure control should be optimized and informed consent and documentation of allergies should be performed in advance of an elective procedure.

Contraindications to Kidney Biopsy

The relative and absolute contraindications for percutaneous kidney biopsies have changed with the improved safety of the procedure. In general, the majority of clinicians and position papers agree that the following are absolute contraindications to kidney biopsy:

1. An uncooperative patient
2. Severe uncontrolled hypertension
3. Refractory bleeding diathesis

Relative contraindications include but are not limited to:

1. Hydronephrosis
2. Active skin infection over biopsy site
3. Anatomic abnormalities of the kidney (e.g., multiple bilateral cysts)
4. Solitary kidney

In many of these circumstances, kidney biopsy may be readdressed once the active issue (e.g., infection, hydronephrosis) is resolved. Anatomic abnormalities in one kidney may necessitate the contralateral kidney to be biopsied. Biopsy of patients with a solitary kidney will be discussed as a special consideration later in this chapter, but can now be considered by an experienced operator due to the improved safety reported using real time imaging. For situations in which there is an uncorrectable bleeding diathesis, non-percutaneous techniques (open or transjugular renal biopsy) may be acceptable alternatives.

Complications of Kidney Biopsy

Complications of kidney biopsy include bleeding, infection, puncture of another organ, and arteriovenous fistula formation. Puncture of liver, spleen, pancreas, and small bowel has all been reported but are very rare with real time imaging. Arteriovenous fistula formation may occur in patients if the walls of smaller veins and arteries are damaged. These typically are clinically silent and resolve spontaneously. In rare circumstances where fistulas form and become symptomatic, they can be addressed with arterial embolization. Bleeding complications can occur around the kidney (perinephric) or within the kidney and cause bleeding into the collecting system. This can lead to pain, a prolonged hospitalization, urinary obstruction, or a need for transfusion. As it is the most common and clinically relevant complication that can occur after kidney biopsy, it will be discussed in more detail.

The kidneys receive 20% of the cardiac output. With such a vascular organ, it might be expected that puncturing this would potentially lead to life-threatening blood loss. Fortunately, the majority of bleeding after kidney biopsy is restricted to the capsule and is self-limited. Prospective studies from the 1970s showed that CT imaging after kidney biopsy revealed evidence of perinephric hematoma in 14/20 patients, although only 1 had clinically evident bleeding. The remaining 13 patients that demonstrated bleeding on CT imaging had no change in hematocrit, blood pressure, or heart rate (Rosenbaum et al. 1978).

Minor bleeding complications such as microscopic or gross hematuria occur in the majority of patients and will resolve spontaneously. Major complications are usually defined as need for further treatment or intervention. This includes transfusion of blood products, coil embolization for persistent bleeding, or surgical repair. The overall incidence of transfusion requirements varies between studies, but a meta-analysis showed an overall transfusion rate of 0.9%, with a 0.6% rate of angiographic intervention. Death was reported on two cases out of a total of 8,971 procedures, for an overall incidence rate of 0.02% (Chung et al. 2014). Some single center studies show transfusion rates as high as 5–9%, but these include higher-risk populations (Korbet et al. 2014).

The change in hemoglobin concentration is evaluated postbiopsy to monitor for bleeding. One series reported an average drop in hemoglobin concentration of 0.9 g/dL in patients without clinically evident bleeding (Whittier et al. 2004). As a result of these findings, patients undergoing kidney biopsy can be expected to have a small decrease in hemoglobin concentration. However, a more severe drop of >2 g/dL is more suggestive (but not an absolute indicator) of clinically significant bleeding (Table 1).

Selecting the Needle Gauge

The modern spring-loaded devices use 14-, 16-, or 18-gauge needles, with an outer diameter of 2.11, 1.65, and 1.27 mm, respectively. The majority of renal biopsies are performed using 14- and

Table 1 Complication rate of native kidney biopsy

Complication	Reported frequency (%)	Number needed to harm
Gross hematuria	3	33
Perirenal infection	0.2	50
Arteriovenous fistula	0.4	250
Transfusion requirement	1	100
Intervention required to stop bleeding	0.6	166
Nephrectomy	0.01	1000
Death	0.02	500

16-gauge needles, with 18-gauge needles reserved for children or very small individuals. There is no significant difference in adequacy when comparing 14- and 16-gauge needles, but some studies have noted a lower yield with the smaller 18-gauge needles (Hogan et al. 2016). Some studies have shown a higher rate of transfusion with the use of 14-gauge needles although the risk was still quite low at 2.1%. Other studies have demonstrated no differences in complication rates or transfusion requirements based on needle size (Corapi et al. 2012). Based on a balance of yield and bleeding risk, most institutions use 16-gauge automated needles as the standard of care, with larger or smaller gauges available for unique circumstances (Fig. 10).

Fig. 10 Examples of the modern spring loaded automated cutting needles used for kidney biopsy. The length of needle can vary from 15 to 25 cm, and the gauge from 14 to 18. The Inrad device (bottom) also allows the operator to select the length of core to be taken (13 mm, 23 mm, or 33 mm)

Technique for Native Kidney Biopsy

Various institutions have differing protocols for performing kidney biopsies. In general, the patient should have peripheral intravenous access placed beforehand. The patient is then placed prone, and a pillow or towel can be placed under their abdomen if this does not cause significant discomfort. Some institutions will use ultrasound guidance to localize the kidney only, and then perform the biopsy with a "blind" approach. However, most institutions use real-time ultrasonography to visualize the entire procedure, as this leads not only to a lower rate of major complications, but also increases diagnostic yield. Once an appropriate path to the kidney has been identified, the skin is prepped and draped, and local anesthesia (usually 1% buffered lidocaine) can be injected to numb the skin and the tract of the biopsy needle. If the kidney is particularly deep, then a spinal needle may be necessary to apply anesthesia to the appropriate depth. A scalpel may be used to create a small skin incision to facilitate passage of the larger biopsy needle bore. Variations in kidney position with inspiration and expiration should be noted, and the patient should be instructed if and when to hold their breath in or out. If real time ultrasonography is available, then the biopsy needle will be guided directly into the lower pole via direct visualization, and the biopsy gun is deployed to take the core. Either kidney can be accessed for

sampling depending on the patient's position, anatomy, and surrounding tissue structures.

If the "blind" approach is being taken, the kidney is localized with ultrasonography prior to the procedure. The depth of the kidney is measured along with the angle of the ultrasound probe relative to the skin. Visualization of the kidney with inspiration/expiration is particularly important if the procedure is performed with this method. After skin prep and anesthesia is applied, anesthesia to the capsule is performed with a smaller gauge needle, and the operator will inject anesthesia down to the depth of the kidney measured during imaging. Oftentimes, the kidney can be felt with the finder needle, and tactile resistance can be noted as the needle tip enters through the capsule. Similar to the original description by Kark and Muehrcke, placing the needle to the level of the kidney and asking the patient to inhale and exhale deeply should cause the hub of the needle to smoothly swing cranially during inspiration and caudally during exhalation. Once the operator is comfortable with their positioning, the anesthetizing needle is withdrawn, a skin incision is made, and the blind approach is replicated with the biopsy needle.

Regardless of which approach is performed, once the spring loaded mechanism of the biopsy gun is deployed, the needle is withdrawn and the tissue in the chamber is mounted onto a slide for direct analysis. If necessary, more cores are taken until the clinician is satisfied with tissue adequacy. Once the procedure is complete, a local adhesive is placed over the skin incision, and the patient is turned supine which applies pressure over the biopsy site. Most protocols advise that the patient lie on their back over the next 4–6 h with frequent monitoring of vital signs during this time period.

There are few studies comparing the "blind" approach versus real time ultrasound imaging during kidney biopsy. One study evaluated post-biopsy complications by comparing these two techniques while also comparing the primary operators (nephrologists vs. interventional radiologists). No difference in complications was noted regarding the two techniques (Maya et al. 2007). Other studies have shown a higher complication rate and lower yield when using the blind approach. As a result, most institutions have moved away from using ultrasonography for localization only and have embraced the real time imaging approach.

Technique for Transplant Kidney Biopsy

Transplant renal biopsy is generally performed to evaluate for renal allograft dysfunction. Acute or chronic rejection, recurrence of primary disease, and other etiologies can only be definitively diagnosed with direct histologic examination of the tissue. Some institutions also perform protocol transplant biopsies at scheduled intervals to diagnose subclinical allograft dysfunction, but this is not a universal standard. The biopsy technique for transplanted kidneys is very similar to the native organ, but the approach is modified for the graft's new position.

In the early 1990s, it was routine to perform blind biopsies of the graft using ultrasound localization, or even with localization based solely on physical palpation and anatomic landmarks. Today, real time ultrasound guidance is nearly universal at all transplant centers. The preprocedural steps of optimizing coagulopathy and blood pressure are the same as described above for native biopsies. However, as the transplanted kidney lies in the iliac fossa overlying the iliopsoas muscle, it occupies the extraperitoneal space. Depending on the thickness of the subcutaneous tissue, the kidney is very superficial, and either the upper or lower pole can be accessed depending on the position it was transplanted. On rare occasions, the kidney transplant may be placed intraperitoneally; real time imaging will confirm this location so the procedure can be modified accordingly with special attention to avoiding surrounding bowel.

Kidney Biopsy Procedure in Unique Circumstances

Special considerations need to be given to specific populations that require percutaneous kidney biopsy. We will discuss:

- Pregnancy
- Solitary Kidneys
- Mechanical Ventilation

Pregnancy

There are many issues that arise when considering percutaneous kidney biopsy in a pregnant patient. The physical space occupied by the gravid uterus has an impact on the organ location and may also detract from the patients ability to lie in the prone position. Additionally, the risks of the procedure apply not only to the mother but also her fetus. Due to these concerns, most practitioners are wary of performing a kidney biopsy during pregnancy. Unless the diagnosis will alter management before delivery, the biopsy should be deferred until the postpartum period. However, a histologic diagnosis during pregnancy often needs to be emergently confirmed. These include scenarios such as evaluating for preeclampsis versus de novo glomerular disease or determining treatment options for lupus nephritis, which may be limited due to their teratogenic nature.

Data on complications after kidney biopsy in pregnancy are sparse. A meta-analysis showed that the risk of complications was highest in a "grey area" of pregnancy between 23 and 28 weeks gestation. The total complication rate remained relatively low at 1.3%. Interestingly, the results of the kidney biopsy altered therapeutic management in about two-thirds of patients (Packham et al. 1987). This information can be extremely useful in counseling regarding continuation or termination of pregnancy and maternal-fetal morbidity. Needless to say, if percutaneous kidney biopsy is deemed to be necessary in pregnancy, real time imaging is recommended if possible.

Solitary Kidneys

As outlined above, a solitary kidney is considered a relative contraindication for kidney biopsy. The rationale is not because of a higher incidence of complication, but rather that the consequence of an adverse event (e.g., nephrectomy) will be much more deleterious in these individuals. Prior to the 1990s, a solitary kidney was considered an absolute contraindication to percutaneous biopsy. However, an improved safety profile arrived with the acceptance of real-time ultrasound guidance and in automated biopsy guns. As a result, some institutions began performing biopsy of solitary kidneys with small but encouraging results (Mendelssohn et al. 1995). In the event that biopsy of a solitary kidney is performed, the procedure should be performed by an experienced operator under real time imaging guidance, and an extended observation to monitor for bleeding should be the standard of care.

Mechanical Ventilation

The intensive care is fraught with acute kidney injury from sepsis, ischemia, and toxins. However, severe systemic diseases such as ANCA associated vasculitis and thrombotic microangiopathy are also frequently encountered in this setting. A percutaneous kidney biopsy can still be obtained cautiously in this critically ill population. Particularly, patients on mechanical ventilation pose unique positional problems for the percutaneous approach. This can be overcome if the intubated patient can be prone positioned for the short period of time needed to perform the biopsy. Real time imaging can often reveal a satisfactory approach in the lateral decubitus position if proning is not possible. The movement of the kidney with the ventilator can be predicted if the patient is maintained on assist control ventilation. This allows the proceduralist to specifically time when the cutting edge is deployed into the kidney. One paper evaluated renal biopsy in ICU settings, with 57% of the patients on mechanical ventilation. A total of 98% of patients had sufficient yield, with 21 mean glomeruli per biopsy. Bleeding complications were higher in this study, with 22% having bleeding severe enough to warrant transfusion. However, baseline levels of hemoglobin were lower, and the biopsy may not necessarily have caused the transfusion requirement in all of these

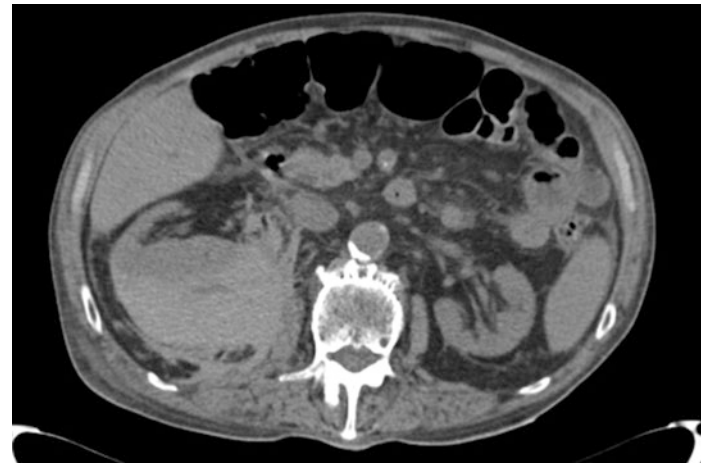

Fig. 11 Computed tomography of the abdomen without contrast reveals a large right retroperitoneal hematoma following kidney biopsy

patients. Despite the increased bleeding risk, 21% of these patients had biopsy findings that modified their treatment (Augusto et al. 2012). With most intensive care units now adopting point of care ultrasound technology, mechanical ventilation should not be a significant barrier to pursuing a kidney biopsy when indicated.

Addressing Postbiopsy Complications

Despite the relative safety of percutaneous kidney biopsy, prompt recognition of postprocedural complications and knowledge of available institutional resources is of utmost importance. The majority of complications occur within the first 24 h after the procedure. Suspicion for bleeding can be obvious (severe pain, hypotension) or subclinical (drop in Hb concentration of 2 g/dL). Immediate assessment of the patient's hemodynamic stability to rule out life-threatening hemorrhage is the first step followed by imaging to evaluate for perinephric bleeding. Ultrasound scanning can be performed relatively quickly and can identify up to 70% of hematomas, but is not as sensitive as CT imaging. There is no universal consensus on the routine use of any postprocedure imaging, and these scans are typically reserved for when there is suspicion for bleeding.

In the event that perinephric bleeding is substantial and is accompanied by a corresponding drop in hemoglobin, transfer to an intensive care setting for close monitoring is warranted. Transfusions and serial blood counts can be given, and stabilization of the hemoglobin suggests that the bleeding is contained. Continued bleeding warrants evaluation for arterial embolization of the vascular supply (typically performed by interventional radiologists) or surgical evaluation (typically performed by transplant surgeons or urologists) (Fig. 11).

Future Directions for Kidney Biopsy

The future era of information derived from the kidney biopsy is moving towards precision and personalized medicine. Molecular information has led to targeted chemotherapy in the field of oncology, as it moves beyond diagnosis by also predicting response to treatment. The fields of nephrology and nephropathology are moving beyond light microscopy and immunofluorescence into areas like proteomics (study of individual proteins), which has already transformed our understanding of diseases that were formerly lumped into the bucket of "renal amyloid." Using glomerular laser-capture microdissection and subsequent mass spectrometry on the samples has allowed us to identify the protein precursors of amyloid such as transthyretin, apolipoprotein A1, or beta-2 microglobulin.

Similarly, extraction of tissue from biopsy samples can provide insight into the molecular mechanisms that lead to their pathogenesis. This

has already been performed in diabetic nephropathy using gene microarray to determine overexpressed genes in diabetic nephropathy compared to healthy individuals (Baelde et al. 2004). Another exciting endeavor that will aid our understanding of diseases is the Precision Medicine Project, which was launched by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Using human kidney biopsy specimens from participants, the initiative aims to create a kidney tissue atlas using single cell RNA sequencing to define and identify cells, pathways, and targets for specific diseases. The future of kidney biopsy interpretation looks bright and will incorporate morphology, immunopathology, serology, genetics, and molecular information. Using these new technologies, the information from the kidney biopsy will provide the clinical information needed to optimize disease-specific treatment on an individualized basis.

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Mechanisms of Glomerular Disease

2

John F. O'Toole, Dhruti P. Chen, and John R. Sedor

Contents

Abstract

Glomerular diseases, clinically manifesting with proteinuria, hematuria, or azotemia, result from complex disease processes. This complexity is driven by an individual's genome, unique environmental exposures, and, importantly, through their interaction mediated by innate and adaptive immune responses. The astonishing complexity of each of these aspects is emerging through the lens of new technologies that provide the ability to interrogate human biosamples, including kidney biopsies, in exquisite molecular detail. An individual's genetic background, their immune responses, and environmental exposures interactively contribute to disease pathogenesis to shape complex disease phenotypes such as glomerulonephritis. In this chapter we review the general pathogenic mechanisms that drive multiple glomerular disease diagnoses and have selected a few specific examples to illustrate how these pathogenic mechanisms influence disease initiation or progression. We have divided the disease mechanisms into the general domains of genetics and innate and adaptive immunity and highlight how genetic background modifies the immune response to cause glomerular diseases in susceptible individuals.

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Glomerular injury · Glomerular disease · Innate immunity · Adaptive immunity · Heredity · Genetics

Introduction

Hematuria and proteinuria are the hallmark phenotypes of glomerular diseases, which are grouped by shared clinical presentations and kidney histopathology. However, patients diagnosed with the same glomerular disease can have variable disease progression and responses to treatment. In this chapter, we will review general mechanisms of glomerular injury; disease-specific mechanisms are discussed in subsequent chapters. The pathogenesis of glomerular diseases is quite complex. We will focus on their genetic mechanisms and the role of the immune response to environmental and self-antigens, emphasizing, where appropriate, that genetic modification of the immune responses confers host susceptibility to glomerular diseases.

Genetic Mechanisms

Advances in technology now permit genome-wide molecular characterization of individual patients in timescales that can impact clinical decision-making. Among these emerging technologies, the contribution of genetic variation to glomerular disease pathogenesis has been best elucidated. Some genetic variants can drive glomerular disease in all individuals who carry them, such as autosomal recessive mutations in the podocin gene (*NPHS2*) leading to focal segmental glomerulosclerosis (FSGS) (i.e., complete penetrance). Genetic variants can also be associated with glomerular diseases in a less predictable fashion, where the presence of the genetic variants does not invariably predict the appearance of the disease phenotype (i.e., incomplete penetrance). An important example of an incompletely penetrant genetic variation is the kidney disease risk variants in the *APOL1* gene, which have been associated with FSGS, hypertension-associated kidney disease, and HIV-associated nephropathy (HIVAN) in African Americans (Genovese et al. 2010; Kopp et al. 2011). The association of *APOL1* variants with these diseases is strong, but most individuals who carry the disease-associated genetic variants do not develop kidney disease. Although most single-gene disorders are associated with one disease diagnosis, different mutations in a single gene can manifest as distinct glomerular disease phenotypes (i.e., pleiotropy). For example, mutations in type IV collagen are known to cause Alport syndrome, thin basement nephropathy, and hereditary FSGS (Malone et al. 2014).

Glomerular diseases are characterized by the structural and functional damage to the glomerular filtration barrier. The glomerular filtration barrier is made up of three distinct structures, which assemble a size and molecular charge barrier to allow solute clearance while retaining plasma proteins within the intravascular space. These components are (1) podocytes and interposed slit diaphragm, (2) the fenestrated endothelium of the glomerular capillaries which maintains a negative charged surface, and (3) the glomerular basement membrane (GBM), an extracellular matrix sheet composed of four major protein components. Genetic variants, which cause defects in structure or function of any of the components of glomerular filtration barrier, can lead to proteinuric kidney diseases. Here we will discuss selected single-gene mutations associated with glomerular filtration barrier function and highlight principles illustrated by these specific examples. Subsequent chapters will discuss specific genetic contributions for each particular glomerular disease.

Single-gene mutations have been identified in many glomerular diseases, and the pathogenic contribution of these monogenic causes can differ according to the population studied. For example, monogenic causes of glomerular diseases are most common in pediatric populations, and their prevalence declines as the median age of the patient population increases. With the increasing application of molecular genetic diagnostic studies to patients with early onset chronic kidney disease (patients less than 25 years old), single-gene mutations have been identified in approximately 20% of cases. The number of disease-causing genes also continues to increase

illustrated by a recent review where over 200 genes have been implicated in the pathogenesis of early onset kidney diseases, which includes glomerular disease (Vivante and Hildebrandt 2016). Additional variability in the contributions of genetic mutations to disease pathogenesis arises from the degree of penetrance, as well as, inheritance modes that include autosomal recessive, autosomal dominant, or X-linked patterns.

FSGS and diffuse mesangial sclerosis (DMS) highlight the contributions of molecular genetic diagnostics to our understanding of glomerular diseases. FSGS and DMS are defined by their renal histopathology, and both present clinically in young children as steroid-resistant nephrotic syndrome (althpough FSGS usually presents later in adolescence or adulthood). Genetic studies have revealed that both diseases are caused by genetic variants that disrupt podocyte function. Podocytes have a central role in the maintenance of glomerular filtration barrier, and their function is based on an adaptive cytoskeleton that ramifies into extensive, interdigitating foot processes. Podocytes are terminally differentiated and are no longer able to proliferate; therefore, any insult to podocytes (i.e., podocytopathy) leading to irreversible injury or loss results in the development of chronic glomerulosclerosis. Podocyte depletion, a phenotype that characterizes glomerular and other chronic kidney diseases, can result from genetic and acquired mechanisms of injury and has been proposed as the final common pathway for progressive chronic kidney diseases (Hodgin et al. 2015). Podocytopathies develop when there are major defects in the structure of the slit diaphragm, the cytoskeleton, or the foot processes of podocytes (Wiggins 2007). Family-based genetic studies have revealed that heritable mutations are important contributors to the pathogenesis of FSGS/DMS and the gene products of these genes are expressed in the podocyte, supporting podocyte dysfunction as a mechanisms of glomerular diseases. At least 23 mutations with recessive mode of inheritance and 7 mutations with autosomal dominant inheritance have been associated with steroid-resistant nephrotic syndrome (Hildebrandt 2016). Interestingly, the genes associated with podocytopathies can be clustered into signaling modules that disrupt podocyte cytoskeleton and mitochondrial function (Hildebrandt 2016).

Nephrin (*NPHS1*) encodes a transmembrane protein that is a critical component of the slit diaphragm and a member of the immunoglobulin superfamily of cell adhesion proteins (Pleasant 2014; Hinkes et al. 2007). *NPHS1* mutations are associated with early onset proteinuria, also known as congenital nephrotic syndrome (CNS) of the Finnish type (CNF). CNF is caused by two specific nephrin mutations: Fin-major is a two-base pair deletion in exon 2, and Fin-minor is a single base substitution in exon 26, both leading to premature truncation of the protein. However, these mutations are not common in non-Finnish populations, although other nephrin mutations have been found to cause CNS in these populations. The different allele frequencies of Fin-minor and Fin-major highlight the importance of ancestry in the genotype-phenotype associations. While the exact mechanisms initiated by these *NPHS1* mutations are not understood, their association with clinical glomerular disease illustrates the concept that disruption of critical podocyte function is causal.

Podocin, encoded by *NPHS2*, is the most common monogenic cause of FSGS and is an integral membrane protein, which localizes to the slit diaphragm and interacts directly with nephrin. Podocin, as part of a multi-protein complex, links the slit diaphragm to the actin cytoskeleton (Roselli et al. 2002; Schwarz et al. 2001; Huber et al. 2001, 2003). The podocin-nephrin interaction is required for signal transduction from the slit diaphragm to the cytoskeleton (Huber et al. 2003) that regulates actin dynamics and the foot process cytoarchitecture necessary for normal glomerular filtration barrier function. Interestingly, as predicted from their shared role in podocyte slit diaphragm signaling, mutations in podocin and nephrin associate with similar clinical disease phenotypes (Hinkes et al. 2007), although patients with nephrin mutations tend to present at an earlier age. This highlights the concept that genes in common functional pathways generate similar clinical phenotypes.

While some monogenic causes of glomerular disease are associated with isolated kidney disease phenotypes, many single-gene mutations have extrarenal manifestations. *WT1* mutations are major contributors to development of early onset steroid-resistant nephrotic syndrome and associate with DMS (Hinkes et al. 2007). The *WT1* gene encodes a zinc finger transcription factor that is critical for normal kidney and gonadal development. It also controls nephrin expression, which is a key protein component of the slit diaphragm as previously discussed. *WT1* mutations, however, not only cause podocyte dysfunction and glomerular diseases but are also associated with Denys Drash and Frasier syndromes, which are characterized by additional urogenital abnormalities including increased incidence of Wilm's tumor (which may be the first symptom of disease) and pseudohermaphroditism (Niaudet and Gubler 2006). Knowing these extrarenal manifestations has clinical utility. While treatments of glomerular diseases associated with a single-gene mutation (like *WT1* variants), these patients and their families need counseling for the associated phenotypes that can be actionable.

Another important point illustrated by genetic studies is that there can be overlap between diseases that are typically considered to be phenotypically distinct. Genetic testing has been able to provide a molecular diagnosis in some cases that have been misclassified by clinical phenotyping. This is has been demonstrated in patients clinically diagnosed with FSGS, who carry mutations in collagen genes typically associated with Alport syndrome (Malone et al. 2014). In these cases, the molecular genetic diagnosis may provide useful information about disease pathogenesis. As opposed to FSGS where most mutations have been identified in genes expressed in the podocyte, Alport syndrome is caused by genetic defects in genes encoding for type IV collagen, one of the four components of the GBM (Gubler 2008). These genetic defects presumably cause increased mechanical fragility of the GBM eventually leading to progressively damaged and thickened basement membrane (Savige 2014). In spite of distinct genetic mechanisms, the clinical phenotype can overlap.

Single-gene defects can have onset later in life and may be common. As we and others have reviewed (O'Toole et al. 2017), excess risk in African Americans for nondiabetic chronic kidney diseases, including FSGS in adults and children, is largely explained by large effect, genetic variations in the *APOL1* gene, which encodes apolipoprotein L1 (APOL1). A recessive inheritance model best explains this association, suggesting a loss of function is responsible for kidney disease. Despite a recessive mode of inheritance, the kidney disease risk genotype is common in the African American community; between 12% and 15% of African Americans carry two *APOL1* risk alleles. Most kidney disease risk allele carriers do not develop disease, consistent with the idea that a "second hit" is needed to cause kidney disease. APOL1 is an innate immune molecule that is toxic to many trypanosome species, emphasizing the role of immune response modification by genetic variation in glomerular disease pathogenesis. However, a trypanosome subspecies, responsible for some African sleeping sickness, expresses a protein that blocks the trypanolytic effect of APOL1. A single kidney disease variant circumvents the block and restores APOL1's trypanolytic function, conferring a selective advantage to carriers and explaining the frequency of the kidney disease risk alleles in the African American community. The mechanisms of variant APOL1-associated kidney injury are not understood (O'Toole et al. 2017). Although the circulating APOL1 mediates its trypanolytic function, APOL1 is synthesized by the podocyte and likely drives glomerular injury. Many investigators believe that variant, but not reference, APOL1-dependent podocyte cytotoxicity causes glomerular disease.

Genome-wide association studies (GWAS), which assay genetic variation across the entire genome in large numbers of subjects with specific phenotypes, have proved to be powerful tools to identify genetic loci regulating complex traits and have identified loci associated with immune-mediated renal disease. Disease susceptibility loci have been most robustly mapped in IgA nephropathy (IgAN), a form of progressive

glomerulonephritis characterized by mesangial cell proliferation and IgA deposition (Wyatt and Julian 2013; Kiryluk and Novak 2014). IgAN is a leading cause of ESRD among East Asians and the most common form of primary glomerulonephritis among Europeans. The defect in IgAN may be extra renal due to aberrant glycosylation of IgA (Silva et al. 1982; Bumgardner et al. 1998; Moldoveanu et al. 2007). GWAS loci include genes that fit within a multi-hit pathogenesis model, providing molecular bases for IgAN disease pathogenesis. These "hits" include increases in circulating galactose-deficient IgA, the production of anti-glycan antibodies leading to formation of immune complexes which deposit in the mesangium and initiate injury (Kiryluk and Novak 2014; Magistroni et al. 2015). A number of the candidate IgAN genes within associated loci are shared with other immune-mediated diseases, such as rheumatoid arthritis, lupus, and inflammatory bowel disease (Magistroni et al. 2015).

Interestingly, loci within the genes encoding major histocompatibility complex (MHC) class II molecules have been associated several glomerular diseases including IgAN, ANCA vasculitis, idiopathic membranous nephropathy, and steroid sensitive nephrotic syndrome. These associations suggest that genetic modification of immune responses (discussed below) is a critical component of glomerular disease pathogenesis. The MHC is the most diverse region of the human genome (Vukmanovic et al. 2003), and this diversity has been maintained by selective pressures. MHC molecules initiate immune responses by presenting short peptides to T lymphocytes, which can both protect the host against an environmental stress or dysregulate autoimmune and inflammatory processes causing disease. The association of MHC loci with some glomerular diseases suggests these molecules initiate and maintain an immune response that disrupts the glomerular filtration barrier. Although specific antigens presented by the MHC to cause glomerular disease remain obscure, a GWAS in primary membranous nephropathy demonstrated significant associations between variants in the MHC region (*HLA-DQA1*) and the phospholipaseA2 receptor gene (*PLA2R1*), which encodes the podocyte autoantigen targeted in the majority of patients with this kidney-specific, autoimmune disease (Salant 2013). Although these associations were independently significant, the risk for developing membranous nephropathy substantially increased in patients homozygous for susceptibility variants in both loci. This observation suggests an interaction consistent with genomic modification of the immune response to specific antigenic exposure (in this case, the PLA2R protein) to result in disease in a genetically susceptible host. The mechanisms by which the *PLAR2* gene variants modify the PLA2R protein remain ill defined.

Mechanisms of Immune-Mediated Kidney Injury

The immune response, which can be broadly divided into the innate and adaptive immune systems, is a major contributor to the pathogenesis of glomerular disease. The immune system functions at the interface of the individual and the environment and as such must be capable of recognizing both self and nonself, responding to virulent microbial threats or tissue damage and regulating inflammatory responses. Dysregulation of these immune functions often plays a central role in glomerular pathology, a fact that is highlighted by the importance of treatments that target the immune system.

Innate Immunity

The innate immune system is more evolutionarily ancient than the adaptive immune system (Hoffmann et al. 1999). It is composed of physical barriers, molecules in the circulation or secretions that suppress microbial infection, and immune cells with pattern recognition receptors (PRRs) on their cell surface. These PRRs recognize molecular motifs common to microbial pathogens known as pathogen-associated molecular patterns (PAMPs). Damage-associated molecular pattern (DAMP) molecules are derived from host cells under stress and, similar to PAMPs, activate the

innate immune system. The innate immune system is constitutively present and ready to respond to pathogens. Unlike the adaptive immune system, it does not rely upon gene rearrangements or clonal expansion to engage and suppress microbial challenges. On the other hand, the innate immune system lacks the exquisite flexibility and lasting immunologic memory that is characteristic of the adaptive immune system. The major effectors through which the innate immune systems mediate glomerular injury are the complement system and immune cells, such as dendritic cells (DCs), macrophages, and neutrophils.

The complement pathway occupies a central role in the innate immune system where it provides protection from infection and regulates inflammation. Primary defects in the complement components or its dysregulation by activating or inhibiting autoantibodies can mediate kidney injury. In addition, processes that originate outside of the complement system, such as those triggered by the adaptive immune system, may lead to downstream processes that eventually lead to the engagement of the complement pathways, which then modify the disease phenotype (Mathern and Heeger 2015; Thurman and Nester 2016).

The complement cascade can be initiated through three different pathways: the classical pathway, the lectin-binding pathway, and the alternative pathway. Each of these pathways is comprised of different molecular components that respond to distinct molecular triggers. The classical pathway is responsive to apoptotic cells or the Fc portion of IgM or IgG molecules encountered within the proper antigen-antibody context. The lectin-binding pathway is triggered by the recognition of carbohydrate modifications that are often found on the surface of microorganisms. In contrast to the classical and lectin pathways, the alternative pathway is maintained in a constitutive state of low-level activation, referred to as the "tickover" mechanism (Mathern and Heeger 2015; Thurman and Nester 2016). This low-level alternative pathway activity results from structural instability of the C3 factor allowing interaction with factor B at a slow basal rate. This slow rate of activation can be accelerated upon encountering bacterial surfaces or products. Upon activation the mature C3 convertase of the alternative pathway is formed, C3bBb, which consists of the two cleavage products of C3 and factor B.

The alternative pathway can be activated in fluid phases, but a critical component of tissue injury involves the targeting to and activation of these molecules on the cell surface. Bacteria or bacterial toxins can also be molecular triggers. Triggering stimuli in each of these pathways activates pathway-specific proteases leading to a cascade of proteolytic events that amplify the response and converge on the final common complement pathway that generates membrane attack complex (C5b-9). Some complement cleavage products have important ancillary functions such as the C3a and C5a cleavage products, known as anaphylatoxins, which mediate inflammation through binding to their G-protein coupled receptors on immune cells. In addition to binding microbes and immunoglobulins, the complement system has additional roles in the clearance of immune complexes and the chemoattraction of macrophages and neutrophils to sites of inflammation.

The classical pathway is activated by the binding of the Fc domain of IgM or IgG to a heteromeric complex composed of six C1q subunits, two C1r subunits, and two C1s subunits, ultimately leading to the cleavage of C2 and C4 by C1s. Following these cleavage events, the cleavage products C2a and C4b combine to form the C3 convertase, which it shares with the lectin-binding pathway and is capable of cleaving C3 into C3a and C3b, thereby amplifying and perpetuating the complement response.

The lectin pathway is activated when mannose-binding lectins recognize and bind cell surface glycoproteins commonly encountered on microbes, but not human cells. This leads to activation of serine proteases, the MASP proteins, which cleave C4 and C2 leading to the formation of C3 convertase, the point of convergence with the classical pathway.

Once C3 is cleaved into C3a and C3b by a C3 convertase specific to each complement activation pathway, an additional molecule of C3b is bound

to the C3 convertase of the classical/lectin pathway (C4bC2a) or the alternative pathway (C3bBb). The addition of C3b to the C3 convertase transforms it into a C5 convertase, thereby activating the terminal complement pathway. The terminal complement pathway is initiated by the cleavage of C5 to C5a with the subsequent recruitment and binding of C6–9 forming the membrane attack complex for the destruction of targeted cells and microorganisms.

Several types of mononuclear immune cells also have important roles in the pathogenesis of glomerular diseases. These cells include the dendritic cells, which are the primary antigen presenting cell of the immune system and the macrophage, whose central role is the phagocytic removal of microorganisms and cell debris. Cell surface markers distinguish macrophages from dendritic cells. Mononuclear phagocytes expressing CD11c + are classically defined as dendritic cells and CD11c negative mononuclear phagocytes as macrophages. However, the markers used to define each of these cell types and their subtypes are not strictly unique to each cell lineage, leading to phenotypic and functional overlap between these immune effector cell types (Weisheit et al. 2015). The emergence of single cell, genome-wide RNA sequencing techniques is likely to redefine these populations and may provide a clearer understanding of the defining functions for macrophages and dendritic cells.

Neutrophils are the most abundant type of white blood cell in the circulation, and they are instrumental in the immediate response to localized tissue damage or infection. As they circulate, they recognize and bind to infection- or inflammation-activated endothelium, which express adhesion receptors for neutrophils. The endothelium is activated by cytokines derived from nearby macrophage or dendritic cell after binding DAMPs or PAMPs in the surrounding tissue (Caster et al. 2017). When the interactions between a neutrophil and endothelial cell are sufficiently strong, the neutrophil adheres to the endothelial surface and transmigrates across the vessel wall into the interstitium. Within the interstitium, the neutrophil migrates toward chemoattractant signals; these include inflammatory cytokines, antibodies, or complement components, to the site of inflammation or infection. Upon reaching extravascular sites of inflammation, neutrophils are able to recruit additional neutrophils through the secretion of other chemoattractants and eliminate microbial invaders through phagocytosis or trapping of microbes through the process of NETosis (Gupta and Kaplan 2016). NETosis is a specialized form of cell death unique to neutrophils involving the extravasation of a lattice of decondensed chromatin, associated intracellular molecules derived from neutrophilic granules, and histone proteins. NETosis can be stimulated by a variety of pathogens through signaling pathways, which involve calcium release from the endoplasmic reticulum that ultimately leads to the downstream decondensation of chromatin. Extracellular presentation of this decondensed chromatin with associated accessory molecules traps microorganisms and stimulates dendritic cells, macrophages, and T cells to mount a vigorous antimicrobial response. Disordered NETosis has been implicated in the initiation and progression of several glomerular diseases (discussed further below), including lupus nephritis and antineutrophil cytoplasmic antibody associated vasculitis.

Adaptive Immunity

The adaptive immune response is characterized by its exquisite ability to distinguish self- from nonself-antigens and the ability to establish immunologic memory after exposure to foreign antigens. The specificity of the adaptive immune system is imparted by gene rearrangements in the DNA encoding T-cell receptors, B-cell receptors, and antibodies in T and B cells, respectively. These molecules undergo a selection process both centrally and peripherally to ensure that they are able to recognize foreign antigen in the context of the proper major histocompatibility complex (MHC) but do not mount an immune response against self-antigens. Foreign antigen is derived from the environment and includes allergens and infections. These foreign antigens, especially in the context of infection, are important

contributors to the pathogenesis of glomerular disease. There are a number of pathways by which infection can cause glomerulonephritis, and distinct molecular mechanisms may drive each of these pathways. Infection is capable of inducing autoimmunity, which may then contribute to the pathogenesis of glomerulonephritis in susceptible individuals (Couser and Johnson 2014). In the following section, we will summarize the major mechanisms that may contribute to the generation of autoimmunity, thereby leading to glomerular pathology.

Presentation of hidden antigens. Presentation of antigens not normally seen by the immune system may occur in the setting of tissue damage. This may be sterile tissue injury or after infection leading to tissue destruction such as a lytic virus infection. The process of NETosis, a specialized form of neutrophilic cell death discussed above, is a specific example of a setting where antigens normally sequestered intracellularly may be presented to the adaptive immune system. This mechanism may be particularly relevant in the pathogenesis of systemic lupus erythematosis (SLE) nephritis (Gupta and Kaplan 2016). Autoantibodies against several components of the neutrophil extracellular traps (NETs) are found in the setting of SLE, including double-stranded DNA and histones. Dysregulation of NETosis, due its aberrant activation or the impairment of NET clearance, has been proposed to contribute to the initiation and progression of SLE and other glomerular pathologies involving autoantibodies.

Molecular mimicry. Autoantibodies may be formed when a self-antigen has sufficient molecular similarity to a pathogenic antigen to be recognized by antibodies that initially target the pathogenic antigen. Importantly, cross-reactivity of antibodies to self-antigens is determined by the secondary sequence and does not necessarily depend upon the presence of shared primary sequence between the pathogenic and self-antigens. This mechanism may be an important contributor to autoantibody generation against the α-3 type IV collagen in glomerular basement membrane disease (Li et al. 2017).

Generalized activation of preexisting autoreactive T and B cells (adjuvant or bystander effect). The bystander effect is characterized by engagement of pattern recognition receptors on innate immune cells by microbial molecules, which releases inflammatory cytokines that are capable of activating quiescent autoreactive T and B cells generating an autoimmune response (Root-Bernstein and Fairweather 2014).

Epitope conformational changes. Environmental exposures have been hypothesized to cause protein modifications or oxidative damage that lead to conformational change of the endogenous protein, exposing previously masked epitopes that can trigger the generation of autoantigens. An example of a conformational change that may in part contribute to glomerular disease is the loss of cross-linking between the non-collagenase domain 1 of α3-α4-α5 type IV collagen chains. This change in conformation generates a neo-antigenic epitope from approximation of two discontinuous peptides within the α3 type IV collagen chain and formation of the autoantibodies that cause anti-glomerular basement membrane disease (Dammacco et al. 2013).

Epitope spreading. An adaptive immune response can shift from an initial, highly antigen-specific and very narrow T- or B-cell response to an increasingly diversified response over time. The original T- or B-cell epitope expands to include additional epitopes on the antigenic molecule (i.e., Intramolecular) or even to different antigenic molecules entirely (i.e., Intermolecular) (Cornaby et al. 2015). In the case of infection, this leads to a more robust immune response against microbial antigens; however, in the case of autoimmunity, this can reinforce the immune response against self-antigens. Epitope spreading has been observed in cases of membranous nephropathy with anti-PLA2R1 antibodies and has been associated with worse clinical outcomes (Seitz-Polski et al. 2017).

Antigen and antibody complementarity. This mechanism of autoimmunity can be induced by peptide fragments that are complementary to autoantigens. This concept is based upon the observation that peptides translated from RNA transcribed from the sense and antisense strands of DNA are complementary, that is, they can bind together based upon the hydrophobicity of their amino acid side chains.

Peptides with complementarity to autoantigens may be derived from microbial proteins or may be transcribed from the antisense strand of an endogenous self-protein.

In addition to synthesis of a peptide complementary to an autoantigen, this mechanism of autoimmunity also requires generation of antibodies that recognize specific peptide sequences of other, target antibodies, collectively referred to as an antibody's idiotype. The idiotype of an antibody or T-cell receptor (TCR) is determined by stretches of amino acid sequence in their variable regions that are conformationally available for antibody binding. These immunogenic regions include but are not limited to the antigen binding site. The idiotype of an antibody or TCR is defined by the sum total of the regions, including the variable region, which is able to act as epitopes for interaction with other antibodies. Therefore the idiotype is unique to each antibody, and an antibody that recognizes one of these regions is referred to as an anti-idiotypic antibody.

Autoimmunity may result when a peptide complementarity to an autoantigen is present, either introduced by a microbe or translated from the antisense strand of the self-protein. Antibodies specific to the complementary peptide are generated. This then leads to the formation of anti-idiotypic antibodies with specificity against the antigen binding region, encoded by the complementary peptide binding variable region. These anti-idiotypic antibodies will also have specificity against the native self-protein and are therefore the autoimmune antibodies. An example of this has been demonstrated in the generation of the antineutrophil cytoplasmic antibody (ANCA) against proteinase 3 (Pendergraft et al. 2004) associated with ANCA vasculitis.

A corollary to the anti-idiotype theory is based upon the observation that viruses utilize cell surface receptors to infect cells. Antibodies, which are generated against viral proteins that interact with the cell surface receptors, may lead to the generation of anti-idiotypic antibodies. These anti-idiotypic antibodies would then be capable of binding to the cell surface protein and function as an autoantibody (Root-Bernstein and Fairweather 2014; Plotz 1983).

An important concept related to antibody mediated glomerular disease is that once autoantibodies are formed, they may contribute to glomerular pathology through distinct mechanisms. First, autoantibodies may directly recognize antigens that are localized to the glomerulus as in the case of glomerular basement membrane disease or membranous nephropathy associated with antibodies against the podocyte PLA2R1 antigen. Alternatively, antibody deposition may occur through the trapping of circulating immune complexes as in the case of IgA nephropathy promoting local inflammatory responses (Rodrigues et al. 2017). Another mechanism of autoantibody-induced tissue injury has been suggested for ANCA-associated diseases. Here, the pathogenic antineutrophil cytoplasmic antibody activates neutrophils to release degradative enzymes, reactive oxygen species, and NETs NETsosis. These mediators cause local inflammation and tissue destruction characterized by pauci-immune glomerulonephritis on renal histopathology (Jennette and Falk 2014).

Although B cell-derived autoantibodies have a central role in the pathogenesis of glomerular diseases, T cells also have critical roles in glomerular injury mediated by the adaptive immune response. T-cells support B-cell antibody production and independently promote inflammation and tissue damage by cell-cell interactions, T-cell effector functions, synthesis, and secretion of cytokines (Suarez-Fueyo et al. 2017). The immune system is highly integrated and dysregulation of one component triggers responses, either adaptive or maladaptive, in other branches of the immune system.

Conclusion

Glomerular diseases result, in part, from an exposure that initiates a dysregulated immune response in a genetically susceptible individual. Keen observations by astute clinicians have driven the basic and translational laboratory research that generated this mechanistic framework for glomerular disease pathogenesis. Currently, glomerular diseases are classified by histopathologic patterns.

However, this ontology often fails to predict treatment responses and patient outcomes. With the evolution of new tools, deep molecular phenotypes, such as whole genome expression and protein patterns, can be integrated with clinical data contained in medical records to develop glomerular disease classifications based on mechanisms that will more effectively guide patient management and treatment (Mariani et al. 2016).

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Diagnostic Testing in Glomerular Disease 3

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Contents

Abstract

Glomerular diseases are among the hardest diseases to diagnose. They can affect multiple organs (and thereby cause multiple symptoms) or only the kidney. While specific diseases may have a "classic" presentation, the overlap among presentations is considerable, and often the only way to diagnose a glomerular disease is by a kidney biopsy. There are many diagnostic tests that can help diagnose a glomerular disease, and more are being identified. This chapter focuses on serologic and urine tests that can be used to help diagnose a glomerular disease. The main diagnostic considerations of the two glomerular syndromes, nephritic and nephrotic, are discussed individually. In a patient with nephritic or nephrotic syndrome,

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clinical judgment based on the presentation will always be needed to determine if other diagnostic tests should be sent off in place of a kidney biopsy or along with a kidney biopsy.

Keywords
Glomerulonephritis · Nephritic syndrome · Nephrotic syndrome · suPAR · Phospholipase A2 receptor 1 antibody (PLA2R1 ab) · Anti-neutrophil cytoplasmic antibody (ANCA ab)

Introduction

Glomerular diseases can present as part of a systemic disease, with multiple symptoms, or with only renal findings and perhaps no symptoms. The variety of presentations, and general rarity of the individual diseases (and therefore a lack of familiarity), makes diagnosing glomerular diseases difficult. Defining the different presentations of glomerular diseases is the first step to recognizing, and then diagnosing, them. Glomerular diseases are generally divided into two classic syndromes: nephrotic and nephritic. Nephrotic syndrome is generally defined by >3.5 g of protein in the urine per 1.73 m^2 of body surface area and the constellation of findings that result from the spilling of a large amount of protein in the urine, namely, edema, hypoalbuminemia, hyperlipiduria, and hyperlipidemia. Nephritic syndrome is defined by hematuria, proteinuria, and kidney damage, with glomerular inflammation (glomerulonephritis) resulting in the clinical findings. While this division into the syndromes provides an organized approach to the different glomerular diseases, overlap of the two syndromes does occur. For example, glomerulonephritis (GN) from a vasculitis can also cause nephrotic range proteinuria. Likewise, a patient with nephrotic syndrome can present with some hematuria and a rising creatinine. Sometimes, pathology consistent with both nephritic and nephrotic syndrome can be present on the same kidney biopsy specimen, as is often found in a systemic disease like systemic lupus erythematosus.

Dividing glomerular disease presentations into nephrotic and nephritic (while recognizing there can be overlap) allows us to define an approach to diagnosing the diseases. The three most common primary renal diagnoses that present as nephrotic syndrome are minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis. It is also important to note that certain systemic diseases, like diabetes and amyloidosis and other paraproteinemias, can also present with nephrotic syndrome and should be considered in the differential diagnosis. It is important to note that a disease, like diabetes, can also cause nephrotic range proteinuria, without the other finding s of the nephrotic syndrome (e.g., no hyperlipidemia, lipiduria, or edema). The differential diagnosis for nephritic syndrome is a bit more complicated and can be divided based on the general findings seen on kidney biopsy. Note that glomerulonephritis is associated with proliferation and inflammation on the kidney biopsy; so light microscopy showing proliferation suggests glomerulonephritis but does not help further classify it. Immunofluorescence studies and electron microscopy look for different types of immune deposits and help diagnose the cause of the glomerulonephritis. If the kidney biopsy shows proliferation on light microscopy and evidence of immune complex deposition on either immunofluorescence or electron microscopy, the main diagnoses to consider are post infectious glomerulonephritis, systemic lupus associated GN, IgA nephropathy, or membranoproliferative GN (which can often present with nephrotic features). If there is no evidence of immune complex deposition on light microscopy or immunofluorescence, a pauci-immune GN should be considered – typically microscopic polyangiitis, granulomatosis with polyangiitis, or eosinophilic granulomatosis with polyangiitis. Proliferation with a linear staining on immunofluorescence suggests direct damage to the glomerular basement membrane from anti-GBM disease.

The definitive diagnosis of glomerular diseases often rests with a kidney biopsy, and a brief description of the biopsy findings is included in Table 1. A more detailed description of the pathology of of glomerular diseases is beyond the scope of this chapter; however, the kidney biopsy remains the gold standard by which glomerular diseases are diagnosed. This chapter focuses on

Table 1 Immune complex glomerulonephritis

	IgA	PIGN	SLE	MPGN
Presentation: History and demographic	Most common GN Hematuria after URI, exertion, stress Younger, Asian	Usually 1–3 weeks after sore throat (Group A b-hemolytic strep) or other infections More classic in children	Any of the many signs or symptoms of SLE	Based on cause (see Table 5)
Presentation	Nephritic syndrome HTC, hematuria	Nephritic syndrome HTN, hematuria	Nephritic syndrome Findings related to organs involved	Nephritic syndrome Other findings based on underlying diagnosis
Serologic tests:	None currently	Low complement levels Evidence of infection	Low complement levels + ANA, + dsDNA	Based on cause: Hepatitis serology Protein electrophoresis Complement evaluation
Biopsy light	Proliferation	Proliferation	Proliferation (depends on class)	Proliferation
IF	IgA is dominant	C3, IgG	IgG, C3, C4 (can be all = full house)	Depends on type
EM	Deposits usually mesangial	Subepithelial humps	Deposits everywhere (Subepi, subendo, mesangial)	Subendo and Subepi deposits (depends on type)
		Pauci-Immune GN		**Anti-GBM disease**
	Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)	*Microscopic polyangiitis*	*Churg-Strauss*	*(Goodpasture's)*
Clinical presentation	Sinus issues, lung issues (cough)	Lung issues	Asthma	Lung and kidney (hemoptysis)
	Vasculitis symptoms (fever, rash, fatigue)	Vasculitis symptoms (fever, rash, fatigue)	Can have vasculitis	
	Depends on organ (rash, sinus, renal failure, lungs)	Depends on organ (rash, lung infiltrates, renal failure)	Wheezing eosinophilia	Hypoxia, renal failure
Serology:	C-ANCA > P-ANCA	P-ANCA slightly more than C-ANCA	Moreso P-ANCA	Anti-GBM antibody
Biopsy light	Proliferation	Proliferation	Proliferation	Proliferation
IF	Minimal (pauci)	Minimal (pauci)	Minimal (pauci)	Linear staining (along GBM)
EM	Minimal deposits (pauci)	Minimal deposits (pauci)	Minimal deposits (pauci)	
Nephrosis				
	Minimal change disease	*Focal and segmental glomerulosclerosis*	*Membranous*	*Systemic disease*
Presentation:	Sudden onset edema Kids	Edema, progressive kidney disease African-American > other	Edema (can be sudden) moreso adult	H/o diabetes, paraprotein
	Association with: Lymphoma, meds	Association with: Obesity, HIV, GU reflux	Association with: Cancers	
	Edema	Edema	Edema	Edema

(*continued*)

Table 1 (continued)

	IgA	PIGN	SLE	MPGN
		Signs of systemic associations	Signs of systemic associations	Signs of systemic disease
Biopsy:		(five variants – perihilar, tip, collapsing, cellular, NOS)		
Light:	Normal	Scarring and sclerosis of glomeruli	Thickened capillary loops	Depends on disease
IF	–	–	Granular deposits, near GBM	Depends on disease
EM:	Foot process effacement (Diffuse)	Foot process effacement If diffuse – primary FSGS If focal – secondary FSGS	Subepi deposits in the GBM	Depends on disease
Serology	None specific	None specific (suPAR)	Anti-PLA4 antibodies	SPEP, UPEP with immunofixation, hemoglobin A1C

the serologic testing available for glomerular diseases, following the approach to classification summarized in Table 1.

Nephrotic Syndrome

Minimal Change Disease

Minimal change disease presents with the nephrotic syndrome, typically in children though also in adults. Minimal change disease describes the findings on light microscopy – no changes are noted; however, diffuse effacement of foot processes is seen on electron microscopy. Minimal change can be either primary (idiopathic) or secondary. If secondary minimal change disease is diagnosed or considered, further evaluation for paraproteinemia and cancer (lymphoma) and review of the medication list for medications associated with minimal change disease should be undertaken. There are currently no serologic tests or urinary markers to identify idiopathic minimal change disease. There are some recent data regarding potential future diagnostic tests. Podocytes have been found to be able to express CD80 (Reiser et al. 2004). It was later shown that urinary CD80 was higher in patients with idiopathic minimal change disease compared to nephrotic syndrome from other causes (Garin et al. 2009), and more recent studies have shown discriminating ability of urinary CD80 for minimal change disease compared to focal segmental glomerular sclerosis (Ling et al. 2015). Although promising, the use of urinary CD80 is not yet established, and further studies are needed to validate this test. Newer approaches to minimal change disease place it as part of a spectrum with focal segmental glomerulosclerosis, with minimal change disease being responsive to steroids (Maas et al. 2016).

Membranous Nephropathy

Membranous nephropathy also presents with the nephrotic syndrome, although rarely there can be overlapped with nephritic syndrome by the presence of an abnormal serum creatinine and/or blood in the urine. Membranous nephropathy can also be found with the presence of a glomerulonephritis. For example, lupus nephritic can present with multiple histologic lesions, and membranous nephropathy and a proliferative GN can be found on the same biopsy sample. Like minimal change disease, membranous nephropathy also can be a primary kidney disease or secondary to another process. If secondary membranous nephropathy is considered, further work-up should include age-appropriate cancer screening, evaluation for autoimmune diseases (especially lupus), a review of the patient's

medication list for agents that can be associated with membranous nephropathy, and an evaluation for infections (with specific attention to hepatitis B). On histology, certain features can be useful to distinguish a primary from secondary membranous lesion (Murtas and Ghiggeri 2016). Among the usual tests done on a kidney biopsy, immunofluorescence staining for IgG4 is more typical with primary membranous, while staining for the other IgG subtypes may be more consistent with a secondary membranous nephropathy. Finding immune deposits in locations other than the glomerular basement membrane or immunofluorescence staining for other markers like C1Q, IgA, or IGM also suggests a secondary form of membranous nephropathy. Serologic tests (e.g., for systemic lupus erythematosus or hepatitis B) also might direct the diagnosis toward a secondary cause of membranous nephropathy.

The report of the association of the M-type phospholipase A_2 receptor 1 (PLA_2R1) with primary membranous nephropathy in 2009 has created considerable excitement (Beck et al. 2009). Further evaluation PLA_2R1 antibody has shown it to be positive in 50–80% of cases, with a sensitivity of 70–80% and a specificity of >90% for primary "idiopathic" membranous nephropathy. The performance variation of the test may result from disease activity (and also possibly ethnicity) (Francis et al. 2016). Further studies have shown correlation between PLA_2R1 antibodies and proteinuria and response to treatment (Radice et al. 2016). Although studies are still ongoing, PLA_2R1 antibodies seem to be a helpful test for distinguishing primary from secondary membranous nephropathy and may even be used to track response to treatment.

Along with PLA_2R, another antibody has been found in primary membranous nephropathy. Patients with primary membranous nephropathy who were PLA_2R antibody negative were tested for an antibody to thrombospondin type-1 domain-containing 7A (THSD7A). It is estimated that up to 14% of patients with primary membranous (who are negative for PLA_2R1 antibodies) may have anti-THSD7A antibodies (Tomas et al. 2014). While the role of anti-THSD7A antibodies is not yet elucidated, the continued discovery of possible causative antibodies for what was once described as "idiopathic" membranous nephropathy is exciting. A new diagnostic approach to membranous nephropathy based on anti-PLA2R1 antibodies has been proposed (De Vriese et al. 2017).

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is diagnosed by histology and classified into one of five subtypes (collapsing, perihilar, tip, cellular, and not otherwise specified). The pathogenesis of FSGS is complex and not well understood, and it is likely different pathogenic mechanisms may lead to different lesions. There are currently no available serologic tests validated to help identify FSGS. Serum soluble urokinase receptor (suPAR) has been shown to be elevated in two thirds of patients with primary FSGS (Wei et al. 2011); however, subsequent studies have shown that specificity for primary versus secondary FSGS, and even other glomerular diseases, is not as clear as originally hoped. Some confounders for suPAR being a more reliable marker are the exact time in the course of disease when suPAR is checked (e.g., suPAR may be more accurate if the nephrotic syndrome is ongoing), and also suPAR levels can also be affected by glomerular filtration rate (GFR). So while suPAR as yet has no diagnostic role, research into the complex pathophysiology of FSGS may yet uncover a specific role for suPAR or other markers in the diagnosis of FSGS. It is also important to note that many genetic causes of nephrotic syndrome, including FSGS, are being uncovered, and testing for these may become more routine.

Table 2 summarizes diagnostic serology in nephrotic diagnoses

Systemic Diseases Causing Nephrotic Syndrome

When a patient has nephrotic syndrome, initial evaluation should include a search for a systemic cause as the etiology of the nephrotic syndrome. Medications should be reviewed and infections (hepatitis B, hepatitis C, HIV, and others) should

Table 2 Diagnostic tests for causes of primary nephrotic syndrome

Diagnosis	Test	Comments
Minimal change disease	Urinary CD80	Not well established, not readily available
FSGS	suPAR	Associated with FSGS, but possibly other causes of nephrotic syndrome. May be issue with test or heterogeneity of renal injury in FSGS
Membranous nephropathy	PLA_2R1 antibodies	Sensitivity 70–80%, specificity over 90% in some studies. Becoming more available commercially
	Thrombospondin type-1 domain-containing 7A (THSD7A)	Accounts for a smaller percentage of idiopathic membranous that is not anti-PLA2R1 positive (up to 14%)

be considered. Certain systemic diseases, most notably diabetes and paraproteinemias, also can cause nephrotic range proteinuria, though they may or may not cause nephrotic syndrome. With the recognition of many types of renal involvement from paraproteins, a serum protein electrophoresis, urine protein electrophoresis, and an assay for serum free light chains are now often part of the work-up for kidney disease and proteinuria of uncertain etiology (in the right demographic group) (Hogan and Weiss 2016).

Nephritic Syndrome

Among the diagnoses that generally present with nephritic syndrome, history and demographic factors can often suggest a diagnosis; however, the kidney biopsy is the only means to definitively make a diagnosis. The classification of glomerulonephritis (GN) used in this chapter is based on the findings from a kidney biopsy. Recognizing that light microscopy alone is often not able to differentiate the different GNs, the classification system is based on the presence and type of pathology identified on immunofluorescence and electron microscopy. The GNs are divided into immune complex, pauci-immune, and anti-GBM disease (see Table 1).

Immune Complex Glomerulonephritis

The four main glomerulonephritis diagnoses that show evidence of immune complex deposition on immunofluorescence or electron microscopy discussed in this chapter are lupus glomerulonephritis, post infectious glomerulonephritis, IgA nephropathy, and membranoproliferative glomerulonephritis. While certain patterns on light microscopy may suggest one of these diagnoses, the findings on electron microscopy and immunofluorescence confirm the diagnosis.

Lupus Glomerulonephritis

Systemic lupus erythematosus (SLE), called "the great masquerader," could garner this appellation from findings on kidney biopsy alone. Lupus glomerulonephritis is divided into six main classes, and one or more can be present on the same biopsy specimen (see Table 3) (Weening et al. 2004). The strict diagnosis of SLE is made based on the clinical presentation. The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics (SLICC) have certain criteria used to help guide clinicians. Lupus renal involvement (proteinuria or urinalysis findings) constitute one of those criteria. Due to the varied nature of lupus presentations, these criteria may be too selective, particularly early in the disease course (Kaul et al. 2016). The immunologic tests used for diagnosing SLE are summarized in Table 4. Lupus involvement in the kidney manifests as urinary findings (proteinuria, hematuria, pathologic casts) with or without a rise in serum

Table 3 Classification of lupus nephritis (Modified from Weening et al. 2004)

Class I: Minimal mesangial lupus
Class II: Mesangial proliferative lupus nephritis
Class III: Focal lupus nephritis
Class IV: Diffuse lupus nephritis
Class V: Membranous lupus nephritis
Class VI: Advanced sclerotic lupus nephritis

Note: Class III and IV are further divided by the amount of activity and chronicity as well as whether the glomerular lesions are global or segmental

Table 4 Serologic testing for SLE (Modified from Petri et al. 2012)

Anti-nuclear antibodies
Anti-dsDNA
Anti-Sm antibodies
+ Anti-phospholipid antibody
Low complement levels (C3, C4, or CH50)
Direct Coombs without a hemolytic anemia

creatinine. The specific criteria listed for renal involvement are a urine protein > 500 mg/dL or red blood cell casts (Petri et al. 2012). Lupus nephritis is often confirmed by kidney biopsy, with the results showing one or more of the classes of lupus nephritis (Table 3) mentioned earlier. As lupus nephritis can have immune complex deposition noted on immunofluorescence and electron microscopy, it is grouped with the immune complex GNs.

Serologic tests for SLE are included in the criteria to diagnose lupus (Table 4). The tests include a positive ANA, or a positive anti-dsDNA antibody, positive anti-Sm antibody, or positive anti-phospholipid antibodies. While these tests help diagnose lupus, no test has been shown to be reliably predictive of lupus nephritis. Currently, complement levels, anti-dsDNA antibody levels, and proteinuria are followed to track lupus activity, although these tests lack sensitivity and specificity (Moy 2016). Even the urinalysis has been shown to give misleading results, perhaps due to imprecise identification of urinary elements by standardized laboratory techniques (Rasalpour et al. 1996). The American College of Rheumatology only recommends following urinalysis findings (e.g., casts) if the manner of identification is reproducible (ACR 2006).

Many new serum and urine biomarkers have been identified for SLE and were reviewed extensively by Moy in 2010. Urinary levels of CC chemokine 2 (monocyte chemoattractant protein 1), tumor necrosis like factor inducer of apoptosis (TWEAK), and neutrophil gelatinase-associated lipocalin (NGAL) have the most evidence supporting them, but are still not validated (Moy 2016).

Postinfection Glomerulonephritis

Postinfectious glomerulonephritis (PIGN) classically presents 4–6 weeks after an infection. PIGN initially was named post-streptococcal GN because of the predominance of cases after group A B-beta-hemolytic streptococcal throat infections in children. With time, other infections were noted to cause PIGN pathology, so the name evolved to PIGN. PIGN is diagnosed by light microscopy showing proliferation and immune complex deposition identified by immunofluorescence (C3 positive, as well as usually IgG and other immunoglobulins) and electron microscopy. The electron microscopy deposits are the classical "subepithelial humps" located along the basement membrane on the epithelial side. Many infections have been associated with PIGN, including gram-negative bacteria, viruses, parasites, fungi, other streptococcal serotypes, and staphyloccus. PIGN resulting from staphylococcus deserves special mention as it is associated with IgA dominant deposits and therefore has a different pathophysiology than "classic" post-streptococcal GN (Stratta et al. 2014).

Excluding a kidney biopsy, diagnostic tests for PIGN would rely on the identification of a culprit infection with a positive culture. For classic PIGN from a streptococcal infection, an antistreptolysin O (ASO) titer can be sent, but it is often high soon after infections (and PIGN may not be noticed until weeks later). Anti-DNAse can be high in streptococcal skin infections. Neither of the tests is very reliable and culturing organisms is the best approach to diagnosis.

Complement levels are useful in PIGN, as C3 is usually low. After resolution of the PIGN (usually after about 4 weeks), the C3 level should return to normal. If the C3 remains low, other diagnostic considerations are membranoproliferative GN (MPGN), endocarditis, and C3 glomerulonephropathy (Stratta et al. 2014). Recent clarification of pathogenesis of MPGN and C3 nephritis has helped establish a diagnostic approach to these conditions. MPGN will be discussed in an upcoming section. C3 glomerulopathy, although rare, has been the subject of much interest due to both a clearer understanding of pathophysiology as well the success of treatment with complement inhibitors. C3 glomerulopathy can look very similar to PIGN, but if no infection is identified, or C3 levels stay persistently low, a complement regulatory disorder should be considered. A new approach defines glomerulonephritis with dominant C3 and suggests an assessment of the complement system when the clinical course does not follow the typical PIGN course (persistent glomerular injury or persistently low C3 levels) or the pathology is not quite typical for PIGN (Pickering et al. 2013).

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) refers to a pattern of findings on light microscopy. MPGN is classified as an immune complex GN in this chapter because there are usually findings on immunofluorescence and electron microscopy. Previously classified by the type and location of deposits on electron microscopy, a more recent classification system has emerged that attempts to define the types of MPGN based on the cause, as is determined by renal biopsy findings, specifically immunofluorescence (Masani et al. 2014). Table 5 summarizes an approach to MPGN. It is important to note that diseases that present with an MPGN pattern of injury can present with both nephritic and nephrotic features.

Serologic tests for MPGN would include any blood tests that might point to a possible etiology of the MPGN. Using Table 5 as a guide for a differential diagnosis, if an MPGN lesion is found with positive immunoglobulins, a serum and urine protein electrophoresis and immunofixations should be sent, as well as serum free light chains. If the immunoglobulin is polyclonal, investigations for systemic diseases (Sjogren's syndrome, RA, mixed connective tissues disease, and SLE) (Zand et al. 2014) should be evaluated for, as well as infections, most commonly hepatitis B and C. If the immunofluorescence is C3 dominant, C3 glomerulopathy or dense deposit disease should be entertained as diagnoses. Electron microscopy patterns can help in differentiating these, and evaluation for complement abnormalities should be considered (Pickering et al. 2013). An MPGN pattern with essentially negative immunofluorescence findings for complement or immunoglobulins should prompt consideration for a chronic or resolving thrombotic microangiopathy (TMA), such as from thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, sickle disease, chronic transplant glomerulopathy, drug-induced TMA, or antiphospholipid antibody (Sethi and Fervenza 2012).

IgA Nephropathy

IgA nephropathy is diagnosed by finding a predominance of IgA deposits in the mesangial area on kidney biopsy. IgA nephropathy is the most common primary GN in the world and is caused by galactose-deficient IgA1 molecules that have abnormal exposure of part of the IgA1 molecule which can form immune complexes with IgA1 or IgG and avoid clearance by the liver. These immune complexes can then deposit in the kidney and cause kidney damage (Wyatt and Julian 2013). As the immune complexes are visible on immunofluorescence and electron microscopy, IgA nephropathy is considered an immune complex GN. While a noninvasive test to diagnose IgA nephropathy would be welcome, there are none currently available. Based on the pathophysiology of IgA nephropathy, assaying blood for galactose-deficient IgA1 levels was tested as a noninvasive marker for IgA nephropathy. Although there is some correlation with the

Table 5 Approach to membranoproliferative glomerulonephritis (Adapted from Masani et al. 2014)

MPGN Pattern of light microscopy
Immunofluorescence positive for:
Immunoglobulins – determine if monoclonal or polyclonal
Monoclonal: send serum and urine protein electrophoresis and immunofixation, serum free light chains (evaluation for paraproteinemia – e.g., multiple myeloma, Waldenstrom's macroglobulinemia, lymphoma, leukemias, paraprotein deposition disease, cryoglobulinemia)
Polyclonal: evaluated for systemic disease (autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, SLE or mixed connective tissues disease) or infections (hepatitis C, hepatitis B, endocarditis)
Immunofluorescence notable for C3 predominance:
(Differentiated based on patterns of deposits on electron microscopy)
C3 glomerulopathy
Dense deposit disease
May be caused by dysregulation of complement cascade, so sending complement investigations may be helpful (Pickering et al. 2013)
Immunofluorescence negative for immunoglobulin and complement:
Thrombotic microangiopathy
(Hemolytic uremic syndrome, TTP, sickle cell disease, kidney transplant glomerulopathy, anti-phospholipid antibody syndrome)

diagnosis of IgA nephropathy, the test has not performed well enough to be used diagnostically, but may be able to detect patients more likely to progress (Canetta et al. 2014). Other tests being considered but not yet validated for diagnosing or monitoring disease activity in IgA nephropathy are antibodies to galactose-deficient IgA1 (anti-glycan antibodies) and urine proteomics.

Pauci-immune Glomerulonephritis

Glomerulonephritis that presents with proliferation/inflammation on light microscopy but no or minimal immune deposition noted on immunofluorescence or electron microscopy is classified as pauci-immune. The main diagnostic considerations in this category are the anti-neutrophil cytoplasmic antibody (ANCA) positive diagnoses (microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and granulomatosis with polyangiitis). If a kidney biopsy reveals a pauci-immune glomerulonephritis, but the ANCA is negative, the disease is classified as ANCA-negative GN (or ANCA-negative pauci-immune GN).

Due to the varied presentation of a small vessel vasculitis, and the different criteria used to diagnose them, there can be clinical overlap of the diagnoses. Classification by ANCA subtype may help determine clinical course (Lionaki et al. 2012). The ANCA immunofluorescence staining patterns are typically cytoplasmic (C-ANCA), which is associated with anti-PR3 antibodies, or perinuclear (P-ANCA), usually associated with anti-MPO antibodies. There are also atypical patterns associated with other targets for the antibodies like cathepsin G and lactoferrin. Many of these atypical ANCAs are not yet associated with specific disease presentations (Cornec et al. 2016). Anti-human neutrophil elastase antibodies, however, are an atypical ANCA associated with cocaine induce vasculitis (Weisner et al. 2004). Cocaine induced vasculitis can also be associated with both c-ANCA and p-ANCA positivity (McGrath, Isakova 2011).

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is a vasculitis that usually affects small vessels, with the kidney and lung often affected. Few or no immune deposits are found, and necrotizing arteritis can be present, but granulomas are not (Jennette et al. 2013). Diagnosis is made by histology in the appropriate clinical setting. While the cause of MPA is not known, ANCA antibodies seem

pathogenic in the correct patient milieu. A little over 80% of MPA patients with be positive for ANCA and most (about two-thirds) of the ANCA detected in MPA are antibodies to myeloperoxidase (MPO), and about one third of the ANCA antibodies in MPA are to proteinase 3 (PR3) (Hagen et al. 1998). ANCA titers have not been shown to reliably correlate with disease activity.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly called Wegener's granulomatosis, is a necrotizing granulomatous inflammation and vasculitis affecting small and sometime medium vessels, with predilection to the upper airway (nose, sinuses) and the lung and kidney. Of patient's with GPA, more than 80% usually have a positive ANCA test, and most of these ANCA tests are positive for PR3 (more than two-thirds) as opposed to MPO (Hagen et al. 1998). Diagnosis of GPA is based on the clinical features and histology. ANCA testing forms part of the clinical features, but alone should not confirm or refute a specific diagnosis.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis (eGPA) combines features of both a small vessel vasculitis and hypereosinophilic syndrome. Renal involvement can occur, but is usually less frequent than with the other ANCA-associated vasculitides. Eosinophilic granulomatosis with polyangiitis is diagnosed by the proper clinical picture with histology of the affected organs (usually the respiratory tract) showing necrotizing granulomatous inflammation that is eosinophil-rich and a necrotizing vasculitis of usually small and medium vessels (Jennette et al. 2013). Although the main manifestations are pulmonary, the kidney can be involved in approximately 25% of cases. When the kidneys are involved in eGPA, the ANCA is more likely to be positive. Only 25% of patients without renal involvement had a positive ANCA, while about 75% percent with renal involvement did. If the renal pathology in eGPA was a necrotizing glomerulonephritis, the ANCA was most often positive. Most of the ANCA were MPO anca (three-fourths) as opposed to PR3 ANCA (one-fourth) (Sinico et al. 2006).

ANCA-Negative Pauci-immune Glomerulonephritis

Up to 30% of pauci-immune vasculitis can be ANCA-negative, depending on how pauci-immune is defined. The pathophysiology of ANCA-negative pauci-immune GN is not well understood, but perhaps another yet unidentified antibody is stimulating the inflammatory response. The ANCA-negative pauci-immune GN tends to have less systemic clinical findings and a more aggressive course of renal disease (Chen et al. 2009). Antibodies to human lysosome-associated membrane protein-2 (hLAMP-2) have emerged as a possible pathogenic antibody in ANCA-negative pauci-immune GN, although these results have not been confirmed in other studies (Peschel et al. 2014).

Anti-glomerular Basement Membrane Disease

Anti-glomerular basement membrane disease (Anti-GBM disease) is a rare cause of glomerulonephritis caused by the direct binding of an antibody (anti-GBM antibody) to the non-collagenous domain 1 of the alpha 3 chain of type 4 collagen. This collagen is expressed in the glomerular basement membrane and alveolar basement membrane and some other tissues. The expression in the kidney and lung accounts for the major clinical findings in anti-GBM disease – glomerulonephritis and alveolar hemorrhage. Immune complex deposition is detected on kidney biopsy of patients with anti-GBM, with a classic linear immunofluorescence pattern. Because the immune injury is a result of direct binding of antibody to antigen in the affected tissue, it is different from the other immune complex glomerulonephritides which are caused by immune complex deposition that may

be assembled elsewhere or are not the result of a direct antibody-antigen interaction in the target tissue. Anti-GBM disease is diagnosed by the detection of anti-GBM antibodies either in the serum and/or in the tissue biopsied, along with the appropriate clinical presentation. Patients can sometimes have negative serum anti-GBM antibody tests but be tissue positive. Such findings may result from less sensitive detection of serum antibodies or perhaps disappearance of the serum antibody before the tissue antibody, as tissue antibodies tend to persist longer. The result may also be a false positive, which can happen with immune trapping and has been reported in diabetes. Patients can also be serum positive and tissue negative. This scenario may result from extensive damage to tissue, ruining the linear appearance, or from other deposition of immune complexes making the underlying pattern of the hard to delineate (Hellmark and Segelmark 2014). ANCAs, usually p-ANCA, present in up to 35% of patients with anti-GBM disease.

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Histopathology of Glomerular Diseases

4

Leal C. Herlitz and J. Charles Jennette

Contents

Abstract

Glomerular diseases are complex and establishing the correct diagnosis often requires a renal biopsy. This chapter describes the main techniques used in the evaluation of renal biopsies and how these techniques help to establish a diagnosis. Normal glomerular structure is described along with the variety of pathologic patterns recognized in a wide variety of glomerular diseases. The common glomerular lesions encountered in glomerulonephritis, nephrotic syndrome, and thrombotic microangiopathies are defined. An overview of how glomerulonephritis is classified based on a combination of pattern of injury, pathogenies mechanism, and etiology is provided.

Keywords

Immunofluorescence microscopy · Electron microscopy · Normal glomerular structure ·

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Proliferative glomeruonephritis · Mesangial hypercellularity · Endocapillary hypercellularity · Crescent formation · Fibrinoid necrosis · Glomerular basement membrane remodeling · Sclerosis · Fibrosis · Immune complex mediated glomerulonephritis · Pauciimmune glomerulonephritis · anti-GBM nephritis · Monoclonal immunoglobuline mediated glomerulonephritis · C3 glomerulopathy · Thrombotic microangiopathy · Chronic glomeruonephritis

Introduction

Renal biopsy is often necessary to distinguish among the numerous glomerular diseases that can have similar and overlapping clinical presentations. The primary purpose of the renal biopsy is to provide information about the cause of disease as well as how active and chronic the process is, so that appropriate therapy can be selected. This chapter will describe the commonly used stains and techniques in renal biopsy interpretation as well as the common lesions and patterns of glomerular injury encountered in renal biopsies. This is intended to provide a practical framework for better understanding the descriptions and diagnoses encountered by nephrologists when reading renal biopsy reports.

Basic Pathologic Examination of the Renal Biopsy

Pathologic examination of renal biopsy specimens involves dividing the biopsy cores for separate evaluation by light microscopy, immunofluorescence microscopy, and electron microscopy. Each of these diagnostic modalities plays an important role in the diagnosis of glomerular diseases.

Light microscopic evaluation is typically based on tissue that has been fixed in formalin, embedded in paraffin, and sectioned at 2–3 microns. These tissue sections are then stained with the four essential stains used in renal pathology including hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), a Masson trichrome stain, and a Jones silver stain (Fig. 1). Each of these stains highlights different structures and pathologic changes. PAS and Jones stains highlight basement membrane morphology and help in distinguishing matrix from cellular cytoplasm. Trichrome staining is often used to highlight fibrosis versus necrosis, because both stain pink in an H&E stain. With a trichrome stain, collagen and matrix material stain blue or green depending on the recipe used, while fibrinoid necrosis stains red. Congo red or thioflavin staining may be used in select cases to evaluate for the presence of amyloid. Light microscopy is essential to establishing what types and patterns of glomerular lesions are present and is also the main way of establishing the degree of activity and chronicity of a given disease process.

Immunofluorescence staining is usually performed on sections of fresh frozen tissue or tissue that has been placed in a room temperature transport medium such as Zeus or Michelle's media. The tissue is frozen and then sectioned for direct immunofluorescence microscopy. The routinely utilized immunofluorescence panel includes stains for IgG, IgA, IgM, kappa and lambda light chains, and complement components C3 and C1q. Positive staining can take on different appearances, appearing more granular or linear, depending on the disease process and where the deposits are located (Fig. 2). Immunofluorescence microscopy allows identification of the composition of glomerular deposits that is essential for the classification of glomerulonephritis described later in this chapter.

Electron microscopy is often required in the most precise diagnosis of glomerular disease. Abnormalities of podocyte foot processes, deposits with certain substructure (such as fibrillary and immunotactoid deposits), and structural abnormalities of glomerular basement membranes (as seen in genetic abnormalities of type IV collagen) all heavily depend on ultrastructural examination for accurate diagnosis (Fig. 3). Electron microscopy is also useful in more precisely localizing immune deposits, for example, determining the subepithelial, subendothelial, or intramembranous location of glomerular capillary wall deposits.

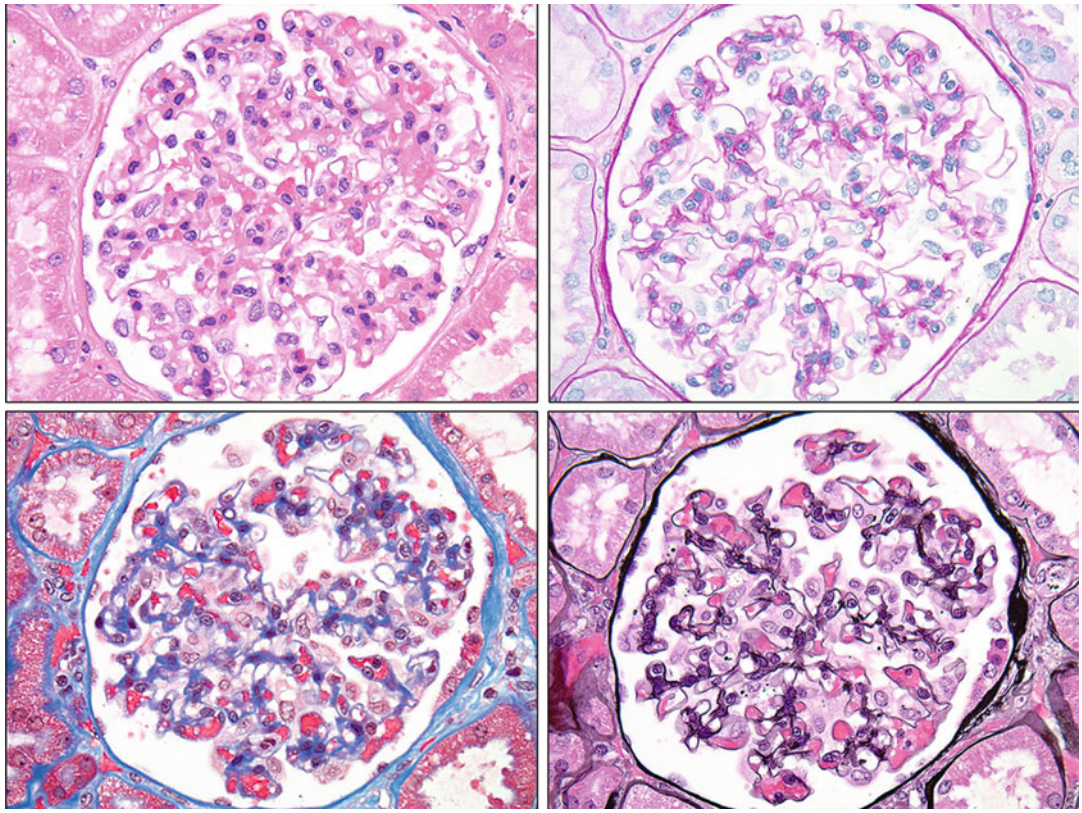

Fig. 1 A normal glomerulus stained with hematoxylin and eosin (H&E) (upper left), periodic acid-Schiff (PAS) (upper right), Masson trichrome (lower left), and Jones methenamine silver stain (lower right). PAS and Jones stains are particularly good at highlighting glomerular basement membrane morphology. Trichrome staining highlights mesangial matrix and surrounding interstitial collagen

Normal Glomerular Structure and Frequent Pathologic Findings

In order to recognize the various patterns of glomerular disease, understanding of the basic structure of a normal glomerulus is important. The main cells present in the normal glomerulus are the mesangial cells that are specialized smooth muscle cells that form the structural core of the glomerulus, endothelial cells that line the inside of glomerular capillaries, and podocytes that surround the outer surface of the glomerular basement membrane (Fig. 4). The glomerular basement membrane invests the glomerular capillaries and then reflects over mesangial areas and is ultimately continuous with Bowman's capsule. In 2–3-μm-thick sections, a normocellular glomerulus will have mesangial areas with three or fewer mesangial cells, and glomerular capillaries will be patent, containing only occasional endothelial cell nuclei and transiting blood cells (Fig. 1).

Electron microscopy allows evaluation of ultrastructural features that can be abnormal in diseased glomeruli and useful for diagnosis. In the normal state, podocytes have interdigitating foot processes connected by slit diaphragms that are an essential component of the glomerular filtration barrier. The glomerular basement membrane (GBM) has three distinct layers, the lamina rara interna beneath the endothelial cells, lamina densa, and lamina rara externa beneath the podocytes.

Light microscopic abnormalities that are important for pathologic diagnosis include glomerular endocapillary and mesangial hypercellularity, endothelial cell swelling, capillary wall thickening, GBM

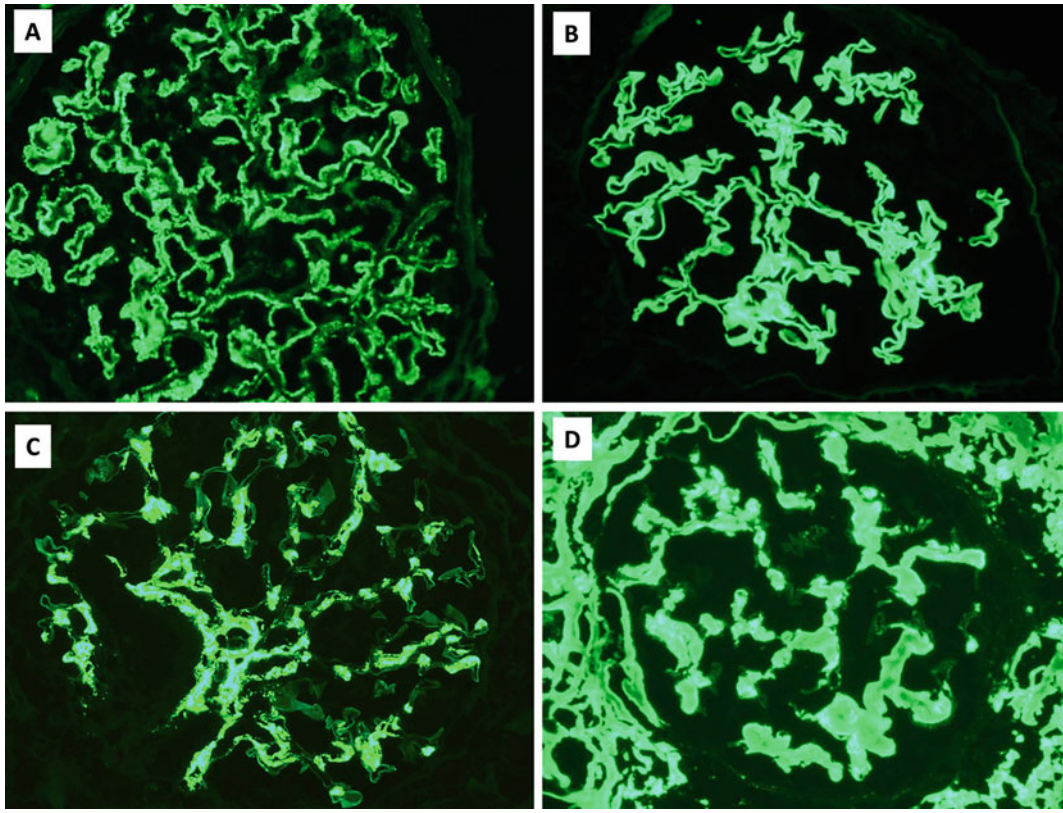

Fig. 2 Patterns of glomerular staining encountered in immunofluorescence. Panel (**a**) shows granular staining outlining the contour of the glomerular capillaries, characteristic of immune complex deposition involving the glomerular basement membrane (GBM). Panel (**b**) shows distinctly linear staining of the GBM that is seen in anti-GBM nephritis. This smooth linear staining contrasts with the granular immune complex deposition seen in panel (**a**). Panel (**c**) shows granular immune complex deposition localizing within mesangial areas as opposed to the GBM. Panel (**d**) shows the "smudgy" texture of staining that can be seen with infiltrative processes such as amyloidosis. Note that in this example, the staining involves not only the glomerulus but the surrounding interstitium

irregularities and replication, sclerosis (scarring), necrosis, thrombosis, and hypercellularity in Bowman's space. Electron microscopy may reveal effacement of podocyte foot processes, microvillous projections from the surface of podocytes, GBM abnormalities (e.g., thinning, lamination, remodeling), expansion of the lamina rara interna, loss of endothelial fenestrations, increased mesangial matrix, abnormal capillary wall of mesangial deposits (e.g., amorphous dense deposits, fibrillary deposits, microtubular deposits), and intracellular inclusions (e.g., myeloid bodies of Fabry disease). Immunofluorescence microscopy can identify the composition of abnormal deposits (e.g., the type of immunoglobulin in immune complex deposits, the dominance of complement in C3 glomerulopathy deposits, and the protein comprising amyloid). The interpretation of pathologic findings may lead to molecular testing, such as genomic testing in a patient with GBM alterations indicative of Alport's syndrome or glomerular proteomic testing in a patient with amyloid that is not positive by routine immunofluorescence staining.

Glomerular Lesions in Glomerulonephritis

The most general definition of glomerulonephritis is inflammation of glomeruli. There is a broad spectrum of lesions that indicate the presence of

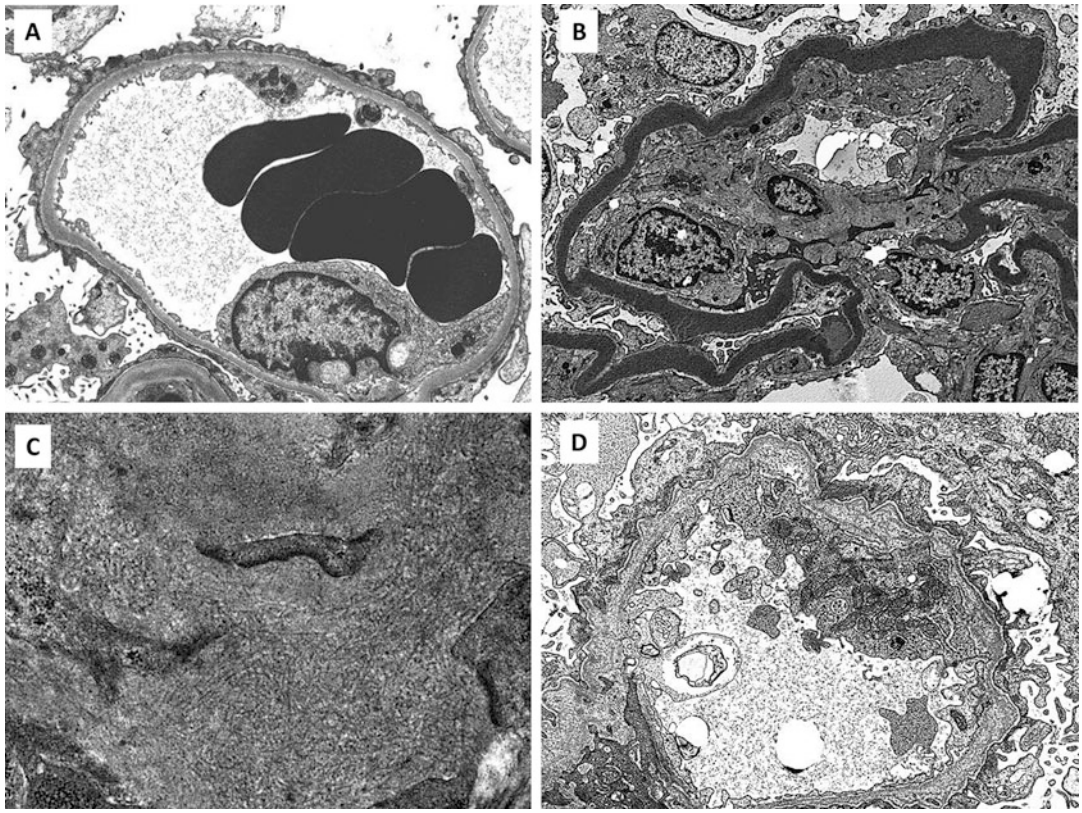

Fig. 3 Utility of electron microscopy in diagnosing glomerular diseases. A case of minimal change disease with its characteristic diffuse podocyte foot process effacement is shown in panel (**a**) (×10,000). Evaluation of podocyte effacement is one important capability of electron microscopy. Panel (**b**) shows the highly electron-dense ribbonlike deposits that help to define dense deposit disease (×8000). Panel (**c**) shows an example of deposit substructure, in this case the randomly oriented 20 nm fibrils characteristic of fibrillary glomerulonephritis (×30,000). Hereditary abnormalities of type IV collagen that cause Alport's syndrome show splitting and lamellation of the glomerular basement membrane, visible by electron microscopy (panel (**d**), ×10,000)

active glomerulonephritis, as well as chronic sclerosing lesions that result from earlier active glomerulonephritis. The names and definitions of many of these lesions have been formulated in the ISN/RPS classification of lupus nephritis (Weening et al. 2004) and the Oxford classification of IgA nephropathy (Roberts et al. 2009). Representative images of these lesions are shown in Fig. 5 along with selected ultrastructural correlates in Fig. 6.

Mesangial hypercellularity, defined as greater than 3 mesangial cells per mesangial area, is commonly seen in response to mesangial immune complex deposition but may be seen as a reactive change in the absence of deposits as well. Alone, mesangial proliferation does not generally cause substantial glomerular scarring and may cause only asymptomatic hematuria and subnephrotic proteinuria.

Endocapillary hypercellularity is the presence of increased numbers of cells within the glomerular capillary lumen, resulting in luminal narrowing. The increased cellularity is caused primarily by influx of leukocytes, but there may be a minor component of endothelial proliferation. Because this pattern of injury was historically thought to be caused primarily by proliferation of constitutive glomerular cells, it is often called proliferative glomerulonephritis. Subendothelial immune complex or complement dominant deposits are particularly prone to cause endocapillary hypercellularity ("proliferative

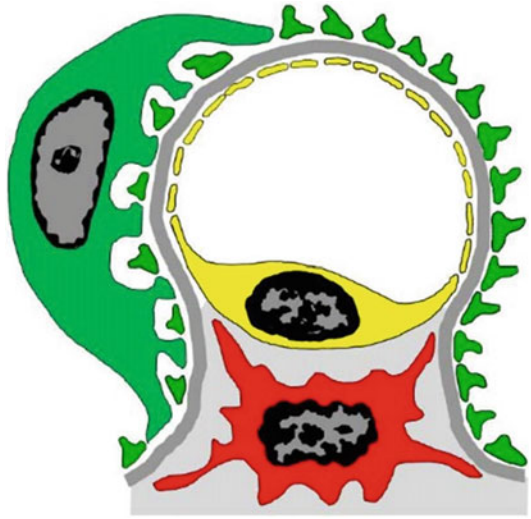

Fig. 4 Basic cells and structure of the glomerular capillary. The mesangial cell (red) is a specialized smooth muscle cell that, along with the mesangial matrix, forms the structural core of the glomerulus. The endothelial cell (yellow) and its fenestrations line the inside of the glomerular capillary. The podocyte (green) gives off the foot processes that are essential to the glomerular filtration barrier. The glomerular basement membrane is present between the endothelial cell and the podocyte and reflects over the mesangium

changes") because these are in close proximity to cellular and humoral mediators in inflammation in the blood. Endocapillary hypercellularity is more likely to cause glomerular scarring than mesangial hypercellularity alone.

Crescent formation (extracapillary hypercellularity) is a result of destructive glomerular inflammation that has caused rupture of capillaries with release of inflammatory mediators into Bowman's space. Crescents can be acute (cellular), subacute (fibrocellular), or chronic (fibrous). A crescent must consist of at least three layers of cells overlying the glomerular tuft occupying Bowman's space. For a crescent to qualify as "cellular," it should be composed of more cells than matrix material. A "fibrocellular" crescent is a subacute lesion that has begun to scar. It is still composed of cells (<50%) but is composed predominantly of matrix. A "fibrous" crescent is comprised almost entirely of matrix material (>90%) with little or no cellularity.

Fibrinoid necrosis, which is a lesion most commonly seen in anti-glomerular basement membrane glomerulonephritis (anti-GBM) or antineutrophil cytoplasmic antibody (ANCA) glomerulonephritis, is characterized by a lytic destruction of portions of the glomerular tuft with activation of the coagulation system, resulting of an irregular zone of fibrin accumulation. Fibrinoid necrosis often is accompanied by crescent formation.

Glomerular basement membrane remodeling (duplication) is the presence of two or more layers of glomerular basement membrane, often separated by immune deposits or cellular interposition. This duplication can be the result of subendothelial or intramembranous immune complex or complement deposition, but can also result from chronic endothelial injury (e.g., caused by hemolytic uremic syndrome) causing basement membrane remodeling.

Sclerosis is defined as obliteration of glomerular architecture and capillary lumina by increased matrix material. Areas of sclerosis may have hyaline (glassy proteinaceous material) accumulation or foam cells (lipid laden macrophages). Sclerosis is the result of the chronic scarring produced by inflammation or other destructive glomerular lesions. Sclerosis is a common end result of numerous pathologic processes and is not specific for glomerulonephritis. For example, glomerular sclerosis is a typical feature if focal segmental glomerulosclerosis and diabetic glomerulosclerosis.

Pathologic Diagnostic Classification of Glomerulonephritis

Glomerulonephritis is classified based on a combination of pattern of injury, pathogenies mechanism, and etiology (Jennette et al. 2014). For example, hydralazine-induced (etiology) ANCA associated (pathogenic mechanism) focal necrotizing and crescentic (pattern of injury). The Mayo Clinic/Renal Pathology Society Consensus Classification of glomerulonephritis (Sethi et al. 2016) recognizes five categories based on pathogenesis (Table 1): immune complex glomerulonephritis, pauci-immune (ANCA)

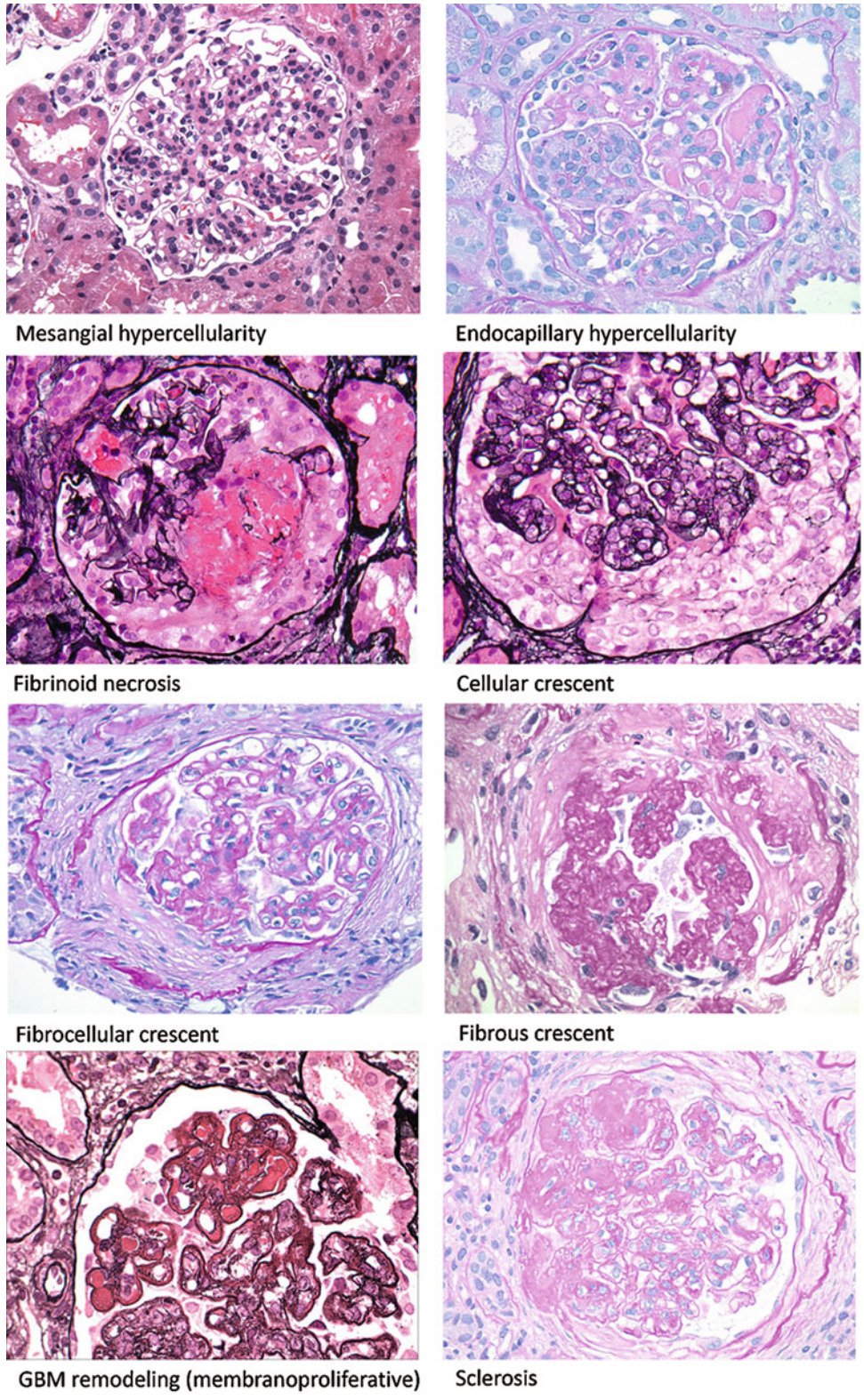

Fig. 5 Common acute and chronic lesions encountered in glomerulonephritis. Mesangial hypercellularity (H&E, ×400) is characterized by mesangial areas with greater than three mesangial cells. Endocapillary hypercellularity

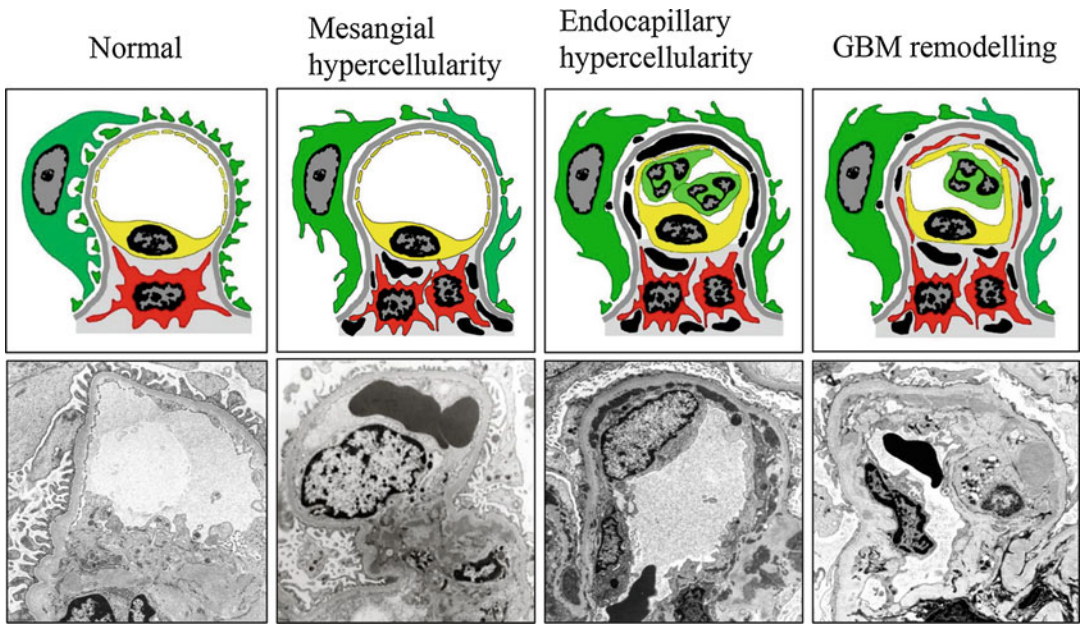

Fig. 6 Ultrastructural lesions of glomerulonephritis. Illustrations with corresponding electron microscopy images are provided for mesangial hypercellularity, endocapillary hypercellularity, and glomerular basement membrane (GBM) remodeling. Note that electron-dense deposits are associated with these lesions, restricted to the mesangium in mesangial hypercellularity, extending into the subendothelial distribution, resulting in endocapillary hypercellularity, and finally resulting in remodeling of the GBM with interposition of mesangial processes

glomerulonephritis, anti-GBM glomerulonephritis, monoclonal immunoglobulin glomerulonephritis, and C3 glomerulopathy. This classification is based largely on findings by immunofluorescence microscopy. An example of how this classification can be expanded and used to make a more concrete clinical diagnosis is shown in Fig. 7.

Immune complex-mediated GN has deposition of polyclonal immunoglobulins within glomeruli. More precise classification and underlying etiology are suggested by the type of immunoglobulins deposited and their distribution. Examples of immune complex-mediated GN include IgA nephropathy, lupus nephritis, and infection-related glomerulonephritis. The lesions (patterns of injury) seen by light microscopy are classified as focal or diffuse and as mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, and sclerosing. A biopsy specimen may have a combination of lesions, e.g., focal necrotizing and crescentic glomerulonephritis.

Anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) typically has

Fig. 5 (continued) (PAS, ×400) is the narrowing of the capillary lumen due to cellular infiltration. Fibrinoid necrosis (Jones silver ×400) is characterized by fibrin accumulation and is often accompanied by rupture and destruction of the glomerular basement membrane. Crescents can be characterized as cellular (Jones silver ×400), fibrocellular (PAS ×400), or fibrous (PAS ×400) depending on the relative proportion of cells to matrix. Glomerular basement membrane remodeling or duplication (Jones silver ×600) can occur in a variety of settings but here is secondary to large subendothelial immune deposits which are between the two layers of GBM. Sclerosis (scarring) is the accumulation of matrix material which obliterates normal glomerular architecture (PAS ×400). Sclerosis is not specific for glomerulonephritis and is the result of numerous types of glomerular injury

Table 1 Mayo Clinic/RPS guidelines on classification of GN

GN pathogenic type	Specific disease entity examples	Pattern of injury: focal or diffuse	Scores or class
Immune complex GN	IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple	Oxford/MEST scores for IgA nephropathy
			ISN/RPS class for lupus nephritis
Pauci-immune GN	MPO-ANCA GN, PR3-ANCA GN, ANCA-negative GN	Necrotizing, crescentic, sclerosing, or multiple	Focal, crescentic, mixed, or sclerosing class (Berden/EUVAS class)
Anti-GBM GN	Anti-GBM GN	Necrotizing, crescentic, sclerosing, or mixed	
Monoclonal Ig GN	Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple	
C3 glomerulopathy	C3 GN, dense deposit disease	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple	

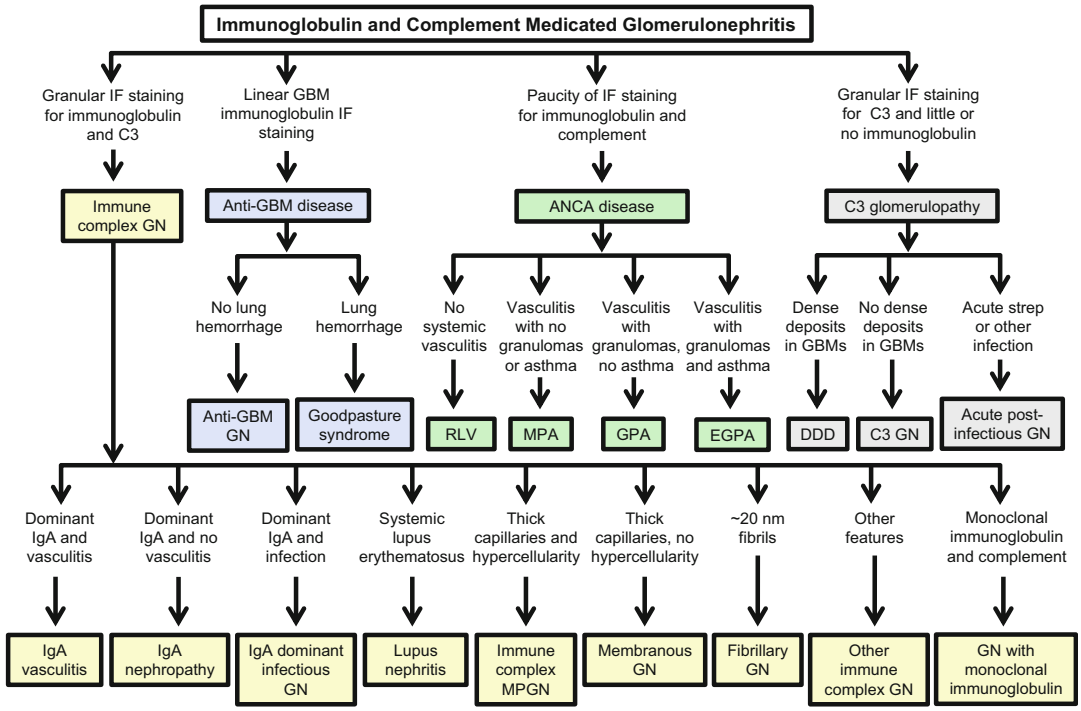

Fig. 7 Classification of immunoglobulin and complement glomerulonephritis illustrated in a flow chart. Monoclonal immunoglobulin-related diseases are not included in this diagram. Immunofluorescence findings are the starting point, allowing for categorization into broad categories. Based on clinical, serologic, and other histologic parameters, more specific entities can be diagnosed

abundant necrosis and extensive crescent formation by light microscopy and is characterized by intense linear staining of the glomerular basement membrane with IgG, which is in contrast to the granular immunoglobulin staining seen in immune complex-mediated GN. The linear staining is due to the deposition of circulating antibodies directed against the GBM (Pedchenko et al. 2010). Despite the positive staining by immunofluorescence, electron microscopy in anti-GBM GN does not show electron-dense deposits.

Pauci-immune necrotizing GN (ANCA GN), similar to anti-GBM disease, also typically has fibrinoid necrosis and crescent formation by light microscopy, though usually glomerular injury is less severe than in anti-GBM GN. In contrast, immunofluorescence in pauci-immune GN shows little if any immunoglobulin staining, and electron microscopy usually has few or no electron-dense deposits. Approximately 90% of pauci-immune necrotizing GN is associated with detectable circulating ANCA, though ANCA negative cases do occur.

C3 glomerulopathy (C3G) is defined by strong glomerular staining for C3 that is two scoring units more intense than any other immune reactant (Hou et al. 2014). Light microscopy shows the full range of patterns of injury seen with immune complex glomerulonephritis, and electron microscopy shows various combinations of mesangial, subendothelial, intramembranous, and subepithelial electron-dense deposits. C3G is subdivided into dense deposit disease and C3 GN based on appearance by electron microscopy. DDD has characteristic intramembranous dense deposits, whereas C3 GN lacks this degree of intramembranous deposits. C3G is driven by dysregulation of the alternative complement pathway, resulting in over-activation of complement and glomerular proliferation (Cook and Pickering 2015).

Monoclonal immunoglobulin-mediated glomerulonephritis is caused by the deposition of monoclonal light and/or heavy chains accompanied by complement components within the glomerulus. Light microscopy shows the full range of lesions caused by immune complex GN, and electron microscopy shows dense deposits that may be indistinguishable from those caused by immune complex deposition containing polyclonal immunoglobulin. Proliferative glomerulonephritis caused by monoclonal immunoglobulin deposits (Nasr et al. 2009) is distinct from "monoclonal immunoglobulin deposition disease" (Lin et al. 2001) that causes nodular glomerulosclerosis and has finely granular GBM deposits by electron microscopy that do not resemble immune complex GN.

Glomerular Lesions Associated with Nephrotic Syndrome

In contrast to the types of lesions described above for glomerulonephritis, the patterns of injury associated with nephrotic syndrome generally lack inflammatory lesions such as glomerular endocapillary hypercellularity ("proliferative lesions"), necrosis, and crescents (Figs. 8 and 9).

Minimal change disease (MCD) is a podocytopathy, characterized ultrastructurally by extensive effacement of podocyte foot processes (Fig. 9). As the name implies, minimal change disease is associated with essentially normal light microscopic findings. Immunofluorescence microscopy reveals no glomerular immune deposits. In a patient with substantial proteinuria, a pathologic diagnosis of MCD is appropriate when there is diffuse podocyte foot process effacement in the absence of pathologic evidence for any other glomerular disease that could be causing foot process effacement.

Focal segmental glomerulosclerosis (FSGS), in the early stages, has focal (i.e., involving some but not all glomeruli) and segmental (involving some but not all glomerular segments) sclerosis (Fig. 8a). FSGS is a pattern of injury that can be caused by many etiologies and pathogenic mechanisms. Because of this, FSGS is very heterogeneous with respect to pathology, clinical presentation, response to therapy, and outcome.

As with glomerulonephritis, FSGS can be classified based on etiology and pathogenesis (if known), as well as by histopathologic pattern of injury. The FSGS patterns recognized by the Columbia classification are perihilar variant, tip

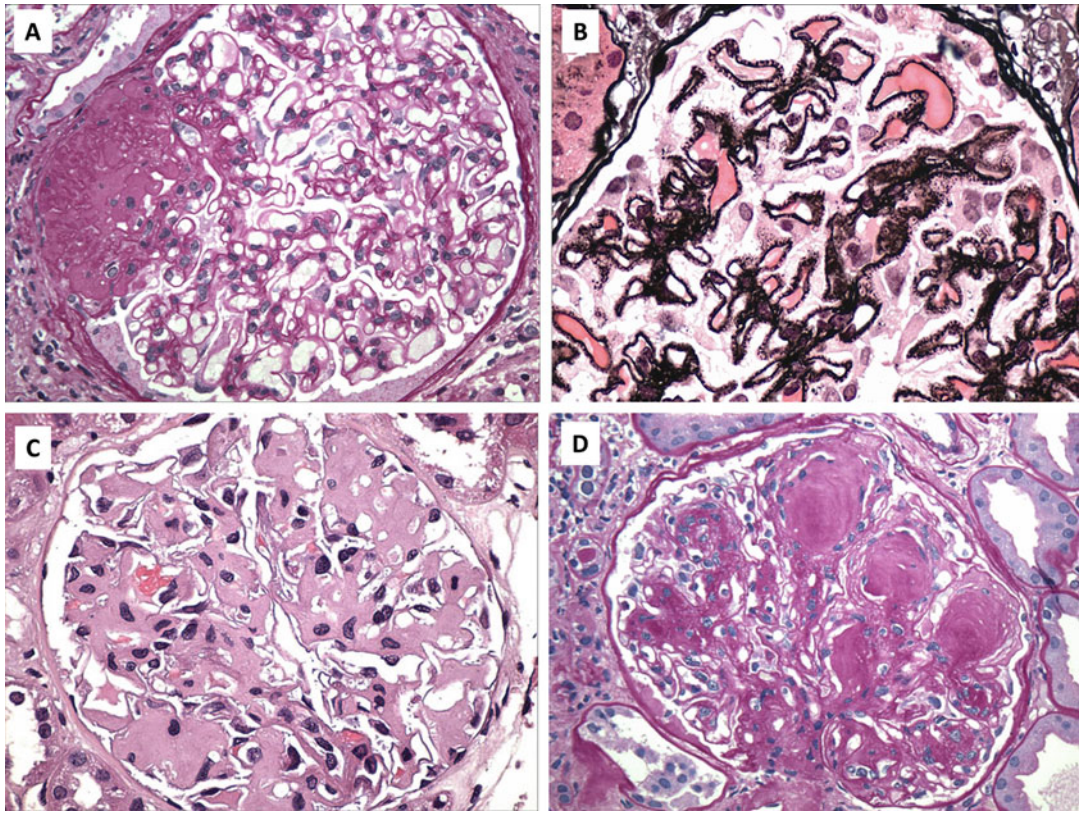

Fig. 8 Histologic lesions associated with nephrotic syndrome. A case of focal segmental glomerulosclerosis is pictured in panel (**a**) (PAS ×400) and shows a segmental lesion characterized by consolidation of the glomerular tuft, hyaline insudation, and adhesion to Bowman's capsule. Membranous nephropathy is shown in panel (**b**) and highlighted with the Jones silver stain (×600 magnification). Immune deposits are separated by black spikes protruding from the glomerular basement membrane into Bowman's space. A glomerulus showing prominent mesangial infiltration by amyloid is pictured in panel (**c**) (H&E, ×400). This type of mesangial expansion can be confused with other causes of mesangial expansion, such as diabetic nephropathy, illustrating the necessity of using a panel of special stains, combined with immunofluorescence and electron microscopy. Panel (**d**) shows the characteristic Kimmelstiel-Wilson nodules of nodular diabetic glomerulosclerosis (PAS ×400)

lesion variant, cellular variant, collapsing variant, and not otherwise specified (NOS) variant that lacks the defining features of the specified variants (D'Agati et al. 2004). As the names imply, perihilar FSGS preferentially affects perihilar glomerular segments, tip lesion FSGS preferentially affects the glomerular segment adjacent to the origin of the proximal tubule, cellular FSGS has numerous foamy macrophages in capillary lumens, and collapsing FSGS has collapse of glomerular segments with adjacent epithelial cell hypertrophy and hyperplasia. These histopathologic patterns of injury correlate with demographic and clinical features, and some etiologies correlate with specific pathologic variants. For example, FSGS secondary to obesity and other hemodynamic stress typically has a perihilar pattern, whereas FSGS associated with HIV or caused by pamidronate therapy has a collapsing pattern. Tip lesion FSGS has a clinical presentation similar to MCD with rapid onset of edema and is more responsive to steroid therapy than other variants of FSGS.

Membranous nephropathy (Figs. 8b and 9) is a form of glomerular injury defined by extensive deposition of immune complex deposits along the outer (subepithelial) surface of the glomerular basement membrane. Immunofluorescence staining reveals granular glomerular

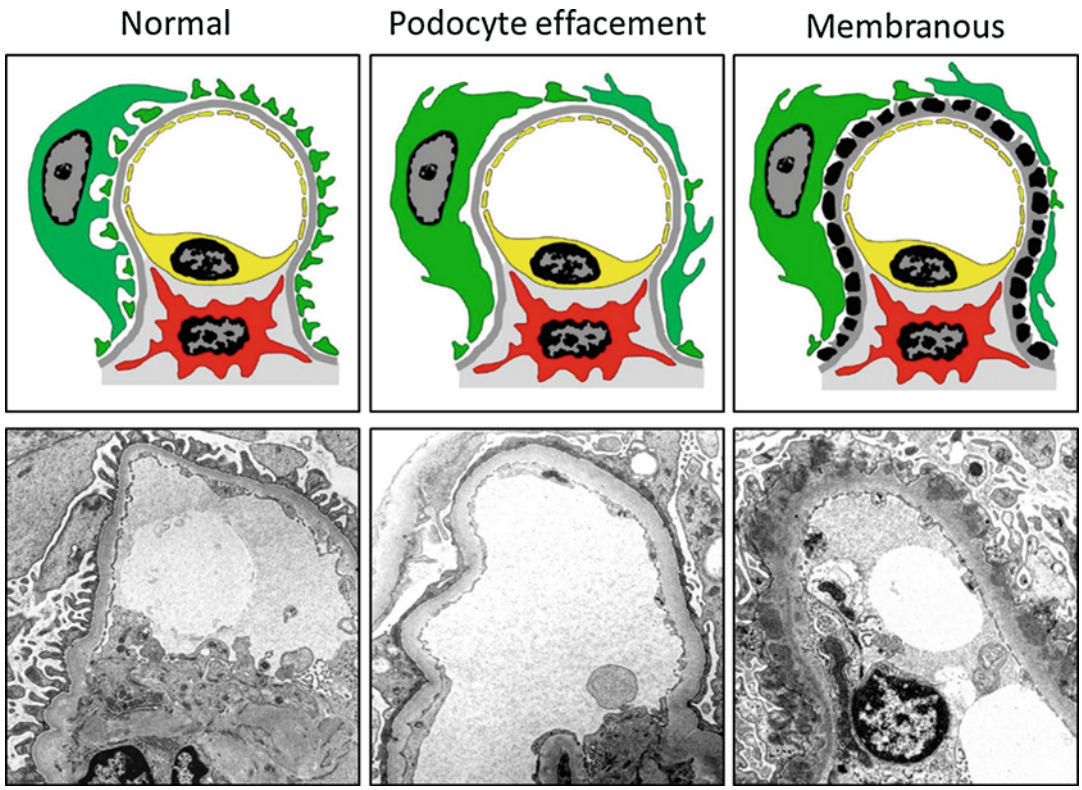

Fig. 9 Ultrastructural lesions of nephrotic syndrome. Podocyte foot process effacement is an ultrastructural hallmark of nephrotic syndrome. Effacement can occur as an isolated ultrastructural finding (middle panels) or due to immune complex deposition, as in membranous glomerulopathy

capillary wall staining for IgG and often C3. The presence of these immune deposits leads to GBM alterations that are visible by light microscopy, including GBM thickening, and spike formation and vacuolization, best demonstrated with PAS and Jones stains. The subepithelial deposits in membranous nephropathy cause extensive podocyte foot process effacement and nephrotic syndrome. As is discussed in later chapters, membranous nephropathy can result from multiple pathogenic mechanisms, including localization of subepithelial immune complexes composed of autoantibodies bound to phospholipase A2 receptor protein (PLA2R) or thrombospondin type-1 domain containing 7A protein (THSD7A). These causes for membranous nephropathy can be detected in renal biopsy specimens using immunofluorescence microscopy with antibodies specific for PLA2R or THSD7A.

Nodular glomerulosclerosis (Fig. 8d) is a pattern of glomerular injury characterized by the accumulation of matrix or other material that causes a nodular expansion of mesangial areas. A wide variety of disease processes can produce a nodular appearance and immunofluorescence, and electron microscopy studies are often required to differentiate among these entities. All of these nodular sclerosing glomerulopathies can be associated with substantial proteinuria or full nephrotic syndrome.

The most common cause of nodular sclerosis is diabetic nephropathy which has a nodular increase in PAS-positive and silver-positive mesangial matrix. Electron microscopy shows increased collagenous matrix material, glomerular basement membrane thickening, and the absence of immune-type electron-dense deposits. Immunofluorescence microscopy typically reveals mild

to moderate linear staining of GBMs for polyclonal IgG without significant staining for complement. Almost identical to nodular diabetic glomerulosclerosis is idiopathic nodular glomerulosclerosis that is most frequently seen in older patients who have a history of heavy tobacco exposure and chronic hypertension. Nodular glomerulosclerosis can be caused by monoclonal immunoglobulin deposition disease with monoclonal linear GBM staining and finely granular dense deposits in GBMs. Chronic membranoproliferative glomerulonephritis may cause mesangial nodularity; however, immunofluorescence microscopy and electron microscopy revel the characteristic features of the various forms of MPGN, such as immune complex MPGN, C3 glomerulopathy MPGN, and MPGN with monoclonal immunoglobulin.

Amyloidosis (Figs. 2d and 8c) has accumulation of proteins molecularly configured as antiparallel beta-pleated sheets. This molecular structure results in characteristic histologic and ultrastructural features. Using routinely stained sections for light microscopy, amyloid deposits in glomeruli are amorphous accumulations of material that stains pink with an H&E stain and stains weakly with PAS and silver stains. This is unlike collagenous scar that also stains pink with an H&E stain, but stains intensely with PAS and silver stains. Amyloid stains positively with histochemical stains including Congo red and thioflavin T. Ultrastructurally, amyloid is composed of fibrils that are randomly oriented and typically measure between 8 and 12 nm. Amyloid can be composed of many different types of polypeptides, including immunoglobulin light chains, amyloid A, apolipoproteins, leukocyte chemotactic factor 2 (ALect2), and many others. Regardless of the molecular composition, the histologic and ultrastructural appearance is the same. Light chain amyloidosis (AL amyloidosis) can typically be diagnosed through the use of routine immunofluorescence microscopy that includes antibodies for kappa and lambda light chains. Detection of other forms of amyloidosis requires immunostaining with antibodies specific for the constituent proteins (e.g., anti-AA protein) or proteomic analysis using mass spectroscopy.

Glomerular Lesions of Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is the spectrum of pathologic lesions associated with endothelial injury and microvascular thrombosis (Fig. 10). The underlying causes of injury vary widely, despite the substantial overlap in histologic appearance. The differential diagnosis of TMA is broad and includes thrombotic thrombocytopenic purpura (TTP), Shiga toxin-mediated hemolytic uremic syndrome (HUS), complement-mediated forms of TMA ("atypical" HUS), preeclampsia, accelerated hypertension, antiphospholipid syndrome, scleroderma renal crisis, systemic infections including HIV, and drug- or toxin-induced TMA. Many, but not all patients with histologic findings of TMA, have microangiopathic hemolytic anemia and thrombocytopenia. Renal biopsy alone cannot reliably distinguish among the varied etiologies of TMA, which must be investigated clinically (D'Agati et al. 2005).

In some forms of TMA, such as TTP, glomerular capillary thrombi will predominate (Fig. 10a) with fewer thrombi in arterioles and small arteries. These thrombi cause progressive remodeling in adjacent vessel walls. Overt thrombosis of capillaries and arterioles is not a requirement for the diagnosis of TMA as the histologic spectrum of endothelial injury extends beyond thrombosis. Glomerular capillary walls often appear thickened due to widening of the subendothelial zone. This is most easily observed by electron microscopy (Fig. 10c). Soon after the acute injury causing subendothelial widening, a new layer of glomerular basement membrane may begin to form, resulting in double contours of the GBM (Fig. 10b). Mesangiolysis is the loosening and unraveling of the normal mesangial matrix resulting in loss of the typically PAS- and Jones-positive mesangial matrix (Fig. 10b). Glomeruli and arterioles may have fibrinoid necrosis with minimal influx of leukocytes. In the acute phase, arteries have edematous (myxoid) intimal thickening, followed later by intimal fibrosis. Areas of mesangiolysis, fibrinoid necrosis, and acute intimal thickening may contain red blood cell fragments (schistocytes). Thrombi may be present in

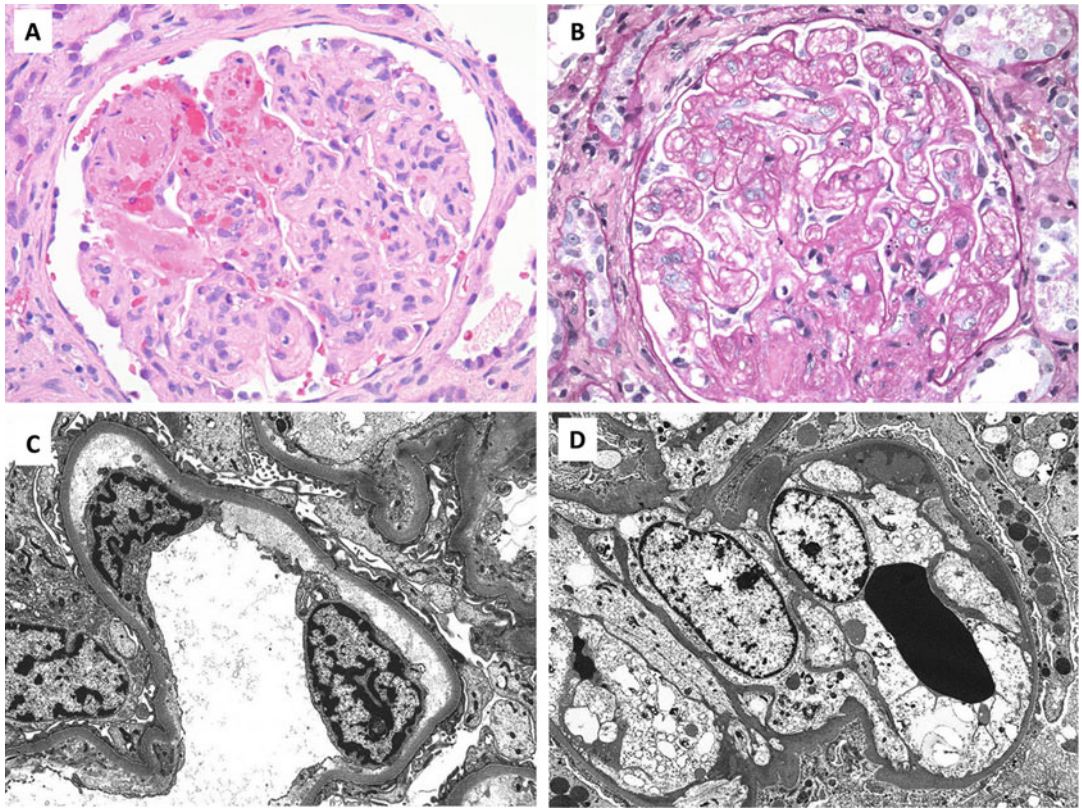

Fig. 10 Histologic lesions in the spectrum of thrombotic microangiopathy. Panel (**a**) (H&E ×400) shows a glomerulus with several glomerular capillary fibrin thrombi which are admixed with schistocytes. In contrast, panel (**b**) (PAS ×400) shows prominent mesangiolysis (loss of the PAS-positive mesangium in a normal glomerulus) as well as extensive double contouring of the glomerular basement membrane. Electron microscopy can be helpful in the diagnosis of thrombotic microangiopathy. Panel (**c**) shows the subendothelial widening commonly seen in a variety of endothelial injury (×6000), and panel (**d**) shows the severe endothelial swelling (endotheliosis) that is classically seen in preeclampsia/eclampsia

injured glomerular capillaries, arterioles, or arteries, but thrombosis is much less conspicuous in other forms of TMA compared to TTP. Some glomeruli may display prominent congestion by red blood cells if flow out of the glomerulus is compromised due to a downstream occluded vessel. Ischemic wrinkling of glomeruli is frequently seen in the setting of severe injury of arteries and arterioles leading into glomeruli. In preeclampsia/eclampsia, often the most obvious lesion is endotheliosis, which is profound swelling of glomerular endothelial cells (Fig. 10d). There may be segmental subendothelial expansion with accumulation of slightly electron-dense material. In later phases, there is usually mild GBM remodeling and replication.

Assessment of Chronic Changes in Glomerular Disease

Chronic scarring is the end result of most of the glomerular diseases discussed above. While chronic changes are generally considered to be irreversible, accurate assessment of chronicity is important for predicting prognosis and guiding therapy. The need to more consistently grade chronic changes in native kidney biopsies has been recently addressed by a team of pathologists and nephrologists who proposed a chronicity score based on chronic scarring in the glomerular, tubulointerstitial, and vascular compartments (Sethi et al. 2017). This chronicity

Table 2 Scoring of chronic lesions

Renal compartment	0 points	1 point	2 points	3 points
Glomerulosclerosis (globally sclerotic + segmentally sclerotic + ischemic glomeruli)	<10%	10–25%	26–50%	>50%
Interstitial fibrosis (% of cortex with increased fibrosis)	<10%	10–25%	26–50%	>50%
Tubular atrophy (% of cortical tubules showing atrophy)	<10%	10–25%	26–50%	>50%
Arteriosclerosis	Thickness of intima < medial thickness	Thickness of intima ≥ medial thickness		

Adapted from Sethi et al. 2017

score ranges 0 points to a maximum of 10 points, with up to 6 of those points awarded for tubulointerstitial scarring, up to 3 points awarded for glomerular scarring, and up to 1 point awarded for vascular disease (Table 2). Chronicity scores of 0 or 1 are considered to represent minimal chronic disease, a score between 2 and 4 is considered to be mild, a score between 5 and 7 is equivalent to moderate chronicity, and scores of 8 or more points are considered to represent severe chronic changes.

Conclusions

Renal biopsy is an important tool in the clinical management of glomerular disease. The pathologic evaluation identifies the pattern of injury, the degree of activity and chronicity, and often provides evidence for the pathogenic mechanism and/or etiology. Biopsy can guide selection of therapy and provide prognostic information. It is important to remember that a wide variety of pathologic processes can produce similar patterns of glomerular injury. For this reason, routine evaluation of renal biopsies must include immunofluorescence microscopy and electron microscopy. In addition, it is critical that the pathologic findings be interpreted in the setting of adequate clinical information, including relevant serologic testing. This allows for the more precise diagnosis of disease entities (such as lupus nephritis or ANCA GN) rather than limiting the diagnosis to a description of the patterns of injury.

Cross-References

- Alport Syndrome and Other Collagen Disorders
- ANCA-Associated Vasculitis, Adult
- ANCA-Associated Vasculitis, Pediatric
- Anti-glomerular Basement Membrane Disease
- C3 Glomerulopathy
- Fibrillary Glomerulonephritis
- Focal Segmental Glomerulosclerosis, Adult
- Focal Segmental Glomerulosclerosis, Pediatric
- Hemolytic Uremic Syndrome
- HIVAN, Adult
- HIVAN, Pediatric
- Idiopathic Immune Complex Glomerulonephritis
- IgA Nephropathy: Clinical Features, Pathogenesis, and Treatment
- IgA Nephropathy and Henoch Schönlein Nephritis, Pediatric
- Immunotactoid Glomerulopathy
- Light Chain (AL) Amyloidosis and the Kidney
- Lipoprotein Glomerulopathy, Non-AL Amyloidosis, LCAT, ING
- Lupus Nephritis (Including Antiphospholipid Antibody Syndrome), Adult
- Lupus Nephritis (Including Antiphospholipid Antibody Syndrome), Pediatric
- Membranoproliferative Glomerulonephritis, Adult
- Minimal Change Disease in Adults
- Minimal Change Disease, Pediatric
- Membranoproliferative Glomerulonephritis, Type 1, Pediatric

- ▶ PLA_2R- and THSD7A-Associated Primary Membranous Nephropathy
- ▶ Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits
- ▶ Thrombotic Thrombocytopenic Purpura, Genetic and Secondary

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Overview of the Current Approach to Glomerular Disease Classification

5

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Abstract

Classification systems of disease states are created to help stratify disease to help guide clinical evaluation and treatment and provide insights into prognosis. Glomerulonephritis is a term used to broadly characterize kidney diseases that occur as a result of immunologic and inflammatory injury to the glomeruli. There are several types of glomerular diseases and these diseases can be classified based on their clinical presentation, etiology, histology, or pathogenesis. Since the incorporation of the kidney biopsy into routine practice, histopathological classification of glomerular diseases has emerged and is now most commonly used method to characterize the different glomerular lesions identified and classify the different glomerular diseases. In this chapter, we will review the current classification systems used in clinical practice to characterize and differentiate glomerular diseases.

Keywords

Glomerulonephritis · Glomerular disease · Classification · Kidney disease · Kidney histology · Nephritis · Nephrotic syndrome · IgA nephropathy · Lupus nephritis · Focal segmental glomerulosclerosis · Histopathology

Introduction

Clinical classification of glomerular disease can be dated to the Hippocratic aphorisms. Then, renal diseases were divided according to whether bubbles appeared on freshly voided urine samples (Black 1980). We now recognize the bubbles appearing on freshly voided urine as evidence of the detergent effect of large amounts of protein in the urine allowing stable bubbles to form. The abundant bubble formation is indicative of nephrotic range proteinuria.

In 1905 Müller introduced the term "nephrosis" to describe noninflammatory kidney diseases in contrast to inflammatory kidney diseases or "nephritis" (Muller 1905). Subsequently, a clinical classification system for glomerular diseases emerged. Glomerulonephritis could now be classified as nephritis, nephrosis, or nephrosclerosis (Arneil 1971; Black 1980) and later stratified as acute, subacute, or chronic based on the timing of clinical presentation (Addis 1948).

In the 1950s, the introduction of the percutaneous renal biopsy revolutionized the study and classification of glomerulonephritis. Renal biopsy allowed for the microscopic study of active renal disease. In so doing, it launched the field of nephropathology and led to new insights into disease pathogenesis and underlined the importance of renal histology to classify glomerular diseases. For example, in 1958 Kark and colleagues further used histopathologic findings to differentiate diabetic nephropathy, lupus nephritis, and other forms of glomerulonephritis (Kark et al. 1958). Importantly, from this newly acquired information, etiology-specific treatment strategies could be applied and studied.

With the routine incorporation of the kidney biopsy into clinical practice, histopathological classifications of glomerular diseases emerged. Nephrologists and Pathologists attempted to

correlate the static snapshot of the renal biopsy to the clinical course of a disease, with the idea of creating classifications that more specifically describe individual diseases and better inform on treatment and prognosis than classifications based on clinical criteria alone. A recent example is the Oxford IgA nephropathy classification system in which a histologic score is provided that has been shown in some studies to help guide treatment decisions and prognosticate outcomes (Cattran et al. 2009).

Over the past 30 years, there have been new insights into the pathophysiology of various glomerular diseases. This includes the discovery of viruses such as hepatitis C and HIV causing glomerulonephritis, the emergence of antiphospholipase A2 receptor antibodies in membranous nephropathy, the role alternative complement dysregulation as a major cause of membranoproliferative glomerulonephritis, and the APOL-1 gene variants in African Americans which predispose them to focal segmental glomerulosclerosis (FSGS). The current challenge is to incorporate our emerging understanding of disease pathophysiology into the existing classification systems. A recent example is the new classification for membranoproliferative glomerulonephritis (MPGN), which is now classified as C3 glomerulopathy (dense deposit disease or C3 glomerulonephritis), immune complex-mediated MPGN, or MPGN due to neither of these mechanisms (Sethi and Fervenza 2011).

Efforts are continuing to be made to improve upon the existing classifications and incorporate new information as it emerges with the goal to better stratify and treat disease and predict long-term kidney outcomes. An effective classification system must satisfy the following criteria: (1) be simple and precise so it can be generalized, (2) provide clear diagnostic delimitations, (3) provide prognostic information of the likely clinical course of the disease, (4) provide specific information related to disease pathogenesis so that treatment can be individualized, and (5) be flexible so that it can undergo modification as new knowledge is gained.

In this chapter, we will review the existing clinical, morphologic, and pathophysiologic criteria used to classify glomerular diseases and will discuss the emerging pathophysiological evidence that may lead to improvements in the existing classification systems in the future.

Clinical Classification of Glomerular Diseases

The presence of glomerulonephritis as opposed to other forms of intrinsic renal disease, such as tubulointerstitial disease or vascular disease, is usually suspected from the history, physical examination, and specific urinary findings. However, the clinical manifestations may be heterogeneous and frequently there are no specific findings for a particular glomerular disease, and despite the clinical clues, glomerular disease can easily be mistaken for tubulointerstitial disease or vascular disease. Therefore, the diagnosis of glomerulonephritis poses a diagnostic challenge. However, there are several findings on the clinical presentation that allow for stratification of the different glomerular diseases. Clinical findings that suggest glomerulonephritis include hallmarks such as glomerular hematuria, proteinuria, and renal dysfunction at presentation. Clinical manifestations including hypertension, edema, proximity to infection and extra-renal manifestations that suggest a systemic disorder may help classify the type of glomerulonephritis present and further differentiate primary glomerulonephritis from systemic causes of glomerulonephritis. Ultimately, a kidney biopsy is usually needed for definitive diagnosis; however, the clinical classification serves as a useful tool for Clinicians to establish a prebiopsy working diagnosis and guide further evaluation.

As mentioned above, glomerular diseases can present with a variety of manifestations ranging from macroscopic glomerular hematuria to asymptomatic patients who are incidentally found to have abnormal findings on urinalysis or urine microscopy such as microscopic hematuria, subnephrotic proteinuria, or nephrotic range proteinuria without nephrotic syndrome. Those with

Table 1 Clinical classification of glomerular diseases

Presentation	Specific presentation	Definition	Examples
Macroscopic glomerular hematuria	Gross hematuria	Visible hematuria of glomerular origin	IgAN Thin-basement membrane disease Alport's syndrome
Asymptomatic urinary abnormalities	Microscopic glomerular hematuria	Glomerular hematuria (≥3 RBC/hpf)	IgAN Thin-basement membrane disease Alport's syndrome
	Non-nephrotic proteinuria	Proteinuria between 150 mg and 3.5 g in 24 h	IgAN FSGS
	"Nephrotic" range proteinuria w/o nephrotic syndrome	Proteinuria ≥3.5 g/24 h + serum albumin ≥3.5 g/dl, w/o edema	Secondary FSGS Diabetic nephropathy
Nephritic syndrome	Mild	Glomerular hematuria ± proteinuria ± hypertension ± preserved renal function	Secondary FSGS Lupus nephritis Mesangioproliferative GN
	Severe	Glomerular hematuria ± proteinuria ± hypertension ± diminished renal function	Immune-complex mediated GN Infection-related GN C3 glomerulopathy
	Extreme (rapidly progressive GN)	Renal failure over days or weeks + proteinuria + glomerular hematuria	Immune-complex mediated Paucimmune (AAV) Anti-GBM
Nephrotic syndrome	Nephrotic proteinuria with evidence of glomerular permeability	Proteinuria ≥3.5 g/24 h + serum albumin <3.5 g/dl ± edema ± lipiduria	Minimal change disease Membranous nephropathy Primary FSGS Lupus nephritis
Chronic kidney disease	Established long-standing kidney disease	Evidence of chronic kidney damage + proteinuria ± hematuria	Secondary FSGS Diabetic nephropathy Monoclonal gammopathies

Abbreviations: *RBC* red blood cells, *hpf* high-power field, *IgAN* IgA nephropathy, *GN* glomerulonephritis, *FSGS* focal and segmental glomerulosclerosis, *HTN* hypertension, *AAV* ANCA-associated vasculitis, *GBM* glomerular basement membrane

nephrotic syndrome or acute nephritis (*defined below*) demonstrate more obvious clinical features. Specific definitions for these clinical presentations and their associated clinical classifications are detailed in Table 1.

Presentation of Glomerular Diseases: Glomerular Syndromes

Here we will describe the current and most widely accepted approach to classifying glomerular diseases. While there is little evidence available to guide this approach, it is considered the classical approach to the clinical evaluation of glomerular disease.

Glomerular Hematuria

Macroscopic Glomerular Hematuria

Glomerular diseases can manifest as macroscopic painless hematuria with otherwise normal renal function. This presentation is observed primarily in children and young adults and is rare in those over 40 years (Rockall et al. 1997; Youn et al. 2006). In evaluating a patient with macroscopic hematuria, it is important to differentiate glomerular from nonglomerular origin. Importantly,

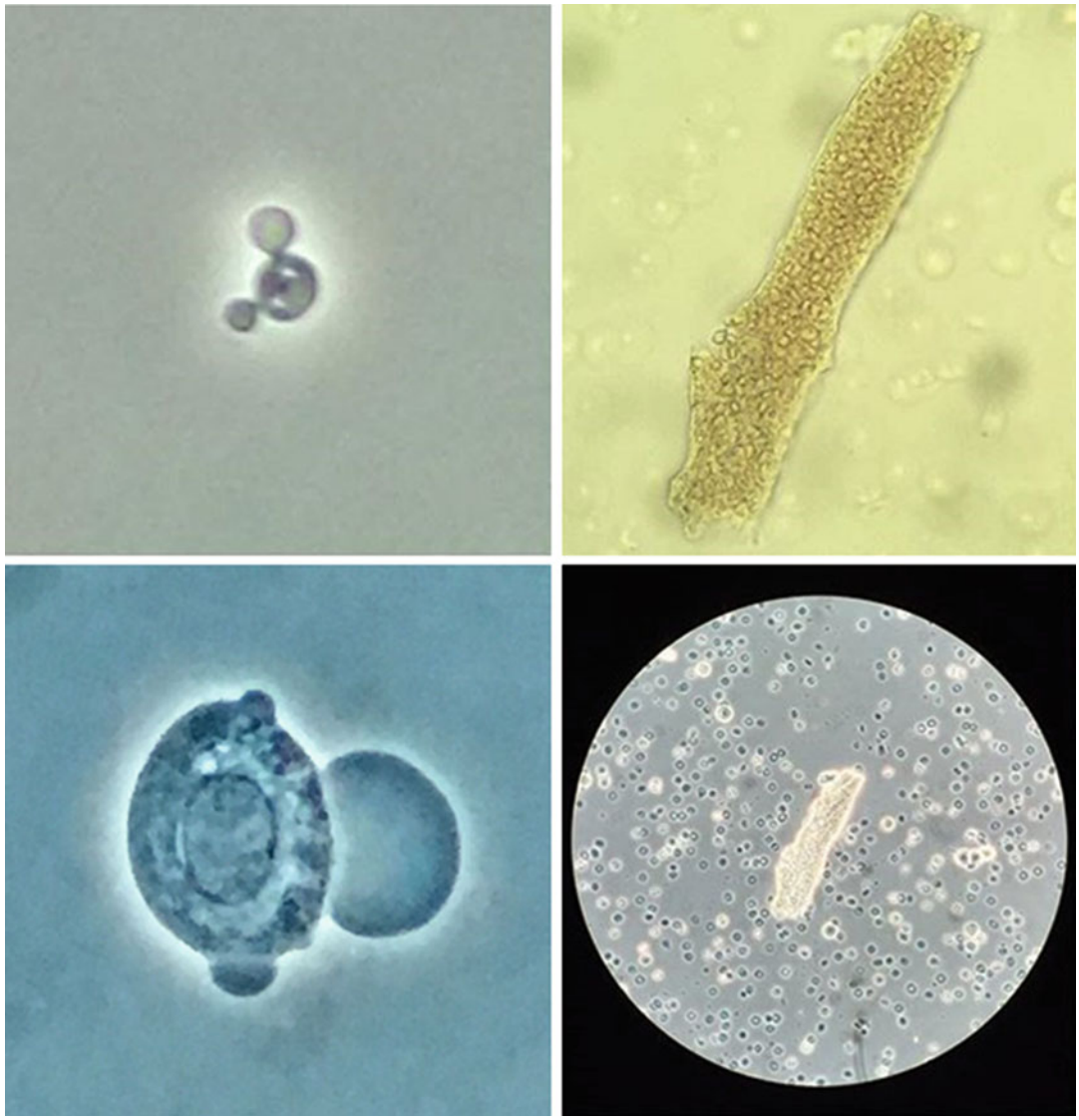

Fig. 1 Acanthocytes and red blood cell casts (Reproduced with permission courtesy of Dr. F. Buchkremer. www.swissnephro.org)

macroscopic hematuria can occur in a variety of nonglomerular conditions including cystic renal disease, nephrolithiasis, and disease of the lower genitourinary tract. If clots are present, a lower genitourinary source is likely. Alternatively, the presence of a brown, cola-colored urine, dysmorphic red blood cells [especially acanthocytes, (Köhler et al. 1991)], red-blood cell casts, and albuminuria (Ohisa et al. 2008) is highly suggestive of a glomerular origin for the hematuria (Fig. 1).

The most common glomerular disease presenting as macroscopic hematuria is IgA nephropathy. A history of recent upper respiratory tract infection can be obtained and typically occurs within days before the start of hematuria. Hereditary nephritis or Alport's syndrome and thin basement membrane nephropathy may also present with macroscopic hematuria and is often associated with a strong family history. Other rarer glomerular diseases can present with macroscopic

glomerular hematuria and include loin-pain hematuria syndrome (Spetie et al. 2006) and the recently recognized anticoagulant-related nephropathy (Brodsky et al. 2009). Finally, macroscopic glomerular hematuria has also been reported to be associated with acute interstitial nephritis (Rossert 2001).

Microscopic Glomerular Hematuria

Microscopic glomerular hematuria is more common than macroscopic glomerular hematuria and is defined as the presence of 3 or more red blood cells (RBC) per high-power field in the urinary sediment or more than 10×10^6 RBC per liter by automatized examination. Red cell morphology is critical to differentiating glomerular hematuria from nonglomerular bleeding. Dysmorphic red blood cells, and more specifically acanthocytes, which are ring-shaped red blood cells with vesicle-like protrusions, are highly specific for glomerular bleeding. The presence of red blood cell casts, which are red blood cells encased in an extra-cellular matrix of Tamm-Horsfall protein, on urine microscopy is virtually diagnostic of an acute glomerulonephritis or renal vasculitis (Hebert et al. 2013) (Fig. 1).

Microscopic glomerular hematuria may be seen in both inflammatory and noninflammatory forms of glomerulonephritis (Topham et al. 1994). Noninflammatory forms of glomerular disease that are known to be associated with microscopic hematuria include Alport's syndrome, thin basement membrane nephropathy, and diabetic nephropathy (Akimoto et al. 2008). IgA nephropathy is the most common cause of microscopic glomerular hematuria worldwide and may be asymptomatic or associated with acute nephritis (Wyatt and Julian 2013).

Microscopic glomerular hematuria is present in most forms of acute nephritis such as post-infectious glomerulonephritis and lupus nephritis. In cases where microscopic glomerular hematuria is present but proteinuria is less than 0.5 g/d and renal function is normal, unless there is concern for a systemic illness such as vasculitis, the renal prognosis is generally excellent so the kidney biopsy is generally deferred and patients are instead followed closely for development of worsening renal parameters. In these cases, the hematuria is usually identified incidentally and most commonly reflect a mild form of IgA nephropathy, Alport's syndrome, or thin glomerular basement membrane disease (Hall et al. 2004).

Glomerular Proteinuria

Asymptomatic Non-nephrotic Proteinuria

Non-nephrotic range proteinuria is defined as abnormal proteinuria of less than 3.5 g in 24 h (Glassock et al. 2015b). Although nephrotic proteinuria is usually secondary to glomerular diseases, non-nephrotic proteinuria is far less specific and therefore, tubulointerstitial and vascular conditions should be excluded on clinical evaluation.

When non-nephrotic proteinuria is accompanied by microscopic hematuria ("active urine sediment") and a normal estimated glomerular filtration rate, it has been frequently classified as "mild glomerulonephritis" or "mild nephritic syndrome" (Table 1). Specific associated etiologies are discussed under the mild nephritic syndrome subsection below.

Nephrotic Range Proteinuria Without Nephrotic Syndrome

Some glomerular and nonglomerular diseases can present with proteinuria over 3.5 g/d without other symptoms or signs, and particularly in the absence of hypoalbuminemia. In these cases, proteinuria may be due to defective proximal tubular reabsorption of low-molecular weight plasma proteins as seen in Dent's disease or arise from "overflow" and excessive filtration of low molecular weight plasma proteins such as that seen in light chain deposition disease. When the proteinuria is from a glomerular source, the most abundant protein is albumin. Therefore, in patients with nephrotic-range proteinuria without hypoalbuminemia, a 24-hour urine testing for both total protein and albumin is recommended to differentiate proteinuria of glomerular origin from proteinuria of nonglomerular origin.

Any of the conditions that are associated with nephrotic range proteinuria can cause asymptomatic nephrotic range proteinuria to "full blown" nephrotic syndrome. However, the most frequent glomerular disease presenting with nephrotic range

proteinuria but without nephrotic syndrome is secondary focal and segmental glomerulosclerosis (e.g., glomerular hyperfiltration, obesity-related nephropathy, nephron mass reduction) (Gupta et al. 2008). The distinction from primary glomerular diseases that usually present as nephrotic syndrome is important as the latter are frequently treated with immunosuppressive agents while the former, with only a few exceptions, is treated with supportive measures only (Praga et al. 1991).

Nephrotic Syndrome

Nephrotic syndrome refers to a specific constellation of clinical features and is defined by the presence of heavy proteinuria (>3.5 g/d) with associated lipiduria, hypercholesterolemia, hypoalbuminemia (<3.5 g/dl), and peripheral edema (Glassock et al. 2015b). Nephrotic syndrome is the most common clinical presentation of glomerular disease and may occur in association with both primary and systemic diseases (Rivera et al. 2004).

Approximately 30% of nephrotic syndrome cases in adults are associated with a systemic disease such as diabetes mellitus or amyloidosis, while the remainder are due to primary diseases such as focal segmental glomerulosclerosis (FSGS) or membranous nephropathy (Haas 1997; Rivera et al. 2004; O'Shaughnessy et al. 2017). Meanwhile in children, the most common cause of nephrotic syndrome is minimal change disease. Specific etiologies for nephrotic syndrome vary according to the age group, ethnicity, and region (Table 2).

Figure 2 shows some of the most common etiologies of nephrotic syndrome according to different age groups. As a general approach, in patients less than 15 years of age, minimal change disease is most common representing approximately 40 to 78% of cases (Rivera et al. 2004; Vivarelli et al. 2017). In patients from 15 to 40 years, FSGS, membranous nephropathy, and minimal change disease are the most common forms of primary nephrotic syndrome. In this age group, the incidence of minimal change disease decreases, while the incidence of FSGS increases (Baqi et al. 1998). Finally, in patients greater than 40 years, FSGS, membranous nephropathy, minimal change disease, IgA nephropathy, and fibrillary glomerulonephritis are the most common forms of primary nephrotic syndrome; however, systemic nephrotic syndrome etiologies also become more common and must be therefore considered. Diabetic nephropathy is the most common form of systemic nephrotic syndrome (O'Shaughnessy et al. 2017), while primary amyloidosis, light chain deposition disease, and infection-associated glomerulonephritis may also present in this age group.

Table 2 Prevalence of nephrotic syndrome causes in adults across diverse biopsy registries

Disease	United States[a]	Italy	Spain	Brazil	South Africa	Mexico	India
MCD	8	12	15	21	4	5	30
FSGS	39	12	12	27	6	13	15
MN	20	33	25	19	12	21	21
IgAN	–	5	5	4	–	2	3
MPGN	5	6	7	2	8	1	11
LN	–	11	10	8	17	42	3
Amyloidosis	1	7	9	5	–	3	–
Diabetic GE	22	–	–	–	–	8	–
HIVAN	–	–	–	–	12	–	–
Others	15	14	17	14	41	5	17

Adapted from references O'Shaughnessy et al. 2017, Gesualdo et al. 2004, Rivera et al. 2004, Polito et al. 2010, Okpechi et al. 2011, Mejia-Vilet 2016 (personal communication), Beniwal et al. 2016

Abbreviations: *MCD* minimal change disease, *FSGS* focal and segmental glomerulosclerosis, *MN* membranous nephropathy, *IgAN* IgA nephropathy, *MPGN* membranoproliferative glomerulonephritis, *LN* lupus nephritis, *Diabetic GE* diabetic glomerulosclerosis, *HIVAN* HIV associated nephropathy

[a]Data assigned as diseases "typically presenting as nephrotic syndrome" and not real rates, all lupus nephritis cases were classified under nephritic syndrome

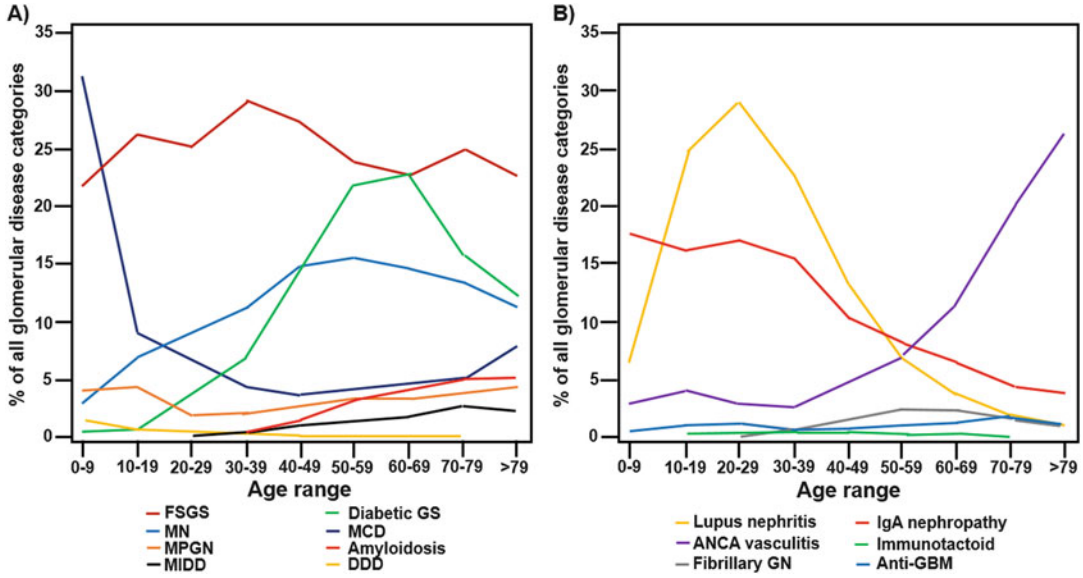

Fig. 2 Age variation of different glomerular diseases according to typical presentation as nephrotic syndrome (**a**) or nephritic syndrome (**b**) (Reproduced with permission from O'Shaughnessy et al. 2017**.** Abbreviations: *FSGS* focal and segmental glomerulosclerosis, *MN* membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *MIDD* monoclonal immunoglobulin deposition disease, *MCD* minimal change disease, *DDD* dense deposit disease, *Anti-GBM* antiglomerular basement membrane disease)

Nephritic Syndrome

In the nephritic syndrome, glomerular inflammation results in the presence of micro- or macroscopic hematuria, acute kidney injury in severe cases, proteinuria, edema, and hypertension. The most severe form of nephritic syndrome is accompanied by a rapid loss of renal function (arbitrarily defined as in less than 12 weeks) and is defined as a rapidly progressive glomerulonephritis. As with nephrotic syndrome, nephritic syndromes can be both primary and due to systemic causes. Many of these syndromes will have characteristic serologic findings as well, including hypocomplementemia in several cases.

Mild Nephritic Syndrome

Nephritic syndrome is classified as mild if there is "active urine sediment" (glomerular hematuria, red cell casts, or mixed red cell/white cell casts) and proteinuria, but the renal function is preserved.

The specific etiologies vary according to the age of the patient (Rivera et al. 2004). In those less than 15 years old, mild nephritis may occur due to postinfectious glomerulonephritis, IgA nephropathy, thin basement membrane disease, hereditary nephritis or Alport's syndrome, Henoch-Schönlein purpura, or mesangial proliferative glomerulonephritis. Between 15 and 40 years, the most common etiologies include IgA nephropathy, thin basement membrane disease, lupus nephritis, hereditary nephritis, and mesangial proliferative glomerulonephritis. In patients over 40 years, IgA nephropathy, thin basement membrane disease, or infection-associated glomerulonephritis should be considered.

Severe Nephritic Syndrome

Severe nephritic syndrome is characterized by glomerular hematuria, proteinuria, hypertension, and acute kidney injury (AKI). AKI refers to an abrupt loss of kidney function that is defined by a usually reversible decline in glomerular filtration rate (GFR) (Kidney Disease: Improving Global Outcomes 2012).

In patients less than 15 years, the most common causes of severe nephritis include postinfectious glomerulonephritis, Henoch-Schönlein purpura (HSP), IgA nephropathy, or C3 glomerulopathy.

In patients 15 to 40 years, IgA nephropathy, HSP, lupus nephritis, postinfectious glomerulonephritis, or C3 nephritis should be considered. Additionally, patients positive for hepatitis C are at risk for cryoglobulinemic vasculitis. ANCA-associated vasculitis is less common in this age group but still may occur. In those over 40 years of age, IgA nephropathy, ANCA-associated vasculitis, cryoglobulinemia, and infection-associated glomerulonephritis should be considered. An example of infection-associated glomerulonephritis is *Staphylococcal aureus* associated glomerulonephritis (SAAGN). SAAGN is different from postinfectious GN in that it occurs in the setting of an ongoing subacute or chronic infection with *Staphylococcal Aureus* species. In comparison, postinfectious glomerulonephritis is rare in this age group.

Rapidly Progressive Glomerulonephritis (Extreme Nephritic Syndrome)

Rapidly progressive glomerulonephritis (RPGN) is the acutest and severe form of glomerulonephritis. It is associated with an abrupt decline in GFR that occurs over days to weeks and is associated with nephritic urine sediment and typically subnephrotic range proteinuria. The etiologies that lead to RPGN can be further subgrouped into 3 main categories: (1) antiglomerular basement membrane disease, (2) immune-complex mediated RPGN which includes lupus nephritis, IgA nephropathy, infection-associated glomerulonephritis, postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, or cryoglobulinemic vasculitis, (3) pauci-immune glomerulonephritis, which is most commonly attributed to ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis). While considered more a vascular than a glomerular disease, thrombotic microangiopathy is not usually included in these categories but should also be considered in the differential diagnosis of RPGN.

Chronic Kidney Disease

Accumulation of chronic kidney damage may occur in all forms of glomerular disease and can occur rapidly in cases of severe nephritis that is not promptly treated. Chronic kidney damage due to an underlying glomerulonephritis is often identified by a clinical course of slowly progressive renal decline and evidence of persistent proteinuria (usually subnephrotic). Ultrasound findings may also show evidence of chronic damage such as reduced kidney size or volume, cortical hyperechogenicity, absence in corticomedullary differentiation, and reduced cortical thickness.

Differentiating chronic from active, proliferative disease represents a diagnostic challenge as chronic kidney damage may look similar to a flare of an active, proliferative glomerulonephritis. For example, proteinuria, a clinical hallmark for glomerulonephritis, may also occur due to glomerulosclerosis that develops due to persistent injury and reflects chronic damage. Therefore, patients may have worsening proteinuria and kidney function due to progressive chronic injury instead of acute flare of the glomerulonephritis. This is particularly challenging in relapsing conditions such as lupus nephritis, ANCA-associated vasculitis, and IgA nephropathy where immunosuppression is needed to treat active disease but would expose patients to unnecessary, potentially toxic therapy if the worsening disease was due to accumulation of chronic damage instead. In these cases, a kidney biopsy may help differentiate active from chronic disease and should be considered prior to modifying therapy (Parikh et al. 2015).

Primary Versus Secondary Glomerular Diseases

As mentioned above, glomerular diseases may be primary (affecting the kidney only) or may occur due to a systemic condition. There are important elements of the patient history that can help orient the diagnosis. Among them are family history, patient's race, the coexistence of a systemic disease that could associate with glomerular damage, and the time course of the development of symptoms. For example, a strong family history of kidney disease and hematuria may suggest Alport's syndrome as the diagnosis. Meanwhile, an African American patient with nephrotic

syndrome is more likely to have FSGS (Korbet et al. 1996). A patient with a long-standing history of diabetes mellitus with associated microvascular complications including retinopathy or neuropathy is most likely to have diabetic nephropathy. This is especially true for patients with type I diabetes mellitus with retinopathy where the development of kidney disease is due to diabetic nephropathy in over 90% of cases (Chavers et al. 1994). Nephritis in a patient with features of systemic lupus erythematosus is most often due to some form of lupus nephritis and not an independent kidney process. This is also the case for a systemic vasculitis although ANCA-vasculitis may also be renal limited.

Acute Versus Chronic Glomerular Diseases

Another type of classification that has been used is to divide glomerular diseases by tempo of disease. Glomerular diseases may occur with a sudden onset (acute) or with a slow evolution over months to years (chronic). For example, abrupt onset nephrotic syndrome suggests minimal change disease, while nephrotic syndrome due to membranous nephropathy may occur over several months.

Although disease's evolution is clear in some cases, often times the temporal evolution of disease can be difficult to determine as many glomerular diseases manifest with asymptomatic abnormalities of the urine sediment or chronic kidney disease. Therefore, this form of glomerular disease classification is of limited value and requires histopathologic evaluation to differentiate active from chronic disease.

Limitations of Clinical Classification of Glomerulonephritis

Clinically classifying glomerular diseases based on presentation and laboratory evaluation is helpful in stratifying the differential diagnosis and guiding the clinical evaluation. However, classifying glomerular disease only by clinical features has several limitations: (1) clinical manifestations frequently overlap between diseases of the glomeruli and tubulointerstitial and vascular renal diseases; (2) in some diseases, the severity of clinical symptoms does not match the severity in the histopathological evaluation; (3) there is frequent overlap between nephritic and nephrotic features; (4) as mentioned above, it is sometimes difficult to differentiate acute from chronic damage based on clinical assessment alone.

Extended Clinical Evaluation of Glomerular Diseases: Laboratory

Perhaps the most important feature of the initial clinical classification of glomerular disease is to guide an extended clinical evaluation to arrive at a working diagnosis. This extended evaluation includes additional serologic studies that can help the clinician define a clinical diagnosis.

Serologic Studies for Clinical Diagnosis of Glomerular Disease

While the initial clinical evaluation can stratify the disease into a particular syndrome (e.g., nephritic versus nephrotic syndrome), additional clinical studies are usually required to arrive at a clinical diagnosis. This is of particular importance when a systemic cause of glomerulonephritis is being considered.

There are many serologic studies that are commonly performed and in some cases will narrow the possibilities for diagnosis to one or a few conditions. For example, in patients with clinical manifestations suggestive of systemic lupus erythematosus (SLE), antinuclear antibody, and anti-double-strand DNA antibody testing may confirm the Clinician's suspicion and make a diagnosis of lupus nephritis more likely. That said, even in patients with SLE where lupus nephritis is likely, 5 to 10% have a disease different than lupus nephritis. Furthermore, for those that do have lupus nephritis, a kidney biopsy is still commonly required to understand the histopathologic classification of disease which often is needed to inform treatment.

Alternatively, in some cases, the identification of a specific marker may help differentiate a primary glomerular disease from a secondary cause. For example, autoantibodies to the phospholipase A2 receptor (PLA2R) are now known to be present in patients with primary membranous nephropathy but negative in patients with secondary membranous nephropathy due to infection, malignancy, or SLE (Beck et al. 2009). Therefore, testing for serum PLA2R can help guide the diagnostic evaluation and inform treatment.

The serologic and genetic markers used to help clinically classify glomerular disease are shown in Table 3.

Classification According to Serum Complement Factors Levels

A frequently used test to evaluate glomerular diseases is the serum levels of complement fragments C3 and C4. In broad terms, low C4 levels (frequently expressed as "*C4 consumption*") suggest classical complement pathway activation, while low C3 levels ("*C3 consumption*") suggest activation of any of the three complement pathways (classical, lectin, or alternative). Therefore, glomerular diseases can be further divided into groups of diseases with normal C3/C4 levels, low C3 with normal C4, low C3 and C4 as shown in Table 4.

Genetic Testing

Genetic mutation analysis is customarily reserved for glomerular diseases that are confirmed by histology. Genetic testing is expensive and not widely available. However, in some cases, genetic testing can help guide treatment and prognosis. There are two entities that frequently require gene evaluation: treatment-resistant nephrotic syndrome in children (Santin et al. 2011) and alternative complement mutations in C3 glomerulopathies (Xiao et al. 2014). For the first, genetic testing is independent of biopsy histopathological evaluation, while for the second, it is generally performed after C3 glomerulopathy

Table 3 Some laboratory biomarkers for evaluation of glomerular diseases

Disease	Diagnostic markers of disease
Focal and segmental glomerulosclerosis	suPAR
	Soluble urinary CD80
	Gene mutations (NPHS2, TRPC6, ACTN4, INF2, PLCε1)
	APOL1 gene variants
Membranous nephropathy	PLA2R-antibodies
	THSD7A-antibodies
C3 glomerulopathy	Serum C3, C3b, CH50
	C3 nephritic factor
	CFHR mutations
	Factor H, factor I, soluble MAC serum levels
Lupus Nephritis	Positive ANA, anti-dsDNA, anti-Sm, serum C3, C4
	Anti-C1q antibodies, anti-C3b antibodies
ANCA-associated vasculitis	ANCA antibodies
	Anti-PR3 antibodies
	Anti-MPO antibodies
Anti-GBM disease	Anti-GBM antibodies
Acute postinfectious glomerulonephritis	Antistreptolysin-O antibodies (ASO)
	Antihyaluronidase (AHase)
	Antistreptokinase (ASKase)
	Antinicotinamide-adenine dinucleotidase (anti-NAD)
	Anti-DNase B antibodies
	C3, C4 (↓C3 most cases, C4 usually normal)
HIV-associated nephropathies	HIV serology
Immune complex membranoproliferative glomerulonephritis	HCV serology
	HBV serology
	Serum/urine immunofixation
	Serum free light chain assay
	Serum complement levels (i.e., ↓C3 in SAAGN)

Abbreviations: *suPAR* soluble urokinase-type plasminogen activator receptor, *APOL1* apolipoprotein L1, *PLA2R* phospholipase A2 receptor, *THSD7A* thrombospondin type 1 domain containing 7A, *CFHR* factor H-related protein, *MAC* membrane attack complex, *ANA* antinuclear antibodies, *anti-dsDNA* antibodies anti-double-strand DNA, *ANCA* antineutrophil cytoplasm antibodies, *anti-PR3* antibodies against proteinase 3, *anti-MPO* antibodies against myeloperoxidase, *anti-GMB* antiglomerular basement membrane antibodies, *HIV* human immunodeficiency virus, *HCV* hepatitis C virus, *HVC* hepatitis B virus, *SAAGN* Staphylococcus aureus-associated glomerulonephritis

Table 4 Approach to differential diagnosis by serum levels of complement factors

C3 and C4 above reference level	Predominant low C4 with variable C3	Predominant low C3 with variable C4	Low C3 and C4
Minimal change disease	Cryoglobulinemic nephropathy	Atypical uremic-hemolytic syndrome	Acute postinfectious glomerulonephritis
Focal and segmental glomerulosclerosis	–	C3 glomerulopathy	Infection-associated glomerulonephritis
Membranous nephropathy	–	Membranoproliferative glomerulonephritis	Proliferative lupus nephritis
IgA nephropathy	–	–	–
ANCA-associated vasculitis	–	–	–
Diabetic nephropathy	–	–	–
Glomerular diseases with organized deposits	–	–	–

is reported on histopathological analysis. The finding of specific mutations can help classify patients into inherited and acquired categories which highly influences therapeutic decisions (Lovric et al. 2016; Bu et al. 2016).

Histopathological Classification

As mentioned above, the introduction of renal biopsy transformed the landscape for diagnosis and management of glomerular diseases. While the clinical classifications described above provide clinicians with a working-diagnosis, renal biopsy is typically required for definitive diagnosis (Kitterer et al. 2015).

Technological advancements in renal biopsy evaluation have led to an increased understanding of the pathophysiological mechanisms involved in specific glomerulopathies and have led to an evolution in the histopathologic classifications for glomerular diseases. For example, histopathologic classification of lupus nephritis has gone through four revisions since the initial World Health Organization classification formulated in 1974. The new classifications take advantage of advances in immunofluorescence and electron microscopy technology with an aim to better guide treatment and predict outcomes (Wilhelmus et al. 2015a).

The renal biopsy is now considered the gold standard procedure for diagnosis and has been shown to significantly influence clinical decisions. For example, in nephrotic syndrome, information obtained from the histopathologic evaluation modifies clinical decisions in up to 86% of cases (Richards et al. 1994).

Histopathologic evaluation and classification of glomerular disease are dependent upon review by an expert nephropathologist after all relevant clinical information has been provided. Additionally, sufficient renal tissue is needed to ensure diagnostic accuracy. The renal biopsy represents a snapshot of a disease and the features seen on biopsy are extrapolated to the rest of the renal tissue. This is of great importance when histopathologic scores are applied and used to classify a glomerular disease as has been described in pathologies such as lupus nephritis, ANCA-associated vasculitis, and diabetic nephropathy, among others (*see below*). Many of these scoring systems will obtain the percentage of damage by dividing the number of glomeruli with the pathologic feature by the total number of observed glomeruli. Therefore, if the denominator (total number of glomeruli observed in the sample) is too small, expressed percentages can be misleading and not representative of the rest of the kidney tissue. As a rule of thumb, for most glomerular disease, a renal biopsy is considered adequate if it contains at least 10 glomeruli and 2 vessels for evaluation. However, pathologies with focal involvement such as focal and segmental glomerulosclerosis may require more than 20 glomeruli for its correct diagnosis and interpretation (Corwin et al. 1988).

Table 5 Definitions for light microscopy findings in the kidney biopsy

Term	Definition
Focal	A lesion involving <50% of total glomeruli
Diffuse	A lesion involving most (≥50%) of total glomeruli
Segmental	Involving <50% of a glomerular tuft
Global	Involving ≥50% of a glomerular tuft
Mesangial hypercellularity	At least three mesangial cells per mesangial region in a 3-um-thick section
Endocapillary hypercellularity	Increased cellularity internal to the GBM due to increased number of mesangial cells, endothelial cells, and infiltrating monocytes and causing narrowing of the glomerular capillary lumina
Lobular	Consolidated expansion of glomerular segments representing major anatomic subunits (lobules) of the glomerular tuft formed by dichotomous branchings of the afferent arteriole (hypersegmentation)
Extracapillary hypercellularity	Increased cellularity in Bowman space of more than one layer of parietal or visceral epithelial cells occupying one-fourth or more of the glomerular capillary circumference
Crescent	Extracapillary hypercellularity other than the epithelial hyperplasia of the collapsing variant of FSGS, often accompanied by fibrin extravasation into Bowman space
Fibrinoid necrosis	Lytic destruction of cells and matrix with deposition of fibrin. Often accompanied by GBM rupture and apoptosis of infiltrating leukocytes
Mesangiolysis	Detachment of the paramesangial GBM from the mesangial matrix resulting in a capillary aneurysm, or lytic dissolution of the mesangial matrix
Sclerosis	Glomerular scarring by expansion of matrix and loss of normal architecture
Hyaline	Glassy acidophilic extracellular material

Abbreviations: *GBM* glomerular basement membrane, *FSGS* focal and segmental glomerulosclerosis

In addition to having a representative sample, the renal biopsy must be evaluated by light microscopy, immunofluorescence or immunoperoxidase evaluation, and electron microscopy (Walker et al. 2004). Each component is necessary to provide a thorough description of the glomerular disease and, in diseases where they exist, provide an appropriate histopathologic score to the glomerular disease. We will briefly review the key histologic findings that may be seen in glomerulonephritis based on these techniques next.

Histopathological Patterns by Light Microscopy

There are several patterns of injury that can be observed by light microscopy evaluation of the renal biopsy. In Table 5, we describe specific terms that are used to describe renal biopsy findings by light microscopy. The classic stains used in light microscopy include hematoxylin and eosin and periodic acid-Schiff reaction (PAS), Jones silver-methenamine, and Masson's trichrome staining. Patterns of glomerular injury as described by light microscopic findings are shown in Table 6.

Evaluation by Immunofluorescence or Immunohistochemistry

Renal biopsy is further evaluated by immunofluorescence or immunoperoxidase staining to identify immune reactants that may be responsible for glomerular injury. These immunoreactants include IgG, IgM, IgA, C3, C1q, fibrinogen, and kappa and lambda light chains.

The pattern of deposition can be classified as continuous (linear) or discontinuous (granular), and the site of deposition (mesangial, subendothelial, membranous, subepithelial, vascular) should be specified. When these reactants are present, they are scored on a semi-quantitative scale (0 to 3+).

Immunostaining can also be used for specific reactants, for example, staining for the α-3, α-4, and α-5 chains of type IV collagen may be used to demonstrate the abnormal distribution of the

Table 6 Patterns of glomerular injury based on light microscopy findings

Pattern	Description
Minimal mesangial	Normal glomeruli by light microscopy but mesangial immune deposits by IF
Mesangial proliferative	Purely mesangial hypercellularity
Active (proliferative)	Any of all of the following glomerular lesions: endocapillary hypercellularity, karyorrhexis, fibrinoid necrosis, rupture of GBMs, cellular or fibrocellular crescents, subendothelial deposits identifiable by LM, and intraluminal immune aggregates
Necrotizing	Segmental or global fibrinoid necrosis
Crescentic	≥50% glomeruli with cellular, fibrocellular, or fibrous crescents (with percentage of crescents always noted in the diagnostic line, even when <50%)
Membranoproliferative	Mesangial and/or endocapillary hypercellularity and thickening of capillary walls caused by subendothelial Ig and/or complement factors
Exudative	Neutrophils accounting for ≥50% of glomerular hypercellularity
Sclerosing	Any of all the following glomerular lesions: glomerular sclerosis, fibrous adhesions, and fibrous crescents

Modified from Sethi et al. (2016)

glomerular basement membrane collagen chains in hereditary nephritis.

Electron Microscopy

Electron microscopy is an essential component to human diagnostic renal pathology. Ultrastructural analysis more clearly delineates immune complex deposits and their location. Additionally, nonimmune complex deposits, such as fibrils seen in amyloidosis, can be identified and help elucidate a diagnosis. This technique may provide a diagnosis for diseases where the light microscopy appears normal as in minimal change disease. Thus, electron microscopy is a valuable tool that is used to help characterize glomerular diseases and its findings are often incorporated into the histopathological classification system of glomerulonephritis.

Classification Systems for Specific Glomerular Diseases

Histopathologic classifications are the most common approach to classify specific glomerular diseases; however, in certain diseases, it does not add information to clinical classification. Classification systems have evolved with improved evaluation techniques and were created to more specifically characterize disease and inform on treatment and prognosis. They are not without pitfalls and how well the classification system accomplishes its goals varies from disease to disease. Here we will present an overview of the classification systems of individual glomerular diseases, both primary and systemic, and briefly discuss strengths and limitations of each classification system.

Focal and Segmental Glomerulosclerosis (FSGS)

FSGS represents a histologic pattern that is nonspecific and can occur in a variety of conditions or superimposed on other glomerular diseases. It may also be primary (or idiopathic) and is a common cause of nephrotic syndrome in children and adults. Two approaches have been described to classify this disease: a clinical and a morphological classification.

The clinical classification of FSGS is based on whether the condition is thought to be primary or secondary. In primary FSGS, patients will typically present with nephrotic syndrome while in

secondary FSGS subnephrotic range proteinuria and often will have evidence of chronic kidney damage (Hebert et al. 2013). This division is important as primary FSGS may be successfully treated with immunosuppression, while in secondary FSGS the underlying cause must be treated (Praga et al. 1991). Secondary FSGS has been associated with several conditions (see ▶ Chap. 9, "Focal Segmental Glomerulosclerosis, Adult" and ▶ 10, "Focal Segmental Glomerulosclerosis, Pediatric"). However, differentiating primary versus secondary FSGS is often difficult clinically, and some features found on kidney biopsy may help elucidate the diagnosis.

The morphologic-based classification system of FSGS was proposed in 2003 (D'Agati 2003) by an international group or renal pathologists. This is now commonly referred as the Columbia classification. Five main light microscopic patterns of FSGS were defined: classical or not-otherwise specified (NOS), perihilar variant, cellular variant, tip variant, and collapsing variant. The description of each pattern is shown in Table 7. The clinical correlation and prognostic significance of these variants have been controversial (Stokes 2014), but it is still the most used classification system for FSGS and can help differentiate primary from secondary FSGS in some cases. However, the Columbia classification does not eliminate the need to evaluate for primary or secondary causes of FSGS.

Table 7 Pathologic (Columbia) classification of focal and segmental glomerulosclerosis

Histologic subtype	Defining features	Associations
NOS	Does not meet criteria for other variant	Most common. Primary or secondary
	Variable foot-process effacement	
Perihiliar	Perihiliar hyalinosis and sclerosis involving the majority of glomeruli	Common in adaptive FSGS
	In adaptive FSGS there is usually glomerular hypertrophy	
	Foot process effacement relatively mild and focal	
Cellular	Expansile segmental lesion with endocapillary hypercellularity with variable epithelial cell hyperplasia	Less common. Usually primary
	Usually severe foot process effacement	
Tip	Segmental lesion involving the tubular pole	Usually primary
	Usually severe foot process effacement and less IFTA	
Collapsing	Glomerular tuft collapse with hypertrophy and hyperplasia of the overlying visceral epithelial cells	Primary or secondary to infections, drugs of vasooclusive disease
	Usually severe foot-process effacement	

Modified from D'Agati et al. (2011)

Advantages

- Clear definitions and mutually exclusive hierarchical system
- Good interobserver reproducibility (except for the cellular variant)
- Widespread acceptance among nephropathologists

Limitations

- Lesions may be lost during histologic preparation or sampling error due to its focal nature
- Lesions may be dependent on the time course of the disease as most diseases end up manifesting as NOS variant
- Controversial prognostic value
- Controversial pathogenic-morphologic correlation
- Not derived from a FSGS cohort (not evidence based conception)
- Glomerular based, does not incorporate tubulointerstitial and vascular compartments

- Does not account for disease pathogenesis. Several mechanisms of injury can arrive at the same histopathological pattern
- NOS category is highly heterogeneous

Membranous Nephropathy

Membranous nephropathy is classified as primary (formerly called idiopathic) which corresponds to 80% of the cases, or secondary as in the case of membranous lupus nephropathy (class V), infection with hepatitis B virus, solid cancer, or other agents such as drugs or toxins.

In 1968, Ehrenreich and Churg proposed a morphologic classification system based on electron microscopy changes that correspond to the pathological sequence of subepithelial immune complex deposition, reactive glomerular basement membrane changes, and mechanisms of resorption and repair (Churg and Ehrenreich 1973). This four-stage classification is widely accepted and used in clinical practice, however, is limited as it does not offer therapeutic or prognostic value.

Recently, the phospholipase A2 receptor (PLA2R), located on podocytes, has been implicated in the pathogenesis of primary membranous nephropathy. Immune complexes predominantly composed of IgG4 directed against the PLA2R are found in approximately 70% of the cases of primary membranous nephropathy (Beck et al. 2009). Anti-PLA2R antibodies can now be tested in the serum and PLA2R antigen stained on kidney biopsy to help differentiate primary from secondary FSGS (Cattran and Brenchley 2017). Finally, antibodies against a second antigen, the thrombospondin type 1 domain-containing 7A (THSD7A), have also been identified and are found in 10% of the negative PLA2R cases (Tomas et al. 2014). Cases positive for THSD7A auto-antibodies are also considered primary; however, a recent report demonstrated THSD7A autoantibody positive membranous nephropathy associated with malignancy (Hoxha et al. 2016). Patients negative for both PLA2R and THSD7A antibodies (and PLA2R tissue antigen) are evaluated for secondary causes.

Therefore, membranous nephropathy can now be classified based on a pathogenesis based classification system that incorporates both clinical and histological findings.

Advantages

- Pathophysiologic approach to classification (this is novel for glomerular diseases)
- Testing can be used to guide work-up and treatment decisions

Limitations

- Commercial assays for serum PLA2R and THSD7A antibodies are still not widely available.
- Limited knowledge regarding the pathophysiology of secondary causes.

IgA Nephropathy

IgA nephropathy is the most common cause of glomerulonephritis worldwide (Wyatt and Julian 2013). Clinical manifestations vary from benign microscopic hematuria to crescentic glomerulonephritis. The diagnosis of IgA nephropathy, however, can only be made by histologic evaluation. Characteristic findings include mesangial hypercellularity with predominant IgA immune complex deposits by immunofluorescence.

In 2008, a working group of experts created a histopathologic classification system for IgA nephropathy (Cattran et al. 2009; Roberts et al. 2009). The purpose of this classification system, known as the Oxford classification system, was to provide an evidence-based classification system that could better predict clinical outcomes for patients with IgA nephropathy and help guide treatment.

The histologic variables identified by light microscopy in the classification system include: mesangial hypercellularity (M), segmental glomerulosclerosis (S), endocapillary proliferation (E), and percentage of tubular atrophy/interstitial fibrosis (T) (Roberts et al. 2009). The criteria for this MEST scoring system are shown in Table 8.

Table 8 Oxford classification for IgA nephropathy

Pathologic feature	Score
Mesangial hypercellularity	M0: <50% glomeruli
	M1: ≥50% glomeruli
Segmental glomerulosclerosis	S0: absent
	S1: present
Endocapillary hypercellularity	E0: absent
	E1: present
Tubular atrophy/interstitial fibrosis	T0: ≤25%
	T1: 26–50%
	T2: >50%
Crescents[a]	C0: absent
	C1: <25%
	C2: ≥25%

[a]Recently proposed to be added. See Trimarchi et al. (2017)

The prognostic value of the Oxford classification has now been validated in multiple cohorts (Tanaka et al. 2013; Coppo et al. 2014). Its role in guiding therapy, however, has not been widely accepted. An initial criticism to this classification was the exclusion of crescents which have previously been shown to have prognostic value in IgA nephropathy (Haas et al. 2017). Recently, crescents have been aggregated in addition to the MEST score as follows: C0, absence of crescents; C1, crescents in 1–24% of glomeruli; C2, crescents in ≥25% of glomeruli (Trimarchi et al. 2017). Another criticism is that the prognostic ability of the Oxford classification is largely determined by the presence of tubular atrophy/interstitial fibrosis (Soares and Roberts 2017). As this is true for most glomerular diseases, it remains unclear whether the Oxford classification system provides any additional value to what is already known regarding outcomes in IgA nephropathy from tubulointerstitial findings.

Regardless, the Oxford classification has now been widely adopted and a MEST score is commonly provided by the nephropathologist when IgA nephropathy is diagnosed on renal biopsy. Some clinicians may use this score educate patients regarding long-term kidney prognosis and to help guide therapy, although the classification system has not been validated for that purpose. It should be noted that this classification has not been validated for other glomerulopathies related to IgA nephropathy such as Henoch-Schönlein purpura, SAAGN, or secondary IgA nephropathy due to liver disease.

Advantages

- Reproducibility and possible prognostic value
- Evidence-based design
- Modifiable according to new discoveries (e.g., crescents)

Limitations

- Not applicable to findings that were not included in the derivation cohort (i.e., patients with mild disease or rapidly progressive disease, Henoch-Schönlein purpura).
- Currently not universally used to help guide therapy.

Diabetic Nephropathy

In contrast to other glomerular diseases, diabetic nephropathy has largely remained a clinical diagnosis. In patients who present with albuminuria and classic microvascular complications including retinopathy and neuropathy, the diagnosis of diabetic nephropathy is generally is made based on clinical criteria alone. In fact, less than 10% of patients started on dialysis with suspected diabetic nephropathy have had a confirmed diagnosis by kidney biopsy.

Kidney biopsy has traditionally been reserved for those who do not present with the typical clinical features of diabetic nephropathy (Fiorentino et al. 2016). Examples include a patient with severe nephrotic syndrome or renal impairment in the absence of diabetic retinopathy or with diabetes vintage less than 5 years, significant glomerular hematuria or rapidly worsening of renal function. Nondiabetic kidney disease may be present in over 30% of patients with diabetes mellitus (Sharma et al. 2013). Therefore, a more liberal application of kidney biopsy in patients with diabetes may identify diseases more amenable to treatment than diabetic nephropathy.

In 2010, the Renal Pathology Society set out to create a consensus classification system for

diabetic nephropathy, applicable to both type 1 and type 2 diabetes (Tervaert et al. 2010). This classification defines 4 classes of diabetic nephropathy based on glomerular findings on light and electron microscopy as shown in Table 9. The standardization of histologic descriptions may help stratify risk for kidney disease progression in diabetic nephropathy and help inform clinical trials for novel therapies.

This histopathological classification has been criticized due to its arbitrary category distinction, high subjectivity, and particularly the assumption that all classes are progressive which remains unproven (Stokes 2014). One other criticism of this classification system is its limited applicability to clinical practice. As described above, kidney biopsy is not routine in diabetic nephropathy and most patients who undergo a kidney biopsy do so because another disease is suspected. Thus, the histologic classification system frequently does not modify clinical practice.

Table 9 Pathologic classification of diabetic nephropathy

Class	Description	Inclusion criteria
I	**Mild or nonspecific LM changes and EM-proven GBM thickening**	Biopsy does not meet any of the criteria mentioned below for class II, III or IV
		GBM > 395 nm in female and >430 nm in male individuals over 9 years of age
IIa	**Mild mesangial expansion**	Biopsy does not meet criteria for class III or IV
		Mild mesangial expansion in >25% of the observed mesangium
IIb	**Severe mesangial expansion**	Biopsy does not meet criteria for class III or iv
		Severe mesangial expansion in >25% of the observed mesangium
III	**Nodular sclerosis (Kimmelstiel-Wilson lesion)**	Biopsy does not meet criteria for class IV
		At least one convincing Kimmelstiel-Wilson lesion
IV	**Advanced diabetic glomerulosclerosis**	Global glomerular sclerosis in >50% of glomeruli
		Lesions from classes I through III

Modified from Tervaert et al. (2010)

Advantages

- Apparently good reproducibility between nephropathologists

Limitations

- Pathologic criteria based on expert opinion only.
- Only includes glomerular lesions. Tubulointerstitial and vascular compartments are not included.
- Clinical relevance still unclear.

ANCA-Associated Vasculitis (AAV)

Antineutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) comprises a group of necrotizing vasculitides with few or no immune complex deposits (pauci-immune) predominantly affecting the small vessels. Traditionally, AAV has been divided under clinical-based algorithms designed by different societies, such as the Chapel Hill Consensus Conference (last modified in 2012) (Jennette et al. 2013) or the European Medicines Agency (EMA) (Watts et al. 2007). These algorithms classify AAV into polyangiitis with granulomatosis (previously Wegener granulomatosis) and microscopic polyangiitis. A third category of AAV that may affect the kidneys is eosinophilic polyangiitis (Churg-Strauss syndrome).

Since the discovery of ANCA in 1985, it has been suggested that these antibodies contribute to AAV pathophysiology. Recent genetic studies have demonstrated that classification of AAV based on ANCA subtype is supported by genetic associations, epigenetic control of major histocompatibility complex, antigen function, and localization (Lyons et al. 2012). Therefore, several groups support the notion that AAV should be

classified by ANCA specificity into proteinase-3 AAV (PR3-AAV), myeloperoxidase AAV (MPO-AAV), and negative antibody AAV (Cordova-Sanchez et al. 2016; Cornec et al. 2016).

A drawback from clinical and serological classification systems for ANCA is that these classifications have not been shown to add prognostic value, with the exception that PR3-AAV is associated with a higher risk of disease relapse compared to MPO-AAV (Lionaki et al. 2012).

In 2010, the European Vasculitis Study Group (EUVAS) proposed a histopathological-based classification system of AAV with the aim to better classify the severity of renal vasculitis and to better prognosticate renal outcomes (Berden et al. 2010). It comprises four categories based on the percentage of glomeruli with either cellular crescents or global sclerosis by light microscopy (Table 10).

Validation cohorts have shown good reproducibility for the polar categories (focal and sclerotic), but significant overlap in patient outcomes for intermediate categories (crescentic and mixed-type) (Bjorneklett et al. 2016). A major criticism of this classification system has been the exclusion of tubulointerstitial lesions that are also likely to add prognostic information (Berden et al. 2012).

Advantages

- Simple
- Validated in different races and ethnicities (focal and crescentic categories)
- Prognostic information

Limitations

- Little information on reproducibility and interobserver variation
- Prognostic differentiation between mixed and proliferative categories is limited
- Lack of inclusion of tubulointerstitium and vascular compartments

Table 10 Histopathologic classification of ANCA-associated vasculitis

Class	Light microscopy findings
Focal	>50% normal glomeruli
Crescentic	≥50% glomeruli with cellular crescents
Mixed	<50% normal, <50% crescentic, <50% globally sclerotic glomeruli
Sclerotic	≥50% globally sclerotic glomeruli

Lupus Nephritis

Lupus nephritis affects over 50% of systemic lupus erythematosus patients (Pons-Estel et al. 2004). Perhaps more so than any other form of glomerular disease, the histopathologic evaluation of lupus nephritis is crucial to understanding the severity of disease and guiding treatment (Parikh et al. 2015). Classification systems based on light microscopy findings were first developed in 1974 under the guidance of the World Health Organization (WHO) and then went through revisions in 1982 and 1995. In 2003, the International Society of Nephrology and Renal Pathology Society (ISN/RPS) revised the original WHO classification with the aim to more accurately align biopsy findings to treatment options and prognosis (Weening et al. 2004).

The ISN/RPS 2003 classification system morphologically categorizes LN based on the location of glomerular immune complexes and severity of the glomerular injury as determined by light microscopy and supported by immunofluorescence and electron microscopy. It attempted to distinguish more specifically between classes of proliferative LN based on the level of glomerular involvement (Table 11). Additionally, the ISN/RPS more clearly differentiated proliferative forms of LN from class V LN or membranous LN.

Unfortunately, despite these changes, the prognostic value of the ISN/RPS criteria remains limited especially for proliferative LN (Haas et al. 2014; Wilhelmus et al. 2015a). The distinction between class III and Class IV LN is arbitrary in nature, and this distinction has not been shown to better predict outcomes in LN. Subcategories of segmental (S) or global (G) were also added to the ISN/RPS to better describe proliferative LN because earlier studies showed global proliferation had a better prognosis than segmental proliferation (Najafi et al. 2001). However, more recent studies have not supported these earlier

Table 11 ISN/RPS 2003 histopathological classification of lupus nephritis

Class	Description
Class I: minimal mesangial lupus nephritis	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II: mesangial proliferative lupus nephritis	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
Class III: focal lupus nephritis	Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
	Subdivided into active (A), active and chronic (A/C) or chronic (C)
Class IV: diffuse lupus nephritis	Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving >50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations
	Subdivided into diffuse segmental (IV-S) and diffuse global (IV-G) as well as into active (A), active and chronic (A/C), and chronic (C) categories
Class V: membranous lupus nephritis	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV, in which case both will be diagnosed
Class VI: advanced sclerosing lupus nephritis	≥90% of glomeruli globally sclerosed without residual activity

conclusions (Haring et al. 2012) and the clinical utility of these subcategories remains unclear.

Another criticism to the ISN/RPS classification is that it does not account for tubulointerstitial and vascular findings. Tubulointerstitial disease more closely correlates with kidney function than glomerular lesions and is associated with poor long-term kidney outcomes in most forms of kidney disease (Yu et al. 2010), while vascular lesions have also been associated with long-term prognosis (Wu et al. 2013; Mejia-Vilet et al. 2017).

To supplement the ISN/RPS classification, "activity" and "chronicity" indices were developed by The National Institute of Health to better forecast outcomes in LN (Austin et al. 1983). These indices incorporate histopathological lesions suggesting active inflammation in an activity index and those lesions suggestive of chronic damage in a chronicity index. Activity index (AI) represents the degree of inflammatory injury to the renal parenchyma that is generally thought to be reversible with anti-inflammatory therapies, while the chronicity index (CI) represents kidney damage thought to be irreversible. These indices are reported with the ISN/RPS classification to provide the clinician a detailed description of the level of active disease as well as the level of chronic damage already sustained.

Despite this level of detail, there are still several limitations to LN classification. First, the findings are subjective with considerable interobserver variability (Wilhelmus et al. 2015b). Additionally, it continues to be debated whether this histopathologic classification meets its stated goals of informing treatment and predicting long-term outcomes in LN. Even with the inclusion of the NIH AI/CI indices, the predictive utility of the ISN/RPS remains suboptimal (Wilhelmus et al. 2015a). Finally, the value of the classification system in follow-up biopsies has yet to be determined. However, due to the lack of concordance between clinical findings and histopathological findings (i.e., patients with apparent clinical quiescence can have active immune complex deposition in the glomeruli), renal biopsy remains the gold standard for diagnosis in lupus nephritis (Malvar et al. 2015).

Advantages

- More clearly differentiates proliferative from nonproliferative forms of LN than previous classifications.
- Better differentiates proliferative forms of LN from Class V LN.
- The addition of NIH AI/CI indices more completely describes the level of kidney injury

compared to ISN/RPS alone and may better predict prognosis.

Limitations

- Not a clear difference in clinical usefulness of class III and IV, segmental and global subclasses.
- Glomerular based, tubulointerstitial, and vascular compartments not included (although tubulointerstitial injury is considered when incorporating the NIH AI/CI indices).
- The arbitrary differentiation between Class III and IV LN does not help guide treatment
- Classification is not evidence-based.
- Does not account for nonimmune complex mediated kidney disease which can be the cause of kidney injury on about 5% of patients with SLE (i.e., thrombotic microangiopathy, podocytopathy, tubulointerstitial nephritis)

Membranoproliferative Glomerulonephritis

The term "membranoproliferative glomerulonephritis" (MPGN) refers to the presence of a glomerular lesion characterized by the thickening of the glomerular capillary wall and the increase in mesangial matrix and cellularity. Thus, MPGN is a morphological lesion that may be caused by several etiologies. MPGN was historically subclassified into 3 types (I, II, and III) based on the ultrastructural location of the electron-dense deposits (Table 12).

In the past decade, significant strides have been made in understanding the pathophysiology of MPGN. Dysregulation of the alternative complement pathway is now thought to be the cause of what was previously known as type II MPGN. These advances in our understanding led to a revised classification for MPGN (Sethi and Fervenza 2011) that relies on immunofluorescence as opposed to light microscopic findings. It divides MPGN as either immune complex- or complement-mediated. The first occurs when there are increased levels of circulating immune complexes as is commonly seen in monoclonal gammopathies, while the latter may occur because of dysregulation of the alternative pathway of complement. If neither of these causes is present (null complement and null immune deposits), then chronic thrombotic microangiopathy should be suspected. Figure 3 provides a classification for MPGN based on histopathologic findings.

Advantages

- Pathophysiological basis for classification
- Probable diagnostic and therapeutic implications although not yet determined

Limitations

- Reproducibility has not been evaluated
- Evolving field that requires a more complete understanding of the role of complement dysregulation in driving disease

Renal Diseases with Organized Deposits

Glomerular diseases with organized deposits include amyloidosis, fibrillary glomerulonephritis, and immunotactoid (Herrera and Turbat-Herrera 2010). While there is no formal classification system

Table 12 Classification systems for MPGN

Morphologic Classification of MPGN	Pathophysiologic Classification of MPGN
Type I: subendothelial electron-dense deposits	**Immune-complex mediated** (immunoglobulins and complement on IF)
Type II: intramembranous electron-dense deposits (dense deposit disease)	**Complement-mediated** (C3-dominant deposits on IF, "C3 glomerulopathy")
Type III: both subendothelial and subepithelial electron-dense deposits	**MPGN not related to complement or immune deposits** (Idiopathic MPGN)
	Negative IF (thrombotic microangiopathy)

Abbreviations: *IF* immunofluorescence, *MPGN* membranoproliferative glomerulonephritis

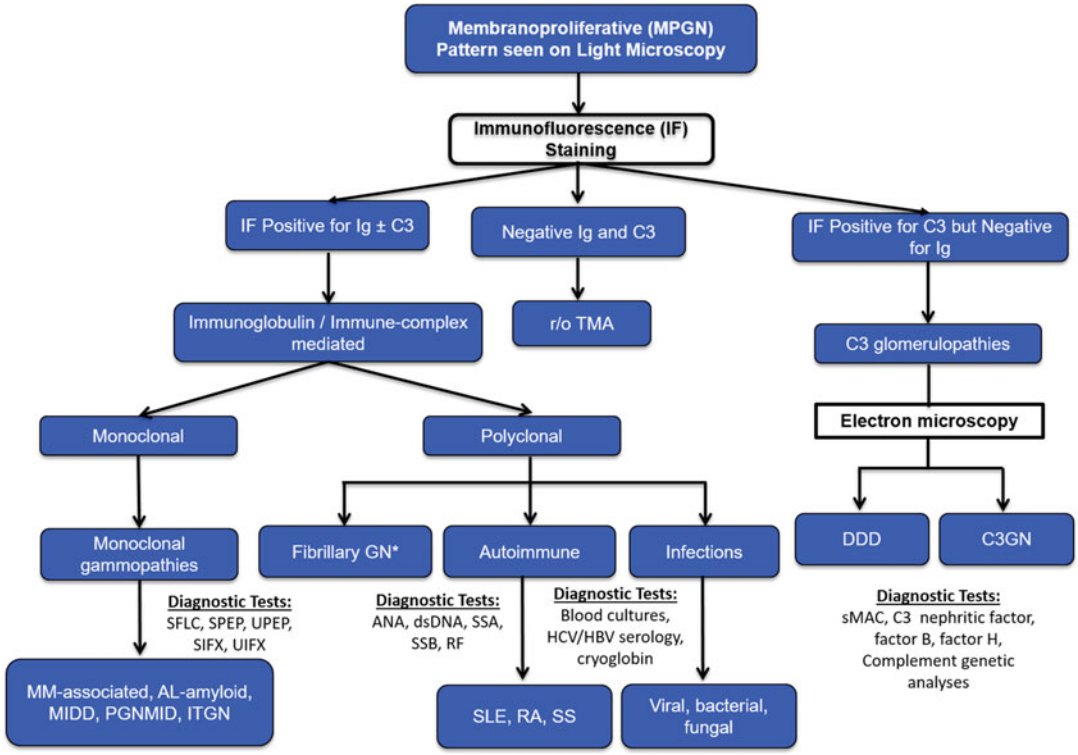

Fig. 3 Histopathologic classification for membranoproliferative glomerulonephritis (*Fibrillary GN can be monoclonal in 10–15% of cases. Abbreviations: *MPGN* membranoproliferative glomerulonephritis, *Ig* immunoglobulin, *C3* complement factor 3, *TMA* thrombotic microangiopathy, *SFLC* serum free light chains, *SPEP* serum protein electrophoresis, *UPEP* urine protein electrophoresis, *SIFX* serum immunofixation, *UIFX* urine immunofixation, *MM* multiple myeloma, *MIDD* monoclonal immunoglobulin deposition disease (includes heavy and light chain deposition diseases), *PGNMID* proliferative glomerulonephritis with monoclonal immunoglobulin deposits, *ITGN* immunotactoid glomerulonephritis, *ANA* antinuclear antibodies, *dsDNA* antibodies against double strand DNA, *SSA/SSB* antibodies against antigens SSA and SSB, *RF* rheumatoid factor, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SS* Sjogren syndrome, *DDD* dense deposit disease, *C3GN* C3 glomerulonephritis, *sMAC* soluble membrane attack complex)

for these diseases, an algorithmic approach is used for diagnosis and is shown in Fig. 4.

This approach involves stratifying diseases based on staining techniques (Jones' silver methenamine, Congo red) and electron microscopy on kidney biopsy. Organized deposits that are positive by silver stain include collagenofibrotic glomerulonephritis, diabetic fibrillosis, and glomerulosclerosis. If silver stain is negative, then Congo red staining is performed. For organized deposits that are silver stain negative, the size of the fibrils on electron microscopy and staining for Congo red help differentiate the disease. Amyloid fibrils are Congo red positive with fibrils ranging from 7 to 15 nm in size. Meanwhile, fibrillary glomerulonephritis and immunotactoid glomerulonephritis are Congo-red negative and their fibrils are 15-30 nm and greater than 40 nm in size, respectively. If microtubules are present, then cryoglobulinemic glomerulonephritis must be considered.

Postinfectious Glomerulonephritis and Infectious-Related Glomerulonephritis

Recently, a suggestion was made to review the terminology of glomerular diseases associated with infectious events (Glassock et al. 2015a). This classification has important pathophysiologic

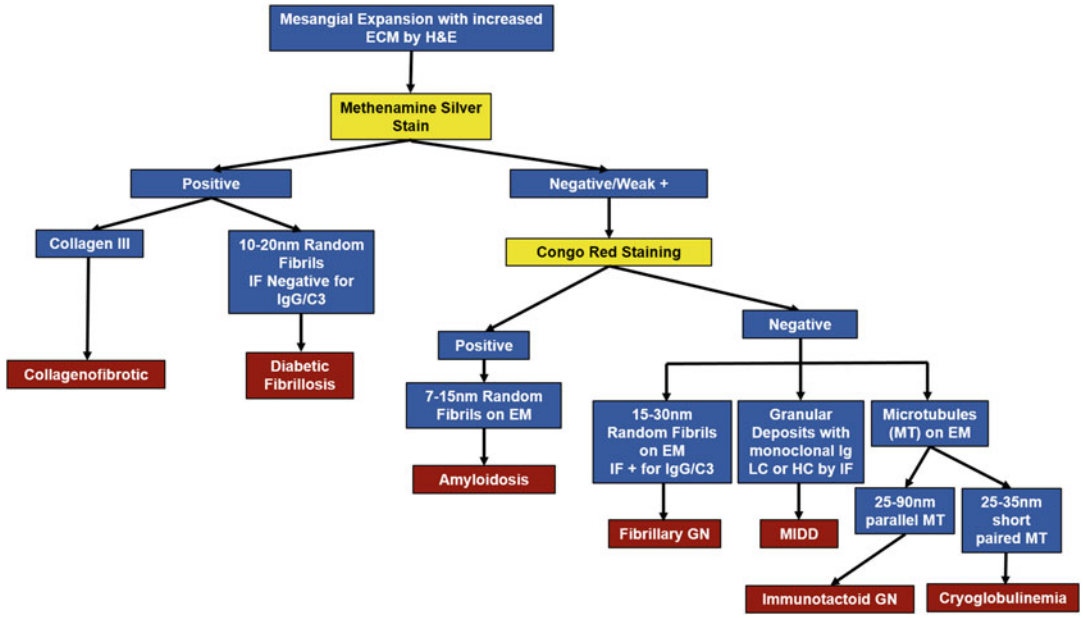

Fig. 4 Classification of glomerulonephritis with organized deposits (Abbreviations: *ECM* extracellular matrix, *IF* immunofluorescence, *MIDD* monoclonal immunoglobulin deposition disease). Reprinted from [Herrera and Herrera, Renal Diseases with Organized Deposits. Arch Pathol Lab Med. 2010;134:512–531 with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2010 College of American Pathologists

and therapeutic implications. These diseases can be subclassified into postinfectious glomerulonephritis and infectious-associated glomerulonephritis. The main differentiation between these two subgroups comes from the knowledge that the first group (postinfectious glomerulonephritis) is characterized by the generation of an immune response that becomes clinically apparent 2–4 weeks after the infection has already resolved. Poststreptococcal glomerulonephritis is the most common example of postinfectious glomerulonephritis. While most cases of poststreptococcal glomerulonephritis are self-limited with excellent outcomes and do not require aggressive therapy, in severe cases, immunosuppression with corticosteroids can be considered since the infection has already resolved.

In comparison, infection-associated glomerulonephritis occurs in the setting of a chronic, active infection. An example is *Staphylococcus aureus*-associated glomerulonephritis, which is a devastating complication of *Staphylococcal aureus* infection (Satoskar et al. 2017). Outcomes are more variable with over 50% of patients reported to be left with chronic kidney damage (Nast 2012). Importantly, immunosuppression should not be used to treat glomerular diseases that occur in the setting of an active infection. Treatment should be focused on eradicating the infection. Indeed, in the setting of *Staphylococcal aureus*-associated glomerulonephritis, treatment with immunosuppression did not improve renal outcome and increased morbidity and mortality (Satoskar et al. 2006). The proposed criteria for classification of glomerulonephritis associated with infection are outlined in Table 13.

Future Directions

Recent years have seen rapid advancements in biomedical research which has led to great interest in understanding the molecular basis for disease. In recent years, a need has been identified to move beyond traditional pathology-based classifications by integrating translational and clinical data to develop new classifications and novel

Table 13 Proposed criteria for classification for glomerulonephritis associated with infection

Postinfectious glomerulonephritis
Criteria
• The GN is preceded by an infection that resolves or is resolving with or without antimicrobial therapy
• A latent period of a few days to 4 weeks follows in which there is no evidence of GN
• The latent period ends with the acute onset of GN
Cause
• Post-*Streptoccocal* glomerulonephritis
Infection-associated glomerulonephritis
Criteria
• An acute glomerulonephritis occurs in the setting of a subacute or chronic infection that has not resolved (i.e., bacterial endocarditis, osteomyelitis, hepatitis C infection)
• The GN is a manifestation of an ongoing infection (i.e., it is not a postinfectious GN)
Cause
• Several bacterial (including staphylococcal aureus-associated glomerulonephritis"), viral, fungal and parasitic infections

Abbreviation: *GN* glomerulonephritis

therapeutic targets for glomerular diseases to improve patient outcomes (Wiggins et al. 2014). Moving forward, this systems biology approach that incorporates molecular information with clinical and histological data will allow for a more comprehensive and precise classification of glomerular disease which will more precisely define disease, guide treatment, and predict long-term renal outcomes.

Conclusions

Glomerular diseases are classified in multiple forms along the evaluation process of the disease. Clinical and serological approaches help formulate a provisional diagnosis that is frequently followed by a renal biopsy. Then histopathological classification adds substantial information. An ideal classification system should include data from all phases of the diagnostic evaluation and provide pathophysiological, therapeutic, and prognostic information. Actual classification systems are continuously evolving to meet these goals.

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Integration with Kidney Disease Improving Global Outcomes (KDIGO)

6

Raja Ramachandran and Vivekanand Jha

Contents

Abstract

Kidney Disease Improving Global Outcomes (KDIGO) guidelines assist nephrologist worldwide in managing patients with glomerular diseases. Despite the use of a robust methodology, quality and generalizability of guidelines is limited by absence of high-quality randomized trials, lack of pathological details to guide therapy, limitations related to the use of histological pattern rather than pathophysiology-based classification system, inability to incorporate emerging data, and limited adverse event coverage. Overcoming these limitations requires innovative approaches such as periodic updates using electronic platform. More discussion is needed on integrating pathological details and helping generation of evidence that could inform the guideline development, such as formation of a global consortia for collecting data and conducting trials in glomerular disease to fill the gap to address variation in race/ethnicity, system, and healthcare providers, to include orphan glomerulonephritis, and to encourage the practice of personalized and precision medicine.

Keywords

Glomerulonephritis · KDIGO · Guidelines · Implementation · Global disparities

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Introduction

Glomerulonephritides occupy a special place in the practice of nephrology. Despite sharing a common feature – damage to glomerular filtration barrier with potential to progress to advanced kidney failure – these diseases are highly diverse in etiology, pathogenesis, clinical presentation, disease course, response to treatment, and outcomes. The diagnosis of glomerular disease (GD) rests on kidney biopsy; its interpretation by appropriate techniques including light microscopy, immunofluorescence, and electron microscopy; proper understanding of the nuances of pathology; and integration with other information collected by context-specific investigations. Such diversity of information presents a vast combination of possibilities, making the management of a patient with GD challenging for both the patient and the nephrologist.

Global Epidemiology of Glomerular Diseases

It is hard to make an accurate estimate of the variations in the epidemiology of GD worldwide because of lack of large studies and/or registries from all parts of the world. Moreover, accurate identification and classification of GD also depends on the diagnostic strategy. A low threshold of performing kidney biopsy (e.g., on detecting abnormalities in routine urine screening in the school children and prior to employment) facilitates earlier diagnosis (Iseki et al. 2004; Kitagawa 1988; Cho et al. 2001). In the developed world (Schena 1997), an asymptomatic urinary abnormality is the most common indication for renal biopsies, whereas in the developing world, it is nephrotic syndrome (Golay et al. 2013). Screening programs help identification of GD in asymptomatic individuals. Genetic and environmental factors impact the epidemiology of GD. The former is exemplified by the demonstrated effect of APOL1(Papeta et al. 2011) gene in determining predisposition to focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy in the black population and the effect of mutations in minimal change disease (MCD), FSGS, membranous nephropathy (MGN), and Alport syndrome. The effect of environmental influence is reflected in the relatively high prevalence of infection-associated glomerulonephritis (GN) in the developing world (Dhanapriya et al. 2017) (Golay et al. 2013). A recent example of the impact of environment is the recently demonstrated association between the prevalence of MGN and air pollution in China (Xu et al. 2016). In general, FSGS and IgA nephropathy are the commonest GD among adults and MCD in children globally. Table 1 summarizes the frequency of primary glomerular disease in different parts of the world.

Clinical Practice Guidelines

Clinical guidelines are "systematically developed evidence-based statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Field and Cohr 1990). Guidelines are developed by experts in the field who are supported by an evidence review group, following a structured methodology (see below). Guidelines improve the quality of clinical decision-making and discourage practitioners from performing dangerous or ineffective procedures or therapeutic interventions but are not designed to define a "standard of care" or suggest an exclusive way of delivering care. Guidelines can be addressed to different stakeholders, but the most frequent intended users are physicians.

General Review and Methodology of the Guidelines: KDIGO

Kidney Disease Improving Global Outcomes (KDIGO) has been at the forefront in developing evidence-based best practice guidelines for patients with kidney diseases using rigorous methodology that represents the best global science to optimize the care of patients with kidney disease. KDIGO recognizes, however, that variations in implementing the recommendations

Table 1 Epidemiology of primary glomerular disease worldwide

Author	Country	Year	Number	Age (years)	FSGS	MN	MCD	IgAN
Sim et al. (2016)	USA	2000–2011	2501	50.66 ± 16.67	973 (38.9%)	317 (12.7%)	274 (11%)	255 (10.2%)
Polito et al. (2010)	Brazil	1992–2007	9617	35.07 ± 18.65	1135 (24.6%)	957 (20.7%)	717 (15.5%)	928 (20.1%)
Schena (1997)	Italy	1987–1993	13,835	–	11.8%	20.7%	7.8%	35.2%
Golay et al. (2013)	India	2010–2012	666	28 ± 14.62	120 (18%)	80 (12%)	134 (20.1%)	56 (8.4%)
Wu et al. (2011)	China	2005–2009	1550	–	62 (4%)	170 (11%)	476 (30.7%)	380 (24.5%)
Sugiyama et al. (2013)	Japan	2009–1010	7442	–	1952 (27.7%)			2180 (31%)
Nadium et al. (2013)	Sudan	2010–2011	71	34.6 ± 18	29.6%	NA	16.9%	5.6%
Okpechi et al. (2016)	Africa	1980–2014	12,093	–	15.9%	6.6%	16.5%	2.8%
Briganti et al. (2001)	Australia	1995 and 1997	2030	–	2.5/ 100,000/ year	1.8/ 100,000/ year	0.7/ 100,000/ year	5.7/ 100,000/ year
Zhou et al. (2009)	China	1993–2007	3331	–	110 (3.30%)	500 (15.1%)	364 (10.9%)	1809 (54.3%)
Li and Liu (2004)	China	1979–2002	9278	–	557 (6%)	918 (9.89%)	86 (0.93%)	4199 (45.26%)
Malafronte et al. (2006)	Brazil	1999–2005	1131	34.5 ± 14.6	29.7%	20.7%	9.1%	17.8%
Spanish Registry.2010 (http://www.nephropathology-esp.org/uploads/user-3/lectures/first-international-renal-pathology-conference-la-coruna-1/rivera-f-spanish-registry-of-gn.pdf)	Spain	1994–2008	16,444	–	9%	10.7%	7.2%	14.4%
O'Shaughnessy et al. (2017)	USA	1986–2015	21,374	48.3 ± 18.3	25.3%	14.2%	5.3%	10.3%

FSGS focal segmental glomerulosclerosis, *MN* membranous nephropathy, *MCD* minimal change disease, *IgAN* IgA nephropathy, *USA* United States

will be required after taking into account local models of care, available resources, and needs of individual patients and encourages users of the recommendations to evaluate the need and appropriateness of applying the guidelines in a given setting. KDIGO guidelines have been adapted and/or adopted by several professional organizations and disseminated through publications, seminars, webinars, symposia, and in digital format.

The KDIGO guidelines for management of glomerulonephritis were published in 2012 (Kidney Disease 2012), with the goal to reduce global variations in practices and improve health outcomes of patients with common glomerular diseases. The guideline development process took 2 years, during which the expert workgroup and the evidence review team (ERT) screened abstracts, full articles, and systemic reviews based on predefined eligibility criteria by conducting a thorough search of biomedical databases through January 2011. The evidence was graded (based on each outcome), and data were summarized in a tabular form by the ERT. The workgroup reviewed the articles, the summary tables, and data forms for accuracy and undertook the primary role in making the recommendation, assigning grade, and developing the statements accompanying the narrative. A hierarchy of evidence was used to develop recommendations regarding treatment, with meta-analyses of randomized control trials (RCT) being on top, followed by individual RCTs. Non-RCT comparative studies were included to strengthen the evidence or to make recommendations where no RCTs were available.

Studies were graded on a scale from A to D, with A indicating a high level of confidence that the true effect lies close to the estimate of effect and D when the estimate of effect was very uncertain and often faraway from truth. The strength of the recommendation was graded as Level 1, implying most patients would benefit from recommended course of action, whereas Level 2 implied less certainty regarding the recommended course of action; however, many would not receive the treatment/intervention indicating scope for subjectivity to the decision.

The critical issue that impacts all guidelines is the quality of available primary evidence. Well-planned/powered RCTs provide the best quality evidence. The shortage of high-quality RCTs lowers the evidence quality and impacts the strength of recommendation.

What Should a GN Guideline Look Like?

An ideal intervention for GN would be one that is required for a short period to induce disease remission, is able to prevent relapses and development of complications, and arrests disease progression. Such an agent should act at a key point in the disease pathogenesis that can affect multiple effector pathways. Finally, the intervention should be free of both short- and long-term adverse events. Since the manifestation and course of GN are heterogeneous, such an intervention should be preferably applied only to those at increased risk of adverse outcomes. Unfortunately, we are limited in our ability to do reliable risk stratification, and current disease-specific treatment for GN is based on potentially toxic drugs.

Using KDIGO GN Guidelines

As explained previously, the KDIGO GN guidelines provide the path to making informed decisions based on the best available global literature. The strength and quality of the guideline depends on the nature of available evidence. Only 28% of the GN guideline recommendations are carrying a strong (Level 1) label (Kidney Disease 2012). In terms of the grade, evidence for only 2% of the guideline statements was graded as A, whereas 20, 40, and 38% were grade B, C, and D, respectively (Kidney Disease 2012). Almost all the agents used for GN were first developed in the treatment of cancers. Further, most glomerular diseases progress over the years, and RCTs that examine the effect of interventions at hard clinical endpoints (such as rates of end-stage kidney disease) need to be conducted for several years (Jha

et al. 2007). Such trials are expensive. GN clinical trialists have been long trying to develop a consensus among all stakeholders on alternate endpoints for GN clinical trials. Complete remission of proteinuria is widely accepted to be a reliable indicator of good outcome (Avasare and Radhakrishnan 2015). The place of partial remission remains contentious, however. Emerging literature also suggests improvement in serum albumin as an indicator of response to treatment (Kaartinen et al. 2008). In terms of change in GFR, the US FDA has accepted 40% decline in eGFR as a reliable endpoint (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072127.pdf), but there is a move to lower this to 30%. Finally, GN clinical trials have historically been hard to recruit, as nephrologists are often not convinced of equipoise. For the same patient, different nephrologists may feel it unethical to either withhold therapy or giving potentially toxic therapy!

Applicability to a single patient: As with all clinical practice guidelines, the KDIGO GN guidelines are able to provide guidance only for limited variations in disease presentation and are able to account for the variations in clinical presentation, patient characteristics, and healthcare provision only imperfectly. Most studies that contribute to the evidence used to support guideline development use stringent inclusion and exclusion criteria, thereby limiting generalizability. In addition to clinical variability, there is not enough data on the effect of the same interventions in various ecosystems (different races, age groups). Radhakrishnan and Cattran demonstrated the lack of applicability/inability to adapt the KDIGO GN guideline in various clinical situations with selected clinical vignettes (Radhakrishnan and Cattran 2012). A typical example is in the case of membranous nephropathy, where the KDIGO guideline recommends the use of a restrictive strategy for 6 months before starting immunosuppressive therapy in an uncomplicated patient (normal renal function, no thromboembolism, or life-threatening symptoms). However, even with a stable nephrotic range proteinuria, the patient may continue to have severe hypoalbuminemia, disabling edema, and acute decline in GFR. Appropriate guidance is not available whether eschewing the use of disease-specific immunosuppressive therapy is appropriate in such cases despite the risk of protein-energy wasting and its consequence. Another difficulty is the inability of the best global science to provide sufficient help for managing patients in resource-constrained environments. Despite the fact that most of the commonly used drugs used for treatment of GN are off patent, and generic formulations have lowered the cost barrier in many countries, certain populations continue to remain deprived. Emerging therapies, especially with biological agents, will lead to exacerbation of the rich-poor disparity. An example concerns the use of eculizumab for atypical hemolytic uremic syndrome (Legendre 2013). This drug is not available outside the developed world, not just because the local population cannot afford it (which is indeed the case) but also because the drug manufacturer does not market it in developing countries (Sethi et al. 2017).

Renal pathology: In addition to the main histological diagnosis, appreciation of additional pathological nuances is crucial for proper risk stratification, prognostication, and fine-tuning management of a given patient. An indicative example can be provided through a case of lupus nephritis. KDIGO guideline provides a class 1B recommendation for the use of steroids and cyclophosphamide or mycophenolate mofetil in the management of a patient with diffuse proliferative (class IV) lupus nephritis. However, additional findings that could impact therapeutic decisions include the presence of thrombotic microangiopathy (Pattanashetti et al. 2017), the presence of segmental/global endocapillary proliferation (Nasr et al. 2008), and the presence of necrotizing GN/tubulointerstitial inflammation (Hsieh et al. 2011). For example, presence of thrombotic microangiopathy might prompt consideration of adding plasma exchange to immunosuppressive therapy (Li et al. 2016). Similarly, it would be prudent to evaluate for antineutrophil cytoplasmic antibody-associated vasculitis in cases with fibrinoid necrosis (Nasr et al. 2008). Some biopsy findings predict an aggressive disease course (Pattanashetti et al. 2017; Hsieh et al.

2011; Markowitz and D'Agati 2007), and there is a lack of RCT for induction therapy in these scenarios. Renal biopsy findings could also point to treatment futility. For example, the use of aggressive immunosuppressive therapy in a patient with widespread interstitial scarring/tubular atrophy or advanced vascular disease is unlikely to lead to equivalent outcomes compared to patients without such lesions.

Use of standard definitions: Several terminologies, definitions, and treatment protocols that define the course of glomerulonephritides are based on tradition rather than evidence. For example, standard definitions for remission and relapse developed in children have been used to manage adult patients with minimal change disease or focal segmental glomerulosclerosis. KDIGO guidelines (Kidney Disease 2012) recommend longer duration of steroids in adults with these conditions. However, whether the current definition (developed in children) with regard to frequency of relapses is appropriate for adults treated with longer courses of steroids is not known. Misclassification as infrequent relapser could cause the patient to continue to receive steroids instead of steroid-sparing agents, leading to avoidable toxicity.

Disease classification: The GN guideline group used the then current system of classifying GN, which was (and still remains) based on histological patterns rather than understanding of pathophysiology. That situation is changing, however, and is likely to be recognized in the next guideline revision. The most notable change has been in the entity of mesangiocapillary or membranoproliferative GN (Sethi et al. 2012). The current guideline document makes common treatment recommendation for all cases with this pattern. Last few years have shown us that abnormalities in several unrelated pathophysiologic pathways can lead to this pattern of injury that require different therapeutic approach. Another example is that of membranous nephropathy (MGN). No specific therapy was recommended for MGN if it was found in association with a known condition (e.g., cancer or hepatitis infection). Discovery of PLA2R (Beck et al. 2009) and THSD7A (Tomas et al. 2014) as candidate pathogenic antigens has led to better understanding of disease pathogenesis, and monitoring of circulating antibody levels has changed the way these patients are managed. Recent experience has led to the appreciation that many so-called secondary cases are actually PLA2R-related and respond to immunosuppressive therapy (Ramachandran et al. 2018). Finally, no solution has yet been found that would allow a reliable distinction of the underlying pathogeneses between MCD and FSGS purely on histology.

Adverse events: The extent of discussion of adverse effects of treatment in the current KDIGO GN is limited. Given the nature of immunosuppressive drugs in the current treatment regimens, side effects are to be expected, but the limits of acceptability have not been defined. If the guideline development group were to provide estimates of risk with different therapeutic regimes, healthcare systems would be able to choose from a menu of choices according to the local limits of acceptability. This will become increasingly important as new (and oftentimes expensive) therapies are tested against older (and oftentimes cheaper) regimes. An example is the emerging use of rituximab in membranous nephropathy, a condition where there are established, less expensive (Ramachandran et al. 2017), albeit more toxic treatments (van den Brand et al. 2017). A similar situation is applicable in lupus nephritis (MMF vs. azathioprine) (Houssiau et al. 2010).

The TESTING trial (Lv et al. 2017) for IgA nephropathy was halted prematurely because the infection rate was disproportionately high among patients treated with steroids compared to the placebo arm. The study, however, showed a signal for benefit in the intervention arm. The investigators have modified the treatment regimen in the low-dose TESTING trial (NCT01560052) and instituted appropriate safeguards, which will hopefully allow a definitive answer to the vexed question of steroid use in this condition.

Emerging evidence: The existing KDIGO GN guideline is a static document, current only till the date of evidence review. Not only has the disease understanding progresses continuously but evidence continues to become available

regarding the use and development of drugs in GD. Other GN therapies are in development. New knowledge makes some of the guideline statements dated. Access to information has been revolutionized by increasing penetration to the World Wide Web on all platforms, including mobiles. Online resources of highly variable provenance provide often-conflicting information. Patients and physicians want to know the place of new, even experimental therapies in therapeutic armamentarium and are disappointed that clearer guidance to patient or practitioners is not available that could help them navigate this area, as has been done in some other areas of medicine.

How Do We Deal with Limitations?

The KDIGO GN guideline document has been used as a "digest" in the developing world. In the absence of local guidelines, treatment standards, and limited training on how to apply emerging evidence to clinical practice, clinical practitioners continue to look up to the GN guideline for managing their GN cases on a day-to-day basis. The following measures may help address some of the barriers:

Keeping the guidelines current and increasing dissemination: At this time, publication of the guidelines marks the end of guideline development. As discussed above, some of the guideline statements become redundant as new evidence emerges. In the new era, KDIGO will likely embrace a process of more frequent review, update the evidence table, and change the guideline if needed. Releasing these updates in electronic format, followed by dissemination through social media platforms and regional nephrology societies would be a cheap and effective way of overcoming this limitation, as has been successfully executed by UpToDate.com. An attractive and popular way of explaining the real-world application of guidelines is by presenting cases and describing how the guideline could be applied in their management. This process – embraced by KDIGO – is particularly relevant to the GN world given the large variations in presentation.

Integrating pathology details: GN classification is becoming increasingly sophisticated with addition of information beyond histological findings and exploration of correlations with clinical presentation and outcome. It is reasonable to assume that the use of this information is likely to improve personalized application of therapeutic recommendations in GN. However, recommendations can only be made if the primary clinical trials have used this information, which makes this hope a distant one. One possibility could be for researchers to perform secondary analysis of existing clinical trial data to generate hypotheses which could then be tested independently. More fruitful, however, is for the influential KDIGO GN guideline group to make a strong recommendation for GN clinical trials to collect histology information and, where possible, apply them in designing trials.

Strengthening evidence: The historic difficulty in recruiting patients in GN clinical trials requires the global GN community to come together and form global consortia. Existing networks like the Nephrotic Syndrome Study Network (NEPTUNE) (Gadegbeku et al. 2013) provide a blueprint for other countries in Asia, Latin America, and Africa. This would allow inclusion of patients from a diversity of racial and sociodemographic backgrounds, making the findings more generalizable. The global clinical trial capacity needs to be strengthened. The ACT (Advancing Clinical Trials) initiative of the International Society of Nephrology (ISN) might contribute to meeting this need. While high-quality RCTs are important to guideline development, inputs from KDIGO guideline WG in designing high-quality pragmatic clinical trials would be important.

Developing guidelines for orphan glomerulonephritides: Developing guidelines for GNs that are not commonly encountered in the advanced countries is an important challenge to the global GN community. Examples include infection-associated GN (Golay et al. 2013) and APOL1 nephropathy (Papeta et al. 2011), which is usually restricted to patients of the African ancestry. The scope of KDIGO Common Elements in Rare Kidney Diseases initiative that addresses challenges in diagnosis, management including disease

progression, clinical study design, and provision of practical and integrated support needs to be expanded to include these conditions.

Precision medicine and treatment of GN: Most of the current evidence from clinical trials is not precise as they adopt a "one size fits all" approach. The expanding era of personalized medicine will inevitably change the nature of treatment guidelines into a more algorithmic rather than linear approach. Examples where this is already a reality are management of MPGN where precise pathophysiological classification directs patients into different treatment pathways (Sethi et al. 2012). Similarly, the use of biomarkers like anti-PLA2R levels might allow more precise tailoring of the nature and/or duration of treatment (De Vriese et al. 2017). Recommendations regarding such approaches might be based on observational studies rather than RCTs. In addition to offering the most suitable therapy, such personalized approaches could also minimize therapeutic toxicity. The increasing acceptability of sophisticated genomic and/or biomarker measurement will likely increase the global rich-poor gap in clinical practice. As the science advances, it would be important to retain some guidelines for applications in areas where these facilities are not available.

In conclusion, KDIGO GN guideline is a valuable resource to nephrologists around the world that promoted provision of evidence-based care. Compilation of such knowledge has also helped in identification of evidence gap in GN management. Implementation of guidelines reinforces the need to apply the recommendations judiciously based on disease, patient, and healthcare system characteristics. The quality of future GN guidelines will improve by more efficient scientific collaboration worldwide and more frequent updates. Incorporation of emerging knowledge into guidelines in a way that maintains global equity presents an ethical challenge for the GN guideline development community.

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Minimal Change Disease in Adults

7

Sanjeev R. Shah and Michael Choi

Contents

Abstract

Minimal change disease (MCD) is a classic cause of nephrotic syndrome that is often overlooked in the adult population. Abrupt onset and remission with heavy proteinuria and preserved GFR with normal light microscopic architecture on pathology are hallmarks of this disease. Pathogenesis appears to be due to abnormalities in podocyte function, with newer data suggesting a two "hit" hypothesis whereby there is an initiating event that affects podocyte cytoskeletal features and a second hit that then potentiates this abnormality, potentially through altered T-cell regulation. Unlike most diseases with heavy proteinuria, minimal change disease is somewhat unique in that preservation of GFR is robust even after many years of a relapsing, remitting course. Treatment is thus

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geared towards preventing morbidity. Nonimmunosuppressive therapies are typically not used. First line therapy for MCD in adults is corticosteroids. In those patients with frequently relapsing or steroid-dependent MCD, use of alkalyting agents or calcineurin inhibitors are considered standard of care. In those patients that are unable to tolerate these therapies, use of mycophenolate mofetil or rituximab may be of utility.

Keywords
Minimal change disease · Epidemiology · Pathology · Immunosuppression · Pathogenesis · Treatment

Introduction

The cardinal symptom of nephrotic syndrome – namely edema – has been noted since the time of Hippocrates, who astutely noted "when bubbles settle on the surface of the urine, it indicates a disease of the kidney and that the disease will be protracted" (Chadwick 1950). It was not until 1722 that one of the first descriptions of nephrotic syndrome in children was accurately described by Zwinger and by 1827, Bright and his collaborators fully described the cardinal symptoms of nephrotic syndrome – namely proteinuria, generalized edema, and hypoalbuminemia (Zwinger 1974; Bright 1827). Further differentiation into the nature of the abnormality causing proteinuria occurred in 1905 when Muller noted it was possible to differentiate "nephritis" from "nephrosis," the latter being associated with noninflammatory diseases of the kidney (Müller 1905). Minimal change disease (MCD) was first coined as an entity in 1913 (Munk 1946). By 1931, the term "nephrotic syndrome" was introduced formally in the medical lexicon (Leiter 1930) and by the 1950s, there were multiple studies looking at use of corticosteroids or adrenocorticotropic hormone (ACTH) in the treatment of idiopathic nephrotic syndrome in adults and children (Barnett et al. 1951; Lange et al. 1957).

Epidemiology

MCD is the prototype pathological archetype that is associated with the syndrome of nephrotic syndrome. Also called *nil* disease (short for *nothing in light microscopy*), it is characterized by minimal abnormalities on light microscopy, heavy proteinuria (usually >3.5 g/day), hypoalbuminemia, generalized edema, hyperlipidemia, and hyperlipiduria and historically has been classified alongside other primary glomerular diseases such as primary FSGS, membranous nephropathy, and MPGN. MCD is predominantly a disease of children, accounting for up to 90% of cases of nephrotic syndrome in children less than the age of 10, and up to 50% of children above the age of 10 (Waldman et al. 2007). That being said, up to 15% of cases of nephrotic syndrome in adults can be attributed to MCD, making it an important entity in the differential diagnosis of not only children but adults as well. Different worldwide series show a higher prevalence of MCD in Asian populations as opposed to European and North American cohorts (Sharples et al. 1985). MCD is much rarer in patients with African ancestry, where the predominant pathological lesion is usually consistent with FSGS. There is no conclusive evidence of male vs. female preponderance.

Pathology

The diagnosis of MCD is suggested by the presence of heavy proteinuria in the absence of notable light microscopic findings on kidney biopsy. The glomeruli are usually normal in appearance or at most have the appearance of mild mesangial prominence, such that no more than three mesangial cells are seen by high powered field with capillary lumens that are delicate and patent. Although light microscopy may show tubular protein and lipid resorption droplets, the presence of tubular atrophy and fibrosis is rare and in isolation – especially in a young patient – should make one consider the possibility of FSGS. In older patients – especially ones with concomitant hypertension – MCD pathology can occur in the setting of patchy areas of interstitial fibrosis.

Immunofluorescence studies in MCD stay true to the name: there is a paucity of immune deposits including absence of IgG, IgA, C3, C4, and C1q. It is possible to have low-level staining of the mesangium with IgM, but notably, this staining is not accompanied by the presence of immune deposits on electron microscopy. When IgM is present in the setting of electron dense deposits on electron microscopy, the prognosis of these patients is worse, steroid resistance is more common, and the diagnosis is more aptly classified as IgM nephropathy. Similarly, it is possible for immunofluorescence studies to show staining of C1q, C3, and IgG, IgM in the presence of light microscopic findings consistent with minimal change disease. Assuming these patients do not have serological/clinical evidence of systemic lupus erythematosus (SLE), they are classified as having C1q nephropathy, an umbrella term for a number of other disorders with C1q staining. As noted below, MCD can also occur in class II lupus nephritis and be associated with IgA nephropathy.

The hallmark of MCD, however, is found on electron microscopy where there is almost always evidence of diffuse podocyte foot process effacement. This hallmark of podocytopathy is not specific for minimal change disease but in conjunction with no light microscopic findings and is highly suggestive of the diagnosis. As mentioned above, pure MCD is not associated with the presence of electron dense deposits. If present, they suggest an alternative diagnosis such IgM nephropathy or C1q nephropathy.

Pathogenesis

As with most diseases, the pathogenesis of MCD has been perplexing, but recent insights have given rise to the notion that MCD represents a fundamental derangement of the podocyte cytoskeleton and slit diaphragm, perhaps in relation to the production of a soluble immune factor. The basis of these arguments stems from overlapping work in immunology, basic structural biology, and biochemistry (Cara-Fuentes et al. 2016).

The glomerular capillary wall is comprised of three portions: the endothelium, the glomerular basement membrane, and podocyte, and our understanding of MCD has been based in large part on a deeper understanding of these three structures. In general, the fenestrae pock marking the endothelium – measured at up to 100 nm – have not been traditionally been thought to be a major target of pathology in MCD owing to their rather large size relative to the albumin macromolecule (Cara-Fuentes et al. 2016). The GBM, by contrast, has been traditionally implicated in the pathogenesis of MCD on the basis of its negative charge. Characterized by a lamina densa flanked on either side by the lamina rara interna and externa, the GBM has been thought of as being a charge specific barrier for various proteins due to the abundance of negatively charged proteoglycans in the lamina rara (Kanwar and Farquhar 1979). In line with this hypothesis, biopsy samples from MCD patients have shown decreased staining for heparin sulfate specific antibody and there has been evidence of increased excretion of heparan sulfate moieties in patients with relapse of MCD (van der Born et al. 1993; Mitsuhashi et al. 1993).

A number of mechanistic explanations for these observations have been put forward. One novel hypothesis put forth is that an expressed protein specifically attacks the GBM to eliminate anionic charges and thus predispose to proteinuria. Angiopoetin-like protein 4 (Angptl4) represents a PPARy target gene that is normally expressed in adipose and liver tissue under conditions of fasting but has also been found to be upregulated in injury models of the podocyte (Clement et al. 2011). When specifically overexpressed in rat podocytes, Angiopoetin-like protein 4 was found to be associated with the phenotype of severe albuminuria along with foot process effacement. In line with the idea of the GBM being a structural etiology for proteinuria on the basis of charge, the GBM was found to have less heparin sulfate moieties in the presence of this upregulation of *Angptl4*. Furthermore, $Angptl4^{-}/Angptl4^{-}$ mice developed less proteinuria as compared to $Angptl4^{+}/Angptl4^{+}$ mice in

the presence of a glomerular injury model. Finally, the same authors were able to show that of the various peptide fractions of Angptl4 were enriched in populations that had an isoelectric point (pI) >8, suggesting that mechanistically, high pI fractions may promote movement of positively charged Angptl4 into the GBM, thus explaining how this peptide can interact with the GBM at physiological pH. Similar arguments have been made for a separate peptide called hemopexin. Normally synthesized in the liver, this compound has been suggested to induce proteinuria and reduce GBM anion charge when a series of proteins (one of which was hemopexin) was infused directly in the renal arteries of rodents (Cheung et al. 1996, 2000). The authors of these works have hypothesized that hemopexin may act as a protease, thus cleaving part of the GBM to create the phenotype of proteinuria.

Despite the obvious attractiveness of a charge-dependent etiology for proteinuria seen in MCD, the role of the GBM has been questioned with knockout experiments involving various proteoglycan moieties found in the lamina rara. Similar studies have all shown that while loss of proteoglycan production in rodent models is associated with decreased charge in the GBM, it is not associated with the phenotype of heavy proteinuria (Goldberg et al. 2009; Chen et al. 2008) The potential dissociation between structure and function has also been noted with Angptl4 and hemopexin, the two putative candidate proteins mediating proteinuria in MCD. For example, although Angptl4 induced proteinuria in animals, sera from patients in relapse did not induce increased Angptl4 production in human podocytes when compared to sera from patients in remission (Cara-Fuentes et al. 2016). Similarly, hemopexin does not have a receptor in the glomerulus (Hvidberg et al. 2005) and surprisingly, MCD patients have a lower serum level of hemopexin than healthy control patients (Bakker et al. 2005). Thus, while the idea of a charge selective barrier seems attractive, there are still remaining questions about attributing the pathogenesis of MCD solely to the GBM.

In contrast to the GBM, more recent studies on the biology of minimal change disease have focused on the podocyte and its associated cytoskeletal structure. The basic structural relationship of the podocyte to the GBM is that it makes contact with the lamina rara externa via foot processes that interdigitate with one another, forming a lattice-like structure over the GBM. The spaces between these interdigitating foot processes are further characterized by slits that are bridged by overlapping proteins that form the slit-diaphragm. The foot processes are dynamic entities that contract and expand in response changes in polymerization of microtubules within the cytoplasm. A full characterization of all the proteins that are involved in the biology of the podocyte is beyond the scope of this monograph, but a few salient points regarding normal cytoskeletal proteins are important to the discussion of MCD.

Visually, when viewed in profile, the podocyte foot processes are connected via the protein nephrin, a transmembrane protein that can be phosphorylated/dephosphorlyated to signal changes internally to affect microtubule polymerization and by extension, podocyte contraction or migration over the underlying GBM (see Fig. 1). Structurally, nephrin is stabilized by forming heterodimers with adjacent proteins called NEPH1, NEPH2, and NEPH3. These signaling cascades appear to be transmitted via proteins associated with lipid rafts (podocin, Nck1, Nck2, Fyn) and effector proteins (WASP or Wiscott-Aldrich Syndrome protein) that form the connection between phosphorylated nephrin and the actin cytoskeleton (Cara-Fuentes et al. 2016).

Interestingly, despite its key role in cytoskeletal structure, diminished expression of nephrin has not uniformly been associated with the phenotype of MCD (Patrakka et al. 2001). In line with this, clustering of families with MCD has not truly been observed. What has been noted is that diminished phosphorylation of nephrin is associated with the phenotype of minimal change disease in both animal models and in human subjects (Uchida et al. 2008). This absence of true familial clustering of MCD, speaks against an inherited structural abnormality as being solely explanatory for MCD (Lahdenkari et al. 2005). This is in contrast to FSGS, where up to 24 associated mutations have been found despite the fact

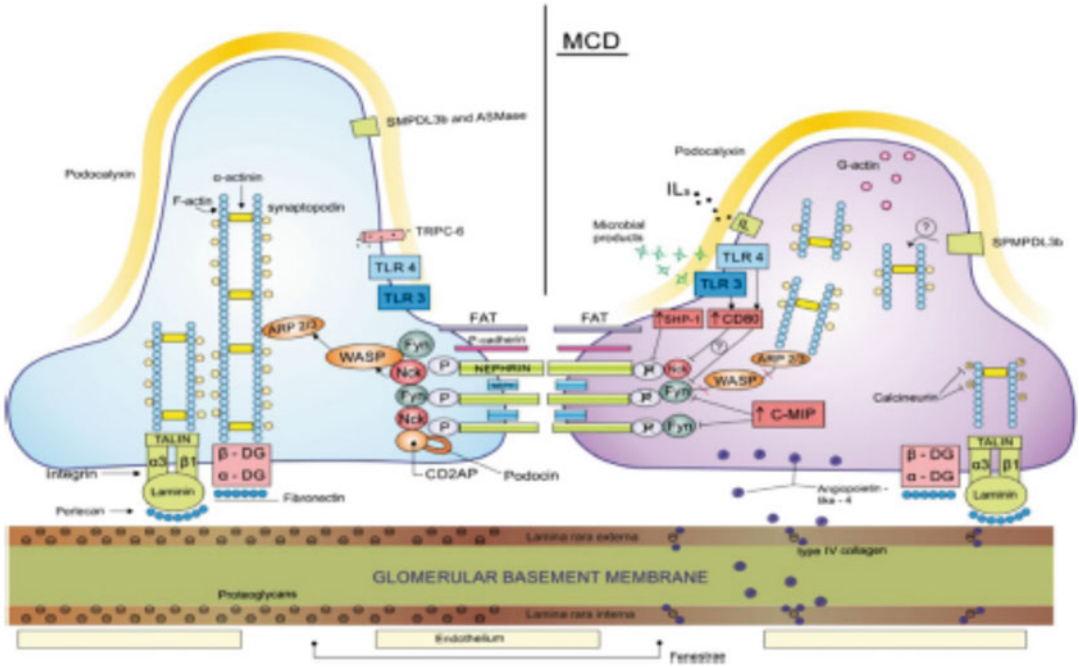

Fig. 1 The podocyte in health (*right* panel) and in minimal change disease (*left* panel). Normally, the protein nephrin forms the link between adjacent foot processes in podocytes. Nephrin itself interacts with the podocyte cytoskeleton via adapter proteins (WASP) and lipid rafts(Nck, Fyn, podocin). Phosphorylation of nephrin (P) stabilizes podocyte processes. MCD is postulated to occur when nephrin is dephosphorylated. This can occur via upregulation of CD80 via engagement of Toll-like receptors (TLR3, TL4) by microbial products or cytokines which block interaction with adapter proteins/lipid rafts. C-MIP has similar downstream effects which can manifest as decreased phosphorylation of nephrin and foot process effacement (taken with permission from Cara-Fuentes et al. 2016)

that both though both share common ultrastructural characteristics of podocyte effacement (McCarthy et al. 2013).

While an inherited etiology has been elusive, clues regarding the potential for immunomodulation affecting podocyte structure in a reversible fashion have been present for many years. For example, MCD is often quite sensitive to the effects of corticosteroids and alkalyting agents – agents that have profound effects on immunity – especially in children (Cattran et al. 2007). Multiple reports also associate the induction of MCD with viral infections, allergic responses, and lymphoma, and after hematopoetic stem cell transplantation (Singer et al. 1985; Laurent et al. 1987; Audard et al. 2006; Stevenson et al. 2005). Within the idea of immunomodulation, numerous reports have pointed to a role for T-cells in the pathogenesis of MCD. For example, infection with measles, a virus that often suppresses cell-mediated immunity, has been associated with remission in MCD (Shalhoub 1974). Other studies have shown that skewed ratios between Th1 and Th2 subpopulations in patients with MCD, with predominance of Th2 subtypes being associated with MCD (Kanai et al. 2010; Kaneko et al. 2002). More recently, this hypothesis has been refined to show that perhaps it is skewing in the population of T-regulatory cells – cells that normally dampen immune responses – that predisposes to proteinuria (Araya et al. 2009; Le Berre et al. 2009; Liu et al. 2011). That being said, as was the case with the GBM, T-cell dysregulation alone as a mechanistic explanation has been questioned as mice with SCID (severe combined immunodeficiency syndrome) are still able to manifest heavy proteinuria (Reiser et al. 2004).

More recently, there has been a shift in focus from looking purely at cell-mediated immunity to how the absence or presence of various

"permeability factors" – potentially secreted by T-cells – can affect final effector molecules on the podocyte. As an example, Koyama and colleagues were able to show that infusion of supernatant from T-cell hybridomas derived from patients with MCD could induce heavy proteinuria in rats (Koyama et al. 1991). Moreover, transplantation of a kidney from a donor with refractory minimal change disease resulted in complete amelioration of proteinuria in the recipient (Pru et al. 1984). Both of these cases point to a potential secreted factor that affects permeability of the podocyte. To date, the identity of this permeability factor has been elusive.

Recently, two molecules – CD80 and c-mip – have been put forth that may tie together the structural and immunological features seen through various experiments. CD80 (also known as B7) is a key co-stimulatory molecule found on T-cells whose activation is required to induce cellular immunity. In addition to its role on T cells, CD80 is also found as a transmembrane protein on podocytes. It has been shown that injection of lipopolysaccharide (LPS) activates Toll-like receptor 3 (TRL3) and upregulates CD80 expression in podocytes with the associated phenotype of heavy proteinuria and foot process effacement (Reiser et al. 2004). Moreover, sera from patients with relapsed MCD but not patients in remission induced CD80 podocyte expression in vitro (Ishimoto et al. 2013). This CD80 was also found in increased quantity in the urine of patients with MCD but not FSGS (Garin et al. 2010). Increased CD80 expression has also been linked to decreased nephrin phosphorylation in the podocyte and cytoskeletal reorganization, the latter phenotype associated with proteinuria (Cara-Fuentes et al. 2016; Reiser et al. 2004). Based on this, it has been hypothesized that a trigger (allergen, drug, or microbial epitope) could potentially affect CD80 expression via interaction with toll-like receptor 3 (TL3) and affect the phenotype of foot process effacement and proteinuria. Interestingly, another molecule – c-mip has been associated with decreased nephrin phosphorylation as well. C-mip is an 86 kDa protein that binds fyn, a lipid raft associated protein that forms the link between nephrin and the actin cytoskeleton in podocytes. Overexpression of c-mip leads to decreased nephrin phosphorylation and the phenotype of heavy proteinuria (Zhang et al. 2010). Interestingly, Reed-Sternberg cells in Hodgkin's lymphoma associated with MCD express c-mip but those Hodgkin's patients without MCD express do not (Audard et al. 2010).

Based on these observations, a "two-hit" hypothesis has been put forward regarding the pathogenesis of minimal change disease (Shimada et al. 2011). In this hypothesis, the first "hit" is the induction of CD80 via a triggering event, potentially the induction of cytokines that affect TL3 (i.e., an allergen or viral pathogen) or via direct action of a hereto unknown circulating factor. The second "hit" works to then prolong CD80 expression, which in normal circumstances is rapidly downregulated. Based on the above data, this may happen via altered T-reg/T-effector set ratios or various cytokines (Shimada et al. 2011; Saleem and Kobayashi 2016). Stabilization of this phenotype occurs when this process is halted and CD80 expression reverts back to normal. Clinically, this may be explained as both steroids and alkylating agents affect T-cell populations by classical teaching. More recently though, steroids have been shown to directly affect podocytes by increasing nephrin phosphorylation (Ohashi et al. 2011). In addition, cyclosporine – another potent IS medication that has efficacy in MCD – has direct effects on the podocyte cytoskeleton in addition to modulating T-cell function (Faul et al. 2008). Lastly, case series have been put forth recognizing the utility of the monoclonal anti-CD20 antibody rituximab in the treatment of refractory MCD (Bruchfeld et al. 2014; Iijima et al. 2014). Given its mechanism of action, this poses the question as to whether B-cell modulation of T-cells may be playing a part (Saleem and Kobayashi 2016). Interestingly, though, newer data suggests that rituximab may also directly affect the actin cytoskeleton (Fornoni et al. 2011). These hypotheses are far from definite but provide new avenues for approaching therapy and monitoring of disease and break with traditional teaching as MCD as disease solely of altered T-cell function, focusing more on the structural changes that affect the podocyte, the key player in the story of the pathogenesis of this phenotype.

Clinical Manifestations and Etiology

MCD is characterized by the sudden, explosive onset of massive proteinuria, and development of edema shortly thereafter. It may occur spontaneously (sometimes triggered by a viral, bacterial, or allergic cause) or as part of a secondary presentation (see below). Nephrotic range proteinuria (>3.5 g/day) is the rule, but unlike most other nephrotic diseases, the clinical course is characterized by either heavy proteinuria or complete remission (<0.3 g/g creatinine). Partial remission (50% decrement in proteinuria from baseline and proteinuria values less than 3.5 g/g creatinine but >0.3 g/g creatinine in adults) should prompt one to question the diagnosis of MCD. Edema usually is generalized and most pronounced in the dependent areas of the body but also areas with low subcutaneous fat content such as the perioribital area. The edema is felt not to be due solely to arterial underfill as has classically been taught but rather an issue with abnormally increased sodium reabsorption, potentially due to altered function of the ENAC channel (Zacchia et al. 2008). This is potentially triggered by proteinuria as has been suggested in selective micropuncture experiments done in an aminoglycoside model of heavy proteinuria (Ichikawa et al. 1983). Heavy loss of protein in the urine is characterized clinically by the presence of foamy urine. Heavy loss of protein can lead to loss of various proteins beyond albumin including antithrombin III, vitamin D-binding protein, and immunoglobulins. These losses in turn can predispose to venous and arterial thromboemboli, vitamin D deficiency, and predisposition to infection, respectively. Children in particular may manifest issues with spontaneous bacterial peritonitis and ascites. Adults with MCD often do not have this infectious complication as they have developed adaptive immunity by a certain age to encapsulated bacteria. It is for this reason that children with nephrotic syndrome are recommended to have immunization against encapsulated bacteria such as pneumococcus (Overturf 2000).

The natural history of MCD suggests that it has a relapsing-remitting course. Almost 73% of adult patients have at least one relapse after remission and up to 28% have a frequently relapsing course (Waldman et al. 2007). In pediatric patients, the relapse rate can be as high as 80–90% in patients treated with 2 months of steroids (Koskimies et al. 1982; Tarshish et al. 1997). Unlike most diseases with heavy proteinuria, MCD is somewhat unique in that preservation of GFR is robust even after many years of a relapsing, remitting course. CKD can ensue if the patient experiences ATN and residual injury, a phenomenon often seen in adult patients with underlying HTN (Waldman et al. 2007).

Beyond a primary disorder, MCD can also be a secondary disorder associated with the use of various drugs, the most common of which are the NSAID class which can cause concomitant AKI secondary to interstitial nephritis. Other less commonly reported drugs include lithium, rifampin, and interferon. Exposure to allergens including dust, pollen, and bee stings have all been reported in association with MCD as well. Viral associations with MCD include HIV and occasionally hepatitis C. Both IgA nephropathy and class II lupus nephritis can be associated with a podocytopathy resembling MCD (KDIGO 2012c). In both cases, a treatment regimen akin to MCD can result in remission. Finally, there is a well-described association between lymphoma and MCD, something buttressed by the interesting findings regarding Reed-Sternberg cells noted above. A list of more common potential associations is listed below. It is unclear if all of these are causal relationships or merely associations (Glassock 2003) (Table 1).

Laboratory Abnormalities

Nephrotic syndrome in MCD is associated with four major laboratory abnormalities: proteinuria, hypoalbuminemia, hyperlipidemia, and hyperlipiduria. We cover each in greater detail below.

Proteinuria

Nephrotic range proteinuria is quantified in adults as protein excretion >3.5 g per 24 h (KDIGO 2012b). Given a primary defect in the podocyte and slit diaphragm, urine protein electrophoresis will show that the majority of spilled protein is albumin in nature although other proteins,

Table 1 Associations with MCD

Medications
NSAIDS
Lithium
Interferon
Gold
Antimicrobials (ampicillin, cefiximine, rifampin, penicillamine)
Probenecid
Malignancy
Hodgkin lymphoma
Non-Hodkin lymphoma
Leukemia
Some solid tumors (rare)
Autoimmune disorders
Class II Lupus nephritis
IgA nephropathy
Stem cell transplantation
Dermatitis herpetiformis
Immunization
Allergy
Food allergies
Pollen
Bee stings
Poison ivy
Poison oak
Viral
HIV
Hepatitis C

including immunoglobulins, are also lost in higher than normal quantities. Proteinuria in MCD is almost always in the nephrotic range and abrupt in appearance as well as disappearance. In most cases, the urine sediment is unremarkable. Exceptions to this rule can occur in those patients that are older and hypertensive (who can present with concomitant hematuria), those patients on nonsteroidal medications (where patients can present with findings of interstitial nephritis) and those patients with severe intravascular volume depletion (where the urine sediment can show evidence of ischemic injury) (Waldman et al. 2007).

Hypoalbuminemia

Hypoalbuminemia is a direct consequence of high permeability of the glomerular filtration mechanism to albumin. In MCD, it can be quite severe and can lead to extremely low albumin levels (less than 2 g/dl). The mean level of hypoalbuminemia was 2.2g/dl in one retrospective study of adults (Waldman et al. 2007). The pathogenesis of hypoalbuminemia is multifactorial beyond merely protein loss as the degree of hypoalbuminemia is not equivalent to other diseases/states with significant protein loss (i.e., secondary FSGS). This may be attributable to increased catabolism of albumin in proximal tubular cells (especially under situations of protein restriction) as well as decreased compensatory hepatic synthesis of albumin due to secretion of a hereto uncharacterized circulating factor (Katz et al. 1963; Sun and Kaysen 1994). These hypotheses have not been conclusively proven as there have been conflicting reports about albumin catabolism (Kaysen et al. 1986).

Hyperlipidemia

Hyperlipidemia is a characteristic finding in patients with nephrotic syndrome and like hypoalbuminemia is multifactorial in nature. In general, two patterns of hyperlipidemia can be seen: hypercholesteremia and hypertriglyceridemia, either together or separately.

The pathophysiology of hypercholesteremia is a function of increased hepatic synthesis of cholesterol as well as decreased clearance (Appel 1991; Demant et al. 1998). Increased hepatic synthesis of cholesterol has been postulated to occur due to low sensed oncotic pressure given that infusion of oncotically active substances (such as albumin) in some cases has promptly decreased lipid abnormalities (Baxter et al. 1961a, b).

The pathophysiology of hypertriglyceridemia appears to be multifactorial as well. Radiotracer experiments show that VLDL delipidation (both $VLDL_1$ and $VLDL_2$) is markedly abnormal (Warwick et al. 1991). These steps are characterized by lower than usual lipoprotein lipase and hepatic triglyceride lipase activity (Demant et al. 1988). One hypothesis to explain this phenomenon is that there is loss of a substance that normally promotes lipoprotein lipase activity. In fact, the urine of nephrotic

patients has been found to contain Apoliprotein CII (an activator of lipase activity) as well as a lipase cofactor which is a glycosaminoglycan (Warwick et al. 1991; Staprans et al. 1980). Interestingly, more recently, upregulated Angptl4 has been found to be associated with inhibition of lipoprotein activity and hypertriglyceridemia, providing an exciting and novel link between the phenotype of proteinuria, podocyte effacement, and hypertriglyceridemia (Clement et al. 2014).

Hyperlipiduria

Hyperlipiduria is the last laboratory hallmark noted with nephrotic syndrome (Klahr et al. 1967). It is highly prevalent in MCD given the high degree of proteinuria exhibited in this disease type at presentation. High urinary lipid excretion often results in the presence of lipid droplets in sloughed cells in the urine (so called "oval bodies"). When incorporated within a cast structure, they are referred to as fatty casts (Greenberg 2014). Lipid is noted to be oval shaped and clear under bright field microscopy. Use of polarized light is key to determining what type of lipid is present. For example, triglycerides are isotropic whereas cholesterol is anisotropic. More specifically, lipid-laden cells often exhibit particular refractile characteristics, with the most famous being the presence of birefringent "Maltese Cross" appearance under polarized light. It is important to note that a number of artifacts can lead to this birefringent appearance, the most common of which is the starch molecule (often found in contamination during handling of urinary specimens via latex glove use). Lipiduria can be distinguished from this artifact on the basis that starch molecules have an irregular appearance whereas true cholesterol will have symmetrical arms of the "Maltese-Cross" configuration (Etter et al. 2009).

Treatment

As mentioned above, the natural history of minimal change disease is different from most other diseases with heavy proteinuria: almost all patients remit even without treatment. Thus, the goal of therapy is primarily to mitigate the morbidity during the period of severe albuminuria and immunoglobulin loss as opposed to preventing progression of kidney disease. In this sense then, it is even more important that therapy must be tailored to minimize potential side effects given the excellent overall renal prognosis.

Therapy can be thought of in terms of both nonimmunosuppressive and immunosuppressive paradigms. Before embarking on this, it is useful to review common definitions utilized in characterizing the response of adults with MCD as these definitions of response directly affect immunosuppressive choices (KDIGO 2012a) (Table 2).

Nonimmunosuppressive Therapy

In general, nonimmunosuppressive therapy such as ACE-inhibitors, ARBs, and cholesterol-lowering agents are not routinely advocated for treatment of MCD on the basis that most patients respond to immunosuppressive therapy and thus long-term sequela of heavy proteinuria such as CV disease are minimal, even in people that relapse (Lechner et al. 2004). They can be considered, however, for patients who fail to achieve remission of proteinuria in a reasonable period of time (16 weeks).

Table 2 Common definitions used in the therapy of glomerular disease specifically applied to MCD

Definition	Adults
Complete remission	Reduction in proteinuria to < 0.3 g/24 h
Partial remission	Reduction in proteinuria between 0.3 g/24 h and 3.5 g/day with $\geq 50\%$ decrease in proteinuria from baseline. NOT SEEN IN MCD
Relapse	Increase in proteinuria to > 3.5 g/day after 1 month of complete or partial remission
Frequently relapsing	>2 relapses in 6 months of initial response
Steroid dependent	Two consecutive relapses occurring during therapy or within 14 days of completing therapy
Steroid resistant	Persistence of proteinuria without significant reduction despite prednisone therapy at 1 mg kg^{-1} for 16 weeks

Immunosuppressive Therapy

The majority of trial data for MCD in adults have been extrapolated from more robust randomized controlled trial (RCT) data in populations in children. More often than not, data when present in adults, have come from retrospective analysis of patients rather than RCTs (Hogan and Radhakrishnan 2013). Where present, RCT data often involves small numbers of patients or involve trials looking at both children and adults. Thus, overall, the level of evidence for treatment of MCD in adults is weak although there are consensus guidelines as to how to systematically treat this disorder in adults (Cattran et al. 2007; KDIGO 2012a). When possible, emphasis has been placed on RCT data related to each individual immunosuppressive agent, when available.

MCD in Adults: Corticosteroids

Corticosteroids remain the bedrock of therapeutic options for treatment for adults based on the data that shows that almost 90% of children with MCD respond to treatment (Koskimies et al. 1982; Tarshish et al. 1997) with the majority of children responding in less than 4 weeks period of time (J Pediatr 1981). Unlike with children, RCT data for the use of corticosteroids in adults is limited to four small RCTs. Two of these RCTs have looked at corticosteroid use vs. placebo while two have looked at IV steroids vs. oral steroids. The earliest trial noted is from 1970 and although not specific only for MCD, compared patients with minimal change disease, membranous nephropathy, and proliferative GN using an average of 30 mg of prednisone as opposed to placebo therapy (Black et al. 1970). Of the three pathological diagnoses considered, only patients with MCD fared better with steroid therapy as opposed to placebo. Similarly, a later RCT in 1986 showed that alternate day therapy with steroids induced remission more quickly than placebo alone (Coggins 1986). Both trials, however, suggested that at >2 years follow-up, outcomes were similar in both the placebo arm and the treatment arm, suggesting that the major benefit of immunosuppressive therapy (similar to what has been found with children) is an earlier remission and mitigation of morbidity as opposed to improvement in renal survival. Two trials looking at IV vs. oral steroids have suggested that IV steroids are likely inferior to oral steroids and for this reason pulse therapy is not recommended in the therapy of MCD (Yeung et al. 1983; Imbasciati et al. 1985). There is no evidence that alternate day therapy is superior to daily oral therapy with corticosteroids (Waldman et al. 2007).

On this basis, current guidelines suggest that an initial episode of biopsy proven MCD should be treated with prednisone at a dose of 1 mg/kg (maximum 80 mg/day) or 2 mg/kg/every other day (maximum 120 mg every other day) for a minimum of 4 weeks after which time steroids can be tapered over the course of 6 months (KDIGO 2012a). This latter time frame has been extrapolated from an earlier meta-analysis of children's data suggesting a lower relapse rate when a slower taper was used (Hodson et al. 2005). An update to this analysis using newer children's RCTs up to 2015, however, noted that the prior result in 2005 may not have accounted for bias in prior studies. When studies with low risk of bias were included in the analysis, including newer trials, a benefit in reducing frequently relapsing MCD was not seen in children with a longer course of therapy (Hahn et al. 2015). Thus, the 6 month time period for therapy in adults is not based on high-level evidence although a theoretical reason for a slower tapering schedule is that those patients with abrupt cessation of steroid therapy may have adrenal suppression and a higher rate of relapse in adults (Leisti and Koskimies 1983). The optimal schedule for tapering is thus not known and is often left to the discretion of the practitioner. Failure to achieve remission by 16 weeks from the initial date of therapy in adults is deemed to be a measure of steroid resistance and thought should be given to reevaluation of the diagnosis of MCD (i.e. potential for sampling error and an actual diagnosis of FSGS).

Treatment for relapse in adults is predicated on whether the patient is classified as having infrequent or frequently relapsing MCD using the definitions above. There is no guideline information or RCT data to guide how infrequent relapses are treated in adults. Options include using a shorter steroid course (as is the case with children) or

repeating the original regimen noted above. If relapse does occur with a shorter regimen, thought should be given to a longer taper of steroids to prevent subsequent relapse. This appears to be based on one RCT in children that compared 7 months of steroid therapy with a regimen that abrogated therapy 4 weeks after initiation of alternate day therapy in unpublished data (Jayantha 2004). There was a lower risk of relapse in those patients treated with the longer duration of steroid therapy.

Frequently relapsing MCD (FRMCD), by contrast, is treated differently. If steroid toxicity is not an issue, some advocate low dose alternate-day steroid therapy to maintain remission. More often than not though, both FRMCD and SDMCD require alternative immunosuppressive agents to maintain remission. These alternative agents include use of cytotoxic agents, such as cyclophosphamide and chlorambucil, calcineurin inhibitors, such as cyclosporine and tacrolimus, as well as mycophenolate mofetil and rituximab. We cover the evidence for and against the use of these medications in MCD below.

MCD in Adults: Cytotoxic Agents

Alkylating agents are attractive agents to use conceptually for MCD given their diffuse effects on lymphocyte biology. In general, alkylating agents are used in the treatment of FRMCD or SDMCD but have to be used sparingly given the concern for adverse events, inclusive of gonadal toxicity, that are possible. If given, they are prescribed as a course only once due to the higher rate of side effects at higher cumulative doses (although the evidence against doing this is scant). Of the two potential cytotoxic agents, chlorambucil is used sparingly as opposed to cyclophosphamide given the much higher side effect profile with the former (Latta et al. 2001). Analysis of multiple RCTs in children as well as observational data suggest that cyclophosphamide is superior to prednisone in maintaining remission in those patients with MCD and thus is of benefit in those patients with FRMCD or SDMCD (Pravitsitthikul et al. 2013). This information is tempered by a lower response rate in those children with SDMCD as opposed to FRMCD (Latta et al. 2001) as well as the mitigating factors of age of therapy and prednisone dosage required to maintain remission. Specifically, data suggest that children that require higher doses of steroids have less of a sustained response to cyclophosphamide as opposed to those requiring lower doses of steroids (Zagury et al. 2011).

Multiple retrospective series have confirmed these pediatric results when looking at cyclophosphamide use in adults with FRMCD or SDMCD (Waldman et al. 2007; Nolasco et al. 1986; Mak et al. 1996). In comparison to corticosteroids, cyclophosphamide has consistently shown a higher sustained remission rate in retrospective series. The earliest series to look at this was from London, where cyclophosphamide was given in 36 patients with MCD, 23 for which were deemed FRMCD or SDMCD (Nolasco et al. 1986). Relapse rate was noted to be 76% in those patients given steroids in comparison to a relapse rate 41% in those patients given cyclophosphamide ($p < 0.01$). Sustained remission was noted to be 66% at 4 years in the cyclophosphamide group but only 34% at 2 years in those patients treated with corticosteroids. Similar discrepancies in sustained remission have been noted in later analyses (Waldman et al. 2007; Mak et al. 1996). As is the case with children, subgroup analyses of FRMCD as opposed to SDMCD suggests a better response rate in the former when considering cytotoxic agents (Mak et al. 1996).

On this basis and robust data from the pediatric literature, current guidelines recommend cyclophosphamide at a dose of 2–2.5 mg/kg for a period of 8 weeks (KDIGO 2012a) although some have advocated for 12 weeks of therapy based on an earlier pediatric report (Report of Arbeitsgemeinschaft fur Padiatrische Nephrologie 1987). Therapy is usually started after remission has been achieved with steroid therapy. Concomitant use of corticosteroids with cytotoxic agents is not recommended as retrospective series have not shown that this alters outcomes (Nolasco et al. 1986). As in children (Bircan and Kara 2003), IV cyclophosphamide has been successfully described in the treatment of adult MCD (Li et al. 2008, 2012) although it is not often used in the North American or European experience for treatment of MCD.

MCD in Adults: Calcineurin Inhibitors

Calcineurin inhibitors include the medications cyclosporine and tacrolimus. These agents modulate the immune response through downregulation of interleukin 2 by T-cells but also have inhibitory effects on antigen-presenting cells as well and indirect activation of B cells (Cattran et al. 2007). As mentioned above, these agents also appear to have direct effects on the podocyte skeletal structure making them attractive agents in the treatment of podocytopathies such as MCD. Both agents can cause nephrotoxicity. Cyclosporine is associated with a higher incidence of cosmetic side effects and hypertension and hyperlipidemia, while tacrolimus is associated with a higher incidence of diabetes mellitus and neurotoxicity. In general, the majority of clinical trials looking at calcineurin inhibitors have investigated use of cyclosporine over tacrolimus although in practice, nephrologists use both agents depending on clinical comfort level with each medication.

An overall overview of the literature shows that there is much stronger evidence looking at MCD in children as opposed to adults. RCTs in children have shown that cyclosporine alone or in conjunction with low-dose prednisone is more effective than prednisone alone in preventing relapses of MCD while therapy is continued (Pravitsitthikul et al. 2013; Tejani et al. 1991; Hoyer and Brodehl 2006). Unfortunately, as is the case with other GNs treated with cyclosporine, relapse is common if the medication is withdrawn abruptly. Two RCTs in children have also shown that cyclosporine is equivalent to alkylating agents in terms of inducing remission although sustained remission rates were markedly lower at 2 years in comparison to alkylating agents (Niaudet 1992; Ponticelli et al. 1993). This may be explained by interruptions in therapy which predisposed to a rebound effect and may make subsequent reintroduction of cyclosporine less efficacious.

Unlike the stronger RCT data seen for children, use of calcineurin inhibitors in adults is limited to small trials or registry data. The separate works of Meyrier and Waldman echo a relatively high response rate with ongoing therapy in retrospective analysis of registry data (Waldman et al. 2007; Meyrier et al. 1994). The French Collaborative experience showed complete remission rates of 73% while Waldman and colleagues also found a remission rate of 61%. One RCT that has considered cyclosporine use in adults that has been noted previously is the one by Ponticelli and colleagues that looked at both children and adults with MCD (Ponticelli et al. 1993). This trial of 31 patients with FR/SD MCD showed that although treatment with 9 months of cyclosporine led to statistically similar remission rates to 8 weeks of oral cyclophosphamide therapy, sustained remission was only 25% in the cyclosporine arm compared to 63% in the cyclophosphamide arm at 2 years. This lower rate of remission has also been found in registry data as almost 41% patients relapsed after cyclosporine discontinuation (Waldman et al. 2007), confirming the pediatric experience of a higher relapse rate with use of calcineurin inhibitors.

Based on the above data, it is recommended that cyclosporine be considered as an agent when corticosteroids or cyclophosphamide are not an option, or if the patient has failed the former two therapies. Cyclosporine is initiated at a dose of 2 mg/kg/day and titrated at 2 week intervals until either (A) the patient enters remission, (B) toxicity occurs, or (C) the patient has reached a total daily dose of 5 mg/kg/day (Cattran et al. 2007). This latter dose is based on the experience of Meyrier and colleagues who noted that no changes were noted in renal function below a threshold dose of 5.5 mg/kg/day (Meyrier et al. 1994). Therapy is continued at this dosing schedule for a minimum of 3 months at which point tapering can commence to the lowest acceptable level. Expert opinion-based consensus guidelines advocate maintaining target cyclosporine trough levels of 80–120 ng/ml, although in practice the lowest possible level that will maintain remission should be considered. This approach may minimize stripe fibrosis and arteriolopathy. Based on a high rate of relapse and rebound effect with interruption of calcineurin inhibitor therapy noted above, expert guidelines advocate uninterrupted treating for at least 1 year to minimize risk of relapse and subsequent loss of efficacy that may be noted upon attempts to reintroduce therapy (Cattran et al. 2007).

Although there is one small, unblinded RCT suggesting that tacrolimus is as efficacious as cyclosporine in MCD in children (Choudhry et al. 2009), data for use of tacrolimus is scant in the adult population. Two series have looked at use of tacrolimus in comparison to cyclophosphamide in an East Asian population (Li et al. 2008, 2012). Despite this paucity of data, tacrolimus is often used by practitioners on the basis of its preferred cosmetic side-effect profile and familiarity of use in the transplant population.

Given the high rate of relapse once therapy is stopped and potential nephrotoxicity, calcineurin inhibitors can thus be considered as an efficacious alternative agent if a patient cannot tolerate steroids or has a contraindication to cytotoxic therapy.

MCD in Adults: Mycophenolate Mofetil (MMF)

MMF is the pro-drug of mycophenolic acid and induces immunosuppression by suppression of the inosine monophosphate dehydrogenase pathway, the rate limiting step in purine synthesis (Franklin and Cook 1969; Eugui et al. 1991). As both B and T cells utilize this de novo pathway extensively, MMF has the advantage of being relatively lymphocyte specific and has already been used extensively in the posttransplant arena for maintenance immunosuppression as well as treatment for proliferative lupus nephritis (Appel et al. 2009; Ong et al. 2005; Dooley et al. 2011). Given strong basic science data showing the role of T cells in the pathogenesis of MCD (see above), there has been interest in using MMF as a steroid sparing agent in MCD.

Data for the use of MMF in the adult population is scarce and limited to case series (Choi et al. 2002; Day et al. 2002; Pesavento et al. 2004; Sui et al. 2008). MMF, however, has shown efficacy in both prospective and retrospective series as well as RCTs for the treatment of MCD in the pediatric literature. Salient points can thus be extrapolated from this pediatric data. Two RCTs in children with FRMCD/SRMCD have studied the use of MMF dose at values of 1200 mg/m^2/day in comparison to use of cyclosporine (Dorresteijn et al. 2008; Gellermann et al. 2013). A 2008 Dutch and Belgian study randomized 12 patients each to MMF or cyclosporine therapy (Dorresteijn et al. 2008). Relapse rates were found to be higher in the MMF group although the small number of patients made this value statistically insignificant. GFR was statistically improved over the course of the study in the MMF vs. the cyclosporine arm. Interestingly, the relapse rate appeared highest in those patients with the lowest area under the curve (AUC) concentration of MMF. These results were to some degree replicated in a much larger multicenter crossover RCT comparing MMF to cyclosporine in 60 pediatric patients (Gellermann et al. 2013). This study showed a statistically higher rate of relapse in the first year but not in the second year after crossover, suggesting that the lower relapse rate in the second year may have been attributable to prior treatment with cyclosporine. Like the Dutch trial, GFR was significantly improved over the course of the study ($>$ 20 cc/min) in those patients taking MMF as opposed to cyclosporine. And interestingly, this study showed that AUC values $>$50 μg·h/ml had a lower relapse rate, suggesting the potential role of MMF level monitoring in all patients. Doses commonly used in adults have usually used 1–2 g/day and have been given concomitantly with low-dose corticosteroids. Observational studies suggest MMF can be used at least up to 45 months without issues related to long-term toxicity (Afzal et al. 2007).

Based on extrapolation from the pediatric literature and adult case series then, it is not unreasonable to use MMF as a third line agent when there are contraindications to steroid, cytotoxic, or CNI-based therapy, with the caveat that better preserved renal function may come at the expense of lower rates of sustained remission. If used, these studies also suggest that therapeutic monitoring has a role in minimizing the chance of relapse.

MCD in Adults: Rituximab

Rituximab is a monoclonal antibody directed against CD20 that was originally designed for the treatment of lymphoma. As has been noted for all other immunosuppressive agents in adults, use of rituximab has similarly been limited to case series (Francois et al. 2007; Hoxha et al. 2011;

Takei et al. 2013; Bruchfeld et al. 2010, 2014; Munyentwali et al. 2013). One of the largest series from Sweden has shown an impressive remission rate: 13 of 16 patients with biopsy proven MCD had induction of complete remission with rituximab in those patients that were deemed to have frequently relapsing or steroid dependant-disease (Bruchfeld et al. 2014). At up to 28 months of follow-up, however, 7 of these patients relapsed.

There have been a number of RCTs looking at MCD with relapsing or steroid-dependent disease in children (Zhihong et al. 2015; Ruggenenti et al. 2014; Iijima et al. 2014; Ravani et al. 2015). The information from these pediatric cases can thus be useful when faced with the adult patient with refractory disease. Different dosing regimens have been used in the pediatric literature, with rituximab given at a dose of 375 mg/m^2 between 1 and 4 times to the patient. Almost all studies, including RCTs, have used concomitant steroid dosing which has then been progressively back titrated (Zhihong et al. 2015; Ruggenenti et al. 2014). One study used measured B-cell populations to assess if repeat dosing of rituximab was required (Ruggenenti et al. 2014). A meta-analysis of four pooled studies showed that rituximab significantly improved relapse-free survival compared to conventional therapy (HR = 0.49, 95% CI, 0.26–0.92, P = 0.03) (Zhihong et al. 2015). A 2014 observational study by Ruggenenti et al. echoed these findings, with an impressive 18 of 32 pediatric patients with SDNS achieving remission without the use of additional medications, and a full 14 of these 18 patients never having further relapses (Ruggenenti et al. 2014). Subsequent newer larger RCTs have confirmed these results from both older RCTS and observational reports showing rituximab to be steroid sparing (Iijima et al. 2014; Ravani et al. 2015). The only major adverse reactions mentioned in all of these studies related to infusion-related reactions which included rash, arthritis, or bronchospasm, all of which promptly responded to changes in infusion rate or supplemental medications such as NSAIDs. Even in studies with longer follow-up, no major infectious complications were noted (Ruggenenti et al. 2014; Ravani et al. 2015).

In summary, steroid therapy remains the first-line therapy for MCD in adults as the disease is exquisitely sensitive to its effects, to the point that if remission is not garnered by its use, the diagnosis of MCD should be questioned. That being said, if the disease will be deemed to be FRMCD or SDMCD, steroid sparing agents are a necessity if steroid intolerance intervenes. Of these, cytotoxic agents (specifically oral cyclophosphamide for a period of 8 weeks) have the best level of evidence but these agents have a high side effect profile and thus should be given more than once. Frequently relapsing disease has a higher response rate than steroid-dependent disease. If there remain contra-indications to cytotoxic therapy, calcineurin inhibitors are a second line option with equivalent efficacy, although sustained remission will likely be lower and with the concern for worsening renal function over time. Rituximab is quickly becoming a novel and potentially safe alternative to patients with SRMCD or FRMCD. High cost and less robust follow-up time data are caveats to this medication that preclude use as initial therapy. Further RCTs are needed to see if rituximab can be used as a first line alternative to steroid/cytotoxic therapy in relapsing disease as standard of care. Similar arguments can be made for MMF, which has much less robust data in the adult population.

Conclusion

MCD as an entity is quickly moving from a realm of pathological diagnosis only to one tied intimately to genetics, structural biology, and immunology. New advances in our understanding may impact future therapeutic options. To date, MCD can best be thought of as a podocytopathy that is exquisitely sensitive to corticosteroids, although other agents – including cyclophosphamide and CNIs – have an important role in those patients deemed to have FR/SD MCD. The efficacy of agents such as rituximab are illuminating the complex immunoregulatory processes that effect a phenotype of MCD and refining our understanding of MCD, with further hope that bench to bedside research will shed light on pathogenesis-directed therapeutic options that offer less toxicity.

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Minimal Change Disease, Pediatric

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Abstract

Minimal change disease (MCD) is the most common glomerular disease encountered in children and one of the most commonly encountered kidney diseases in this age group. The disease commonly presents with the classic tetrad

that characterizes nephrotic syndrome (NS): generalized edema, high-grade proteinuria, hypoalbuminemia, and dyslipidemia. Increased risk of thrombosis and infection are uncommon, but potentially life-threatening associated features. The manifestations of MCD are thought to be the result of the impaired glomerular permselectivity, leading to urinary losses of albumin and other peptides. Although the majority of children with MCD respond well to currently offered therapies and have an excellent long-term prognosis, some children, especially those with frequently relapsing or steroid-dependent nephrotic syndrome, may encounter major challenges related to corticosteroid and other medication-related side effects and impaired quality of life.

Keywords

Nephrotic syndrome · Minimal change disease · Focal segmental glomerulosclerosis · Podocyte · Edema · Immunosuppression · Corticosteroids · Cyclophosphamide · Tacrolimus · Cyclosporine · Plasma exchange · Spontaneous bacterial peritonitis · Acute kidney injury

Historical Background

The underlying histopathology MCD (also known as "Nil disease") became known shortly after the introduction of the renal biopsy by Brun, Iversen, and Muerhke in the early 1950s. In the initial half of the twentieth century, NS was considered fatal in approximately two-thirds of individuals, mainly due to infectious complications. The discovery of antibiotics in the 1940s led to a dramatic reduction in mortality, which was further reduced by the introduction of steroids in the 1950s to approximately 9% (Farnsworth 1950; Muehrcke et al. 1955; Iversen and Brun 1951; Arneil and Lam 1966). The natural course of NS in children and rate of response to therapy was well described in the International Study of Kidney Diseases in Childhood (ISKDC) prospective observational study published in 1978 that included 521 newly diagnosed children with nephrotic syndrome (Anonymous 1978). Newer, large multicenter studies of primary nephrotic syndrome in adults and children, such as the NEPTUNE study (clinicaltrials.gov NCT01209000), have the potential to provide additional insights into MCD pathogenesis, especially with respect to the role of genetic factors (Gipson et al. 2016; Gadegbeku et al. 2013).

Definitions and Nomenclature

- *Nephrotic syndrome (NS)*: the combination of edema, high-grade proteinuria (>40 mg/m^2/h or a urine protein to creatinine ratio >2.0 mg/mg), hypoalbuminemia (<2.5 g/dl), and dyslipidemia (Anonymous 1981b, Clark and Barrat 1998).
- *Complete remission*: a spot urine protein to creatinine ratio of less than 0.2 mg/mg, or urine albumin dipstick readings that are negative or trace for three consecutive days in children with a previous diagnosis of steroid-sensitive nephrotic syndrome (Gipson et al. 2009).
- *Partial remission*: Greater than 50% reduction in proteinuria but without full criteria for complete remission. The clinical significance of partial remission of the disease has not been well defined.
- *Relapse*: A spot urine protein to creatinine ratio ≥2.0 mg/mg, or urine albumin dipstick readings exceeding 300 mg/dl (3^+ or more) (Lombel et al. 2013).
- *Steroid-sensitive nephrotic syndrome (SSNS)*: A remission following a 4–8-week treatment course of daily corticosteroids (Gipson et al. 2009).
- *Steroid-dependent nephrotic syndrome (SDNS)*: Steroid sensitive NS patients who develop a relapse during the tapering phase of the medication or within 2 weeks after the corticosteroid is discontinued (Clark and Barrat 1998; Gipson et al. 2009).
- *Frequently relapsing nephrotic syndrome (FRNS)*. Steroid-sensitive NS patients who have two or more relapses within a 6-month period following the initial course of therapy, or four or more relapses within any 12-month period (Gipson et al. 2009).
- *Steroid-resistant nephrotic syndrome (SRNS)*: Persistent high-grade proteinuria following a

4-week treatment course of daily corticosteroids (Gipson et al. 2009).

Epidemiology

MCD carries an incidence of 2–7 per 100,000 children annually worldwide and has a cumulative prevalence of 16 per 100,000 children (Clark and Barrat 1998; Nash et al. 1992; Srivastava et al. 1999; Hogg et al. 2000; McEnery and Strife 1982). The disease incidence peaks at age 2–3 years, and the disease has a male preponderance in young children, with a ratio of 2:1 (Clark and Barrat 1998; Nash et al. 1992). In children who are less than 10 years of age who present with NS, the underlying histopathologic lesion is estimated to be MCD in 90% of cases. Such estimate is closer to 50% or less in children age 10 years or older. Beyond the first few years of life, the likelihood of MCD histology and response to corticosteroids gradually decreases with age (Anonymous 1978). MCD appears to be more common in Asian children and is relatively uncommon in Africans (Bhimma et al. 1997; Sharples et al. 1985). In contrast, children of African ancestry presenting with NS carry a much higher risk of steroid-resistance, with focal segmental glomerulosclerosis (FSGS) as the predominant underlying histology (Bonilla-Felix et al. 1999; Kopp et al. 2008) (see ▶ Chap. 10, "Focal Segmental Glomerulosclerosis, Pediatric").

Pathogenesis

MCD is thought to result from a disruption of the glomerular filtration barrier (GFB), a complex structure composed of the capillary endothelial cells, the glomerular basement membrane (GBM), and the podocytes. Podocytes, also known as the glomerular epithelial cells, are highly specialized terminal epithelial cells, characterized by major processes and minor (foot) processes. The foot processes interdigitate with others from neighboring podocytes and are linked by a special cell-cell junction, known as the slit diaphragm (Karnovsky and Ainsworth 1972). The GFB allows for the filtration of aqueous plasma while retaining larger biological molecules, such as albumin and other proteins, in the circulation. This retention of macromolecules is maintained through both size selectivity (molecules larger than 42 Å in diameter) and electric charge (negatively charged molecules are less likely to penetrate the GFB) (Brenner et al. 1978) (see ▶ Chap. 2, "Mechanisms of Glomerular Disease").

Proteinuria

Podocyte injury, leading to the loss of charge and/or size selectivity of the GFB, is considered responsible for the high-grade albuminuria seen in MCD as well as in other proteinuric diseases (Taylor et al. 1997; Kitano et al. 1993; Carrie et al. 1981; van den Born et al. 1992; Sorensson et al. 1998; Ciarimboli et al. 1999). The triggering events for such an injury have not been fully elucidated but both immunologic and nonimmunologic factors are believed to be involved (Shankland 2006). Dysregulation of both humoral and cell-mediated immunity probably contributes to the pathogenesis of the disease (Yokoyama et al. 1987; Fodor et al. 1982; Yang et al. 2008; Yan et al. 1998; Sasdelli et al. 1981, Shalhoub 1974). Abnormalities of the immune response may explain why viral infections frequently trigger relapses of MCD, see ▶ Chap. 2, "Mechanisms of Glomerular Disease." In addition, children with a history of atopy or certain malignancies (e.g., Hodgkin's lymphoma) are more likely to develop the disease (Audard et al. 2006; Shalhoub 1974; Abdel-Hafez et al. 2009). MCD responds to steroidal and nonsteroidal immunomodulators, such as calcineurin inhibitors, mycophenolate mofetil, or rituximab, which are known to suppress the cell-mediated and/or humoral immune response (Yang et al. 2008; Anonymous 1978). Although mutations in several genes have been implicated in the pathogenesis of other forms of primary NS (notably FSGS), specific gene defects have been infrequently described, to date, in patients with primary MCD (Gbadegesin et al. 2015; Gee et al. 2014). Similarly, a putative circulating permeability factor, well described in FSGS, has been implicated in only rare cases of MCNS (Ali et al. 1994; Aggarwal et al. 2007).

Edema

MCD and other causes of NS are associated with avid sodium and water retention, which is thought to be mediated by two mechanisms. The first, termed the "underflow" hypothesis, identifies hypoalbuminemia as the primary factor. The resulting decreased oncotic pressure contributes to decreased effective arterial blood volume and, thereby, triggers compensatory mechanisms that are typically seen with volume depletion (e.g., increased proximal tubule sodium reabsorption and activation of ADH). The second, termed the "overflow" hypothesis, postulates that there is a primary abnormality of sodium retention, which is suggested by evidence that sodium and water retention are seen before the serum albumin drops to the level at which oncotic pressure is significantly decreased. Although the mechanism remains poorly defined, it is thought to be related to abnormal collecting tubule sodium handling, likely involving corin-mediated activation of epithelial sodium channels (Teoh et al. 2015).

Dyslipidemia

Active MCD is commonly associated with significant dyslipidemia. Total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, and lipoprotein A [Lp (a)] are elevated while high-density lipoprotein (HDL) is low (Querfeld 1999; Querfeld et al. 1993). Evidence suggests that dyslipidemia in NS is associated with a combination of increased production and diminished cellular uptake of various lipoproteins. However, the precise underlying mechanisms behind such changes remain elusive (Wang et al. 2012).

Clinical Features

Clinical Presentation

Children with MCD often present with painless generalized pitting edema. The swelling is most prominent in gravity-dependent areas, such as the lower extremities in ambulatory children and the sacral region in infants or recumbent children. Periorbital swelling may be most pronounced in the morning and gradually improve as the child ambulates during the day. Often, there is a history of an antecedent viral infections (e. g., upper respiratory infection or gastrointestinal symptoms), although some MCD patients may present without such history. Very commonly, localized periorbital swelling is initially mistaken for allergic symptoms. Patients may have received a course of antihistamines or other allergic therapies without improvement. Since both allergies and MCD often respond dramatically to corticosteroids, maintaining a high index of suspicion for NS should prompt the clinician to collect a urine sample in any child who presents with periorbital edema, prior to initiation of systemic corticosteroids therapy, thereby avoiding an unintended delay in the diagnosis. Other cutaneous areas with weak underlying fasciae that are more prone to edema include the scrotum and labia. Parents may also note abdominal swelling. Gross hematuria, dysuria, fever, weight loss, and/or lymphadenopathy are not typical of MCD and should prompt a thorough evaluation for alternative etiologies.

Physical Examination

The physical examination of a child with suspected MCD aims at evaluating the extent of the edema, monitoring for complications of the disease, and excluding alternative etiologies. A carefully measured weight should be obtained and compared to a recent value (if available). The difference between the two weights is used to reliably estimate the percentage weight gain as a quantitative assessment of the child's volume overload. A blood pressure measurement should also be obtained, preferably manually from the right arm utilizing an appropriate sized cuff. The blood pressure is usually normal in children with MCD. Sustained hypertension, therefore, favors other underlying histologies, such as FSGS.

Evaluation of gravity-dependent regions for pitting edema is performed by applying adequate thumb pressure against the underlying bone, best elicited at the tibial shaft in ambulatory children, or the sacral/occipital bones in

recumbent infants. Careful examination of the skin should be performed, screening for signs of breakdown or cellulitis. Particular attention should be given to the genital inspection to evaluate for scrotal or labial edema and to exclude occult skin breakdown. Chest percussion and/or auscultation may detect pleural effusion, a relatively common finding in children with active MCD that usually remains asymptomatic and without clinical consequence. Moderate to severe ascites may be detected by eliciting an abdominal fluid wave. Abdominal rebound tenderness should raise concern for spontaneous bacterial peritonitis, an uncommon but serious complication of MCD.

Diagnosis

The diagnosis of MCD is typically made based on clinical criteria, including history, physical exam, and laboratory findings. As noted below, renal biopsy is performed in a minority of patients.

Laboratory Evaluation

A urine dipstick, preferably with microscopy, should be obtained in all children who present with generalized edema. In untreated children with MCD, the urine dipstick reveals high-grade proteinuria, defined as 3+ (>300 mg/dL) or 4+ (>2000 mg/dL). This is usually followed by a quantitative assessment of urine protein in the form of a spot urine protein to creatinine ratio in the nephrotic range (normal <0.2 mg/mg; nephrotic range >2.0 mg/mg). A 24 h urine collection of protein, commonly performed in adults with proteinuria, is less commonly requested in children due to the known challenges associated with obtaining an accurate 24 h urine collection. In addition, collection of a random urine sample, or preferably a first morning urine sample, for protein-to-creatinine ratio appears to correlate well with 24 h urine protein quantitation in children (Abitbol et al. 1990). The urinalysis may also reveal microscopic hematuria in 1 out of 5 children who present with MCD. However, as previously mentioned, gross hematuria is rare in MCD and should prompt further evaluation for an alternative diagnosis (Anonymous 1978). In addition to high-grade proteinuria, the diagnosis is further supported by the presence of severe hypoalbuminemia (Serum albumin <2.5 g/dl) and elevated serum cholesterol and/or triglycerides on blood chemistries.

Laboratory evaluation for MCD also includes renal function tests (BUN and serum creatinine), serum electrolytes, a complete blood count, and complement levels (C3/C4). Mild hyponatremia is commonly encountered in children with active nephrotic syndrome, attributed to excessive water retention in response to reduced effective intravascular blood volume associated with hypoalbuminemia. BUN may also be elevated, due to avid proximal tubule sodium retention by the same mechanism. However, serum creatinine is expected to be normal, or even low, except in a small subset of MCD patients who may have coexistent acute kidney injury (AKI). Hemoconcentration, reflected by elevated hemoglobin and hematocrit, is commonly seen as a reflection of relative intravascular volume depletion in children with severe edema. For unknown reasons, thrombocytosis is also commonly seen in children with MCD and may further exacerbate the risk of thrombosis (see ► Chap. 3, "Diagnostic Testing in Glomerular Disease").

Complement levels in MCD are invariably normal. Therefore, the finding of low C3, C4, or both suggests alternative diagnoses (Table 1). The finding of isolated C3 hypocomplementemia could be due to membranoproliferative glomerulonephritis, C3 glomerulonephritis, or postinfectious nephritis. Combined C3 and C4 hypocomplementemia should raise concerns for lupus nephritis. Since sexually transmitted viruses may be associated with secondary causes of NS, Hepatitis B, Hepatitis C, and human immunodeficiency virus screening may be indicated in adolescents, especially those with a history of unprotected intercourse or other high risk behaviors (see ► Chaps. 29, "Glomerular Diseases Associated with Hepatitis B and C Infection, Pediatric," and ► 31, "HIVAN, Pediatric").

Table 1 Secondary causes of nephrotic syndrome (see ▶ Chap. 5, "Overview of the Current Approach to Glomerular Disease Classification")

Autoimmune diseases
Henoch-Schönlein purpura
Systemic lupus erythematosus
Diabetes mellitus
Sarcoidosis
Infections
Hepatitis B
Hepatitis C
HIV
Drugs
Nonsteroidal anti-inflammatory drugs (MCNS)
Gold
Captopril
Penicillamine/ bucillamine
Anti-TNF agents (infliximab and etanercept)
Anabolic steroids
Malignancies
Leukemia
Lymphoma (Hodgkin disease usually associated with MCNS)
Other
Sickle cell disease
Insect stings (Bees and ants)
Food allergies
Preeclampsia
Mitochondrial disorders

A screening test for latent tuberculosis should be considered prior to the initiation of corticosteroids therapy. Screening for latent tuberculosis may be performed utilizing the purified protein derivative (PPD) or the QuantiFERON®-TB test. Note that the QuantiFERON®-TB test is currently considered the preferred method of testing only for children age 5 years and older (Nicol et al. 2009; Lighter et al. 2009).

Decision to Obtain a Renal Biopsy

Prepubertal children (>1 year of age) who present with typical features of NS with normal blood pressure, no history of gross hematuria, normal serum creatinine, and normal complement levels are highly likely to have MCD. A kidney biopsy is not considered necessary in children who fulfill these criteria and they may be empirically treated with corticosteroids without histological confirmation of the disease (Gipson et al. 2009). Epidemiological studies showed that >90% of children who fulfill these criteria have steroid-responsive disease (White et al. 1970, Anonymous 1981b, 1978). However, a kidney biopsy should be performed in children who initially fulfill the criteria for MCD but do not show an appropriate response to 4 weeks of therapy with high-dose corticosteroids (with good medication adherence), as steroid nonresponders have a high risk of having other etiologies for NS (e.g., FSGS) (see ▶ Chap. 10, "Focal Segmental Glomerulosclerosis, Pediatric").

For pubertal children who present with NS, a kidney biopsy should be considered (Gipson et al. 2009). In addition, a renal biopsy is also indicated for children with clinical features suggestive of non-MCD etiologies, such as arthritis, severe hypertension, low complement levels, gross hematuria, or a sustained elevation of serum creatinine. It is important to note, however, that a few children who satisfy the definition of SRNS may still respond to a more prolonged treatment course of glucocorticoids. Therefore, corticosteroids should be continued for an additional 4 weeks even as a biopsy is being arranged.

Pathology

Classic Minimal Change Disease (MCD)

As the name implies, classic MCD is characterized by minimal or no abnormalities on light microscopy (Fig. 1) and absent immune staining for immunoglobulins, C3, or C1q. Glomeruli on biopsy specimens should be screened carefully on light microscopy for any signs of segmental glomerulosclerosis, which, if present, exclude the diagnosis of MCD (and suggests FSGS). On the other hand, occasional global sclerosis or mild mesangial hypercellularity may be occasionally observed in children with MCD (Churg et al. 1970). In untreated children with MCD, EM usually reveals diffuse effacement of the podocyte foot processes (Fig. 2). Effacement of the foot

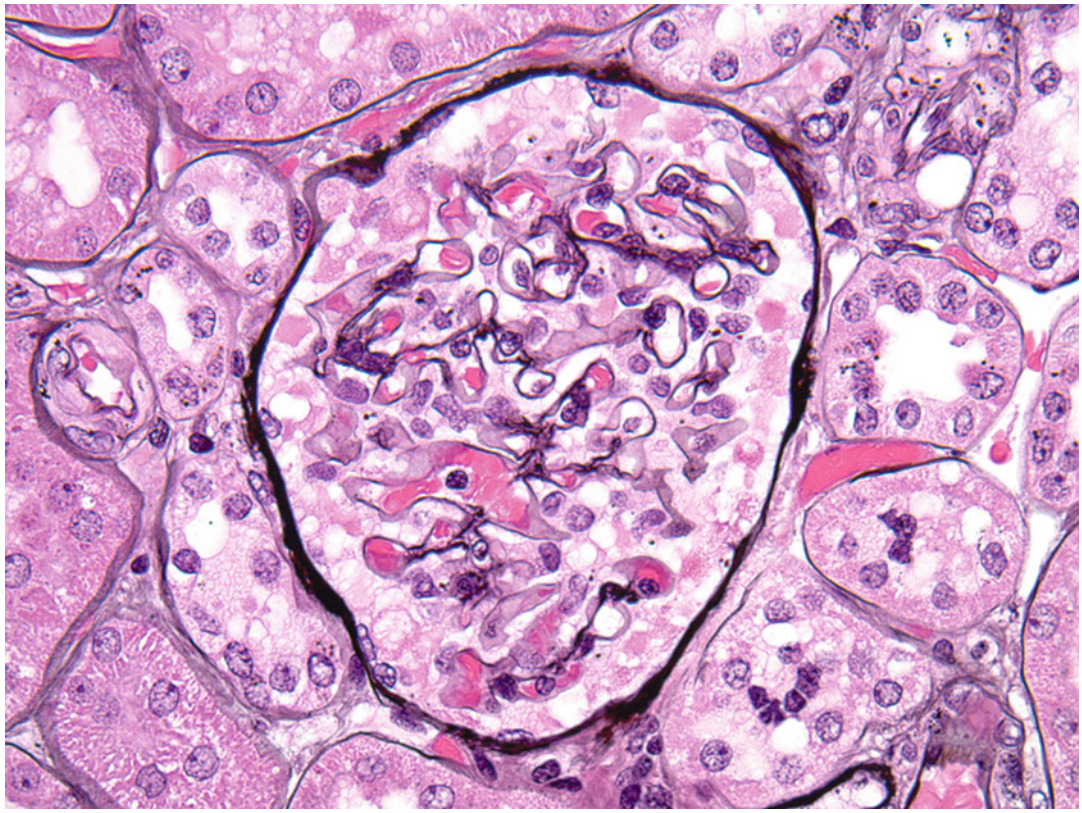

Fig. 1 Light microscopy in MCD. The glomerulus shown illustrates the typical light microscopy appearance of MCD, including the normocellular appearance with patent glomerular capillaries and glomerular basement membranes of normal thickness and contour. The podocytes in Bowman's space appear mildly swollen, a common histologic finding in MCD (Jones methenamine silver staining, 400 × magnification)

processes may be absent or focal in distribution in children with MCD who were previously treated with corticosteroids, particularly those in partial or complete remission of the disease (see ▶ Chap. 4, "Histopathology of Glomerular Diseases").

MCD Variants

Several histological variants of MCD have been described that share many of the clinical and histological characteristics of classic MCD. Observational studies suggest that such variants may be associated with reduced responsiveness to steroids or increased frequency of relapses (Markowitz et al. 2003; Border 1988; Myllymaki et al. 2003).

- *IgM nephropathy*

  This variant is characterized by isolated IgM staining of the glomerular mesangium by immunofluorescence and electron-dense mesangial immune deposits by EM (Border 1988). Increased risk of resistance to corticosteroid therapy or progression to a steroid-dependent course has been associated with this entity (Myllymaki et al. 2003; Swartz et al. 2009).
- *Mesangial proliferative glomerulonephritis*

  Also known as the mesangial hypercellularity variant of MCD, this entity is characterized by mesangial proliferation (Waldherr et al. 1978; Anonymous 1983, 1981a). Children with mesangial proliferative glomerulonephritis often present with history of gross

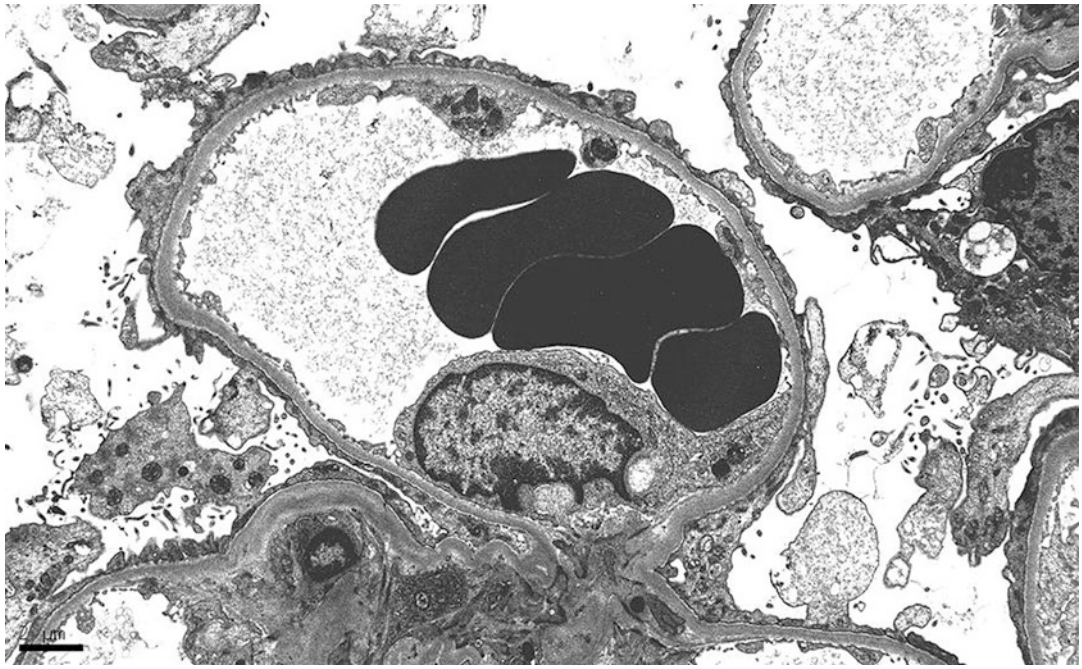

Fig. 2 Electron microscopy in MCD. Electron microscopy shows a glomerular capillary with the typical appearance of diffuse podocyte foot process effacement seen in MCD. No immune type deposits or other abnormalities are present, another defining feature of MCD (6000 × original magnification)

hematuria and/or systemic hypertension, both features that are uncommon in classic MCD. Resistance to corticosteroids has been described in 40% of children with this entity (Anonymous 1983).

- *C1q nephropathy*

  Glomerular C1q deposition is most commonly recognized as a manifestation of lupus nephritis. However, the histological entity "C1q nephropathy" is used to describe predominant C1q mesangial deposition detected on IF in patients who present with no other serological or clinical features of systemic lupus erythematosus. Such IF pattern may be observed in association with minimal changes on LM (thus, as an MCD variant) or with FSGS. This clinical significance of C1q deposition in MCD remains uncertain. Increased risk of steroid dependence, steroid resistance, and progression to ESRD was suggested in small studies (Hisano et al. 2008; Kersnik Levart et al. 2005; Markowitz et al. 2003; Vizjak et al. 2008).

Differential Diagnosis

Primary Focal Segmental Glomerulosclerosis (FSGS)

The hallmark of primary FSGS is the presence of focal (involving some glomeruli) and segmental (involving only certain segments of each involved glomerulus) sclerotic lesions on light microscopy. MCD and FSGS share many similarities in terms of underlying pathophysiology and clinical presentation. Both disorders are believed to be the result of a major insult to the podocytes, reflected by diffuse effacement of the podocyte foot processes on EM. However, FSGS is characterized by its classic histopathology of segmental glomerular scarring. Clinically, both disorders present with an insidious onset of the NS. In addition, children with FSGS may present with isolated high-grade proteinuria detected on a routine urinalysis, commonly associated with systemic hypertension,

but without overt nephrotic syndrome. Classic MCD almost never presents as asymptomatic proteinuria. Responsiveness to therapy and prognosis also differ between MCD and FSGS, with the latter being much less likely to respond to corticosteroids therapy and carrying an increased risk of progression to ESRD (Anonymous 1978). Sampling error and/or a relatively late development of glomerulosclerosis in the course of FSGS may explain why some children with this disease may initially have histological features indistinguishable from MCD (or one of its variants) on an early kidney biopsy (see ▶ Chap. 10, "Focal Segmental Glomerulosclerosis, Pediatric").

Primary Membranous nephropathy

Primary membranous nephropathy (MN) is a very uncommon cause of NS in children. Details about the clinical features, pathophysiology, diagnosis, and treatment of MN are covered elsewhere in the text (see ▶ Chap. 15, "PLA_2R- and THSD7A-Associated Primary Membranous Nephropathy").

Secondary Nephrotic Syndrome/ Podocytopathies

Various autoimmune diseases, infectious agents, metabolic disorders, toxins, medications, and malignancies have been associated with secondary podocyte injury, leading to NS. Such etiologies are far less common that primary MCD and are usually differentiated by the history and associated systemic manifestations (Table 1). Mutations in multiple genes have also been linked to the development of NS, which may or may not be associated with syndromic features. As noted above, however, no significant associations of MCD with specific gene mutations have been reported, to date (see ▶ Chap. 5, "Overview of the Current Approach to Glomerular Disease Classification").

Management

General Approach

The initial management approach for children with suspected MCD is directed at control of symptoms, induction of immunological remission, prevention of complications, and minimizing treatment-associated side effects. As previously discussed, children who fulfill certain clinical criteria for MCD are empirically treated with corticosteroids without histological confirmation with a kidney biopsy (see "Diagnosis") (Gipson et al. 2009). The initial response to corticosteroids and frequency/timing of subsequent relapses of the disease are used to dictate subsequent therapeutic options. All children presenting with NS benefit from supportive nonpharmacologic measures (see below), particularly during the active illness.

Control of Symptoms

Children of NS often present with moderate to severe generalized edema that may interfere with ambulation and place them at risk for skin breakdown. Dietary salt restriction and elevation of the feet should be initially implemented to control the symptoms. Fluid restriction is also commonly implemented but is unlikely to be effective if not coupled with strict restriction of dietary sodium. Oral diuretics, such as furosemide, may be added in more resistant cases. However, the use of oral diuretics in children with NS carries a significant risk electrolyte disturbances (hyponatremia, hypokalemia, and metabolic alkalosis) and depletion of effective blood volume, which, in turn, may increase the risk of acute kidney injury or thromboembolism. Periodic monitoring of electrolytes and renal function is essential in children with active NS, particularly those receiving diuretics.

In hospitalized children, salt-poor 25% human albumin infusions (0.5–1.0 g/kg infused over 4–6 h) with or without concurrent use of loop diuretics (furosemide 1–2 mg/kg IV given midway during or immediately following the albumin

infusion) is an effective strategy that is reserved for those with severe anasarca. The use of IV albumin and diuretics serves to expand the intravascular volume while concurrently inducing brisk diuresis. In one study, each infusion of albumin and furosemide resulted in an average weight loss of 0.4 kg or 1.2% body weight (Haws and Baum 1993). However, the effect is usually transient and such regimen carries a small but significant risk of hypertension, volume overload, and pulmonary edema. Thus, such regimen should be reserved for the treatment of substantial anasarca, especially if associated with major discomfort, difficulty with ambulation, severe scrotal edema, or detectable skin breakdown. Intravenous albumin should be avoided in children with moderate to severe hypertension, left ventricular dysfunction (suspected or confirmed), or advanced oliguric acute kidney injury (Hogg et al. 2000). Similar to children on oral diuretics, serum electrolytes should be monitored at least daily in patients receiving infusions of human albumin with or without concurrent furosemide therapy.

Treatment (Table 2)

Corticosteroids

- *Initial course of corticosteroids:*

  Children age 1–12 years of age who present initially with a clinical picture suggestive of MCD are treated with a 4–6-week course of daily prednisone 2 mg/kg/day or 60 mg/m^2 (maximum 60 mg per day) followed by an additional 4–6 weeks of alternate day therapy at 1.5 mg/kg/dose (maximum 40 mg per dose) (Gipson et al. 2009). Alternatively, alternate day therapy may be given for up to 5 months and tapered over a period of 2–5 months, although this is a less common approach (Hodson et al. 2007; Lombel et al. 2013). Shorter initial treatment courses of corticosteroids, including previously recommended 8 week course of initial treatment (Anonymous 1981b), are no longer advised due to a potential increased risk of future relapses (Brodehl 1991; Hodson et al. 2000; Bagga et al. 1999; Anonymous 1988; Hodson et al. 2007). Two randomized controlled studies (RCT) showed no additional clinical benefit when comparing the current standard 3-month course of steroids with more prolonged courses of 5–6 months (Sinha et al. 2015; Teeninga et al. 2013). Moreover, one RCT showed no differences in the time to remission between children who received prednisone as a once daily dose when compared to divided doses twice daily (Hodson et al. 2007). BSA-based dosing may be preferred in younger children (weight <30 kg) (Saadeh et al. 2011; Feber et al. 2009). The likelihood of achieving complete remission of the disease utilizing the above regimen is estimated to be more than 90%, with most steroid-sensitive patients (94%) responding within the first 4 weeks of treatment (median 7 days) (Vivarelli et al. 2010; Anonymous 1981b).

Table 2 Immunosuppressive treatment of idiopathic nephrotic syndrome in children

Initial course	2 mg/kg/day (max 60 mg) daily for 4–6 weeks *followed by* 1.5 mg/kg/dose (max 40 mg) every other day for 4–6 weeks
Infrequent relapses	2 mg/kg/day (max 60 mg) daily until remission is confirmed *followed by* 1.5 mg/kg/dose (max 40 mg) every other day for 4 weeks
Frequent relapses or steroid-dependent	2 mg/kg/day (max 60 mg) daily until remission *followed by* 1.5 mg/kg/dose (max 40 mg) every other day for 4 weeks *followed by* taper dose slowly over 2 months
Steroid-sparing medications[a]	Mycophenolate mofetil 400–600 mg/m2/dose (maximum 1 g) twice daily Cyclosporine 3–5 mg/kg/day divided twice daily (target 12 h trough 100–200 ng/mL) Tacrolimus 0.1 mg/kg/day divided twice daily (target 12 h trough 4–6 ng/ml) Oral cyclophosphamide 2 mg/kg/day for 12 weeks IV cyclophosphamide (pulse) 500 mg/m^2/dose monthly for 6 months Rituximab 375 mg/m^2/infusion, 1–4 infusions separated by 2 weeks

[a]Choice depends on tolerance of a specific agent, physician, and family preference

- *Relapses*

  Children with MCD who develop their first relapse of the disease are treated for each episode with a course of prednisone similar to that described for initial therapy, but with a more rapid transition to alternate day dosing and a shorter overall course. Once the relapse is confirmed (protein ≥300 mg/dL on dipstick on 3 consecutive days), prednisone is restarted at 2 mg/kg/day, to be continued until remission is achieved (negative or trace for protein on dipstick for 3 consecutive days), then reduced to 1.5 mg/kg/dose given on alternate days. Alternate day dosing of prednisone is continued for 4 weeks then discontinued (Gipson et al. 2009). If subsequent relapses develop and are infrequent (<2 relapses per 6 month period and <4 relapses per year), they can be treated in a similar manner as the first relapse.
- *Frequent relapses and steroid dependency*

  Children with known or presumed MCD who develop ≥2 relapses per 6 month period or ≥4 relapses per year are considered to have frequently relapsing NS (FRNS). Frequent relapses are typically treated in a similar fashion as less frequent episodes (i.e., prednisone 2 mg/kg/day until the urine dipstick is trace or negative for 3 days, followed by 1.5 mg/kg/dose given on alternate days for an additional duration of 4 weeks). However, children with FRNS generally receive an additional gradual prednisone wean rather than abrupt discontinuation, which is usually given over 2 months until discontinued (Gipson et al. 2009).

  Patients who develop a relapse during the tapering of prednisone or shortly after discontinuation (within 2 weeks) are considered to be steroid-dependent. Frequent prednisone treatment courses may be necessary for such patients leading to an increased risk of growth failure and other prednisone-related side effects. Two strategies have been suggested by experts in an attempt to minimize the risk of toxicity from corticosteroids (Lombel et al. 2013): one involves a tailored adjustment of prednisone dosing and the other involves initiation of alternative "steroid sparing" immunosuppression as discussed below. With the first approach, prednisone is tapered to the lowest dose that had previously proven to maintain remission in the same patient. In addition, low dose of prednisone either daily or on alternate day dosing can be given for a prolonged duration (months to years) to maintain remission while closely monitoring for signs of linear growth delay or other side effects. However, the long-term safety and effectiveness of such clinical regimens have not been well studied. In children with FRNS or SDNS, relapses are often triggered by viral infections. Hence, a short (<2 weeks) course of daily low dose of prednisone has been suggested to be administered during episodes of upper respiratory or gastrointestinal infections to minimize the risk of relapses, particularly in children with MCD who are maintained on an alternate day regimen of low-dose prednisone (Gulati et al. 2011; Srivastava et al. 1992; Mattoo and Mahmoud 2000).

Steroid-Sparing Medications

A second treatment strategy for SDNS or FRNS encompasses initiation of immunomodulatory steroid-sparing mediations to allow for complete discontinuation or significant reduction of prednisone. As the term implies, steroid-sparing regimens aim to maintain a prolonged remission of MCD, possibly through immunomodulatory mechanisms, thereby minimizing the long-term cumulative exposure to corticosteroids.

Mycophenolate mofetil, calcineurin inhibitors (cyclosporine or tacrolimus), cyclophosphamide, and rituximab are the most commonly used steroid-sparing medications in this setting. This second strategy is preferred in children with MCD who require relatively high doses of prednisone to maintain remission (>0.2 mg/kg/day) and in children who manifest behavioral changes, growth retardation, or other significant long-term side effects attributed to prednisone (Gipson et al. 2009). Several medications, as discussed below, are considered to be safe and effective in promoting long-term remission. Each has specific short- and long-term toxicities, but none has proven to be clearly superior in clinical studies. The choice of therapy, therefore, is generally based on

tolerance of a specific agent, and physician and family preference (Gipson et al. 2009).

- *Mycophenolate mofetil (MMF)*

  MMF is a noncompetitive inhibitor of inosine monophosphate dehydrogenase. T- and B-lymphocytes are inhibited, both of which are dependent on this enzyme to generate guanosine triphosphate and deoxyguanosine triphosphate (Eugui et al. 1991). MMF is started at a dose of 400–600 mg/m2/dose (maximum 1 g) twice daily (Gipson et al. 2009). During continuous use, MMF may reduce the frequency of relapses and allow for decreased long-term need for corticosteroids (Hogg et al. 2006; Afzal et al. 2007; Fujinaga et al. 2007; Novak et al. 2005; Bagga et al. 2003). Many children who were previously steroid-dependent may be able to reduce the dose or discontinue prednisone (Banerjee et al. 2013). MMF is also considered an attractive choice for the management of MCD in view of its favorable side-effects profile, particularly in terms of avoiding the long-term potential for nephrotoxicity associated with calcineurin inhibitors or malignancy and infertility risks of cyclophosphamide. However, the effect of MMF does not appear to be sustained after the medication is discontinued. The majority of children with MCD (75%) are expected to develop a relapse after stopping MMF (Hogg et al. 2006). MMF is generally well tolerated in the majority of children with MCD. The most common adverse reactions associated with MMF, some of which may require reduction or discontinuation of the medication, include diarrhea, vomiting, leukopenia, and anemia (Butani et al. 1999; Bunchman et al. 2001). MMF is also currently available in an enteric coated formulation, which may be a viable option to minimize the risk of nausea or diarrhea for older children who are able to take tablets (Pape et al. 2008; Vilalta Casas et al. 2006). Since most children with MCD require liquid suspensions, the use of enteric coated mycophenolic acid has limited use in pediatric MCD. Serial monitoring of complete blood counts to detect anemia and/or leukopenia and a metabolic profile to detect liver injury is recommended in all children who are maintained on MMF.

- *Calcineurin inhibitors (CNIs)*

  Cyclosporine A and Tacrolimus (FK506) inhibit a calcium-dependent phosphatase enzyme known as calcineurin. Calcineurin is a major T-cell activator and promoter of IL2 production (Borel 1991). CNIs were initially thought to be effective in NS, including MCD, primarily due to their immunosuppressant properties. More recent data suggest that these agents have a second, nonimmune-mediate effect by which they stabilize the podocyte cytoskeleton directly to induce remission. However, the precise mechanism behind this effect has not been uncovered to date (Faul et al. 2008). Cyclosporine, started at a dose of 3–5 mg/kg per day divided twice daily, has been shown to be safe and effective in the treatment of MCD, even in children with steroid-dependent or steroid-resistant disease (Niaudet and Habib 1994; Niaudet et al. 1991; Kano et al. 1999; Habib and Niaudet 1994; Mahmoud et al. 2005; Gipson et al. 2009). Following initiation of therapy, cyclosporine dose is titrated to maintain 12 h trough serum levels of 100–200 ng/mL. Tacrolimus appears to have a similar effect based on relatively smaller clinical trials, started at a dose of 0.1 mg/kg per day divided twice daily (Sinha et al. 2006), with levels typically targeted at approximately 4-6 ng/ml. Lower levels of each drug, however, can be targeted if they allow for discontinuation of corticosteroids while maintaining remission. Similar to MMF, many children who are maintained on CNIs develop a relapse of the disease after the treatment is discontinued (Ishikura et al. 2012; Niaudet 1992; Ponticelli et al. 1993).

  Adverse effects associated with CNIs are dependent on the dose and duration of therapy. Hypertension, hyperkalemia, hyperglycemia, tremor, and seizures have been reported. Cosmetic side effects, particularly gingival hyperplasia and hypertrichosis, have been associated with cyclosporine, but not tacrolimus. Hyperglycemia, occasionally

progressing to permanent diabetes mellitus and neurotoxicity (tremors, seizures), are more frequently encountered with tacrolimus than cyclosporine A (Dittrich et al. 2006; Trompeter et al. 2002; Anonymous 1994a, b). Chronic nephrotoxicity, manifested as tubulointerstitial scarring, is not uncommonly seen with both cyclosporine A and tacrolimus, particularly after 2 years of continuous therapy (Iijima et al. 2002). The role of serial kidney biopsies to assess tubulointerstitial fibrosis is a subject of ongoing investigation (see ▶ Chap. 45, "Medication-Associated Glomerular Disease").

- *Cyclophosphamide*

  Prior to the introduction of other steroid-sparing agents, alkylating agents such as cyclophosphamide were considered as first-line therapy for SDNS or FRNS. However, in the presence of potentially safer and effective alternatives, these agents have been utilized less frequently in recent years for the prevention of relapses in SDNS or FRNS. Nevertheless, cyclophosphamide remains an effective option for children with known contraindications or MMF and Tacrolimus (Zagury et al. 2011). The typical course of therapy is oral cyclophosphamide given at a dose of 2 mg/kg/day given for 12 weeks. Monthly intravenous "pulse" cyclophosphamide regimens (500 mg/ m^2/dose for 6 months) are also considered safe and effective (Prasad et al. 2004; Gulati et al. 2001) and may be particularly useful for children who cannot tolerate oral medications or are nonadherent to oral therapies. Adverse effects commonly associated with alkylating agents include leukopenia, bacterial infections, and alopecia (Latta et al. 2001). Accordingly, monitoring of the complete blood counts is mandatory during therapy. Less common side effects include alopecia, hemorrhagic cystitis, and increased risk of malignancy or infertility. The latter two adverse effects are rare in NS patients who typically do not receive the high cumulative doses of alkylating agents (>200 mg/kg) that are used for oncologic indications (Guesry et al. 1978, Watson et al. 1985). However, the risk of malignancy and infertility are very concerning for patients and parents, and are likely major factors influencing both physician and patient/parent preferences for treatment.
- *Levamisole*

  Levamisole is an antihelminthic agent that also has immunosuppressant activity. It has demonstrated efficacy as a steroid-sparing agent in SDNS and FRNS. Unfortunately, it is unavailable in many countries including the USA.
- *Rituximab*

  Rituximab, a monoclonal Anti-CD20 antibody, is emerging as a promising therapeutic option in children with FRNS/SDNS. Currently, it is commonly used in children who fail to respond to conventional steroid-sparing therapies. Rituximab (1–4 infusions separated by 2 weeks, 375 mg/m^2 each) results in prolonged depletion of B-cells lasting approximately 6 months with complete recovery of B-cells anticipated 12 months after therapy (Sanz et al. 2007; Maloney et al. 1997). Rituximab therapy appears to induce in a sustained steroid-sparing benefit in children with MCD that lasts at least 6 months (Sellier-Leclerc et al. 2010, 2012; Fujinaga et al. 2010; Guigonis et al. 2008; Ravani et al. 2011). Relapses are anticipated in many, but not all patients, after the recovery of B-cells (Kamei et al. 2009). MMF may be used as maintenance therapy after Rituximab infusions to prevent future relapse (Ito et al. 2011). Although generally tolerated by most children, Rituximab has significant potential side effects including infusion-associated anaphylaxis/acute cytokine release (10% of patients) and increased risk of bacterial infections. Leukopenia is an infrequent complication and, therefore, monthly complete blood counts are advisable until the B-cell population is reconstituted. Hypogammaglobulinemia can occur in a small percentage of patients, who may require intravenous immunoglobulin therapy. In addition, rare cases of a progressive neurologic disorder called progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving rituximab,

although these were primarily patients with lymphoproliferative or rheumatologic disorders who were receiving multiple immune modulating medications.

Additional Therapies

Children who do not achieve full remission despite the above interventions are at high risk for progression to ESRD as well as future development of cardiovascular disease. Use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and/or hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors may help delay or prevent such long-term complications in the small subset of MCD patients who do not respond to immunosuppressive therapies.

ACEI or ARBs are infrequently needed in children with MCD because most do not develop hypertension and the proteinuria resolves promptly with successful immunosuppressive therapy. However, MCD children who develop hypertension, particularly those with steroid-resistant disease, may benefit from ACEI for their antiproteinuric and long-term renoprotective properties (Bagga et al. 2004; Ellis et al. 2003; Montane et al. 2003).

Similar to other causes of nephrotic syndrome, active MCD commonly results in significant dyslipidemia, including elevated levels of total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, and lipoprotein A [Lp (a)]. Low levels of high-density lipoprotein (HDL) are also frequently encountered during active relapses (Querfeld 1999; Querfeld et al. 1993). Such changes in lipoproteins have been considered unfavorable in adults and correlated with increased long-term risk of cardiovascular complications as well as progression of chronic kidney disease (Veverka and Jolly 2004; Moorhead et al. 1989; Keane 1994; Samuelsson et al. 1997; Taal 2004). However, dyslipidemia in most children with MCD is most often transient since the majority respond well to corticosteroids and/or other immunosuppressive therapy. Accordingly, treatment with HMG CoA reductase inhibitors is seldom needed in MCD but has been advocated in older children ($\geq$8 years of age) with refractory steroid-resistant disease (Prescott et al. 2004; Sanjad et al. 1997; Coleman and Watson 1996).

Prevention and Treatment of Complications

Medication-Related Side Effects

Children who receive standard therapy for MCD are frequently exposed to prolonged and relatively high doses of corticosteroids. Clinical providers should carefully monitor for short- and long-term side effects of corticosteroids. Parents should be educated regarding both common side effects of corticosteroids as well as other rare but serious complications. Not uncommonly, the treatment regimen may need to be adjusted, shortened, or discontinued based on clinical judgment of unacceptable toxicity. Common acute adverse effects associated with corticosteroids include hyperglycemia, hypertension and behavioral changes, acne, weight gain, and cushingoid facies. Longer-term adverse effects include growth impairment, obesity, posterior subcapsular cataracts, and osteonecrosis/fractures (Jones 1985; Solomon 1981; Limaye et al. 1988; Hayasaka et al. 2006; Brocklebank et al. 1982; Bachmann et al. 1977; Ng et al. 2001; Leroy et al. 2009; Rees et al. 1988; Emma et al. 2003; Donatti et al. 2003). Alternate-day regimens are generally thought to carry a reduced risk of growth impairment (Polito et al. 1986). Thus, one goal of therapy for FRNS or SDNS is transition to alternate day dosing as soon as possible. In addition, alternate day dosing provided as a single dose in the morning is suggested to minimize effects on growth hormone secretion.

Infection Prevention

Children with MCD are at risk for various infectious complications, including cellulitis, spontaneous bacterial peritonitis pneumonia, bacteremia/sepsis, and UTI (Rheault et al. 2014). Maintaining a high index of suspicion, repositioning of immobilized patients, and frequent monitoring of the skin for areas of cellulitis or skin breakdown are essential. Antibiotics should

be initiated if clinical signs of cellulitis are detected, but preventive antibiotics are not generally recommended in this setting. Some infectious complications of NS are preventable in this era of wide-spread vaccinations. Despite rare reports of nephrotic relapses temporally related to vaccines (Abeyagunawardena et al. 2003), the long-term benefits of immunizations far outweigh the slight short-term risk of relapse. Therefore, children who are not fully immunized should receive the age-appropriate vaccinations based upon guidelines released by the American Academy of Pediatrics (AAP). In addition, children with MCD should receive the 23-valent polysaccharide pneumococcal vaccine (PPSV23) and the conjugated pneumococcal vaccine (PCV13), if the PCV13 series has not been previously given (Gipson et al. 2009). The AAP recommends that all live vaccines, including the varicella vaccine, be delayed if the child is receiving prednisone at a dose greater than the equivalent of 2 mg/kg/day or 20 mg per day, or equivalent dosing of other corticosteroids, for more than 14 days. In such children receiving a relatively high dose of corticosteroids, the live vaccines may be administered starting 1 month after discontinuation of the corticosteroids. If the duration of high-dose corticosteroids is less than 14 days, the live vaccines should be given without further delay as soon as the corticosteroids are discontinued (Anonymous 2012). However, children who are receiving any of the steroid-sparing agents (e.g., CNIs, MMF) should not receive live immunizations while they are being treated with those agents. Children with MCD and their household contacts should also receive the annual inactivated seasonal influenza vaccine.

Thrombosis Prevention

Early ambulation, maintaining physical activity, and avoidance of prolonged bed rest should be implemented to reduce the risk of deep vein thrombosis (DVT), particularly during an active relapse of the NS. Compression stockings should also be used to reduce the risk of DVT. Asymmetric edema of the lower extremity may be sometimes positional but if persistent should also raise concerns for deep vein thrombosis (Haws and Baum 1993). Management of established thrombosis requires initiation of systemic anticoagulation and/or thrombolytic therapy under the guidance of an experienced pediatric hematologist (Lilova et al. 2000). To date, the role, if any, of prophylactic anticoagulation and/or aspirin therapy in children with active NS has not been established (Andrew et al. 1998).

Prognosis

Responsiveness to corticosteroids is considered the most important prognostic factor in children with NS, including MCD; therefore, those who are steroid resistant (or become resistant) have a high risk of progression to end-stage kidney disease (ESKD) regardless of their underlying renal histopathology. Although most children with MCD (70%) who respond to the initial course of corticosteroids are expected to develop at least one subsequent relapse of their disease, the likelihood of relapse declines over time, with most children (80%) entering a prolonged remission 8 years following the initial diagnosis (Tarshish et al. 1997). However, at least 40% of children with MCD continue to develop relapses into adulthood. Not surprisingly, children with frequent relapses during childhood who require steroid-sparing medications are more likely to have one or more relapses during adulthood (Ruth et al. 2005). Hypertension, obesity, cataracts, and osteoporosis are common in adults with history of prolonged exposure to corticosteroids during childhood (Fakhouri et al. 2003; Kyrieleis et al. 2009), although there is some evidence that children receiving intermittent high doses (i.e., during relapses) may not show bone mineral density abnormalities long-term (Leonard et al. 2004).

The current mortality rate in children with MCD is not known. The most recent estimation was reported in the early 1980s to be 2.6% over up to 15 years of follow-up. Such estimation was in dramatic contrast to the two-thirds mortality rate in children with NS observed in the early twentieth century, prior to the discovery of antibiotics (1940s) and corticosteroids (1950s) (Anonymous 1984).

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Focal Segmental Glomerulosclerosis, Adult

9

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Contents

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Abstract

Focal and segmental glomerulosclerosis (FSGS) is the histological manifestation of a variety of clinicopathological entities. The

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hallmark pathologic finding is the presence of segmental glomerular scars in some but not all the glomeruli. Clinically, it presents with varying degrees of proteinuria and progression to end-stage renal disease if untreated. FSGS is the leading cause of primary glomerular disease in adults who present with nephrotic syndrome, occurring at higher rates in black patients. Morphologic variants of FSGS, which include the classic or not otherwise specified (NOS), collapsing, tip, perihilar, and cellular lesions, have prognostic importance with the collapsing lesion having the lowest response to glucocorticoids and thus worst outcomes, whereas the tip lesion is the most glucocorticoid-responsive variant with the best outcomes, resembling minimal change disease. Primary FSGS, often presenting with nephrotic syndrome, is primarily a podocytopathy. Circulating permeability factors are thought to play a central role in podocyte foot process effacement in primary FSSG. Secondary FSGS is a result of irreversible podocyte injury from a diverse group of insults such as viruses and drugs or an adaptive glomerular hyperfiltration in such cases as obesity or loss of nephron mass. Unlike primary FSGS, secondary forms of FSGS tend not to recur after kidney transplantation. Treatment of primary FSGS ranges from conservative management to glucocorticoids to immunosuppressive medications depending on the clinical presentation. Response to therapy is the strongest predictor of long-term renal survival. Treatment of secondary FSGS focuses on identifying and eliminating the underlying culprit.

Keywords

Focal and segmental glomerulosclerosis (FSGS) · Glomerular disease · Nephrotic syndrome · Primary FSGS · Secondary FSGS · Podocytopathy · Foot process effacement · APOL1 · SuPAR · Genetic FSGS · Collapsing · Tip · Cellular · Perihilar · HIV-associate nephropathy · Obesity-related glomerulomegaly · Proteinuria · End-stage renal disease · Steroid responsive · Steroid resistant · Partial remission · Complete remission

Introduction

Focal and segmental glomerulosclerosis (FSGS) is the histological manifestation of a variety of clinicopathological entities. The hallmark pathologic finding of FSGS is the presence of segmental glomerular scars in some but not all glomeruli. Shared clinical features include the presence of varying degrees of proteinuria and progression to end-stage renal disease (ESRD) if untreated. Described by Rich in 1957, FSGS has been distinguished from minimal change disease by hematuria, hypertension, and renal insufficiency at presentation, significantly poorer response to steroid therapy and progression to end-stage renal disease (Habib 1973; Rich 1957). In the past two to three decades, FSGS has become the most common cause of idiopathic nephrotic syndrome in adults (Haas et al. 1997). The incidence is 2–3 times higher in blacks, especially younger blacks under 45 years of age.

FSGS can be either primary or secondary to a variety of underlying processes. There is often significant overlap between clinical and pathological features of primary and secondary FSGS, which makes the distinction difficult. The distinction between primary and secondary FSGS is important as it drives all subsequent aspects of management. Primary FSGS, which represents a primary podocytopathy, tends to present as nephrotic syndrome and frequently responds to immunosuppressive therapy. Secondary FSGS is thought to be an adaptive response to glomerular hyperfiltration as a consequence of nephron mass reduction, scarring from a previous injury or direct toxic injury to podocytes. Secondary forms of FSGS often present with subnephrotic proteinuria and renal insufficiency and do not respond to immunosuppressive therapy. Unlike primary FSGS, secondary forms of FSGS tend not to recur after kidney transplantation. The focus of management in

secondary forms of FSGS is on eliminating the underlying etiology.

Epidemiology

The distribution and incidence of FSGS varies across geographic regions, racial, and age groups (Woo et al. 2010). Among primary glomerular diseases, FSGS is the leading cause of adult nephrotic syndrome worldwide, with an estimated prevalence of 20–30% in adults >15 years of age and 30–35% in adults >60 years (McGrogan et al. 2011). Some geographic variability exists. For example in Spain, FSGS is the fourth common histological finding in adults (ages 15–65) with nephrotic syndrome behind membranous nephropathy, minimal change disease, and lupus (Rivera et al. 2004). In the United States, FSGS is the most prevalent cause of primary glomerular disease (39%) among all racial groups, occurring at a higher rate (50%) in black patients (Sim et al. 2016). Blacks are four times more likely to have FSGS than white patients (Korbet et al. 1996). Although the incidence rate of most other glomerular diseases has remained relatively stable over time, FSGS rates have risen from 1.5 per 100,000 persons to over 5 per 100,000 persons within the last decade (Sim et al. 2016). This follows an 11-fold prior increase in the prevalence of FSGS as the cause of ESRD between 1980 (0.2%) and 2000 (2.3%), even after excluding human immunodeficiency virus (HIV) (Kitiyakara et al. 2004). The reason for the increase in FSGS incidence over time remains unclear. Primary FSGS is the most common cause of nondiabetic glomerular disease leading to ESRD in the United States in the black and white population (Haas et al. 1997). Within the subcategory of adult nephrotic syndromes, it constitutes 35% of all cases and 50% of cases among blacks. The risk of ESRD from primary FSGS is fourfold higher in black patients compared to white and Asian patients and twofold higher in men than women. It is one of the most recurring diseases after kidney transplantation with a 30–40% recurrence incidence in adults and up to 80% in children (Kitiyakara et al. 2004).

An estimation of the incidence and prevalence of FSGS in children is hampered by the fact that most children with nephrotic syndrome do not undergo a renal biopsy. Clinical reports make the presumptive diagnosis of minimal change disease based on steroid responsiveness and thus likely underestimate the 15–20% of children with FSGS that are initially steroid responsive (Bonilla-Felix et al. 1999; Filler et al. 2003). Of the children with nephrotic syndrome who undergo a renal biopsy, approximately 7% have a diagnosis of FSGS (Anon 1985). FSGS is the most common cause of ESRD in black children (23%) but the third most common cause (10%) in white children (Filler et al. 2003; Jungraithmayr et al. 2005). The prevalence of FSGS among all children with nephrotic syndrome who undergo a renal biopsy increases with age (Hogg et al. 2007). The frequency of FSGS in nephrotic syndrome patients presenting before the age of 6 is less than 10% but increases to 20–50% in patients presenting in adolescence (Anon 1981, 1985; Bonilla-Felix et al. 1999; Kim et al. 2005; Srivastava et al. 1999). Much like their adult counterparts, there has been an increase in the incidence of FSGS among children, mainly older children (Chesney 2004; Hogg et al. 2007). The cause of this increase in incidence is unknown but is unlikely to be due to genetic factors, the epidemic of childhood obesity, or ethnic differences (Hodgson et al. 2004; Kambham et al. 2001).

Classification

The "classic" or prototypical FSGS lesion has segmental destruction of the glomerular capillary loops by extracellular matrix often accompanied by hyalinosis (D'Agati et al. 2011) (Fig. 1). Furthermore, prominent parietal epithelial cell, tuft adhesion, intracapillary foam cells, or even collapse of the underlying capillary tuft can be seen

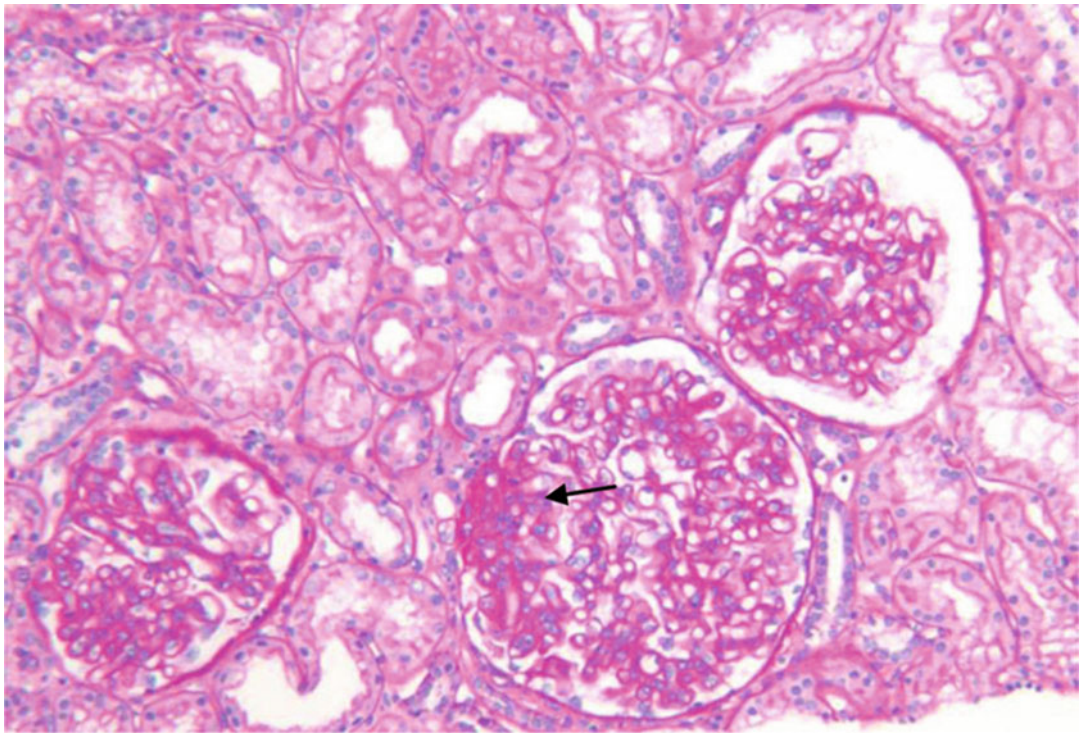

Fig. 1 Classic or not otherwise specified (NOS) lesion of FSGS with segmental scar (arrow), also depicting the focal (some but not all glomeruli) and segmental (involving part but not the entire capillary tuft) nature of FSGS (periodic acid-Schiff stain, original magnification x220) (Courtesy of Dr. David Cimbaluk)

on light microscopy. Segmental lesions can involve any portion of the glomerular capillary tuft, including the hilum, which is adjacent to the vascular pole, up to the tip, which is near the origin of the proximal tubule. Focal global glomerulosclerosis (FGGS) is not synonymous with FSGS and is most frequently a manifestation of aging, vascular injury from chronic hypertension, or a consequence of tubulointerstitial disease (Grgic et al. 2012).

Due to the focal (some but not all) nature of glomerular involvement by the sclerotic lesion in FSGS, adequate glomerular sampling is of significant importance (Schwartz and Korbet 1993b). Sclerotic glomeruli first occur in juxtamedullary glomeruli and thus may be missed in superficial biopsies that only contain cortex (RICH 1957). A glomerulus, which is a sphere of ~200 μm, is often sectioned into 2 μm cuts. Thus single sections can easily miss a segmental lesion. True degree of tuft involvement requires three-dimensional reconstruction through serial sectioning, which is often a limitation of practical histology (Remuzzi et al. 1995). Although response to therapy remains the single most important predictor of long-term renal survival, morphologic classification of FSGS variants may provide additional prognostic information.

The most current histologic classification, otherwise referred to as the Columbia Classification, recognizes five morphological variants that can be applied to both primary and secondary FSGS: classic FSGS, also referred to as FSGS not otherwise specified (NOS), collapsing, tip, perihilar, and cellular (D'Agati et al. 2004). In this classification, renal scarring from other primary glomerular diseases is excluded as a diagnostic possibility.

Classic (NOS)

Classic (NOS) FSGS is the most common variant (Chun et al. 2004) and requires the exclusion of all other variants. Segmental obliteration of glomerular capillaries by extracellular matrix is

the defining lesion, while hyalinosis, endocapillary foam cells, capsular adhesion, and parietal cell coverage of the sclerotic lesions are common features (Stokes and D'Agati 2014) (Fig. 1). Immunofluorescence microscopy shows no immune deposits except the nonspecific trapping of IgM and C3 within the segmental scars. Foot process effacement is often diffuse. The degree of tubulointerstitial fibrosis is variable. FSGS NOS is the most common (41–68%) variant of FSGS (Chun et al. 2004; D'Agati et al. 2013; Thomas et al. 2006).

Collapsing

The collapsing variant of FSGS was first described in 1978 as a malignant form of FSGS due to its rapidly progressive nephrotic syndrome (Albaqumi et al. 2006; Albaqumi and Barisoni 2008). During the HIV epidemic of the early 1980s, "HIV-associated nephropathy" was the term used to describe a similar lesion later found in HIV-negative patients and labeled collapsing FSGS (Weiss et al. 1986b). There are distinct histological and clinical differences between collapsing FSGS, also referred to as collapsing glomerulopathy, and classic FSGS. The finding of segmental or global implosive collapse of glomerular capillaries with overlying visceral epithelial cell hypertrophy and hyperplasia in at least one glomerulus, irrespective of the findings in other glomeruli, defines the collapsing variant of FSGS (Fig. 2). Proliferation of the extracapillary glomerular epithelial cells occupies the Bowman's space, forming a pseudocrescent, distinct from the spindled shaped inflammatory crescents that have pericellular matrix, fibrin, leukocytes, and breaks in

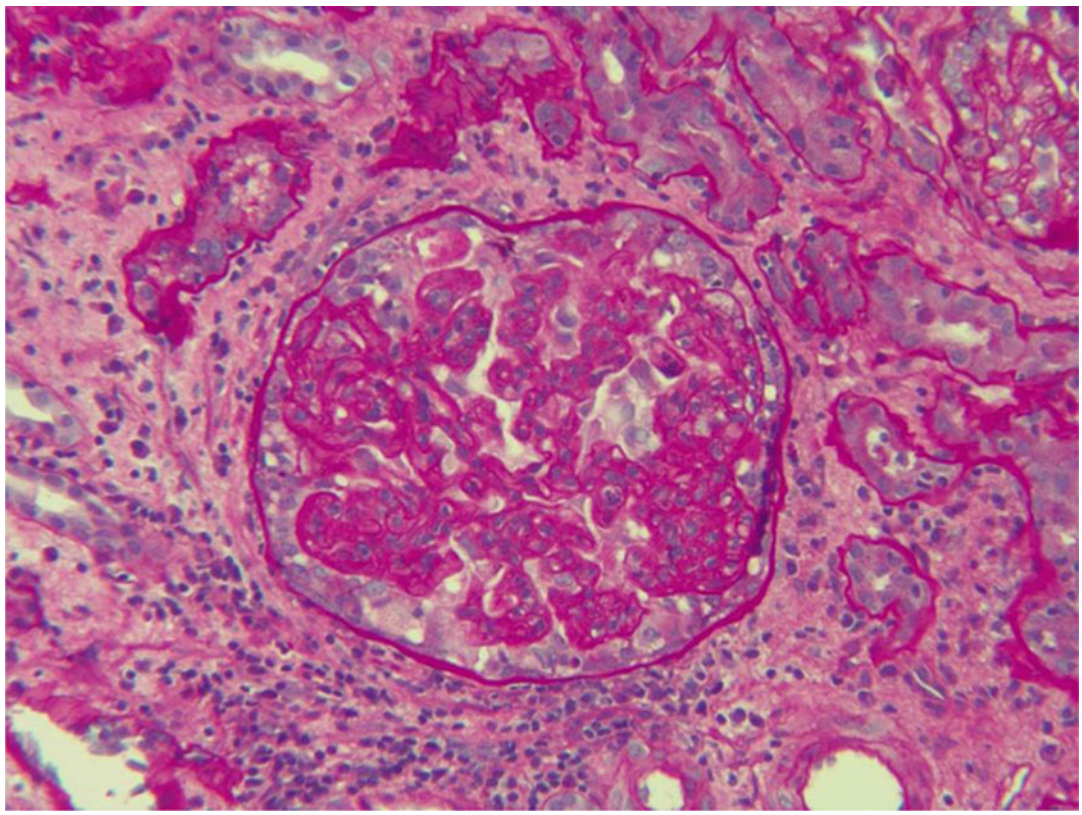

Fig. 2 Collapsing FSGS showing global collapse of the capillary tuft with pronounced podocyte hyperplasia and hypertrophy ("pseudocrescent") filling the Bowman's space. The glomerulus is surrounded by damaged tubules with thickened and wrinkled basement membranes indicating severe tubulointerstitial fibrosis (periodic acid-Schiff stain, original magnification x220) (Courtesy of Dr. David Cimbaluk)

the basement membrane (Valeri et al. 1996b). Proliferation and hypertrophy of the parietal epithelial cells lining the urinary side of the Bowman's capsule also contribute to extracapillary hypercellularity (Dijkman et al. 2005). Foot process effacement is usually diffuse (>80%). Extraglomerular features of collapsing variant often include severe interstitial fibrosis, tubular atrophy, and tubular microcysts containing proteinaceous casts (Detwiler et al. 1994b).

In addition to its distinct histological features, collapsing FSGS differs from other subtypes of FSGS in clinical features. The collapsing variant has the highest black racial association (63%), highest baseline serum creatinine, and heaviest proteinuria (D'Agati et al. 2013). Blacks account for an overwhelming majority (88%) of patients with HIV-associated nephropathy (Abbott et al. 2001). Furthermore, black patients with HIV-associated collapsing FSGS have an increased incidence of a family history of ESRD compared to HIV-infected black patients without renal disease, suggesting a genetic susceptibility contributed by genes such as apolipoprotein 1 (APOL1) risk alleles (Genovese et al. 2010a, b; Kao et al. 2008; Kopp et al. 2008, 2011; Pollak 2008). Compared to patients with classic FSGS, those with collapsing lesions have a more rapid deterioration in renal function, progressing to ESRD over 12–18 months (Detwiler et al. 1994b; Haas et al. 1995a; Schwartz et al. 1995b; Valeri et al. 1996b). Additionally, patients with biopsies demonstrating extensive involvement with collapsing lesions (>20%) are less likely to enter a remission with therapy than those with classic lesion (Chun et al. 2004). In addition to HIV, other secondary causes of collapsing FSGS include parvovirus B19; hemophagocytic syndrome; pamidronate; interferon α, β, or γ therapy; and acute vaso-occlusive disease (D'Agati et al. 1989; Markowitz et al. 2001; Markowitz et al. 2010; Moudgil et al. 2001; Stokes et al. 1999; Thaunat et al. 2006).

Tip

A single segmental sclerotic lesion located at the tip region, near the origin of the proximal tubule, with adhesion or confluence with tubular epithelium, is diagnostic of the tip variant of FSGS (Howie et al. 2005; Howie and Brewer 1984). Collapsing and perihilar variants must be excluded. The lesion is predominantly cellular, containing foam cells, but hyaline-containing sclerosis can be present (Fig. 3). There is little to no immune complex deposition with IgM or C3. Extensive foot process effacement is seen on electron microscopy (D'Agati 2003). The predominant mechanism of injury involves podocyte detachment as a result of shear stress and turbulent flow at the tubular pole (Stokes et al. 2004). Most FSGS tip variants are primary; however, other diseases with heavy proteinuria such as membranous glomerulopathy, diabetic nephropathy, and preeclampsia can lead to the development of tip lesion.

The tip variant of FSGS comprises approximately 13–17% of the adult nephrotics with primary FSGS (Chun et al. 2004; Thomas et al. 2006). Unlike the collapsing variant, blacks have a substantially lower proportion (15%) of the tip variant (Thomas et al. 2006). This lesion may identify a subset of patients who present with sudden onset of nephrotic syndrome and are more likely to respond to glucocorticoid therapy compared to other FSGS variants, features that are similar to minimal change disease (Beaman et al. 1987; Haas and Yousefzadeh 2002; Thomas et al. 2006). On the other hand, 70% of repeat renal biopsies of patients with originally diagnosed tip variant show classic FSGS (Howie et al. 2005). Furthermore, patients with tip lesion who are steroid unresponsive are more likely to progress to ESRD. These features suggest that tip variant may be an early form of classic FSGS. Thus the question of whether the tip lesion should be considered a variant of minimal change disease or FSGS remains unanswered.

Perihilar

The defining feature of the perihilar variant is the presence of at least one segmental hyalinosis and sclerosis at the glomerular vascular pole in more than 50% of the affected glomeruli (D'Agati 2003). Hyalinosis may extend to the adjacent afferent arteriole (Fig. 4). Immunofluorescence

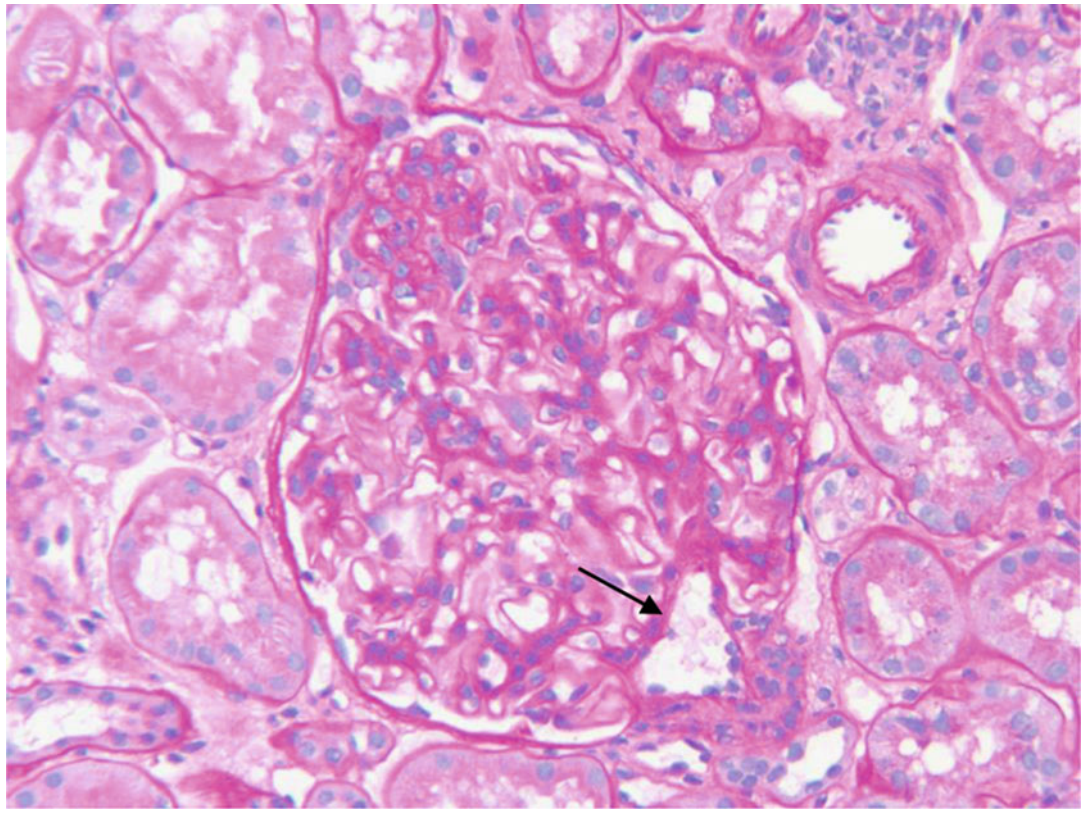

Fig. 3 FSGS tip lesion showing segmental endocapillary lesion at the origin of proximal tubular takeoff, opposite of the vascular pole (arrow), with adhesion to the Bowman's capsule and confluence of podocytes and parietal epithelial cells (hematoxylin and eosin stain, original magnification x220) (Courtesy of Dr. David Cimbaluk)

and electron microscopic findings are similar to classic FSGS. Although this lesion can be seen in primary FSGS, most reported cases are in secondary adaptive forms of FSGS with enlarged glomeruli and focal foot process effacement (Bhathena et al. 1985; Falk and Jennette 1994; Harvey et al. 1992; Herlitz et al. 2010; Hodgin et al. 2009; Kambham et al. 2001; McGraw et al. 1984). The proposed mechanism is afferent arteriolar dilation as a result of hyperfiltration, which leads to shear hydrostatic stress on the perihilar segment where the blood enters the glomerular tuft (Nagata et al. 1992; Nagata and Kriz 1992).

Cellular

Cellular FSGS is defined by presence of at least one glomerulus with segmental expansion of the glomerular tuft by endocapillary hypercellularity, often with foam cells, with or without hyperplasia of overlying visceral epithelial cells (Stokes et al. 2006). Absence of capillary collapse and confluence with the origin of the proximal tubule differentiates the cellular variant from those of collapsing and tip lesions, respectively. In its original 1985 description, cellular lesion resembles what was later classified by the Columbia group as a collapsing lesion (Schwartz and Lewis 1985). Cellular FSGS is the least common (3–5%) morphologic variant of FSGS (Stokes et al. 2006). It often identifies patients with idiopathic FSGS who present with short duration of heavy proteinuria with progression to ESRD if untreated. Also, on deeper sectioning, some cellular FSGS biopsies prove to be tip or, less commonly, collapsing variants. These sampling limitations may explain in part the intermediate outcome of cellular

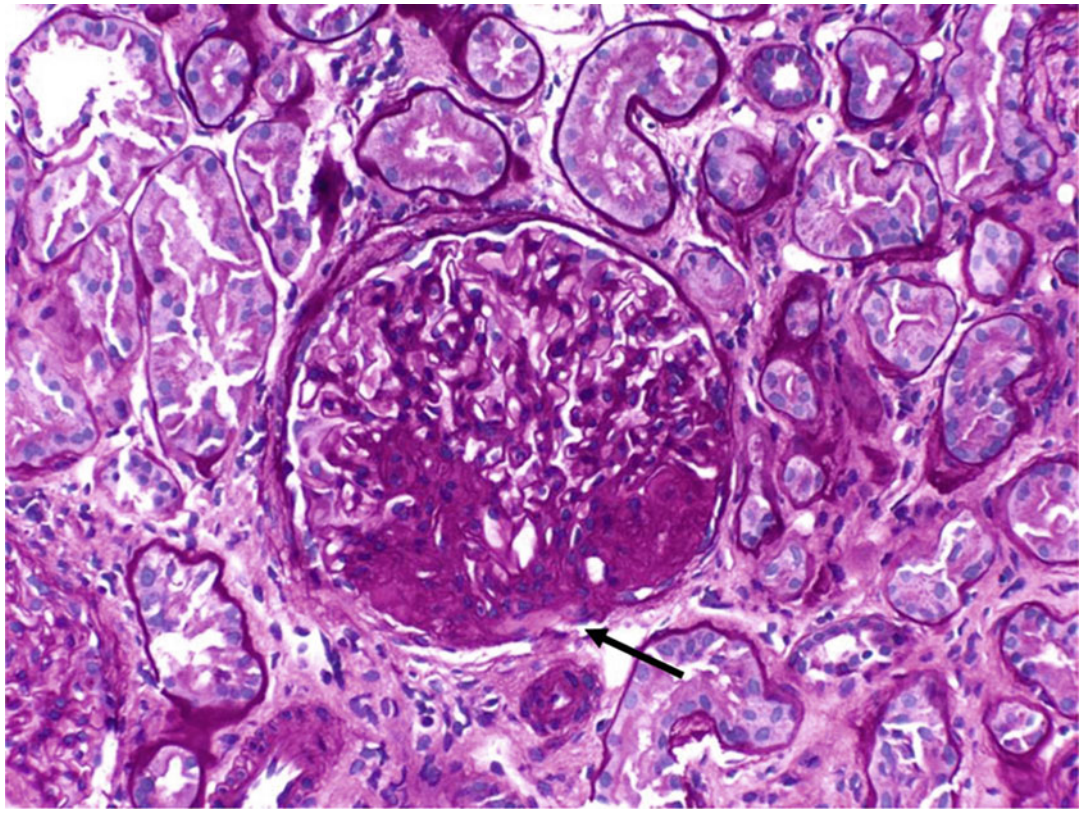

Fig. 4 FSGS perihilar lesion with segmental accumulation of matrix and hyaline at the vascular pole (*arrow*) (periodic acid-Schiff stain, original x220 magnification) (Courtesy of Dr. David Cimbaluk)

relative to collapsing and tip variants (Stokes et al. 2006).

Pathophysiology

The principle site of injury in all forms of primary FSGS is the glomerular epithelial cell or podocyte (Kriz et al. 1994). These highly specialized cells help maintain the integrity of glomerular architecture and hinder egress of proteins into the urinary space. Early electron microscopic changes after podocyte injury observed in post-transplant FSGS patients show podocyte cell body attenuation, foot process effacement, pseudocyst formation, and microvillous transformation, long before the development of visible light microscopic changes (Verani and Hawkins 1986). Podocyte injury, if not recovered, leads to cell death or detachment from the underlying glomerular basement membrane via $\alpha_3\beta_1$ integrin, dystroglycan, and podoplanin, leaving the GBM uncovered (Kerjaschki 2001; Pavenstadt et al. 2003). The uncovered capillary loops balloon toward Bowman's capsule and interact with the parietal epithelial cells (PEC) (Kriz and Endlich 2005). The glomerular PECs deposit matrix between these bridging cells and form a fibrous attachment (tuft adhesion), an irreversible connection which is the earliest light microscopic feature of FSGS (Jefferson and Shankland 2014). Intracapillary deposition of proteinacious material (hyalinosis) and lipid-laden macrophages (foam cells) leads to capillary loop obliteration, the characteristic lesion of segmental sclerosis. A consequence of PEC-capillary loop interaction is the formation of gaps in the parietal epithelial lining where misdirected glomerular filtrate can further strip PECs,

form proteinacious pseudocrescents, and spread along the tubular basement membrane resulting in tubular atrophy (Jefferson and Shankland 2014).

Podocyte injury and subsequent depletion, which seems, at least initially, to be at the center of FSGS pathogenesis, can have a multitude of causes. In rat model of adriamycin-induced nephrotic syndrome, proteinuria precedes podocyte changes (Bertani et al. 1982). This finding is supported by a similar observation in patients suffering rapid recurrence of FSGS after transplantation (Korbet et al. 1988). In addition, in utero transmission of a permeability factor from a nephrotic mother to her child with subsequent resolution of proteinuria within months of birth has been reported (Kemper et al. 2001). These observations suggest a role for a circulating factor that initially impairs perm-selectivity, leading to proteinuria, and then results in podocyte injury. Early reports suggested a nonimmunoglobulin 30–50 kDa circulating protein which is present at low levels in normal subjects and is elevated in patients with recurrent FSGS (Savin et al. 1996).

One such circulating factor candidate is the soluble urokinase plasminogen activator receptor (suPAR) (Wei et al. 2008, 2012). Urokinase plasminogen activator receptor (uPAR), expressed in a variety of cell types throughout the body, is a cellular receptor for urokinase which is involved in orchestration of a number of signaling cascades (Blasi and Carmeliet 2002). After cleavage of its phosphatidylinositol anchor, uPAR can be released as a soluble molecule (suPAR). SuPAR is a 20–50 kDa, multidomain, heavily glycosylated protein that can be present as different fragments and with various degrees of glycosylation (Sier et al. 1998). Serum suPAR levels have been shown to be higher in patients with primary FSGS compared to other glomerular diseases. Patients with pre-transplant elevated suPAR levels have an increased risk of FSGS recurrence after kidney transplantation (Wei et al. 2011). These observations have led to immense interest in suPAR as a pathogenic circulating permeability factor. Circulating suPAR activates podocyte β3 integrin in both native and transplanted kidneys, leading to foot process effacement and proteinuria (Wei et al. 2012). Elevated suPAR levels of >3000 pg/ml are seen in 84% of adults and 55% of children with primary FSGS compared to 6% of healthy controls (Wei et al. 2012). On the other hand, serum suPAR levels are increased due to a variety of other disease states such as paroxysmal nocturnal hemoglobinuria, HIV, malaria, tuberculosis, central nervous system bacterial or viral infections, as well as multiple types of cancers. Furthermore, suPAR levels increase as glomerular filtration rate (GFR) declines, adding an overwhelming confounding effect on the correlation between suPAR and glomerular histopathology (Reiser et al. 2014). Due to these limitations, single measurement of suPAR with currently available commercial assays remains controversial and is not recommended for distinction between primary FSGS and other forms of glomerular diseases (Spinale et al. 2015).

APOL1

The disproportionately higher incidence of end-stage renal disease among blacks in the United States (3.5-fold higher compared with whites) has raised questions about the role of genetics in expression and progression of disease in this population. Blacks are 50 times more likely to develop ESRD if they are infected with HIV (Eggers and Kimmel 2004). Similarly, higher ESRD incidence rates have been noted for blacks if the underlying disease is FSGS, hypertension-attributed nephropathy, or nondiabetic chronic kidney disease (Parsa et al. 2013). Previous health disparity research focusing on socioeconomic differences, although highly consequential, failed to explain these racial differences in disease progression. The observation that many patients of African ancestry with ESRD had close relatives who had also been on dialysis focused the search on genetic factors (Freedman et al. 1993).

Mapping by admixture linkage disequilibrium (MALD) narrowed the association of kidney disease and African ancestry to chromosome 22 (Kao et al. 2008; Kopp et al. 2008; Shlush et al. 2010). Although originally the disease-causing variant was thought to be located in the genes encoding

nonmuscle myosin heavy chain 9 (MYH9), two common variants (G1 and G2) of apolipoprotein L1 (APOL1) gene are thought to infer the risk alleles (Genovese et al. 2010a; Tzur et al. 2010). After controlling for the APOL1 risk variants, the association of kidney disease with the MYH9 haplotype disappears. The two common variants of APOL1 confer resistance to the lethal *Trypanosoma brucei rhodesiense* infection in West Africa. An individual with zero risk alleles (G0) would be susceptible to Trypanosomiasis, otherwise known as African sleeping sickness, a parasitic infection transmitted by the tsetse fly. Individuals with one APOL1 risk allele (heterozygous G1 or G2) are protected from *T. b. rhodesiense* infection and are at lower risk for the development of APOL1-associated nephropathy. Individuals with two APOL1 risk alleles are also protected from *T. b. rhodesiense* infection but are at increased risk for the development of progressive adult kidney disease (Kruzel-Davila et al. 2016).

Polymorphism in the APOL1 gene associated with the FSGS lesion is exclusively expressed in individuals of African descent (Genovese et al. 2010a, b). Inheritance of two APOL1 risk variants does not equal development of kidney disease but certainly increases the risk, in case of FSGS by 20-fold (Kopp et al. 2011). The direct role of APOL1, a lipid-binding protein and a component of high-density lipoprotein class 3, which is involved in protecting low-density lipoprotein from oxidation, is not known. Abnormalities in APOL1 overexpression in the arterial beds including the glomerular arterioles and interlobular arteries may promote vascular sclerosis via autophagy and provide the "first hit" in a two-hit model of progressive kidney disease (Madhavan et al. 2011; Sethi et al. 2015). A "second hit," either environmental, infectious, or genetic, is then required for disease expression (Freedman and Langefeld 2012).

APOL1-associated FSGS presents between ages 15–39 years old and has a rapid clinical progression to end-stage renal disease (Kopp et al. 2011). Histologically, patients with APOL1-associated FSGS have more collapsing variants, more advanced glomerulosclerosis, tubular atrophy, and interstitial fibrosis consistent with their more rapid functional loss (Kopp et al. 2015). Interestingly, patients with APOL1-associated FSGS have a similar response to glucocorticoids, cyclosporine, and mycophenolate/dexamethasone therapy compared to those lacking two APOL1 risk alleles. Given their poor outcome, early and aggressive treatment is warranted (Kopp et al. 2015).

Clinical Presentation

Primary FSGS

Adults with primary FSGS present with nephrotic-range proteinuria (>3 g/d) in more than 70% of cases. Hypertension, microscopic hematuria, and renal insufficiency are seen in 30–45% of presentations (Korbet 2002). In patients with primary FSGS, the onset of nephrotic syndrome is relatively sudden, occurring over weeks to months. In others, more indolent presentation is seen. In this group, non-nephrotic proteinuria, which gradually increases over months to years to nephrotic range, often associated with worsening renal function, is seen. Such patients generally do not develop full-blown nephrotic syndrome with hypoalbuminemia or edema. This presentation is typical of patients with secondary FSGS due to longstanding hypertension, morbid obesity, or reflux nephropathy or in the setting of a solitary kidney due to congenital dysplasia and loss of nephron mass (Kambham et al. 2001; Praga et al. 1999, 2001; Rennke and Klein 1989). The distinction between primary and secondary forms of FSGS is crucial as prognosis and therapy differ substantially.

The level of proteinuria has long been known to have prognostic significance in primary FSGS (Korbet 2002; Troyanov et al. 2005). Patients with non-nephrotic proteinuria have an extremely good prognosis with less than 15% progression to ESRD at 10 years, whereas >50% of patients with nephrotic-range proteinuria progress to ESRD over the same time period. In patients with massive proteinuria (> 10–14 g/d), the course is particularly malignant, resulting in

ESRD over an average of 2–3 years (Beaufils et al. 1978b; Cameron et al. 1978a; Korbet 1995; Velosa et al. 1983a).

In nephrotic adults with FSGS, several clinical and histologic features at biopsy are predictive of progression to ESRD. These include serum creatinine level >1.3 mg/dl, interstitial fibrosis >20%, and the presence of collapsing lesions (Schwartz et al. 1999a). Attainment of remission in nephrotic patients with FSGS is associated with a significantly reduced risk for progression to ESRD (>90% 10-year renal survival) compared with patients not attaining remission (<35% 10-year renal survival) (Chun et al. 2004; Stirling et al. 2005; Troyanov et al. 2005).

Secondary FSGS

Primary FSGS, defined as a primary podocytopathy, often presents with nephrotic syndrome in a patient with light microscopic findings of FSGS and EM findings of widespread foot process effacement without an obvious secondary cause. Secondary FSGS is mediated by a diverse group of insults directed to or inherited within the podocyte (Table 1). Drugs and viruses are among the more common causes of podocyte injury. Another form of FSGS, termed adaptive FSGS, is thought to result from structural and functional adaptations mediated by intrarenal vasodilation, increased glomerular capillary pressure, and plasma flow rates (Rennke and Klein 1989). These maladaptive responses may arise through a reduction in the number of functioning nephrons (unilateral agenesis, reflux nephropathy, surgical ablation, or low nephron endowment from premature birth) or conditions that place hemodynamic stress on initially normal nephron population (obesity, sickle cell, or cyanotic congenital heart disease).

Approximately 80% of cases of FSGS remain primary or idiopathic with the remaining 20% categorized as secondary (D'Agati et al. 2011). The distinction between primary and secondary forms of FSGS can be challenging. One helpful clue is the degree of foot process effacement on electron microscopy. In secondary forms of FSGS, the foot processes are relatively preserved or only focally effaced as compared to primary FSGS, where foot processes tend to be diffusely effaced, with little overlap between the two categories (D'Agati 1994; Deegens et al. 2008; Kambham et al. 2001). There are exceptions to this observation. Cases of collapsing FSGS secondary to HIV, interferon, or pamidronate are characterized by widespread foot process effacement on EM (Laurinavicius et al. 1999a; Markowitz et al. 2001). Another helpful clue is the degree of proteinuria. Patients who present with sub-nephrotic proteinuria (<3.5 g/24 h) or nephrotic-range proteinuria (>3.5 g/24 h) but without full-blown nephrotic syndrome (serum albumin <3.5 g/dL, hyperlipidemia, and edema) more likely have FSGS due to a secondary process (Praga et al. 1999). The slow appearance of proteinuria observed in secondary forms of FSGS

Table 1 Causes of secondary focal and segmental glomerulosclerosis

Hyperfiltration
Unilateral renal agenesis or hypoplasia
Renal ablation
Obesity
Reflux nephropathy
Loss of nephron mass
Oligomeganephronia
Infections
Human immunodeficiency virus (HIV) – associated nephropathy
Parvovirus B19
Simian virus 40
Hepatitis C virus
Cytomegalovirus
Epstein-Barr virus
Toxins
Heroin
Pamidronate
Lithium
Interferon α, β, and γ
Anabolic steroids
Anthracyclines
Ischemia
Atheroembolic disease
Renal artery stenosis
Malignant hypertension
Calcineurin inhibitors
Renal transplant rejection
Sickle cell anemia
Congenital cyanotic heart disease

may allow for compensatory mechanisms of protein loss as opposed to the sudden onset of proteinuria seen in primary forms.

Given the current epidemic of obesity, defined as body mass index (BMI) of >30, the recognition of renal diseases associated with obesity has gained significance. Obesity-related glomerulopathy (ORG) is morphologically defined as glomerulomegaly (mean glomerular diameter of ~230 μm compared to 168 μm in controls with primary FSGS) with or without FSGS (Kambham et al. 2001). The disease is more prevalent in the white population, has a lower incidence of nephrotic syndrome, and has a more indolent course. There is less podocyte foot process effacement on EM of patients with ORG than seen with primary FSGS. Obesity-related increases in glomerular filtration rate (GFR) with subsequent development of intraglomerular hypertension is the proposed pathogenic mechanism (Kasiske and Crosson 1986; Praga et al. 1995). Other risk factors include insulin resistance leading to increased transcapillary pressure gradient and increased synthesis of growth factors promoting glomerular hypertrophy (Juncos and Ito 1993; Verani 1992). There are also confounding factors contributed by obesity-related multi-organ involvement such as obstructive sleep apnea (OSA) and cardiovascular disease. Elevated plasma levels of leptin through upregulation of TGF-β1 in obesity may also predispose to glomerulosclerosis (Wolf et al. 1999). Weight reduction is an effective strategy in management of ORG (Fowler et al. 2009; Shen et al. 2010). In addition to weight reduction, angiotensin blockade has shown reno-protective effects (Praga et al. 1995). In a related fashion, the use of anabolic steroids has also been associated with the development of FSGS (Herlitz et al. 2010). The clinical course suggests a secondary FSGS resulting from a combination of post-adaptive glomerular changes driven by the increased lean body mass and potential direct nephrotoxic effects from anabolic steroids. Discontinuation of the anabolic steroids leads to weight loss which can stabilize and improve proteinuria (Herlitz et al. 2010).

Viruses can act on the podocyte either by direct infection or by release of inflammatory cytokines that interact with podocyte receptors. HIV-1 is the best studied virus known to directly infect the podocytes and tubular epithelial cells (Bruggeman et al. 2000). Podocytes become reservoirs for HIV-1 despite antiviral therapy and normalization of peripheral CD4 (Chen et al. 2011). HIV-associated nephropathy (HIVAN) is typically a collapsing FSGS and progresses rapidly to ESRD (Wyatt et al. 2008). Parvovirus B19 is another virus that can infect podocytes and tubular epithelial cells, leading to collapsing FSGS (Moudgil et al. 2001). Other viruses such as simian virus 40, cytomegalovirus, and Epstein-Barr virus are less well characterized (Li et al. 2002; Tomlinson et al. 2003).

Heroin is the first drug associated with FSGS, though the incidence of this drug-induced disease (known as heroin nephropathy) has fallen sharply in parallel with the increasing purity of modern street heroin (Friedman and Tao 1995). The bisphosphonate pamidronate, an osteoclast inhibitor used to reduce bone resorption in patients with myeloma and metastatic cancers, has been linked to the development of FSGS (Markowitz et al. 2001). Proteinuria and renal failure associated with pamidronate typically improve after withdrawal of the drug. Pamidronate has direct toxic effects on the actin cytoskeleton of osteoclasts with a similar proposed effect on podocyte cytoskeleton. All forms of interferon therapy, including interferon alpha (widely used to treat hepatitis C), interferon beta (indicated for multiple sclerosis), and interferon gamma (formerly used in idiopathic granulomatous disease and malignant osteopetrosis), have been reported to induce FSGS (Markowitz et al. 2010). The podocyte expresses receptors for interferon alpha and beta and expresses major histocompatibility complex class II antigen in response to interferon gamma, suggesting potential direct podocyte effect.

Genetic Causes of FSGS (Familial)

FSGS can be the renal manifestation of a variety of systemic diseases that are secondary to genetic syndromes (syndromal FSGS). Few such examples include Nail-Patella syndrome (*LMX1b* gene mutation), Frasier syndrome (*WT-1* gene mutation), and Fechtner syndrome (*nonmuscle myosin*

IIA gene mutation) (Rood et al. 2012). In these syndromal forms of FSGS, the extrarenal manifestations are most prominent and often diagnostic. In some, FSGS may be the only or the presenting manifestation, thus mimicking sporadic FSGS. Non-syndromal genetic FSGS refers to mutations in genes that encode proteins that play key roles in maintaining podocyte ultrastructure (Table 2) (Conlon et al. 1999; Faubert and Porush 1997; Pollak 2003). These mutations often lead to steroid-resistant nephrotic syndrome (SRNS). Features that should prompt a genetic investigation include a positive family history, early-onset disease, and steroid resistance.

FSGS caused by mutations in nephrin, podocin, *CD2AP*, *PLCε1*, and *MYO1E* is characterized by autosomal recessive pattern of inheritance and manifests mostly in childhood (Hinkes et al. 2007; Santin et al. 2011). Mutation in the *NPHS1* gene encoding for the transmembrane protein nephrin, a major component of the slit diaphragm, leads to a severe form of nephrotic syndrome, which often manifests in utero (Patrakka et al. 2000). Located on chromosome 19q13, nephrin

Table 2 Genetic causes of FSGS

	Gene	Gene product	Inheritance	Associated condition	Remarks
Non-syndromal FSGS	*NPHS1*	Nephrin	AR		Most common cause of CNS Finish type
	NPHS2	Podocin	AR		Most common cause of childhood SRNS
	PLCε1/NPHS3	PLCε1	AR		Associated with DMS
	CD2AP	CD2AP	AR		
	MYO1E	Non-muscle Myosin-1E	AR		
	TRPC6	TRPC6	AD		Non-nephrotic proteinuria, incomplete penetrance
	ACTN4	Alpha-actinin-4	AD		
	INF2	Formin	AD		Most common adult familial FSGS
Syndromal FSGS	*WT-1*	WT-1	AD	– Denys-Drash syndrome – Frasier syndrome	
	Mitochondrial tRNA leucine 1	tRNA(leu)	Maternal	MELAS syndrome	
	LAMB2	Laminin β2	AR	Pierson's syndrome	
	ITGB4	B4-integrin	AR	Epidermolysis bullosa	
	CD151	Tetraspanin	AR	Epidermolysis bullosa	
	SCARB	SCARB2/ LIMP-2	AR	Action myoclonus renal failure syndrome	
	LMX1b	LIM HboxTF1	AD	Nail-patella syndrome	
	Non-muscle myosin IIA	MYH9	AD	– Epstein syndrome – Alport syndrome – Sebastian syndrome – Fechtner syndrome	

AR autosomal recessive, *AD* autosomal dominant, *CNS* congenital nephrotic syndrome, *SRNS* steroid-resistant nephrotic syndrome, *DMS* diffuse mesangial sclerosis (modified with permission from Rood et al. (2012))

mutation has a high incidence in Finland (1 in 8200), often referred to as congenital nephrotic syndrome of the Finish type (Fuchshuber et al. 1996). It has a post-transplant recurrence rate of 25%, likely due to anti-nephrin antibodies (Benoit et al. 2010; Patrakka et al. 2002). Podocin mutation (*NPHS2* gene mutation located on chromosome 1q25-31) is the most common genetic cause of SRNS in Western European children (Boute et al. 2000). Compound heterozygous *NPHS2* mutation has been identified in adult-onset FSGS involving the podocin *R229Q* polymorphism (Machuca et al. 2009). Mutations in *α-actinin-4*, *TRPC6*, and *INF2* cause autosomal dominant FSGS, which present in adulthood and are often non-nephrotic (Lowik et al. 2008; Winn et al. 2005; Zenker et al. 2004). Genetic testing is recommended in all children with congenital nephrotic syndrome (nearly 100% have a mutation), children with familial and sporadic SRNS, and adults with a family history of FSGS with living related donor transplant and donor selection implications (Rood et al. 2012).

Clinical Course and Prognosis

Prior to 1980, primary FSGS in adults was a lesion that was thought to have such a poor prognosis; immunosuppressive treatment was generally not recommended (Beaufils et al. 1978b; Bolton et al. 1977; Cameron et al. 1978a; Jenis et al. 1974; Lim et al. 1974; Newman et al. 1976; Velosa et al. 1975). This was based on data from several different case series from 1974 to 1978, the majority of which demonstrated a complete remission rate with low-dose steroids of less than 20%. Because of this lackluster response to immunosuppressive therapy (low-dose steroids), nephrologists were appropriately reluctant to expose potentially harmful medications to patients with little benefit. This was highlighted in a study from 1987 in which only 42% of nephrotic adults with primary FSGS were treated with immunosuppressive medication (Pei et al. 1987b).

These early studies, however, were small cohort series without control groups. As more studies were completed, with more patients, and with use of higher dose and prolonged therapy with prednisone, it became evident that the prognosis was better than 20% and remissions approximated 50% with treatment (Agarwal et al. 1993a; Cattran and Rao 1998a; Chan et al. 1991a; Chun et al. 2004; Korbet et al. 1986a; Miyata et al. 1986; Nagai et al. 1994a; Pei et al. 1987b; Rydel et al. 1995b; Schwartz et al. 1999a), with some studies higher than 60% (Alexopoulos et al. 2000; Banfi et al. 1991; Shiiki and Dohi 2000). Even more clear was that the long-term prognosis of the patients who responded was far more encouraging than nonresponders, changing the culture of the nephrology community to favor immunosuppressive treatment for nephrotic patients with this lesion.

As the treatment era of FSGS commenced, the question of who has the highest risk of progression, and therefore who would be most appropriate to treat, became paramount. Similar to other glomerulonephropathies, the degree of proteinuria is a strong prognostic indicator for progression to end-stage renal disease (Beaufils et al. 1978a; Cameron et al. 1978b; Chun et al. 2004; Korbet et al. 1986b; Rydel et al. 1995a; Velosa et al. 1983b; Wehrmann et al. 1990) (Table 3). In observational studies, virtually all patients who present with massive proteinuria (>10 grams/day (g/d)) progress to ESRD within 5 years (Brown et al. 1978; Velosa et al. 1983b), but the prognosis improves with lesser degrees of proteinuria. In patients who present with >3.5 g/d, the progression to ESRD is nearly 50% over a 5–10-year period, and in those who have non-nephrotic proteinuria at presentation, it is close to 20% at 10 years (Beaufils et al. 1978a;

Table 3 Proposed definitions of response in proteinuria to therapy for patients with nephrotic -range proteinuria due to primary FSGS

Complete response: Reduction in proteinuria to <300 mg/day
Partial response: Reduction in proteinuria by ≥50% and to less than 3.5 g/day
Relapse: Reoccurrence of proteinuria to ≥3.5 g/day
Steroid dependence: Requirement of ongoing steroids to maintain complete or partial remission
Steroid resistance: Less than partial response to an adequate dose of steroids for at least 16 weeks

Cameron et al. 1978b; Chun et al. 2004; Korbet et al. 1986b; Rydel et al. 1995a; Velosa et al. 1983b). The presenting serum creatinine is another baseline variable that has been shown to be predictive of progression to ESRD in primary FSGS, with a cutoff of >1.3 mg/dl associated with poorer renal survival (Chan et al. 1991b, 2004; Korbet et al. 1986b; Rydel et al. 1995a; Wehrmann et al. 1990). Multivariate analysis of these baseline laboratory parameters, however, has revealed that only serum creatinine, as opposed to proteinuria, is independently predictive of a poor prognosis (Rydel et al. 1995a; Schwartz et al. 1999b; Velosa et al. 1983b; Wehrmann et al. 1990).

In adults, arterial hypertension has been linked to the progression of primary FSGS (Ponticelli et al. 1999a), similar to other glomerulopathies (Hunsicker et al. 2004; Lewis et al. 1999; Pohl et al. 2005). As there is a racial difference in the prevalence of this disease, with it being more common in black patients, some investigators have considered a racial difference in the prognosis (Tune et al. 1995; Waldo et al. 1992). Indeed, black patients tend to present with more proteinuria than whites, and therefore overall, the prognosis is worse, but when stratified by similar levels of proteinuria, there is no difference in the progression between black and white patients (Korbet et al. 1986b; Rydel et al. 1995a).

The last baseline feature that can affect prognosis is the pathology itself (Table 4).

Again, similar to other glomerulonephropathies, advanced tubulointerstitial fibrosis (>20%) is strongly associated with progression to ESRD (Chun et al. 2004; Ponticelli et al. 1999a; Rydel et al. 1995a; Schwartz et al. 1995a, 1999b). Given this, it is surprising that the proportion of focal or global sclerosis is not. Mesangial hypercellularity was associated with progressive renal failure in one study (Ponticelli et al. 1999a), as well as the coexistence of mesangial deposits of IgM and C3 (Zhang et al. 2016). Of all of the variants of primary FSGS, the cellular or collapsing lesion has been shown to have the poorest prognosis (Chun et al. 2004; Detwiler et al. 1994a; Haas et al. 1995b; Korbet and Schwartz 2001; Laurinavicius et al. 1999b; Schwartz et al. 1999b; Singh et al. 2000; Valeri et al. 1996a), and if the lesion is widespread, the prognosis is even more guarded. However, in a study by Chun et al. (2004), a 64% remission rate was noted in the patients with the collapsing lesion, which was attributed to less advanced clinical and histologic disease. Importantly, Chun et al. (2004) reported a 92% remission rate with treatment when the collapsing lesions were in <20% of glomeruli. This was recently confirmed in another study where the collapsing lesion was compared to the not otherwise specified lesion, and after controlling for immunosuppressive treatment, the renal prognosis was similar (Laurin et al. 2016a). Finally, the tip lesion has the most favorable prognosis (Cameron 1996; Howie and Brewer 1985) with the highest response rate to treatment (Cameron 1996; Chun et al. 2004; Schwartz et al. 1995a; Schwartz and Korbet 1993a) (Table 5).

Irrespective of the classification of the lesion, the single most favorable predictive factor over time is achieving a remission (Cattran and Rao 1998b; Chun et al. 2004; Pei et al. 1987a; Ponticelli et al. 1999a; Rydel et al. 1995a; Schwartz et al. 1999b). In patients who are nephrotic at baseline, only 15% will progress

Table 4 Features associated with a poor prognosis in primary FSGS

Clinical	Histologic
Nephrotic range proteinuria	Cellular/collapsing lesion
Serum creatinine >1.3 mg/dl	Tubulointerstitial fibrosis/atrophy
Lack of complete or partial remission	Mesangial proliferation
Hypertension	Mesangial IgM and C3 deposits

Table 5 Likelihood of progression to ESRD based on histologic variant

Variant	Percent of progression to ESRD
Collapsing/cellular	35–75
Tip	20
Perihilar	30
Classic (NOS)	30

to ESRD if a complete remission (defined as proteinuria <0.3 g/d) occurs. A partial remission (variably defined as proteinuria >0.3–0.5 g/d but less than 2–3 g/d, or as a ≥50% decrease in proteinuria) is also predictive of a better outcome compared to patients who remain persistently nephrotic (Banfi et al. 1991; Chun et al. 2004; Korbet et al. 1994; Korbet and Schwartz 2001; Pei et al. 1987a; Wehrmann et al. 1990). Approximately half of the patients with nephrotic range proteinuria who do not achieve a partial or complete remission will progress to ESRD within 5 years. This underscores the importance of active treatment. Unfortunately, spontaneous remissions are rare, occurring in 5–23% of nephrotic patients with primary FSGS (Lewis 1982; Meyrier 1999; Pinn-Wiggins 1987; Weiss et al. 1986a), but occur more frequently in certain clinicopathologic settings, such as the tip lesion, preserved renal function, and/or lower grades of proteinuria. Therefore, since the late 1980s, nephrotic patients with primary FSGS have historically been treated initially with prednisone and, because of it, are up to ten times more likely to achieve a remission compared to untreated patients. However, since no clinical or histologic features can reliably predict outcome in nephrotic patients with primary FSGS, the response to steroids is still the best clinical indicator of outcome (Haas 2005; Korbet 2012).

Treatment

The single most important decision prior to undergoing immunosuppressive therapy is to ensure the patient has primary, as opposed to secondary FSGS or focal and global sclerosis, both of which have different prognoses and treatments (Sethi et al. 2014, 2015). The current treatment of the latter two is conservative care for chronic kidney disease as well as treating the underlying cause (see below). As mentioned above, primary FSGS is a clinicopathologic diagnosis of exclusion, and secondary causes must be ruled out. In the absence of secondary causes, primary FSGS can be diagnosed, and the biopsy will typically feature diffuse foot process effacement (> 80%) on electron microscopy (Sethi et al. 2014).

Conservative Care

Regardless of the degree of proteinuria, severity of chronic kidney disease, or defining FSGS as primary or secondary, conservative care is an important initial and continual therapy throughout the course of the disease (Fig. 5). This consists of optimal blood pressure control along with the use of agents which block the renin-angiotensin aldosterone axis (RAAS), such as angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). In patients who either become or remain non-nephrotic after 6 months of conservative therapy, this remains the ongoing therapy (Korbet 2012), as achieving even a partial remission has been shown to improve renal survival from 80% to 40% compared to no remission (Troyanov et al. 2005). Blockade of the RAAS should therefore be considered standard; however, it may be held or delayed if the nephrotic syndrome is severe, as acute tubular necrosis may occur (Jennette and Falk 1990; Praga et al. 1989).

While the chronic use of ACEi or ARB in FSGS with the nephrotic syndrome is renoprotective by nature of lowering proteinuria and slowing the progressive renal insufficiency (Maschio et al. 1996; Praga et al. 1992; Ruggenenti et al. 2000; The GISEN Group 1997; Troyanov et al. 2005), it is unusual that this therapy alone will induce a complete or partial remission (Korbet 2003a). Furthermore, spontaneous remissions are rare in nephrotic patients with FSGS. When prednisone is added to conservative therapy for nephrotic patients with FSGS, the likelihood of remission significantly increases (Schwartz et al. 1999b; Troyanov et al. 2005). Therefore, although a trial of conservative therapy alone could be considered, the recommendation is that immunosuppressive therapy should be added if a patient is nephrotic. If the patient has complications from the nephrotic syndrome and has acute kidney injury from the glomerular disease or if the nephrotic syndrome is severe, then the immunosuppressive therapy should begin immediately.

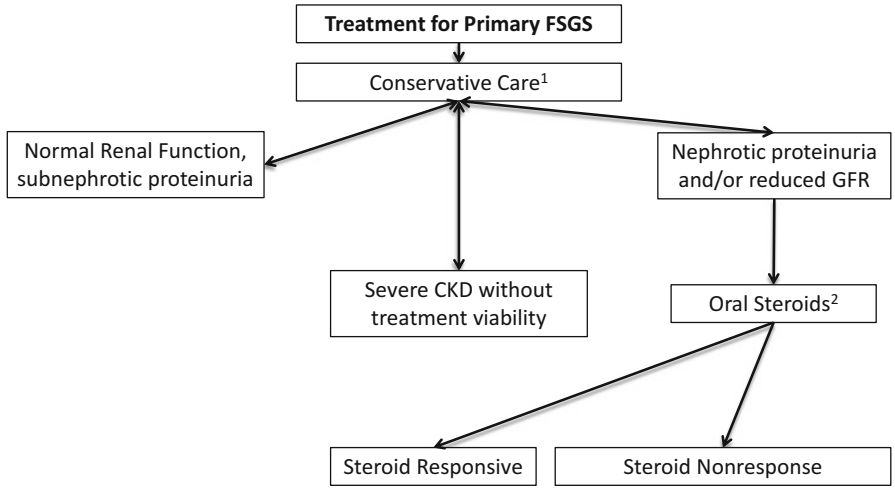

Fig. 5 Treatment for primary FSGS. [1]Blood pressure control to goal 120–140/80–90, use of ACEi or ARB, control of symptoms of nephrotic syndrome (such as edema) if present. [2]Prednisone 1 mg/kg daily (80 mg maximum) or 2 mg/kg (maximum 120 mg) alternate day x at least 4 weeks up to 16 weeks until complete remission. Slow taper over 6 months once remission achieved. *FSGS* focal segmental glomerulosclerosis, *CKD* chronic kidney disease, *GFR* glomerular filtration rate

Other therapy for the nephrotic syndrome should be used, including symptomatic treatment of edema with sodium and fluid restriction and/or diuretics and anti-lipid therapy as indicated (Anon 2012a). The role for prophylactic anticoagulation has not been studied specifically for FSGS and remains controversial (Glassock 2007).

Primary FSGS

Initial Immunosuppressive Treatment

The initial immunosuppressive therapy for nephrotic adults with primary FSGS has most often consisted of high-dose steroids alone (Fernandez-Juarez et al. 2016) (Fig. 5). The standard treatment regimen is oral prednisone at a dose of 1 mg/kg/day for 2–3 months with an additional of 4-month taper (Anon 2012c; Cattran and Rao 1998b; Korbet 2012; Ponticelli et al. 1999a; Stirling et al. 2005). Using this approach, the proteinuria typically decreases gradually over 1–2 months, but can take more time, up to 4–6 months, for remission (Cattran and Rao 1998b; Ponticelli et al. 1999a; Rydel et al. 1995a; Stirling et al. 2005). This extended course of steroids, contrasted to treatment of minimal change disease, is often necessary to achieve remission. In one study of primary FSGS, patients receiving steroids for >16 weeks had a 61% remission rate compared to 15% remission rate for those receiving ≤ 16 weeks (Ponticelli et al. 1999a). Rydel et al. (1995a) also found that patients who entered a remission had received a prolonged course of high-dose steroids (average 3 months) with a total treatment duration of 5 months (including taper) compared to those who received a shorter course (1-month high dose with 3-month taper). There is a limit, however, to how long the course should be. Cattran and Rao (1998b) found that if a patient had not responded by 6 months, additional treatment was not beneficial. Therefore, in primary FSGS, the definition of steroid resistance should be defined by the persistence of nephrotic proteinuria only after a more prolonged course (4-month course of prednisone at 1 mg/kg/day) (Meyrier et al. 1994b). Another group of investigators evaluated the addition of cytotoxic agent to prednisone as the first-line

therapy, but this did not improve the overall remission rate (Banfi et al. 1991). Most of the dismal remission rates prior to the 1980s were in part due to lack of prolonged therapy with prednisone (Korbet 2003b), and with the extended course, overall remission rates with prednisone as first-line therapy are now 47–66%, with complete remission rates of 32–47% and partial remission rates of 19–29% (Agarwal et al. 1993b; Cattran and Rao 1998b; Chun et al. 2004; Ponticelli et al. 1999a; Stirling et al. 2005).

In order to minimize the potential toxicity of long-term high-dose daily steroids, some investigators have evaluated alternate-day high-dose steroids or steroid sparing/minimizing regimens. One study assessed the use of higher-dose alternate-day steroids (120 mg every other day) for 3–5 months in patients with FSGS who were over the age of 60 and attained a complete remission rate of 44% (Nagai et al. 1994b). Mycophenolate mofetil (MMF) has also been used as initial add-on therapy in order to minimize steroid exposure. In one small study, 33 patients were randomized to receive MMF 1 g twice daily for 6 months along with 0.5 mg/kg/d prednisone for 2–3 months compared to the standard of prednisone 1 mg/kg/d for 5 months. Patients in both groups had equal remission and relapse rates, with the former demonstrating less steroid exposure (Nayagam et al. 2008). Lastly, calcineurin inhibitors (CNI) and azathioprine have been evaluated as initial therapy. In one retrospective study, patients received oral prednisone alone (1 mg/kg/d) for 4 months, or low-dose prednisone (0.5 mg/kg/d) combined with cyclosporine (CSA) or azathioprine. Similar remission rates were achieved: prednisone alone, 63%; prednisone plus azathioprine, 80%; and prednisone plus CSA, 86% (Goumenos et al. 2006). In another retrospective analysis, CNIs, with or without glucocorticoids, were not inferior to treatment with glucocorticoids alone, and importantly, all treatment groups showed improved renal outcomes compared to no treatment (Laurin et al. 2016b). Tacrolimus has also been used in a small group of patients with success (Duncan et al. 2004). Thus, in addition to conservative treatment, first-line treatment of primary FSGS with immunosuppression is important to increase the likelihood of sustained remission, but no regimen has been proven to be superior to steroids alone.

Treatment of Relapsing FSGS

In patients who achieve a complete remission with steroids, relapse of the nephrotic syndrome occurs in approximately 33% of the patients but occurs in more than 50% of those who only attain a partial remission (Cattran and Rao 1998a; Pei et al. 1987b; Troyanov et al. 2005). The relapse may occur at variable intervals, from a range of 20 to 36 months when evaluated in studies (Cattran and Rao 1998a; Pei et al. 1987b; Troyanov et al. 2005). The renal survival is best for those patients who achieve a remission and never relapse; however, those who experience a relapse still have a better prognosis than the patients who never achieved a remission. Furthermore, achieving another remission after a relapse leads to a better renal outcome than not (Troyanov et al. 2005). Thus, achieving an initial remission is important, but achieving and maintaining the remission, even in the event of a relapse, is the ultimate objective.

Treatment of relapsing FSGS (Fig. 6) is comparable to that of relapsing minimal change disease (Anon 2012b, c; Korbet 2012). A repeat course of steroids, with a slower taper is one option, as is adding cytotoxic agents or CNIs with or without steroids. Similar to minimal change disease, the response to a relapse for steroid sensitive patients is good, with remission rates of up to 80% (Korbet 2012).

When considering treatment with CNIs or cytotoxic agents such as cyclophosphamide, the main concerns are potential side effects of the therapy as well as which one may more likely lead to a sustained remission. Similar to other relapsing nephrotic syndromes such as minimal change disease (2012b) or membranous lupus nephritis (Austin et al. 2009), cyclophosphamide provides equal remission rates with less chance of relapse compared to CSA. In frequently relapsing steroid-sensitive nephrotic syndrome, Ponticelli et al. (1993a)

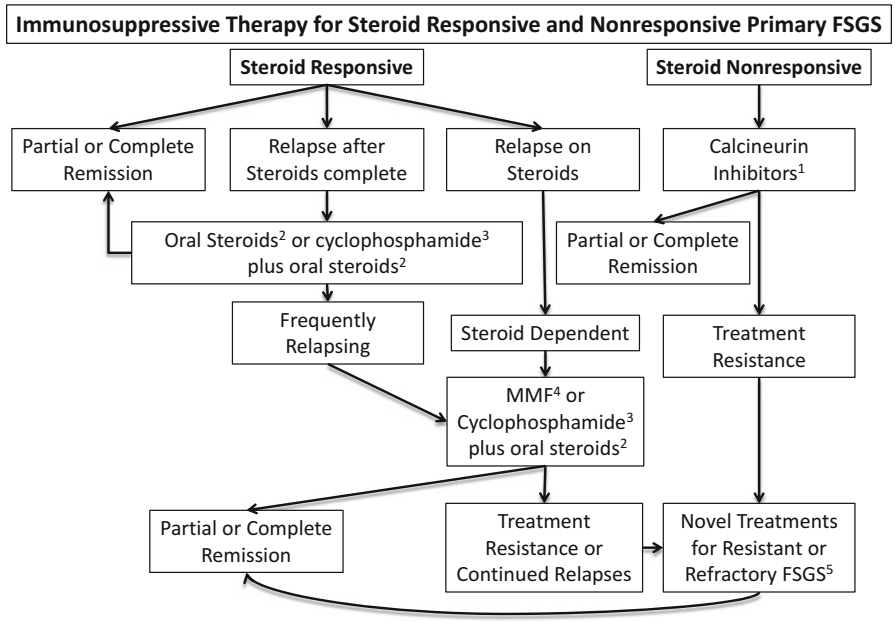

Fig. 6 Immunosuppressive therapy for steroid-responsive and steroid-nonresponsive primary FSGS. [1]Cyclosporine 3–5 mg/kg/day or tacrolimus 0.1–0.2 mg/kg/d in divided doses for 4–6 months with or without low-dose prednisone (0.15 mg/kg/d), followed by slow taper if remission achieved. Alkylating agents or mycophenolate mofetil can also be used. [2]Prednisone 1 mg/kg daily (80 mg maximum) or 2 mg/kg (maximum 120 mg) alternate day x at least 4 weeks up to 16 weeks until complete remission. Slow taper over 6 months once remission achieved. [3]Cyclophosphamide oral 2 mg/kg for 2 months. [4]MMF, mycophenolate mofetil 1000 mg oral twice daily for 6 months. [5]Pulse dexamethasone, rituximab, oral galactose, adrenocorticotropic hormone, abatacept, immunoadsorption columns, low-density lipoprotein apheresis, plasmapheresis. *FSGS* focal segmental glomerulosclerosis

randomized 66 patients to receive oral cyclophosphamide (2.5 mg/kg/d for 2 months) or CSA (5–6 mg/kg/d in two divided doses for 9 months). At the end of 9 months, the rates of relapses were similar (cyclophosphamide, 33%; CSA, 25%). However, when followed out 2 years, 75% of patients who received CSA had relapsed, while only 37% relapsed if cyclophosphamide was used. Keeping patients on CSA for longer courses is a way to avoid a relapse and achieve sustained remission as well as avoiding possible toxicity from cyclophosphamide, but the downside is depending on long-term CSA and developing potential nephrotoxicity (Meyrier et al. 1994a; Tostivint et al. 2007). Lastly, MMF has been studied in small nonrandomized studies (Day et al. 2002; Mendizabal et al. 2005) and has been associated with a benefit. However, relapse with MMF can also occur upon tapering (Day et al. 2002; Mendizabal et al. 2005; Ponticelli and Graziani 2013).

Treatment of Steroid-Resistant FSGS

Steroid therapy, even when the high dose is extended to 16 weeks, still fails to induce remission in up to 50% of cases (Agarwal et al. 1993a; Cattran and Rao 1998a; Chun et al. 2004; Ponticelli et al. 1999b; Stirling et al. 2005). Those that have not responded remain at high risk of progression to ESRD. Options for treatment (Fig. 6) include CNIs with or without low-dose prednisone, or agents such as MMF, and if these fail, novel therapies can be given.

Of all the options, CSA is the most effective agent to induce a remission for adults with steroid-resistant FSGS. Two randomized controlled trials have evaluated CSA for these patients. In 1993, Ponticelli et al. (1993b) randomly assigned 45 patients to receive CSA (5 mg/kg/day for adults and 6 mg/kg/day for children) without

steroids vs. supportive care for 6 months, with a taper of 25% of the dose by 2 months until discontinuation. With this regimen, complete remission was 21% and partial was 36%, compared to 0% and 16% in the control group. Later, Cattran et al. (Cattran et al. 1999) randomized 49 adults with steroid resistance to CSA (3.5 mg/kg/day in two divided doses titrated to a 12 h trough level of 125–225 μg/L) with low-dose prednisone (0.15 mg/kg/d) or placebo for 6 months with a 1-month taper. With this regimen, complete remission was 12% and partial was 57%, compared to 0% and 4% in the placebo group. This remission, however, was not sustained. By 1 year, 75% and 60% of the patients in the respective studies had relapsed. Despite the relapses, the renal survival for patients taking CSA for 6 months was still better, as half of the patients in the placebo group experienced a 50% decline in renal function at 4 years compared to 25% or the patients who were randomized to CSA.

Because of these two landmark trials, a 6-month course of CSA, with or without low-dose prednisone, is considered standard first-line therapy for patients with steroid resistance (2012c). Due to the high rate of relapse after CSA discontinuation, it is recommended that, if a complete or partial response is achieved, CSA be continued for at least 1 year followed by a gradual taper but discontinued at 6 months if no response is evident (2012c). Because CSA can be continued long term or even indefinitely in some patients, trying to minimize or prevent CSA nephrotoxicity is essential. Meyrier et al. (1994a) performed surveillance biopsies in a group of patients with steroid-dependent or steroid-resistant nephrotic syndrome and CSA exposure for 1 year. Based on the nephropathology, CSA toxicity was limited when the dose was $<$5.5 mg/kg/d. CSA nephrotoxicity also occurs in patients without primary kidney disease. In patients treated with CSA for uveitis, the nephrotoxicity has been shown to be worse in those receiving $>$3 mg/kg/d (Korbet 2012). The serum creatinine increased by 0.11 mg/dl for 100 mg of CSA per day. Although this increase in serum creatinine was reversible, there was an irreversible GFR loss (3.3 ml/min/1.73 m^2) noted if the cumulative dose of CSA was over 100 g (Tostivint et al. 2007). Therefore, to maintain remission and minimize the potential for CSA nephrotoxicity, once a complete remission has been achieved, the CSA dose should be slowly tapered by 0.5 mg/kg/month to the lowest effective dose (Cattran et al. 2007). After remission is maintained for 1–2 years with low-dose CSA, an attempt to taper CSA completely is recommended. If no response to CSA has occurred by 6 months of treatment (defined by $\geq$50% reduction in baseline proteinuria), alternative therapy should be considered.

Due to the risk of nephrotoxicity and high relapse rate associated with CSA, a prospective randomized controlled trial was conducted comparing alternate-day prednisone with either CSA or MMF plus pulse dexamethasone for patients (age 2–40 years) with steroid-resistant nephrotic syndrome. In the 138 patients who were randomized, there was no difference in complete and partial remission rates (CSA, 44%; MMF, 33%) (Gipson et al. 2011).

What options exist when CSA has failed or led to dependence (Fig. 5)? Segarra et al. (2002) found that in CSA-dependent or CSA-resistant FSGS patients, use of another CNI, tacrolimus, improved remissions by 15%. In those patients who were initially CSA responsive, the remission rate was 83%. Not surprisingly, perhaps as a class effect, the relapse rate was high: 76% within 4 months after discontinuing tacrolimus. MMF has also been evaluated in steroid-resistant and CSA-resistant FSGS. Cattran et al. (2004) assessed MMF at a dose of 1 g twice daily for 6 months in 18 nephrotic patients, most of whom had failed cyclophosphamide and/or CSA. Although no patient achieved a complete remission, partial remissions were 44%. In addition, Segarra et al. (2007) studied MMF as rescue therapy in resistant patients and found that a complete or partial remission was achieved in 54%, confirming that MMF has utility in resistant patients. Other novel therapies have been evaluated in case reports and small case series with varying results. These include pulse dexamethasone, rituximab, oral galactose, sirolimus, adrenocorticotropic hormone, abatacept,

immunoadsorption columns, low-density lipoprotein apheresis, and plasmapheresis, but there is too little experience to recommend any of them for widespread use.

Treatment of Secondary FSGS

Secondary FSGS is important to differentiate from primary FSGS as there are treatment implications. Secondary FSGS is typically an adaptive lesion and features glomerular hypertension as the primary pathogenic process. This secondary hyperfiltration and FSGS can be seen in nephron loss from vesicoureteral reflux, congenital diseases, or surgical interventions or can also be seen in biopsies with residual scarring from prior segmental necrotizing lesions, such as vasculitis or IgA nephropathy. It can also be secondary to podocyte toxins, such as HIV, parvovirus B-19, or medications (e.g., pamidronate).

With hyperfiltration injury, the therapy involves treating the underlying process as well as conservative care with blood pressure control and use of ACE-I or ARB. As an example, in obesity-related glomerulopathy, which features glomerulomegaly often with segmental scars, treatment with ACE-I and weight loss have both been shown to reduce proteinuria and achieve sustained remissions (Shen et al. 2010). Exposure to anabolic steroids can also lead to the development of proteinuria from secondary FSGS (Herlitz et al. 2010). Once the drugs are discontinued, there is an associated weight loss, stabilization, and/or improvement in proteinuria and stabilization of GFR. Interestingly, repeat exposure to anabolic steroids has led to relapse of proteinuria (Herlitz et al. 2010), supporting the role of androgens in the pathogenesis of this lesion and highlighting the importance of determining and treating the underlying cause.

Although there are no randomized controlled trials of treatment of underlying HIV infection in the setting of HIV-associated nephropathy (HIVAN), observational studies show that there is improvement in proteinuria and GFR with use of antiretroviral therapy (ART) (Atta et al. 2006; Cosgrove et al. 2002; Szczech et al. 2004) and ACE-I (Wei et al. 2003). Steroids for HIVAN can be considered (Eustace et al. 2000; Smith et al. 1996) if interstitial nephritis is present or if the nephropathy is progressing despite the use of ART and ACE-i. The routine use of steroids however is controversial due to the infectious risk. Now, in the ART era, the collapsing lesion seen with HIVAN is less commonly found compared to the classic FSGS lesion (Lescure et al. 2012), and immune complex-mediated GN as well as nephrotoxicity as a side effect from medications is becoming more prevalent (Kumar and Perazella 2014). Thus, medication reconciliation is crucial in the overall management of a patient with HIV-related renal disease.

Familial FSGS in the setting of childhood nephrotic syndrome, due to a variety of different mutations described above, has proven to be elusive in finding successful therapies. Patients with these mutations typically present in childhood with steroid-resistant nephrotic syndrome, and remissions remain dismal after treatment with CSA (Buscher et al. 2016). Thus, treatment with immunosuppression is not warranted. Fortunately, as opposed to primary FSGS, the likelihood of recurrence once transplanted is very low (Rood et al. 2012).

Ultimately, the focus of secondary FSGS includes identifying the underlying cause and treating it when possible, as well as conservative management with blood pressure control and use of ACE-I or ARB for hyperfiltration and chronic kidney disease.

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Focal Segmental Glomerulosclerosis, Pediatric

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Abstract

Focal segmental glomerulosclerosis (FSGS) is an important diagnostic finding in kidney biopsies from patients with proteinuric kidney diseases. Its presence often heralds a relentlessly progressive loss of kidney function over time. An effective treatment is not possible in all, or even most, cases. Advances in our understanding of the causes of this pathological lesion, thought to be based on pathology of the glomerular visceral epithelial cell (the podocyte), may eventually lead to more specific and less toxic treatment for patients having this form of renal pathology.

Keywords

Podocyte · Sclerosis · Glomerulus · Proteinuria

Introduction

Focal segmental glomerulosclerosis (FSGS) is a finding on kidney biopsy of sclerosis of portions of some, but not all, glomeruli. FSGS is a pathological finding often seen in progressive proteinuric glomerular diseases and is ultimately the result of podocyte loss from the glomerular tuft. Thus, FSGS is a finding common to a number of podocyte-associated glomerulopathies, diseases reflecting podocyte dysfunction (causing proteinuria) and podocyte loss (causing sclerosis). Some variants (collapsing FSGS) may involve dysregulated proliferation of podocytes.

The pathological entity FSGS has a significant overlap with, but is not identical to, the clinical entity of steroid-resistant nephrotic syndrome (SRNS). Classically, FSGS has been categorized as primary FSGS or secondary FSGS, based on the presumed etiology. This distinction both obscures and somewhat undervalues our current understanding of the mechanisms of podocyte injury and should therefore be eschewed in any systematic exploration of FSGS. Instead, three broad categories of mechanisms can be considered to cover the majority of cases: genetic, immune-related signaling, and hemodynamic. All these forms share the features of podocyte dysfunction and/or loss. The particular mechanism involved may suggest the most appropriate therapy. This chapter will review the epidemiology of FSGS, highlight the clinical features and disease outcomes, explore the pathology and proposed pathogenic mechanisms, and discuss treatment regimens for SRNS.

Epidemiology of FSGS in Children

Due to its rarity, the incidence of FSGS is quite hard to establish, particularly in pediatrics. Because there are no noninvasive markers of FSGS, estimates of its prevalence in pediatric NS are based solely on biopsy findings. An early population-based study showed an incidence of "lipoid nephrosis" on biopsy of 1.5 per 100,000 per year in 10–20-year-olds (Simon et al. 1994). This presumably sets an upper limit on the incidence of FSGS, as it likely contained cases of minimal change disease as well. Studies in the 1970–1980s, including reports from the International Study of Kidney Disease in Children (ISKDC) and the Southwest Pediatric Nephrology Study Group (SPNSG), suggested that FSGS represents a small fraction of nephrotic syndrome (NS) cases. The ISKDC recruited 521 patients from 4 continents at time of presentation of NS, and kidney biopsy before treatment was initiated (ISKDC 1978). The ISKDC patients were not selected for biopsy on the basis of their failure to respond to a course of oral steroids, as is the usual practice today. The study found 7% of NS patients had FSGS compared with 77% with minimal change disease (MCD). Of note, the study included patients referred to participating sites,

and thus the results are not entirely generalizable to the overall NS population. Similar to ISKDC findings, the SPNSG found a prevalence of FSGS of 7.1% in 1031 biopsies (SPNSG 1985).

There is evidence that the incidence of FSGS has been increasing over time, from ~7% of biopsied NS cases in ISKDC and SPNSG to 23% in the 1980–1990s (Srivastava et al. 1999). In another population-based study of almost 300,000 children with idiopathic NS covering 17 years (1985–2002), there was a significant rise in the percentage of those having FSGS on biopsy from the first half (10.8%) to the second half (24.7%) of the study period; both were greater than the incidence found by the 1978 ISKDC and 1985 SPNSG studies (Filler et al. 2003). An informal meta-analysis has suggested about a doubling of the incidence (based on percentage of cases of nephrotic syndrome or percentage of biopsies) over the last three decades (Borges et al. 2007). Other studies have showed no secular change in FSGS incidence, but probably a greater frequency of steroid resistance among patients with FSGS (Banaszak and Banaszak 2012; Boyer et al. 2007).

Changes in biopsy practices are hard to exclude as a factor impacting the prevalence of FSGS found on biopsy. Only the ISKDC population was biopsied without any prior treatment (thus representing a relatively unselected population) (Churg et al. 1970). Thus, any recent estimates of FSGS incidence based solely on biopsy results may demonstrate selection bias for those patients with steroid-resistant disease. For example, a study of 152 patients recruited at time of NS presentation found that 31% did not undergo biopsy given a positive response to steroids and no or few relapses; of those who underwent biopsy, 31% had FSGS (Bonilla-Felix et al. 1999). Nonetheless, adult studies have similarly found an increase in FSGS incidence over time (Haas et al. 1995). As discussed below, the risk for renal decline in FSGS underlines the significance of a rise in disease incidence for public health.

There appear to be racial differences in FSGS incidence, although these are difficult to precisely define because of differing representations of different racial groups in various studies; the risk is probably greater in African-American children, while the relative risk for Hispanic children is still unclear. The lifetime risk of FSGS overall may be only about 0.24% (Kitiyakara et al. 2004), but clearly shows racial differences. As discussed later in this chapter, the discovery of the apolipoprotein L1 (*APOL1)* high-risk genotype in individuals with African ancestry may explain the ethnic disparities in the disease outcomes. Additionally, the incidence of FSGS is greater in adolescents compared to younger children (Boyer et al. 2007; Hogg et al. 2007).

Statistics on end-stage kidney failure (ESRD) prevalence have been detailed by the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), a multicenter prospective study that has been collecting data on end-stage kidney disease in children since 1987 (Alexander et al. 1990). The first report covering 761 transplants in 754 patients, published in a 1989 report, found end-stage kidney disease due to FSGS as the third most common indication for kidney transplant (Alexander et al. 1990). FSGS was the primary diagnosis in 12% of transplant recipients and was greater for older children: 12% at 13–17 years as compared to 9% at 2–5 years. The most recent report, published in 2010, now encompassed data from 11,603 kidney transplants in 10,632 patients (Smith et al. 2013). Despite 20 years of new patient additions to the registry, FSGS remained the third most common primary diagnosis for ESRD at 11.7%, behind renal dysplasia at 15.8% and obstructive uropathy at 15.3%. Similarly, FSGS as a primary diagnosis again increased with patient age. In adults, review of data from the United States Renal Data Services indicates FSGS is the most common glomerulopathy associated with ESRD (Kitiyakara et al. 2003), consistent with pediatric studies.

Clinical Presentation and Features

FSGS results in proteinuria, and many patients can present with nephrotic syndrome (NS) – the clinical presentation of heavy proteinuria, hypoalbuminemia, and edema. Patients with FSGS have substantial morbidity and mortality,

including a high incidence of progression to end-stage kidney failure and a risk of disease recurrence after kidney transplantation. While FSGS is treated as a single clinical entity, there is in fact a heterogeneous collection of etiologies that eventually result in the FSGS lesion. Over the past several decades, significant research has been dedicated to discovering the molecular mechanisms underlying FSGS, and defining clinical classifications that would permit personalization of prognosis and optimization of therapeutic regimens.

As noted above, studies have revealed that children with FSGS are more likely to present later and with resistance to corticosteroids. The ISKDC found a later age of onset for FSGS, with 50% of children presenting after age 6 versus only 20% of MCD patients with disease onset after this age (ISKDC 1978). Steroid responsiveness as a metric for NS disease classification was recognized from the 1981 report of the ISKDC. The ISKDC reported that 78% of NS patients had clinical remission by 8 weeks of steroid therapy (ISKDC 1981). Seventy percent of FSGS patients did not respond to steroid therapy. Currently, it is well accepted that most FSGS falls into the subset of steroid-resistant NS (SRNS). However, it cannot be assumed that all SRNS is FSGS, as SRNS encompasses other pathological diagnoses such as MCD, membranoproliferative glomerulonephritis (MPGN), and membranous nephropathy (MN).

Outcomes

Children with FSGS can develop a progressive decline in kidney function. A review of the Toronto Glomerulonephritis registry suggested that children with FSGS (not steroid responsive) have a renal survival rate of 60% at 10 years (Cattran and Rao 1998). Additional studies of children with SRNS (either due to minimal change disease or to FSGS) from different populations have found a similar rate of renal survival (60–80%) at 10 years (Martinelli et al. 2001; Mekahli et al. 2009; Paik et al. 2007; Trautmann et al. 2017). As discussed below, other than response to therapy, which predicts outcome in multiple studies, additional factors predicting the risk of kidney functional decline are not well established.

The high morbidity associated with FSGS has prompted a search for factors predictive of disease progression. Analysis of a single cohort of children with biopsy-proven FSGS identified age, serum creatinine, hematuria, and percentage of global sclerosis as factors predicting development of chronic kidney disease (CKD) (Abrantes et al. 2006). However, the best current predictor of progression of kidney disease is remission of proteinuria, which has been confirmed as a prognostic marker in several studies. Renal survival at 3 years can be seen in up to 90% who achieve complete or partial remission, whereas 50% of those who do not achieve remission have progression of CKD (Gipson et al. 2006). Recent analysis of the PodoNet international registry showed that 10-year renal survival for SRNS was 94% for those achieving complete remission in the first year and 72% for those achieving partial remission, but 43% for those with multidrug resistance (Trautmann et al. 2017). Partial remission itself is predictive of renal survival in adults, although those who relapse may have a more rapid rate of renal decline than those without relapse (Troyanov et al. 2005). In addition to remission status, ethnicity is increasingly recognized as a risk factor for renal functional decline. African-American (AA) ethnicity, as compared with non-AA ethnicity, was demonstrated to show increased risk and worse outcome for children with FSGS (Ingulli and Tejani 1991; Sorof et al. 1998). More recently, morphometry from diagnostic biopsies in a cohort of patients with primary proteinuric glomerulopathies has been strongly associated with change in eGFR, suggesting that morphometric analysis may potentially play a future role in estimating risk of renal functional decline (Lemley et al. 2016).

Pathology

The biopsy appearance of FSGS is variable. It was first described in children (Rich 1957). Characteristic (and required for the biopsy diagnosis) is the

presence of segmental sclerotic lesions including capillary obliteration and often intracapillary PAS-positive hyaline deposition. Early on, these are both focal (found in only some glomeruli) and segmental (affecting only part of the glomerular capillary tuft). Also quite typical are various changes in the podocytes (vacuolization, microvillous transformation, protein reabsorption droplets, foot process effacement, condensation of cytoskeletal filaments in the bases of the foot processes); hyperplasia of podocytes on the glomerular basement membrane (GBM), sometimes called a "cap," or conversely patches of bare GBM without any podocyte cover (or sometimes a "halo" of detached podocytes over multilayered, new loose GBM-like material); wrinkling of the GBM; intracapillary foam cells; some degree of mesangial expansion or hypercellularity; and/or synechiae or adhesions of the tuft to the overlying parietal cell layer of Bowman's capsule. The immunofluorescence examination is generally negative or shows (what appears to be) nonspecific or passive mesangial deposition of small amounts of IgM or C3.

Interstitial fibrosis and tubular atrophy (IFTA) may be present to varying degrees for more advanced or more severe cases of FSGS. Foam cells may be present in the interstitium. The presence of IFTA in a biopsy without obvious segmental sclerotic lesions is suggestive of "missed FSGS," since this strongly suggests the obliteration of glomeruli with subsequent atrophy of the attached tubules. Given the segmental presence of glomerular sclerosis, with lesions making up as little at 5–10% of the capillary tuft volume (Remuzzi et al. 1990), the chances of missing involved parts of a given glomerulus with a single sampling section are quite high. The estimated incidence of segmental lesions based on single section may be one third or less of the actual incidence (Remuzzi et al. 1995). Vascular changes are usually associated with hypertension as a secondary phenomenon.

The most commonly used classification system for FSGS is the Columbia classification (D'Agati 2003; D'Agati et al. 2004). In this scheme, five different morphological variants are distinguished: cellular, perihilar, tip, collapsing, and not-otherwise-specified (NOS). There is a general association of morphologic type with outcome (with respect to remission on therapy and loss of renal function), with tip lesions (more common among white patients) having the best overall outcomes and collapsing lesions (more common among African-American patients) having the worst outcomes.

The five Columbia variants are partly defined by exclusion among each other. The most common variant is the **not-otherwise-specified** (NOS) variant, also known as classical FSGS; it shows the required features of a segmentally sclerotic lesion, but lacks the defining characteristics of the other variants. It is thought that several of the other forms may "evolve" toward the NOS variant with time. The **perihilar** variant requires perihilar sclerosis or hyalinosis in >50% of the involved glomeruli. It excludes findings of the remaining variants. Glomerulomegaly and adhesions are common. This variant is commonly associated with hemodynamic (secondary) forms of FSGS. The **cellular** variant involves segmental, endocapillary hypercellularity (involving >25% of the tuft and leading to capillary occlusion). It excludes findings of the tip and collapsing variants. There may be infiltrating monocytes, lymphocytes, and neutrophils. The podocytes may be swollen and hyperplastic, leading to the appearance of a pseudocrescent (an extracapillary cellular aggregate *not* attached to Bowman's capsule). Patients with this form may be more nephrotic and have a more rapid rate of disease development. The **tip lesion** variant has at least one glomerulus with either an adhesion or a confluence of podocytes near or protruding into the opening of the proximal tubule. Collapsing or perihilar lesions must be absent. The most aggressive variant is the **collapsing** lesion. It requires at least one glomerulus with segmental or global obliteration of the capillary lumina with wrinkling or collapse of the GBM, as well as podocyte hypertrophy and/or hyperplasia. A single glomerulus with such features of collapse pre-empts the diagnosis of the other variants. The form often has a malignant course to ESRD with severe NS, although recent evidence suggests that – after controlling for baseline clinical characteristics

and immunotherapy exposure – the chances of remission and the risks of renal failure are similar to NOS (Laurin et al. 2016). Podocytes may be de-differentiated and stain for Ki67, a marker of cell proliferation. Generally, there is a loss of endocapillary cells. Whether the collapsing variant results from dysregulated proliferation of podocytes or – as with other forms of FSGS – there is net loss of podocytes is still unclear. No study using stereologically valid methods to estimate podocyte number in this variant has been reported; in the setting of a shrinking "reference volume" (the glomerular tuft), the subjective impression of crowding of podocytes on the tuft cannot be automatically interpreted as representing an increased number of these cells. The presence of tubuloreticular inclusions in this variant suggests HIV-associated nephropathy (HIVAN).

The pathological form of **C1q nephropathy** is a form of FSGS with variable mesangial hypercellularity with paramesangial C1q deposits (usually also containing IgG, IgM, and/or C3). Most patients with this lesion show NS and some amount of CKD. The lesion of **diffuse mesangial sclerosis** (DMS) will not be specifically addressed (see section on *Genetics*). This form of podocytopathy is substantially different from most forms of FSGS and very likely results from some unique pathobiological features. This histopathology lesion is often seen in infants with congenital NS.

There is some debate as to whether or not the segmental sclerotic lesions of FSGS are reversible (Benigni et al. 2011; Remuzzi et al. 2006), specifically under renin-angiotensin blockade. Such a question is not easily addressed experimentally (even in animal models of FSGS) since one cannot sample the same tissue twice.

The reported higher propensity of glomeruli in FSGS to be in the juxtamedullary region may be an important feature (Rich 1957), although the basis of this reported preferential involvement is not understood. The significance of glomerular hypertrophy in the propensity for FSGS in this region is also not clear, as stereological autopsy studies in adult men showed equivalent or smaller glomerular volumes in juxtamedullary glomeruli (Samuel et al. 2005). It is also possible that hypertrophic glomeruli may reflect preceding glomerular loss (compensatory hypertrophy of remnant glomeruli) or congenital glomerulopenia, both leading to increased susceptibility to subsequent glomerular injury. Children with MCD who have larger glomeruli on their initial biopsy are more likely to "evolve" to FSGS over time (Fogo et al. 1990). The concept of a "morphological transition" from minimal change disease to FSGS has been proposed (Tejani 1985). This relates to the concept of MCD and FSGS lying on a common (connected) spectrum of disease. The difficulties with such a proposal include the potential selection bias of patients receiving follow-up biopsies (suggesting more severe or treatment-resistant disease) and the substantial risk of "missed" FSGS in the early biopsies, especially if the number of glomerular tufts sampled is inadequate (Corwin et al. 1988).

Taxonomy of FSGS

A taxonomy is an organizational principle based on hierarchical relationships resulting from structural similarities. The goal of a taxonomy of FSGS is to predict prognosis and response to therapy. A better molecular understanding of podocyte pathobiology together with advances in histological analysis holds the promise for the development of a taxonomic classification of FSGS that integrates gene expression, cell biology, and histological and clinical manifestations (Barisoni et al. 2007; Kretzler and Sedor 2015). The "new taxonomy" is intended to be mechanistic rather than purely descriptive; it supports the development of targeted treatments (precision medicine). It is based on two axes: an axis of histology (MCN, FSGS, DMS, CG) and one of etiology (idiopathic, genetic, reactive). It is likely that with advances in understanding the underlying unifying mechanisms at work in the NS, additional axes (transcriptomic, biomarker-related) will be added to an expanded taxonomy (Gadegbeku et al. 2013).

Pathogenesis

Three broad categories of mechanisms can be considered to cover the majority of cases: genetic, immune-related signaling, and hemodynamic. Of these, the first category encompasses pathogenic variants of podocyte-expressed genes leading to dysfunction of distinct cellular mechanisms, such as calcium signaling, the actin cytoskeleton, or structural proteins regulating the filtration slit diaphragm. The second has traditionally been considered to be due to the effects of various circulating proteins of the immune system (e.g., products of T lymphocytes) largely based on the salutary effects of immune-modulating agents, such as steroids and cyclosporine. Recent cell biological studies, however, have shown this association to be more complex than a purely immune phenomenon, as several effective immunosuppressive therapeutic agents have been shown to have direct, nonimmune-mediated effects on various components of the podocyte considered to be pivotal to normal function. Various malignancies (Hodgkin lymphoma, adenomas, mesotheliomas) may also release circulating factors that adversely influence the podocyte. Finally, the third broad category reflects structural and functional adaptations to renal mass reduction triggering compensatory hyperfunction (and hypertrophy) at the single glomerulus level. Other stimuli may also lead to intracapillary hypertension with similar results, such as obesity or sickle cell disease. Aside from the three major categories, less frequent causes are podocytopathies associated with infectious agents, specific medications/drugs, and pre-eclampsia, among others (see Table 1).

Primary pathogenic causes of FSGS (genetic, hemodynamic, circulating factors, etc.) must be

Table 1 Causes of focal segmental glomerulosclerosis

Genetic
Podocyte-expressed proteins (*NPHS1, NPHS2, WT1*, etc.)
Mitochondrial (*COQ2*, etc.)
Other (*GLA*, *PAX2*, etc.)
Circulating factors
Products of the immune system (cardiotrophin-like cytokine 1, soluble urokinase receptor)
Malignancy (Hodgkins and non-Hodgkins lymphoma, adenoma, mesothelioma)
Hemodynamic
Due to reduction of functional renal mass (surgical nephrectomy, reflux nephropathy, renal dysplasia, chronic interstitial nephritis, oligomeganephronia, low birth weight/prematurity, unilateral renal agenesis, kidney transplant status, renal cortical necrosis)
Sickle cell disease
Morbid obesity
Cyanotic congenital heart disease
Renal artery stenosis (hypertension) – Contralateral
Pre-eclampsia (reverse causation?)
Other
Associated with prior glomerular diseases (IgAN, TMA, SLE, AAV)
Medication-associated (calcineurin inhibitors, pamidronate*, interferons, heroin, anabolic steroids, sirolimus, lithium, anthracyclines)
Infectious agents (parvo B19*, HIV-1*, CMV)

*Associated with collapsing FSGS

Table is inclusive of some causes predominantly seen in adults. It may be difficult to distinguish between diseases and their treatment in causation of FSGS (anthracyclines and lymphomas; lithium and chronic interstitial nephritis)

IgAN IgA nephropathy, *TMA* thrombotic microangiopathy, *SLE* systemic lupus erythematosus, *AAV* ANCA-associated vasculitis, *HIV* human immunodeficiency virus, *CMV* cytomegalovirus

distinguished from disease modifying factors, which may influence the rate of progression of CKD in the setting of FSGS. Such factors include congenital glomerulopenia (probably represented by glomerulomegaly, as in oligomeganephronia, but also in certain at-risk populations), genetic variants (such as risk alleles in *APOL1*), and obesity, among others. At least some of these factors seem to be related to a relative insufficiency of podocytes.

Genetic Disease

The past two decades have seen a virtual explosion in our understanding of the genetics underlying NS. Initial genetic studies using the time- and labor-intensive method of positional cloning in kindreds with familial FSGS/SRNS discovered causal mutations in several genes (*NPHS1, NPHS2, ACTN4, TRPC6, INF2)*. Recent advances in sequencing technology have facilitated whole-exome sequencing in affected families, resulting in a rapid increase in the discovery of causative genes. Over 30 genes have now been implicated in the pathogenesis of FSGS/SRNS, and most of the gene products localize to the podocyte (Hall and Gbadegesin 2015). These genetic discoveries have provided novel insights into the molecular mechanisms underlying the structure and regulation of the slit diaphragm, the role of the actin cytoskeleton, and the importance of energetics and mitochondrial metabolism in podocytes. Additionally, early studies have suggested that those patients with a monogenic cause of NS may represent a unique subset of NS, with greater resistance to immunosuppressive therapy and lower likelihood of posttransplant recurrence compared with nonmonogenic disease (Benoit et al. 2010; Buscher et al. 2016; Buscher et al. 2010; Ruf et al. 2004; Weber et al. 2004) (see Table 2).

***NPHS1*:** An early discovery of a monogenic form of NS emerged from the study of congenital NS of the Finnish type (CNF), a distinct entity characterized by massive proteinuria, often starting in utero, with early progression to end-stage kidney disease (Hallman and Hjelt 1959). Mutations in *NPHS1*, which encodes the protein nephrin, a 1241 amino acid Ig-like transmembrane protein, was identified as the monogenic cause of CNF (Kestila et al. 1998). Nephrin localizes to the slit diaphragm, the narrow region between interdigitating foot processes of podocytes (Holthofer et al. 1999; Holzman et al. 1999; Ruotsalainen et al. 1999). Using electron microscopy, nephrin has been shown to form strands that resemble the "zipper-like" structure of the healthy slit diaphragm (Wartiovaara et al. 2004). The extracellular domains of nephrin

Table 2 Genes associated with FSGS including protein name, pattern of Mendelian inheritance, function, and any associated extrarenal phenotype and/or syndrome

Gene	Protein	Inheritance pattern	Function	Extrarenal phenotype/syndrome
NPHS1	Nephrin	Autosomal recessive	Slit diaphragm	Congenital nephrotic syndrome, Finnish type
NPHS2	Podocin	Autosomal recessive	Slit diaphragm	
WT1	Wilms-tumor protein 1	Autosomal dominant	Transcription factor	Denys-Drash and Frasier syndromes
ACTN4	Alpha-actinin-4	Autosomal dominant	Actin-binding	
INF2	Inverted formin-2	Autosomal dominant	Actin-binding	
TRPC6	Transient receptor potential cation channel	Autosomal dominant	Ion channel	
LMX1B	LIM homeobox transcription factor 1, beta	Autosomal dominant	Transcription factor	Nail-patella syndrome

have been demonstrated to form homophilic interactions, suggesting nephrin molecules may form cell-cell adhesions between podocytes (Khoshnoodi et al. 2003). However, more recent experimental evidence suggests that nephrin may have different role in a multilayered protein scaffold that maintains the interpodocyte filtration slit (Grahammer et al. 2016). Aside from a structural role, nephrin expression seems to underlie a signaling pathway (Huber et al. 2003a). For example, nephrin has been shown to bind Nck, an adaptor protein that controls the podocyte actin cytoskeleton, and the nephrin-Nck interaction is needed for actin reorganization (Jones et al. 2006). These studies suggest nephrin may serve as a signaling platform, acquiring information from the slit diaphragm and translating it to the podocyte actin cytoskeleton.

NPHS1-related NS has been classified as having an autosomal recessive Mendelian inheritance pattern. Two *NPHS1* variants (Fin-major and Fin-minor) were the most common variants initially identified (Kestila et al. 1998). In the homozygous state, these particular variants lead to a clinically severe phenotype of CNF with early progression to end-stage kidney disease (ESKD) (Patrakka et al. 2000). In addition to early-onset disease, a growing body of evidence has implicated *NPHS1* in the development of FSGS later in life. Santin and colleagues reported 4 children and 1 adult with FSGS-associated *NPHS1* variants (Santin et al. 2009b). In all five of these individuals, there was compound heterozygosity for *NPHS1*. Likewise, Philippe and colleagues reported one familial case and nine sporadic case of *NPHS1* compound heterozygosity (Philippe et al. 2008). Of these, three (all sporadic) had FSGS; of these, all had steroid resistance and two had progression to ESKD in the second decade of life. Given the importance of nephrin to maintaining the slit diaphragm, it is not surprising to see a phenotypic spectrum, with milder variants postulated to result in later onset of disease (Kitamura et al. 2007; Wong et al. 2013).

NPHS2: Positional cloning identified *NPHS2*, which encodes the protein podocin, as a causative gene in familial FSGS (Boute et al. 2000). Podocin is a 383 amino acid transmembrane protein that is localized to the podocyte foot process at the slit diaphragm (Roselli et al. 2002). Podocin may form oligomers in lipid raft microdomains, potentially acting as a protein scaffold (Schwarz et al. 2001). Indeed, podocin has been shown to interact with nephrin at the slit diaphragm, and podocin mutations can disrupt nephrin targeting to lipid rafts, and thus nephrin-dependent signaling (Huber et al. 2001; Huber et al. 2003b). These findings highlight a putative mechanistic role for podocin at the glomerular filtration barrier.

NPHS2-associated FSGS was initially characterized by an autosomal recessive Mendelian inheritance pattern, childhood onset, and early progression to ESKD (Boute et al. 2000). Further studies demonstrated progression to ESKD often within the first decade of life (Hinkes et al. 2008). In addition to familial cases, causal *NPHS2* variants have been identified in sporadic FSGS cases as well (Caridi et al. 2001; Karle et al. 2002). To date, over 100 variants have been identified, extending across *NPHS2*'s entire coding region (Bouchireb et al. 2014). The common R229Q *NPHS2* missense variant is found in about 3% of European individuals (Tsukaguchi et al. 2002). While common, it can cause NS in the setting of compound heterozygosity with other specific *NPHS2* mutations (Machuca et al. 2009; Santin et al. 2011). In these situations, it appears disease-causing variants resulting in C-terminal substitutions exert a dominant negative effect on R229Q podocin's ability to heterodimerize and localize to the slit region (Tory et al. 2014).

WT-1: The *WT-1* gene was initially mapped given its association with Wilms' tumor – one of the most common types of malignancy in children (Call et al. 1990). WT-1 was identified as a zinc-finger containing transcription factor expressed in the kidney, which acts a tumor suppressor, as haploinsufficiency resulted in development of Wilms' tumor (Haber et al. 1990). Further studies of WT-1 identified an association with glomerular diseases, with different phenotypes based on specific patterns of genetic variation. Denys-Drash syndrome involves the constellation of DMS and associated renal functional decline, pseudohermaphroditism, and Wilms' tumor and has

been associated with mutations in exons 8 and 9 (Pelletier et al. 1991). Frasier syndrome involves male pseudohermaphroditism, streak gonads, and FSGS, and involves alternative splicing of intron 9 resulting in inclusion of 3 additional amino acids (KTS isoform) (Barbaux et al. 1997).

***TRPC6*:** Variants in *TRPC6* were first identified in familial FSGS with autosomal dominant inheritance, characterized by development of heavy proteinuria in the third or fourth decade of life and progression to end stage in around 10 years (Winn et al. 2005). Subsequently, nonfamilial cases and childhood-onset presentation have been demonstrated (Santin et al. 2009a). *TRPC6* encodes TRPC6, a member of the transient receptor potential (TRP) family of cation channels, which seem to act as cellular sensors via calcium currents (Clapham 2003). Indeed, some *TRPC6* variants result in altered calcium influx (Reiser et al. 2005; Winn et al. 2005). TRPC6 is located at the slit diaphragm in association with nephrin and podocin (Reiser et al. 2005). Thus, TRPC6 may act to communicate between the slit diaphragm and the intracellular networks of the podocyte and has been highlighted as a potential therapeutic target.

ACTN4: Variants in *ACTN4* were first identified in familial FSGS with autosomal dominant inheritance, characterized by development of mild proteinuria in adolescence and slow progression of renal dysfunction (Kaplan et al. 2000). Subsequently, nonfamilial cases and childhood-onset presentation have been demonstrated (Choi et al. 2008; Weins et al. 2005). *ACTN4* encodes alpha-actinin-4, an actin-binding and cross-linking protein (Weins et al. 2007). Identified variants have been clustered around the actin-binding domain, suggesting variants alter alpha-actinin-4's role in regulation of the podocyte actin cytoskeleton.

***INF2*:** Variants in *INF2* were first identified in familial FSGS with autosomal dominant inheritance, characterized by development of moderate proteinuria in adolescence and early adulthood with subsequent progression to end-stage disease (Brown et al. 2010). The initial phenotype was comparable to *ACTN4*-associated FSGS, and interestingly, *INF2* encodes an actin-binding protein with roles in accelerating actin polymerization. Additional familial cases with childhood-onset and intrafamilial phenotypic variability were subsequently identified (Lee et al. 2011).

LMX1B: A recently described genetic cause of familial FSGS has been a specific mutation in the LIM-homeodomain transcription factor, *LMX1B*. Like many other genes mentioned in this section, *LMX1B* is expressed specifically in the podocyte (in postnatal life). Mutations in this gene have long been known to cause the multisystem disorder, nail-patella syndrome (OMIM 161200). Severe renal manifestations in this disorder do not segregate with the *LMX1B* mutation, even within a family, suggesting that sequence variation in an LMX1B-regulated podocyte gene may be required for the severe renal phenotype (Lemley 2009). Recently, amino acid variation at a single residue (R246Q) in the homeodomain region of the protein has been shown to cause an autosomal dominant, heritable form of FSGS, without the usual skeletal and other extrarenal manifestations of nail-patella syndrome (Isojima et al. 2014). In addition to findings characteristic of FSGS, LMX1B nephropathy also may show the ectopic presence of type III collagen within the GBM. A small minority of patients with nail-patella syndrome may progress to ESRD even during childhood. These individuals will typically have a preceding phenotype including the nephrotic syndrome (Lemley 2009).

In addition to the aforementioned genes, over 20 other genes have been identified, each with important putative roles at the glomerular filtration barrier. While efforts are ongoing to identify novel FSGS-associated genes, a recent focus of research has been identifying the prevalence of monogenic disease using large NS cohorts. The PodoNet Consortium registry contains over 1500 patients with childhood-onset steroid-resistant NS, congenital NS, or subnephrotic proteinuria of potential genetic origin, recruited from over 20 countries. Sequencing of 1174 individuals has identified a genetic cause in 23.6% (Trautmann et al. 2015). In a separate cohort of 1783 unrelated, international families with steroid-resistant NS, sequencing of 27 genes identified a genetic cause for NS in 29.5% of all cases, but a bimodal distribution, with 12–14% having genetic causes among US patients, while 45% of

patient from Middle Eastern countries had definable genetic causes (Sadowski et al. 2015). The incidence of sporadic NS in unselected, admixed populations has also been investigated. Sequence analysis of 312 individuals from NEPTUNE study, which enrolled North Americans with proteinuric kidney disease suspected of being MCD, FSGS, or membranous nephropathy (MN) without a known history of familial disease, and irrespective of response to therapeutics, found an incidence of monogenic disease of only 2.9% in sporadic NS (Sampson et al. 2016a). Through such large scale screening efforts, novel variants are continuously identified in these monogenic genes, and a critical goal of genetic research is appropriate attribution of causality, given the implications for genotype-phenotype correlations and subsequent prognostic and therapeutic decision-making.

Regardless whether considered as either familial or sporadic disease, monogenic disease represents only a fraction of FSGS, and it remains as yet unclear to which degree other non-Mendelian forms may contribute to the burden of genetic FSGS. Digenic inheritance of *NPHS1* and *NPHS2* variants (primarily the R229Q *NPHS2* variant) has been reported in cases of congenital NS, suggesting that non-Mendelian genetic variation could contribute to glomerular phenotype (Koziell et al. 2002; Schultheiss et al. 2004). Sequencing of NS patients may identify causal variants, but may also incidentally identify secondary variants with unknown phenotypic contribution (Weber et al. 2016). However, recent work by Crawford et al. did not identify digenic heterozygosity or oligogenicity in 21 known monogenic NS genes as a contributor to NS in a large US cohort, suggesting that this form of inheritance is unlikely to have a large role in causing NS (Crawford et al. 2017).

In addition to rare causal variants ("mutations"), research over the past decade has highlighted the role of genetic variants that increase the risk of NS in a non-Mendelian manner, such as common variants in *APOL1* in blacks with FSGS, as discussed below.

***Apolipoprotein L1 (APOL1)*:** *APOL1* encodes apolipoprotein L1, a protein component of high-density lipoprotein and of the trypanosome lytic factor in human serum, which confers resistance against potentially lethal African sleeping sickness. Two coding variants in *APOL1*, termed G1 (a non-synonymous coding variant) and G2 (a 6 base-pair deletion), common in individuals with recent African ancestry but absent in European populations, are highly associated with increased risk of FSGS and ESRD (Genovese et al. 2010; Tzur et al. 2010). These *APOL1* variants restore trypanolytic activity, which led to its strong positive selection, and subsequent common frequency in those of recent African origin, particularly west African (Genovese et al. 2010).

APOL1 is only present in a few primate species including humans, suggesting it is not universally required for mammalian kidney development or maintenance. Although APOL1 circulates through bloodstream, plasma levels have not correlated with *APOL1* genotype or CKD (Bruggeman et al. 2014; Kozlitina et al. 2016). The ways by which *APOL1* variants cause kidney disease and damage are not fully understood, although diverse mechanisms have been suggested, such as potassium efflux leading to cytotoxicity (Olabisi et al. 2016). To explore the role of APOL1 variants, several transgenic mouse models have been developed. Transgenic mice with noninducible, podocyte-specific expression of *APOL1* G2 variant did not demonstrate any proteinuria or histologic findings of glomerulosclerosis, as compared to mice with G0 reference allele, but did develop a pregnancy-associated phenotype (Bruggeman et al. 2016). Of note, transgenic *APOL1* expression was noted to be variable in this model system. More recently, transgenic mice with podocyte-specific conditional, inducible-expression of either G1 or G2 variant developed azotemia and albuminuria and had histological findings of glomerulosclerosis, whereas mice expressing reference allele did not display this phenotype; additionally, there was a correlation between risk-variant expression levels and phenotype (Beckerman et al. 2017). At a molecular level, APOL1 variants disrupted endosomal trafficking and hence decreased autophagic flux, enhancing inflammatory-mediated cell death. Further research is needed to expand our understanding of how high-risk variants of

APOL1 contribute to FSGS pathogenesis and progression of any form of CKD.

Initial reports suggested that kidney disease is associated with these *APOL1* variants only in the recessive model (homozygosity or compound heterozygosity) (Genovese et al. 2010). Also known as the "high risk" (HR) genotype, those harboring two risk alleles demonstrate an earlier onset of FSGS and faster progression to ESRD as compared to African-Americans having zero or one variant, the "low risk" (LR) genotype (Kopp et al. 2011). In two cohorts of African-American NS patients with variable histopathologic findings from the NEPTUNE and FSGS Clinical Trial studies, HR genotype was associated with higher tubulointerstitial disease on histopathology (Kopp et al. 2015; Sampson et al. 2016b). Black children with NS and a HR genotype have lower eGFR on presentation, faster decline in eGFR over time, and increased odds of having been born preterm (Ng et al. 2016).

APOL1 variants are common, with 13% of African-Americans having the high-risk genotype, with an associated estimated lifetime FSGS risk of 4% (Kopp et al. 2011). Given this high prevalence, there has been interest in ascertaining the clinical utility of *APOL1* genotyping. One area of prime interest is in regards to kidney transplantation. Recipient *APOL1* genotype status has not been shown to affect 5-year survival of deceased donor grafts (Lee et al. 2012). However, several reports have demonstrated that HR *APOL1* genotype in the deceased donor kidney is associated with earlier allograft failure, controlling for other factors affecting allograft such as cold-ischemic time, HLA match, and various recipient characteristics (Freedman et al. 2015; Freedman et al. 2016; Reeves-Daniel et al. 2011). These studies have introduced the question of whether *APOL1* genotyping should play a role in deceased donor kidney allocation. Some authors have argued that rapid *APOL1* genotyping should become routine for deceased donor kidneys, although others have argued against it (Freedman and Julian 2015; Ross and Thistlethwaite 2016). As donor kidneys are in short supply, further research is needed to define the role of *APOL1* genotyping in organ allocation.

Circulating Factors and Biomarkers

The high recurrence rate of FSGS following renal transplantation and the beneficial effect of plasmapheresis on disease recurrence have led many to hypothesize that a circulating "permeability" factor may contribute to disease pathogenesis in some cases (Hickson et al. 2009; Mahesh et al. 2008). The loss of renal allografts to disease recurrence in pediatric patients is not negligible. Review of the 2001 NAPRTCS registry indicated that 15% of graft failure in patients transplanted for FSGS was due to disease recurrence (Baum et al. 2002). Numerous investigators have sought to identify the putative circulating factor causing disease to better assess risk and suggest effective interventions. Several candidates (e.g., soluble urokinase plasminogen activator receptor [suPAR], hemapexin, cardiotrophin-like cytokine-1 [CLC-1]) have been suggested. However, at this time, the identity of the responsible circulating factor(s) remains unclear.

suPAR was experimentally shown to lead to foot process effacement via activation of αvβ3 integrin, which attaches podocytes to the glomerular basement membrane; integrin activation has been shown to promote cellular motility (Wei et al. 2008). In initial cohort comparisons, patients with FSGS had higher suPAR levels than healthy controls or patients with other glomerular diseases (Wei et al. 2011; Wei et al. 2012). This initial experimental evidence raised the possibility that integrin blockade could prevent downstream effects that lead to podocyte disruption and proteinuria; however, integrin blockade has not thus far been substantiated as a useful therapeutic target. In addition, subsequent studies have failed to demonstrate that higher suPAR levels are specifically associated with FSGS (Bock et al. 2013; Franco Palacios et al. 2013; Spinale et al. 2015).

Biochemical purification methods have been used to attempt isolating the focal sclerosis permeability factor (FSPF) from plasma of FSGS patients (Sharma et al. 2004). Given the potential for a circulating factor to interact with the glycocalyx, galactose-affinity chromatography was applied to plasma from FSGS patients, and identified circulating cardiotrophin-like cytokine

factor 1 (CLC-1) as the putative factor (McCarthy et al. 2010). Galactose therapy was then tried in a case report, as galactose bound the permeability factor (Savin et al. 2008). Use of oral galactose in a series of children did show decreases in bioassayable FSPF, but no change in proteinuria (Sgambat et al. 2013). The FONT trial (Novel Therapies for Resistant Focal Segmental Glomerulosclerosis) attempted to test the efficacy of galactose as a therapy for FSGS, but fell short of patient recruitment goals (Trachtman et al. 2015a). Thus, the role for galactose as a treatment for FSGS remains unclear.

Some biomarkers have been identified that may help to differentiate between MCD and FSGS. CD80 (also known as B7-1), which is present on antigen-presenting cells, is a membrane protein involved in providing a costimulatory signal for T cell activation. CD80 is also in found on the podocyte, where it is upregulated in experimental models of NS, potentially acting as a modifier of glomerular permselectivity and a component of cellular danger signaling machinery (Reiser et al. 2004). Urinary CD80 levels have been found to be elevated in patients with relapsed MCD, but not in patients with MCD in remission or in FSGS patients (Garin et al. 2009; Garin et al. 2010). Thus, urinary CD80 may be useful to discriminate between MCD and FSGS, although studies on larger patient populations are necessary. An inhibitor of B7-1 (CD80), abatacept (cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin fusion protein [CTLA-4—Ig]), which has been approved for treatment of rheumatoid arthritis, has also been investigated as a treatment for FSGS. In a small cohort of 5 patients with either primary or recurrent FSGS, abatacept resulted in partial or complete remission (Yu et al. 2013). In in vitro experiments, abatacept restored *β1* integrin activation and blocked podocyte migration, suggesting a biological mechanism in glomerular disease whereby B7-1 promotes podocyte migration through *β1* integrin inactivation (Yu et al. 2013). Based only on a small collection of case studies, the role for podocyte CD80 targeted inhibition with abatacept remains interesting and is being evaluated in an ongoing randomized clinical trial (Mundel and Greka 2015).

An older biomarker – both of histology and of steroid responsiveness – is the *selectivity* of proteinuria (Cameron 1968; Ellis and Buffone 1981; Lines 1969). This biomarker seems to have been forgotten, rather than disproved or supplanted by a superior alternative. Selectivity refers to the relationship of specific proteins' urinary clearances to their molecular weights (MW), traditionally, the slope of the fit line for several proteins' clearances to their MW, ranging from orosomucoid (MW 40 kD) or albumin (MW 68 kD) to α_2-macroglobulin (MW 840 kD), plotted on a log-log scale; more simply as the relative clearances of IgG (MW 160 kD) and transferrin (MW 90 kD). A more negative slope (or lower ratio) is considered to represent greater selectivity. The predictive ability of the selectivity index to distinguish MCD from FSGS (or steroid-resistant NS) was greater in some studies (absolute, for example, in (Lines 1969)) than in others (Cameron 1968; Ellis and Buffone 1981). Protein selectivity has biological plausibility as a possible index of different forms of podocyte dysfunction, e.g., disruption of normal slit diaphragm function (high selectivity) versus podocyte detachment (low selectivity). Whether a reconsideration of this biomarker (using easier ELISA technology) in comparison to urinary CD80 levels, for example, is worthwhile remains to be seen.

Hemodynamic

FSGS due to hemodynamic derangements would be classically considered as a secondary form of FSGS. Hyperfunction injury is the paradigm case. This results from compensatory hypertrophy and hyperfunction of remnant nephrons attendant to a significant loss of functional renal mass, as occurs following subtotal nephrectomy. Particularly exuberant responses to the hypertrophic stimulus (as seen after unilateral nephrectomy in rapidly growing young rats (Nagata et al. 1992)) result in excessive compensatory glomerular hypertrophy, which may lead to relative podocyte insufficiency, even if no podocytes are lost initially. It is tempting to posit that another example of such imbalanced, exuberant growth may occur in children

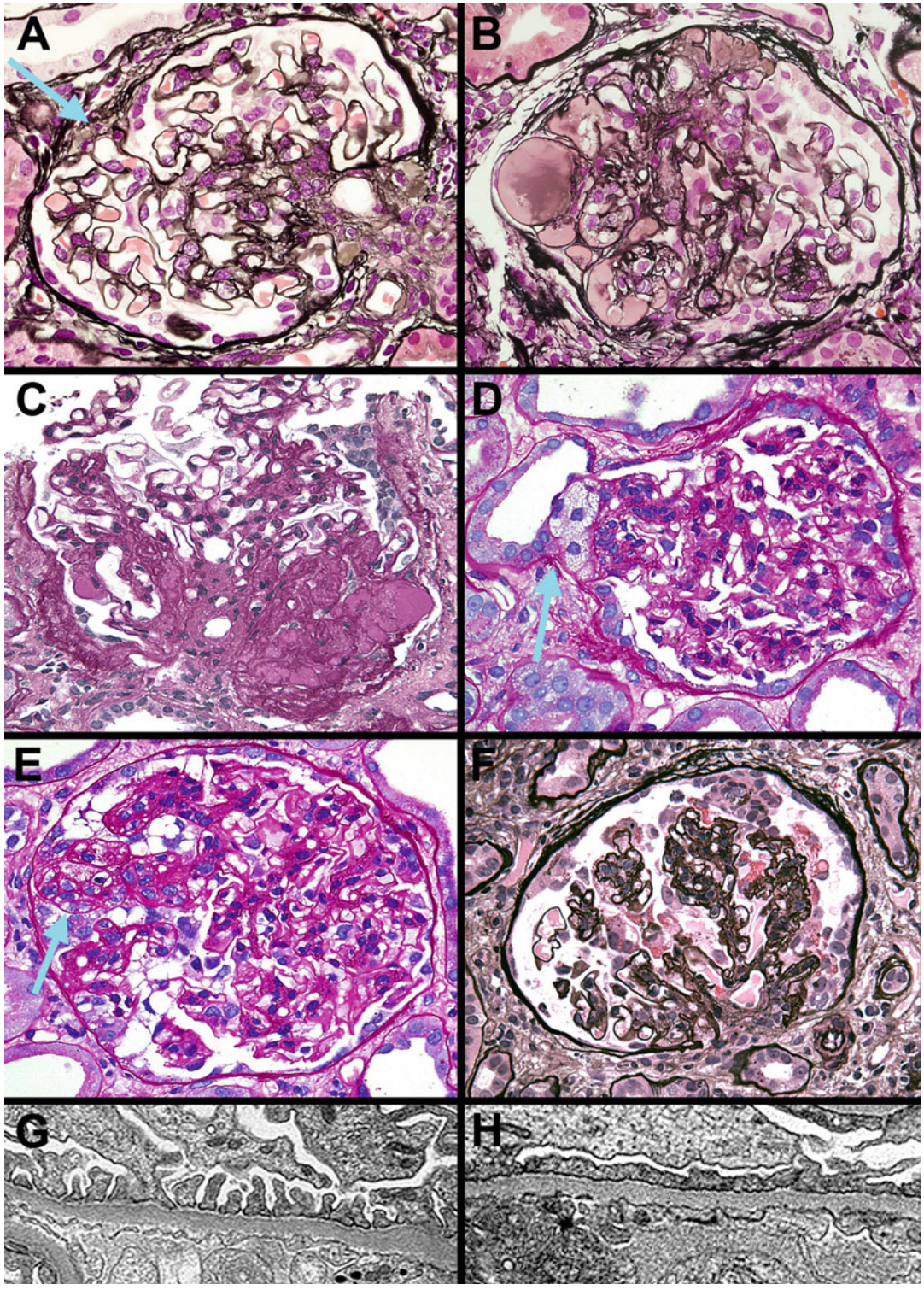

Fig. 1 FSGS features and Columbia classification variants. (**a**) Adhesions or synechiae, a very early sclerosing lesion, may form between the sclerosing segment and Bowman's capsule as podocytes become depleted through detachment or cell death. An open capillary loop connects to Bowman's capsule via minimal matrix deposition (*blue arrow*) (Jones methenamine silver, x400). (**b**) NOS, not otherwise specified, is the usual (classic) histologic pattern

with premature birth or low birth weight (leading to lower glomerular number (Manalich et al. 2000)), especially if coupled with subsequent excessive catch-up growth during childhood leading to excessive glomerular hypertrophy (Barker et al. 2005). This class of FSGS often shows less foot process effacement and greater variability of foot process morphology even among the foot processes of a single podocyte, suggesting the influence of local mechanical (rheological) forces on foot process geometry (Kriz and Lemley 2016).

There seems to be a convergence of various initial etiologies of disease to a final pathomechanism of progression based on podocyte "insufficiency," viz., an inadequate number of podocytes to assure the stability of an enlarged glomerular tuft (Fries et al. 1989). Why this is relentlessly progressive (despite the undeniable beneficial effects of angiotensin blockade) is subject to debate. It has been suggested that "podocyte damage damages [other] podocytes" (Ichikawa et al. 2005)), presumably based on loss of protective autocrine factors. Progression from segmental scarring to global glomerular sclerosis may depend on the role of the RAAS in adapting to the loss of ultrafiltration capacity and compensatory functional effects activated by tubuloglomerular feedback (Lemley 2012). Alternatively, the loss of lateral stabilization against shear forces by slit diaphragms between neighboring podocyte foot processes may explain the fact that after a certain degree of podocyte loss, the further loss of podocytes is autonomously progressive (Fukuda et al. 2012; Kriz and Lemley 2016).

What seems to be indisputable is that for many podocytes, detachment from the glomerular tuft occurs as viable cells (Vogelmann et al. 2003). This has been suggested to result from a very specific mechanism of podocyte detachment in which elevated shear stresses on the filtration slits (from sustained hyperfiltration) result in shearing forces that may strip otherwise viable podocytes off of the GBM, often still attached by intercellular junctions to their neighboring, equally viable podocytes (see Fig. 1) (Kriz and

Fig. 1 (continued) of FSGS. It is defined by segmental obliteration of the glomerular capillary lumina by increased extracellular matrix and/or hyalinosis that does not meet defining criteria for any other variant. It is the most common variant and can present with either nephrotic syndrome or subnephrotic proteinuria. NOS can occur in patients with primary FSGS or diverse secondary forms, including genetic FSGS (Jones methenamine silver, x400). (**c**) Perihilar variant is defined as perihilar hyalinosis and sclerosis at the vascular pole involving the majority (>50%) of glomeruli with segmental lesions. It may be found in primary FSGS but is particularly common in adaptive FSGS, where it is usually accompanied by glomerular hypertrophy (glomerulomegaly). Patients with adaptive FSGS and perihilar variant are more likely to present with subnephrotic proteinuria and normal serum albumin levels (Periodic acid-Schiff, x400). (**d**) Tip variant is defined by the presence of at least one segmental lesion involving the tip domain, next to the origin of the proximal tubule, with either extracellular matrix adhesion to the tubular outlet or confluence of visceral cells with parietal or tubular epithelial cells (*blue arrow*). Intracapillary foam cells are frequently seen. It is more common in Caucasians and typically presents with abrupt onset of full nephrotic syndrome. Most cases are primary. It has the most favorable outcome with the highest rate of steroid responsiveness, the best preservation of renal function, and the least tubulointerstitial injury at biopsy (Periodic acid-Schiff, x400). (**e**) Cellular variant is defined by at least one glomerulus with an expansile segmental lesion featuring endocapillary hypercellularity, often including foam cells and infiltrating leukocytes (*blue arrow*). Segmental sclerosis is not required. This is the least common variant. It usually presents with nephrotic syndrome, and most cases are primary (Periodic acid-Schiff, x400). (**f**) Collapsing variant is defined by the presence of at least one glomerulus with either segmental or global implosive glomerular capillary wall collapse with hypertrophy and hyperplasia of the overlying glomerular epithelial cells. This is the most aggressive variant with worst renal function at presentation, severe markers of nephrotic syndrome, the strongest black racial association, the lowest rate of therapy response, and the most rapid progression to renal failure. It can occur in primary FSGS as well as secondary forms related to interferon therapy, pamidronate therapy, HIV infection, parvovirus B19 infection, acute ischemia, and rare genetic forms (Jones methenamine silver, x400). (**g**) Transmission electron microscopic view of the normal glomerular capillary wall showing intact podocyte foot processes above the glomerular basement membrane (x10,000). (**h**) Transmission electron microscopic view of a glomerular capillary in FSGS showing podocyte foot process effacement above the glomerular basement membrane (x10,000)

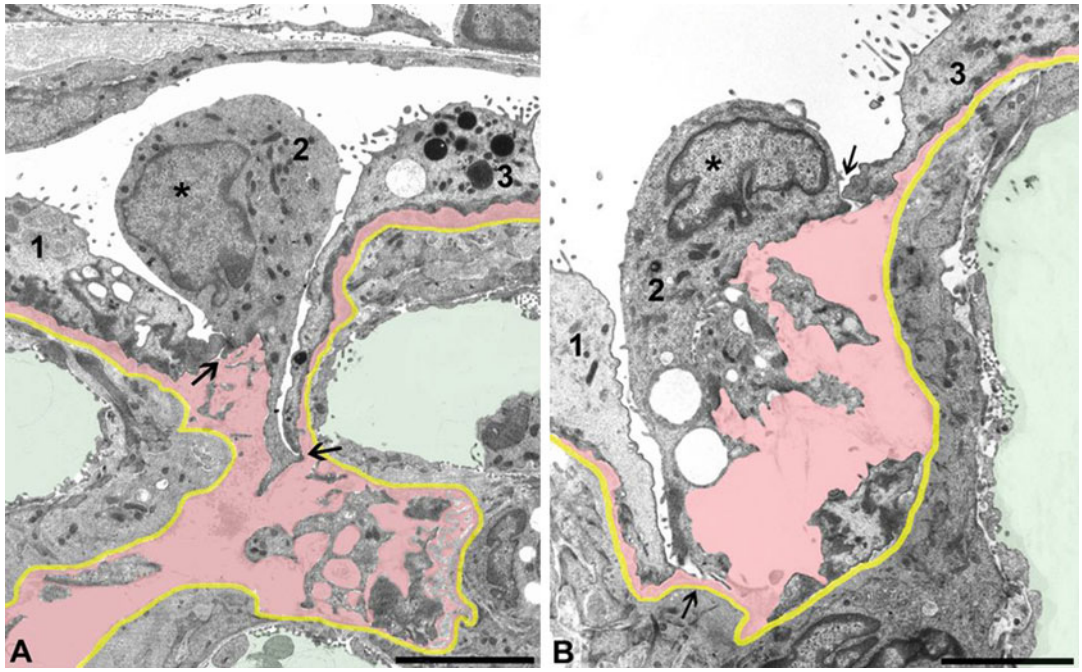

Fig. 2 Detachment of viable podocytes from the GBM (*yellow*). Lumens of capillaries are highlighted in *green* and the space between podocytes and GBM in *pink*. (**a**) Three podocytes are detaching (1–3). Podocytes 1 and 3 have extensive foot process effacement. Podocyte 2 is widely detached from the GBM, although still connected to its neighboring podocytes by intercellular junctions (*arrows*). (**b**) A similar situation of detachment of three podocytes. Cell nuclei of all podocytes have normal chromatin patterns (no apoptosis). Both **a** and **b** from rats with Masugi nephritis (days 28 and 7, respectively). Bar, 5 μm (Reprinted from Kriz et al., Am J Physiol Renal Physiol., 304:F333–47, 2013)

Lemley 2016; Lemley 2016). That shear stress, rather than increased intracapillary hydrostatic pressure, is the major influence on podocyte detachment is suggested by the fact that the typical morphological variant for this type of FSGS is the perihilar one. Local filtration rates and shear stresses in the filtration slits are highest at the beginning of the capillary branching at the afferent arteriole, near the hilum, and fall steadily as ultrafiltration raises the oncotic pressure of the capillary plasma, countering the net hydrostatic driving pressure for filtration and possibly reaching a point where no further filtrate crosses the filtration slits (Fig. 2).

Angiotensin blockade is particularly protective in the setting of hemodynamic glomerular injury. By almost doubling the ultrafiltration coefficient (possibly by capillary remodeling), enalapril likely led to halving the net driving forces for glomerular filtration along the entire length of the glomerular capillaries after subtotal nephrectomy in rats (Lemley 2016).

Hemodynamic factors are probably also drivers of glomerular pathology in obesity-related FSGS (which has also been described in children), low congenital nephron number, polycythemia, sleep hypoxia, sickle cell disease, and cyanotic congenital heart disease (Adelman et al. 2001; Falk et al. 1992; Hida et al. 2002; Hodgin et al. 2009; Kambham et al. 2001; Tejani et al. 1985).

Treatment

Treatment of FSGS is aimed at reducing proteinuria with the overall goal of preserving kidney function. As noted above, achieving partial or complete remission is prognostic for renal survival. Current treatment options to achieve this goal include steroids, immune-based therapies

(calcineurin inhibitors, or CNIs), antimetabolites, biologics), as well as other strategies, such as renin-angiotensin-aldosterone system blockade. FSGS treatment has been reviewed recently (Hodson et al. 2010; Sethna and Gipson 2014). Therapeutic decisions are based on responsiveness to initial treatment with steroids (sensitive or resistant).

In younger children, following the presentation of NS, corticosteroids are empirically started, based upon the findings of the ISKDC study suggesting a high likelihood of favorable histology (MCD) and positive disease response to treatment (ISKDC 1981). Thus, biopsy is often deferred at initial presentation, unless atypical signs (e.g., renal insufficiency, gross hematuria, hypertension) necessitate a histologic diagnosis. In the ISKDC, the majority (70%) of children with FSGS did not respond to steroids, although the sample size was small. Likewise, the SPNSG found that 40 of 56 patients (71%) with FSGS did not respond (SPNSG 1985). A lack of steroid response is often the motivating factor for a kidney biopsy, which can then identify FSGS as the histopathologic diagnosis. In addition, given the importance of achieving remission of proteinuria to renal survival, a lack of steroid response often necessitates administration of other agents to attempt to control proteinuria. In addition, even when FSGS does respond to steroids, the benefits of achieving remission are often balanced with the side effects of prolonged steroid use (growth delay, hypertension, weight gain, and Cushingoid appearance, amongothers). Thus, despite steroid sensitivity, alternate agents are often needed to reduce overall steroid exposure.

As the majority of cases of FSGS represent steroid-resistant NS (SRNS), the following treatment discussion will focus on SRNS. For SRNS, the Kidney Disease: Improving Global Outcomes (KDIGO) organization recommends CNIs – cyclosporine or tacrolimus – as a first-line treatment (KDIGO 2012). Several early randomized trials demonstrated that cyclosporine, as compared to placebo, is better able to achieve remission (Lieberman and Tejani 1996; Ponticelli et al. 1993)). However, cyclosporine does have significant cosmetic side effects, such as hypertrichosis (excess hair growth) and gingival hyperplasia as well as nephrotoxicity, hyperlipidemia, and hypertension (El-Husseini et al. 2005). Thus, tacrolimus, another CNI, has emerged as a treatment with comparable efficacy as cyclosporine but less cosmetic side effects and a better cardiovascular risk profile (Choudhry et al. 2009). CNIs are commonly used for immune suppression following solid organ transplantation, and their successful use in NS has suggested that these agents alter immunological mechanisms underlying NS. However, cyclosporine has been shown to directly stabilize the actin cytoskeleton in podocytes, highlighting a novel mechanism for its antiproteinuric effect (Faul et al. 2008). Nonetheless, since both cyclosporine and tacrolimus can cause hypertension and nephrotoxicity, often prompting the need for surveillance biopsies to assist with risk and benefit analysis of ongoing CNI use, alternative therapies have been sought.

In addition to CNIs, KDIGO recommends use of either angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), agents that alter the renin-angiotensin-aldosterone system (RAAS). Addition of fosinopril to steroid therapy was more effective than steroid only therapy in reducing proteinuria (Yi et al. 2006). Alongside tapering steroid therapy, higher dose enalapril was more effective in reducing proteinuria than lower dose (Bagga et al. 2004). These agents act to decrease GFR and can lead to azotemia and hyperkalemia, necessitating laboratory monitoring; caution should be used in those with significantly decreased kidney function, given the potential for hyperkalemia. Lastly, RAAS inhibition can result in fetal malformations; thus, the use of ACE inhibitors or ARBs is contraindicated during pregnancy.

When the combination of CNIs and corticosteroids fail to achieve remission, KDIGO recommends consideration of the antimetabolite mycophenolate mofetil (MMF) or high-dose corticosteroids therapy. MMF has been shown to be effective in achieving remission in a single-center prospective study (Li et al. 2010). Another observational study that compared MMF alone or MMF following cyclosporine treatment showed no difference in steroid/cyclophosphamide-resistant NS patients (de Mello et al. 2010). Recently, a

randomized trial that compared patients with FSGS receiving oral pulse dexamethasone and mycophenolate versus patients receiving cyclosporine did not find a difference in rates of proteinuria remission, although the study was underpowered to detect moderate effect differences (Gipson et al. 2011). A retrospective study has suggested a role for MMF as "maintenance" therapy following combined cyclosporine/MMF therapy (Gellermann et al. 2012). The exact role for MMF in SRNS/FSGS management remains unclear, and further research is necessary.

The cytotoxic agent, cyclophosphamide, has been used in steroid-dependent and/or frequently relapsing NS. Early case series suggested that cyclophosphamide could potentially be used for steroid-resistant NS, including FSGS (Bajpai et al. 2003; Rennert et al. 1999). While these reports appeared promising, cyclophosphamide does carry small but significant risks associated with its use, including hemorrhagic cystitis, infection, infertility, and late-onset malignancy. Analysis of a small, randomized trial of FSGS patients receiving either steroid therapy or steroid therapy plus oral cyclophosphamide demonstrated no difference in remission rates or adverse outcomes (Tarshish et al. 1996). A randomized trial comparing SRNS patients with various histologies (including a third with FSGS) demonstrated addition of tacrolimus to steroids achieved higher rate of remission than those treated with intravenous cyclophosphamide (Gulati et al. 2012). Based upon review of available data, however, KDIGO currently recommends against use of cyclophosphamide for SRNS. The combination of pulse intravenous methylprednisolone alongside oral prednisone, known as the "Tune-Mendoza protocol," had demonstrated high efficacy in achieving remission (Mendoza and Tune 1992). In this protocol, oral alkylating agents (e.g., cyclophosphamide) were used as an adjunct. Currently, the Tune-Mendoza protocol has fallen out of favor. Rituximab, an anti-CD20 antibody, has demonstrated efficacy in management of steroid-dependent NS; however, results in SRNS have not been promising (Magnasco et al. 2012).

Recurrence of FSGS following renal transplantation poses a significant threat to the kidney allograft, necessitating prompt treatment. Management of recurrent FSGS differs from management of primary disease and has recently been reviewed (Trachtman et al. 2015b). Particularly, plasmapheresis has been highlighted as an important tool for management, with many patients experiencing lasting remission.

Conclusion

FSGS is a histological lesion that can be seen in glomerular proteinuric disease resulting from a variety of pathophysiologic mechanisms. In the past two decades, remarkable progress has been made in understanding the mechanisms leading to FSGS, such as molecular underpinnings of podocytopathies or the hemodynamic mechanical forces leading to podocyte depletion. In addition, the discovery of the *APOL1* risk allele has elucidated a partial explanation for the racial disparity in disease prevalence. Nonetheless, further research is needed to better predict treatment response and prognosis in patients with FSGS. Given the correlation between FSGS and ESKD, research is underway to develop new treatments to mitigate the progression of CKD. The rarity of proteinuric glomerular diseases, such as FSGS-associated disease, necessitates the continued engagement of the pediatric nephrology community in research studies and clinical trials.

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Alport Syndrome and Other Collagen Disorders

11

Michelle N. Rheault

Contents

Abstract

Type IV collagen is a ubiquitous component of basement membranes along with laminin, entactin/nidogen, and heparan sulfate proteoglycans. Six type IV collagen genes (*COL4A1–COL4A6*) encode six unique alpha chains of type IV collagen [α1(IV)–α6(IV)]. Mutations in several of the type IV collagen genes can cause a number of progressive and

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nonprogressive glomerular disorders. Mutations in *COL4A3*, *COL4A4*, and *COL4A5* may cause Alport syndrome (AS), an inherited kidney disease that classically leads to ESKD, sensorineural hearing loss, and eye abnormalities in affected individuals. Mutations in *COL4A6* along with *COL4A5* are associated with AS accompanied by leiomyomatosis. Heterozygous mutations in *COL4A3* and *COL4A4* are associated with thin basement membrane nephropathy (TBMN), a generally nonprogressive kidney disorder presenting with isolated microscopic hematuria. Finally, mutations in *COL4A1* cause hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome. This chapter will review the genetics, clinical manifestations, pathology, diagnosis, and treatment of each of these type IV collagen disorders.

Keywords
Glomerular basement membrane · Type IV collagen · End-stage kidney disease · Hematuria · Proteinuria · Sensorineural hearing loss · Alport syndrome · Familial nephritis

Normal GBM Structure

Glomerular basement membranes (GBMs) are vital for normal functioning of the glomerular filtration barrier and are composed of type IV collagen, laminin, entactin/nidogen, and agrin, a heparan sulfate proteoglycan (Miner 2012). Laminin forms a network within the GBM based on heterotrimeric association of α, β, and γ isoforms. Laminin-521 is the form found in mature GBM and has the composition α5β2γ1 (Miner 2012). Mutations in *LAMB2* encoding laminin β2 cause massive failure of the glomerular filtration barrier with clinical symptoms of congenital nephrotic syndrome and eye abnormalities (Zenker et al. 2004). Laminin and type IV collagen networks closely interact and are bridged by entactin/nidogen and agrin molecules.

There are six isoforms of type IV collagen designated α1(IV)–α6(IV) encoded by one of six distinct genes, *COL4A1–COL4A6*. *COL4A1* and *COL4A2* are present on chromosome 1 and encode α1(IV) and α2(IV). The α3(IV) and α4(IV) chains are encoded by the *COL4A3* and *COL4A4* genes on chromosome 2, while the α5(IV) and α6(IV) genes are encoded by the *COL4A5* and *COL4A6* genes on the X chromosome. Each pair of genes is situated in a 5′-5′ head-to-head orientation, with intervening promoter and transcriptional regulatory sites (Poschl et al. 1988; Segal et al. 2001). All type IV collagen isoforms share several common structural features: a collagenous domain of ∼1,400 amino acids containing the repetitive triplet sequence glycine-X-Y (Gly-X-Y, with X and Y representing other amino acids), a noncollagenous carboxy-terminal (NC1) domain of ∼230 amino acids that includes 12 conserved cysteine residues, and a noncollagenous amino-terminal sequence of 15–20 residues (7S domain). Individual type IV collagen isoforms associate to form trimers determined by specific interactions regulated by sequences in the NC1 domain. Despite the large potential number of trimer conformations, only three major trimeric species have been found in mammalian species: α1α1α2(IV), α3α4α5(IV), and α5α5α6(IV) (Khoshnoodi et al. 2006; Hudson 2004). In contrast to type I collagens that lose their NC1 domains after trimerization and form fibrillar networks, type IV collagen trimers form open, nonfibrillar networks through NC1-NC1 and amino-terminal interactions between trimers.

α1α1α2(IV) networks are ubiquitously present in basement membranes including the developing GBM. The α3α4α5(IV) network is restricted to mature GBM, Bowman's capsule, and distal tubule in the kidney and is also found in alveolar basement membranes and basement membranes of the testis, eye, and ear (Khoshnoodi et al. 2008). The α5α5α6(IV) network is restricted in the kidney to Bowman's capsule and distal tubular

and collecting duct basement membranes and is also found in epidermal basement membranes, the eye, bronchial epithelium, and smooth muscle (Peissel et al. 1995; Yoshioka et al. 1994).

Alport Syndrome

Epidemiology

Familial nephritis was first reported in the medical literature in the early 1900s (Guthrie 1902). In 1927, Cecil Alport published a description of a large family affected by kidney disease and deafness with a male predominance, and this entity thereafter took on his name (Alport 1927). It was not until 1972, after the widespread application of electron microscopy to kidney biopsies, that AS was recognized as a disorder of GBMs (Hinglais et al. 1972). In the 1980s, histochemical investigations determined that type IV collagen chains were missing in the GBM of individuals with AS (Kashtan et al. 1986; Olson et al. 1980). In 1990, mutations in *COL4A5* were identified as causative of X-linked AS (Barker et al. 1990). Shortly thereafter, mutations in *COL4A3* and *COL4A4* were identified in patients with autosomal recessive and autosomal dominant AS (Mochizuki et al. 1994; Jefferson et al. 1997). AS is a rare disease, affecting approximately 1:50,000 people and is seen in all ethnicities and races (Levy and Feingold 2000). AS accounts for approximately 0.5% of adults and 1.7% of children with end-stage kidney disease (ESKD) in the United States (Saran et al. 2016).

Genetics and Pathogenesis

AS can be inherited as an X-linked condition due to mutations in *COL4A5* on the X chromosome (Barker et al. 1990). Affected males are hemizygotes and have only one copy of a mutated *COL4A5* allele, whereas affected females are heterozygotes with one normal *COL4A5* allele and one mutated *COL4A5* allele. Due to X-inactivation, this leads to a mosaic expression pattern for α5(IV) in basement membranes in females. Autosomal recessive inheritance can also be observed due to homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* (Mochizuki et al. 1994). Digenic inheritance was also recently described (Mencarelli et al. 2015). Finally, autosomal dominant AS is caused by heterozygous mutations in *COL4A3* or *COL4A4* (Jefferson et al. 1997). Individuals with heterozygous mutations in *COL4A3* or *COL4A4* may exhibit classic AS or TBMN with non-progressive isolated microscopic hematuria. Classically, approximately 80% of AS was thought to be inherited in an X-linked manner, with 15% autosomal recessive and 5% autosomal dominant inheritance patterns observed. With the advent of next-generation sequencing, it is clear that autosomal dominant AS is more common than previously recognized, accounting for approximately 19–31% of affected families (Fallerini et al. 2013; Moriniere et al. 2014).

Over 1,200 pathogenic mutations have been identified in the *COL4A5* gene in patients with XLAS (Crockett et al. 2010; Hertz et al. 2012). There are no hot spots within the gene and mutations have been found in all 51 exons. *COL4A5* is a large gene and about 10–15% of mutations occur as spontaneous events; therefore a family history is not required to consider a diagnosis of AS. A variety of mutation types have been described: large rearrangements (~20%), small deletions and insertions (~20%), missense mutations altering a glycine residue (Gly-X-Y repeat region) in the collagenous domain of α5(IV) (30%), other missense mutations (~8%), nonsense mutations (~5%), and splice site mutations (~15%) (Jais et al. 2000). Genotype has a strong correlation with kidney disease progression in males with XLAS (Jais et al. 2000; Gross et al. 2002). In males with a large deletion, nonsense mutation, or a small mutation changing the mRNA reading frame, the risk of developing ESKD before age 30 is 90%. In contrast, splice site mutations and missense mutations have a less severe renal phenotype with 70% and 50%

reaching ESKD by age 30 years, respectively (Jais et al. 2000). In addition, the position of a glycine substitution within the gene may also impact the rate of disease progression as those with 5′ glycine missense mutations demonstrate a more severe phenotype than those with 3′ glycine mutations (Gross et al. 2002). In contrast to males with XLAS, there is no genotype-phenotype correlation in females with XLAS (Jais et al. 2003). In patients with autosomal recessive AS, the presence of at least one mutation leading to a premature stop codon was associated with earlier onset renal failure; however a genotype-phenotype correlation was not confirmed in other small studies (Storey et al. 2013; Oka et al. 2014). There does not appear to be a genotype-phenotype correlation in patients with autosomal dominant AS (Marcocci et al. 2009; Kamiyoshi et al. 2016). It is unclear why some individuals with one *COL4A3* or *COL4A4* mutation develop progressive kidney disease while others have a more benign clinical course (Lemmink et al. 1996).

Mutations in any of the *COL4A3*, *COL4A4*, or *COL4A5* genes may alter the composition of affected basement membranes. In the setting of severe mutations in *COL4A5* or severe homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* (deletions, frameshift mutations, premature stop codons leading to the absence of protein expression), the other collagen chains normally present in the type IV collagen trimer are degraded, and no α3α4α5(IV) trimers are deposited in basement membranes (Gunwar et al. 1998). In the absence of the α3α4α5(IV) network, the embryonal α1α1α2(IV) network persists. Missense mutations may produce misfolded proteins that are retained within the endoplasmic reticulum of the cell and degraded (Bateman et al. 2009). Alternately, missense mutations that affect the glycine residues involved in triple helix formation may lead to the formation of abnormally folded trimers that can be deposited into the basement membrane. In this case, an abnormal type IV collagen network is formed. The α3α4α5(IV) is not necessary for development of the GBM; however it is required for normal maintenance of the GBM structure and function due to its increased strength and stability compared to the α1α1α2(IV) network. This may be in part due to the greater number of disulfide bonds in the α3α4α5(IV) network making it more highly cross-linked and thus more resistant to proteases than the α1α1α2(IV) network (Gunwar et al. 1998; Zeisberg et al. 2006). The glomerular capillary walls of AS patients are mechanically weak and provoke pathologic stretch-related responses in glomerular cells (Meehan et al. 2009).

Clinical Features

Individuals with AS may have progressive chronic kidney disease (CKD), sensorineural hearing loss, and ocular abnormalities. The frequency of each finding depends on genotype, gender, and age. In general, patients with autosomal dominant AS and females with XLAS have less severe kidney disease and are less likely to have extrarenal manifestations (Marcocci et al. 2009; Savige et al. 2016).

Renal Findings

Males with XLAS and males and females with autosomal recessive AS have a similar clinical course. Kidney disease in AS progresses predictably through a series of clinical phases (Gross et al. 2012a) [Table 1, Fig. 1]. Phase 0 typically lasts from birth until late childhood or early adolescence and is characterized by isolated microscopic hematuria, with the absence of proteinuria and normal kidney function. Episodes of gross hematuria are common in up to 60% of affected individuals, particularly in association with infection, which may lead to diagnostic confusion with IgA nephropathy (Jais et al. 2000; Gubler et al. 1981).

Table 1 Clinical stages of Alport syndrome

Stage	Definition
0	Isolated microscopic hematuria +/− gross hematuria
I	Hematuria + microalbuminuria (30–300 mg albumin/g creatinine)
II	Hematuria + overt proteinuria (>300 mg albumin/g creatinine)
III	Decline of glomerular filtration rate by >25%
IV	End-stage renal disease

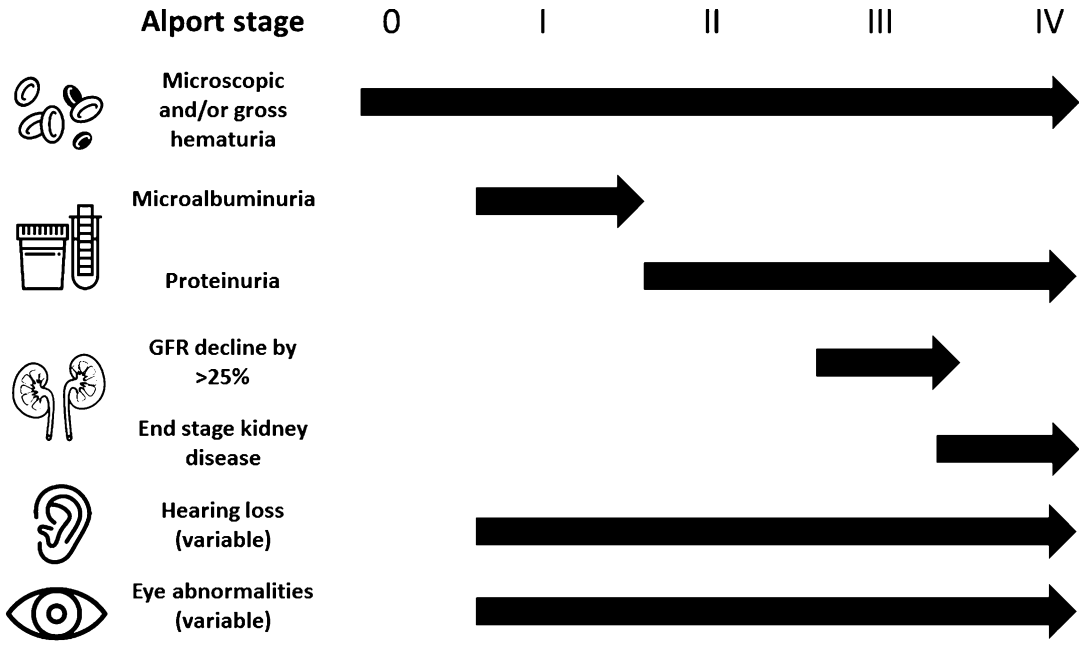

Fig. 1 Clinical stages of Alport renal disease and extra-renal manifestations over time. Alport renal disease follows a distinct progression from hematuria alone to microalbuminuria to proteinuria to GFR decline and ESKD. Onset of hearing loss and eye abnormalities is variable, but is rare prior to the onset of microalbuminuria

Persistent gross hematuria for months or years is also observed. In phase I, microalbuminuria (30–300 mg albumin/g creatinine) develops, but renal function remains normal (Kashtan et al. 2013; Gubler et al. 1981). Overt proteinuria (>300 mg albumin/g creatinine) signals the start of phase II and the beginning of a decline of renal function (Kim et al. 1995). Hypertension may be present in this phase, whereas blood pressures are generally normal prior to this. In phase III, individuals have a progressive decline of renal function with >25% reduction in GFR. The rate of passage through these phases is primarily a function of the causative mutation and gender. Progression from one phase to the next is utilized as an outcome measure in clinical trials of AS (Gross et al. 2012a). Females with XLAS and males and females with autosomal dominant AS demonstrate a similar progression through each phase; however the course may be slow enough that they do not require renal replacement therapy in their lifetime (Jais et al. 2003; Kamiyoshi et al. 2016).

In untreated males with XLAS, the risk of ESKD is 50% by age 25 years, 80% by 40 years, and 100% by age 60 year (Jais et al. 2000). With the adoption of early treatment with angiotensin-converting enzyme (ACE) inhibitor therapy, the age at ESKD may be increasing in this population (Gross et al. 2012b). In patients with autosomal recessive AS, the risk of ESKD is 50% by age 21–22 years; however ESKD as young as 9 years has been reported (Storey et al. 2013; Oka et al. 2014). In patients with autosomal dominant AS, the lifetime risk of ESKD is lower and most often occurs after the age of 40 years (Kamiyoshi et al. 2016; Marcocci et al. 2009). In one retrospective study, the median renal survival in autosomal dominant AS was 70 years (Kamiyoshi et al. 2016).

Females who are heterozygous for *COL4A5* mutations are commonly referred to as "carriers" of AS; however this term is not entirely accurate because almost all have some manifestation of disease (Rheault 2012; Savige et al. 2016). Hematuria is reported in 95.5% of affected women and proteinuria in 75% (Jais et al. 2003). Proteinuria is a risk factor for adverse pregnancy outcomes in general, and there are reports of hypertension,

preeclampsia, and decline in renal function during pregnancy in women with XLAS (Yefet et al. 2016; Hladunewich et al. 2016; Alessi et al. 2014). Females with XLAS have a smaller, but not insignificant, risk of ESKD compared to affected males. There was a 12% risk of ESKD by age 40 years and 30% by age 60 years reported by the European Community Alport Syndrome Concerted Action group (Jais et al. 2003). A more recent European report similarly showed 15.4% prevalence of ESKD in women with XLAS (Temme et al. 2012b). The explanation for the wide variation in outcomes for females with XLAS is unclear, but likely multifactorial. Risk factors for ESKD in females with XLAS include proteinuria and sensorineural hearing loss (Grunfeld et al. 1985; Jais et al. 2003). There does not appear to be a genotype-phenotype to explain the severity of kidney disease (Jais et al. 2003). X-inactivation, the process by which one X chromosome in females is silenced to adjust for gene dosage differences between males and females, may play a role as well in CKD progression in women with XLAS (Guo et al. 1995; Iijima et al. 2010; Rheault et al. 2010). Further studies are necessary to determine how to accurately predict the risk of progressive kidney disease in women who are affected with XLAS.

Sensorineural Hearing Loss

Newborn hearing screening is always normal in AS, but bilateral loss of perception of high-frequency sounds often becomes detectable in late childhood or early adolescence. The hearing loss is progressive and extends into the range of conversational speech with advancing age, often requiring amplification with hearing aids or cochlear implants. Sensorineural hearing loss (SNHL) is present in 50% of males with XLAS by approximately age 15, 75% by age 25, and 90% by age 40 (Jais et al. 2000). Similar to renal disease, genotype can predict the risk of SNHL in affected individuals. Severe mutations such as splice site mutations, deletions, insertions, and nonsense mutations are associated with a 90% risk of SNHL before the age of 30 years; however missense mutations are associated with a lower risk of SNHL of 60% at age 30 years (Jais et al. 2000). SNHL is less common in females with XLAS. About 10% of XLAS females have SNHL by 40 years of age and about 20% by age 60 (Jais et al. 2003). SNHL is common in autosomal recessive AS as well with approximately 40–66% of individuals affected (Storey et al. 2013; Oka et al. 2014). The risk of SNHL in autosomal dominant AS is lower than other genetic forms of the disease, with only 2–13% of individuals affected depending on the series (Kamiyoshi et al. 2016; Marcocci et al. 2009).

The SNHL in AS is due to the absence of the α3α4α5(IV) network in the cochlea (Wester et al. 1995). In normal cochleae, the α3α4α5(IV) network is expressed in a number of basement membranes including the spiral limbus, the spiral ligament, and stria vascularis and in the basement membrane situated between the organ of Corti and the basilar membrane (Kleppel et al. 1989; Cosgrove et al. 1998; Harvey et al. 2001). However, this network is absent in animal models of AS and in men with XLAS (Cosgrove et al. 1998; Harvey et al. 2001; Zehnder et al. 2005). Cochleae from men with XLAS demonstrate separation between the organ of Corti, the structure that produces nerve impulses in response to sound vibrations, and the underlying basement membrane (Merchant et al. 2004). This separation may be responsible for the decreased acuity of hearing observed in patients with AS. An alternative hypothesis is that hearing is impaired by changes in potassium concentration in the scala media, or cochlear duct, induced by the absence of the α3α4α5(IV) network in the stria vascularis (Gratton et al. 2005). Further research is required to elucidate the exact cause of hearing loss in patients with AS.

Ocular Findings

Anomalies of the lens, retina, and cornea are common in patients with AS (Savige et al. 2015). The α3α4α5(IV) network is normally found in several basement membranes in the eye including the lens capsule, corneal basement membrane, Descemet's membrane, internal limiting membrane of the retina, and the retinal pigment epithelium basement membrane (Kleppel et al. 1989; Cheong et al. 1994; Ohkubo et al. 2003; Chen et al. 2003b).

Ocular anomalies are more common in males with XLAS and males and females with autosomal recessive AS, affecting 35–80% of affected individuals (Jais et al. 2000; Wang et al. 2014; Oka et al. 2014; Storey et al. 2013). Ocular findings are less common in women with XLAS (~15%) and are almost never observed in autosomal dominant AS (Jais et al. 2003; Marcocci et al. 2009; Kamiyoshi et al. 2016).

Anterior lenticonus, a conical protrusion of the lens anteriorly through the capsule, is diagnostic for AS and is present in 13% of males with XLAS (Jais et al. 2003). Some reports suggest a higher incidence of anterior lenticonus in autosomal recessive AS with up to 80% affected in one series (Wang et al. 2014). Lenticonus generally presents in middle age, after the development of CKD. Due to the abnormal shape of the lens, vision may be affected. The absence of the α3α4α5(IV) network in the lens capsule leads to abnormal splits in the capsule that may rupture, allowing protrusion of the lens. The lens capsules of Alport patients with anterior lenticonus are thin with focal areas of dehiscence, suggesting that the lens capsule lacks the mechanical strength to maintain normal lens shape (Ohkubo et al. 2003; Sonarkhan et al. 2014; Kato et al. 1998). Increased distensibility in the lens capsule has been demonstrated in experimental models of AS and correlates with the observed clinical findings (Gyoneva et al. 2013). Healing of lens capsule ruptures may lead to cataract formation (Sonarkhan et al. 2014). Anterior lenticonus and cataracts can successfully be treated with lens replacement and do not recur (Liu et al. 2008).

Retinal anomalies are also common in AS including central or peripheral fleck retinopathy. Central fleck retinopathy appears as whitish-yellow perimacular dots and flecks that are present from early adolescence and is more common in patients with more severe kidney disease. It is present in 50–60% of men with XLAS and men and women with autosomal recessive AS and in ~15% of women with XLAS (Wang et al. 2014). Peripheral retinopathy appears as asymmetric patches of confluent flecks and is the most common ocular finding in patients with AS. With either type of retinopathy, visual acuity is normal and no treatment is required.

Corneal erosions can be observed in <10% of patients with AS due to abnormal α3α4α5(IV) network in the corneal subepithelium (Rhys et al. 1997; Burke et al. 1991). Posterior polymorphous corneal dystrophy is a more serious corneal issue that is visualized as vesicular lesions, linear bands, or irregular diffuse opacities of the posterior corneal surface involving Descemet's membrane by slit lamp exam (Teekhasaenee et al. 1991). Affected patients may be asymptomatic or have recurrent episodes of eye watering, foreign body sensation, and photophobia. Treatment may require corneal transplant.

Other Clinical Associations

The association of XLAS with smooth muscle tumors (leiomyomas) of the respiratory, gastrointestinal, and female reproductive tracts has been described in some families (Zhou et al. 1993; Antignac and Heidet 1996; Heidet et al. 1997). Symptoms such as difficulty swallowing, vomiting, epigastric or retrosternal pain, recurrent bronchitis, shortness of breath, cough, and stridor may appear in late childhood or adolescence. This syndrome arises from a contiguous gene deletion on the X chromosome involving exon 1 of *COL4A5*, the common promoter region that regulates gene expression of *COL4A5* and *COL4A6*, and the first two exons of the adjacent *COL4A6* gene (Zhou et al. 1993). The genotype-phenotype relationship in this disorder was put into question recently by a report that showed that deletions in this region may not always lead to leiomyomas and conversely that some families with XLAS and leiomyomas do not have deletions involving the common promoter region and *COL4A6* (Sa et al. 2013).

Deletions that extend downstream of the 3′ end of the *COL4A5* gene are associated with mental retardation, midface hypoplasia, and elliptocytosis in a small number of XLAS males (Jonsson et al. 1998; Vitelli et al. 1999). Abnormalities in arterial vessels have been described in males with XLAS including aortic root dilatation and aneurysms of the thoracic and abdominal aorta, possibly due to abnormalities of the α5α5α6(IV) network normally present in arterial smooth muscle basement membranes (Kashtan et al. 2010).

Renal Histopathology

Children with AS may have normal findings by light microscopy before about 5 years of age. In older patients, mesangial hypercellularity and matrix expansion may be observed. By age 10 years, focal segmental glomerulosclerosis (FSGS), tubular atrophy, and interstitial fibrosis become the predominant light microscopic abnormalities (Kashtan et al. 1998). Although some patients exhibit increased numbers of immature glomeruli or interstitial foam cells, these changes are not specific for AS.

Electron microscopy of kidney biopsy specimens is frequently diagnostic (Fig. 2). In early childhood, the predominant ultrastructural lesion in males is diffuse thinning of the GBM (Fig. 2b). This may be identical in appearance to patients with thin basement membrane nephropathy (TBMN), and differentiation between these two entities can be difficult in young children. The classic ultrastructural lesion in AS is diffuse thickening of the glomerular capillary wall, accompanied by "basket-weave" transformation of the lamina densa and intramembranous vesicles, scalloping of the epithelial surface of the GBM,

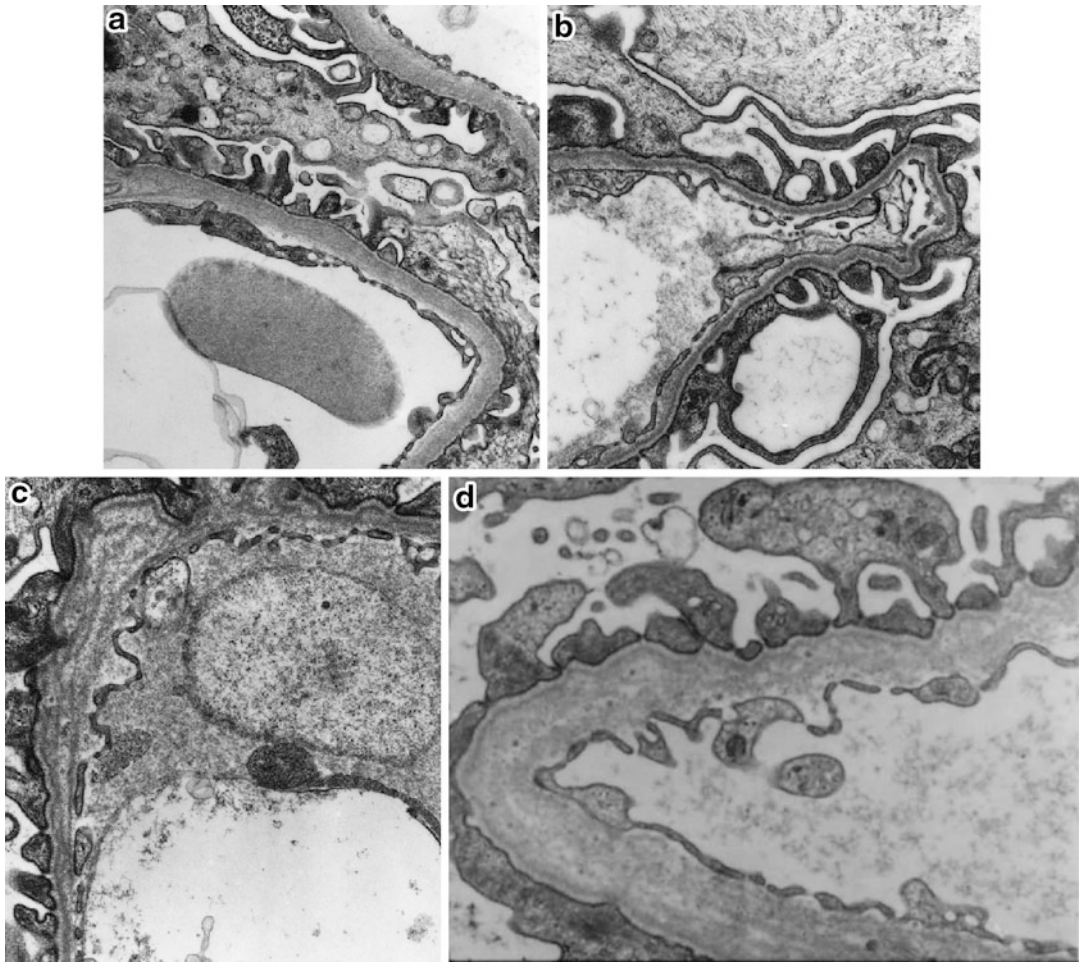

Fig. 2 Electron micrographs from patients with hematuria. Magnifications are similar, but not identical. (**a**) Normal GBM. (**b**) Attenuated GBM in a patient with TBMN. (**c**) This female with a heterozygous *COL4A5* mutation exhibits both thin and split, lamellated GBM. (**d**) This male with XLAS shows diffuse thickening and lamellation of GBM (Reprinted from Kashtan (2002), with permission from Elsevier)

and effacement of overlying podocyte foot processes (Fig. 2c, d). These changes are more prevalent in males with XLAS and males and females with autosomal recessive AS, and the percentage of GBM displaying this lesion increases progressively with age (Rumpelt 1980). Affected females with XLAS can display a spectrum of lesions, demonstrating either predominantly normal-appearing GBM, focal GBM thinning, diffuse GBM thinning, thickening/basket weaving, or diffuse basket weaving. The classic GBM lesion is not found in all kindreds with AS. Recently, a number of families with primary FSGS with or without the classic AS basement membrane lesion have been found to have mutations in *COL4A3* or *COL4A4* (Deltas and Pierides 2015; Malone et al. 2014). These findings expand the spectrum of histopathology phenotype associated with type IV collagen mutations (Miner 2014).

Routine immunofluorescence microscopy is normal or shows nonspecific deposition of immunoglobulins. In contrast, specific immunostaining for type IV collagen α chains is frequently diagnostic and can distinguish between the X-linked and autosomal recessive forms of the disease (Fig. 3). In approximately 80% of XLAS males, immunostaining of kidney biopsy specimens for α3(IV), α4(IV), and α5(IV) chains is completely negative (Kashtan et al. 1996). About 60–70% of XLAS females exhibit mosaic expression of these chains, while in the remainder of females, immunostaining for these chains is normal. It is important to note that normal immunostaining for type IV collagen does not exclude a diagnosis of AS in males or females. Mutations in *COL4A3* and *COL4A4* in patients with autosomal recessive AS may prevent expression of α3α4α5(IV) trimers but will have no effect on expression of α5α5α6(IV) trimers. Therefore, in kidney biopsy specimens from patients with autosomal recessive AS, immunostaining for α3(IV), α4(IV), and α5(IV) chains is negative in

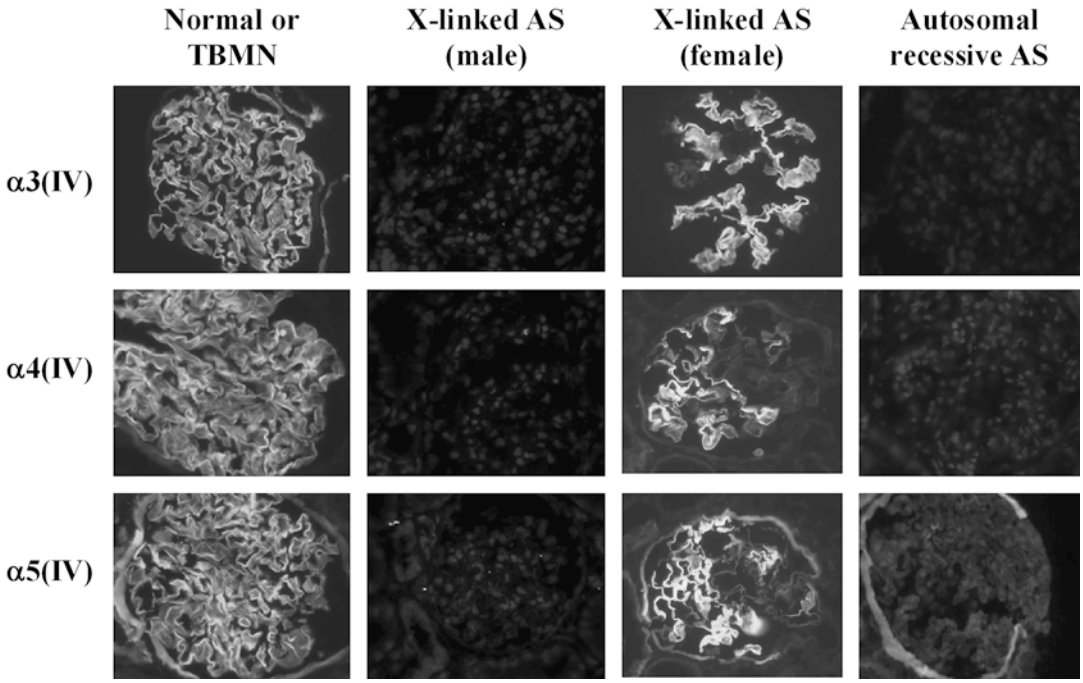

Fig. 3 Glomerular immunofluorescence microscopy in XLAS and ARAS. α3(IV), α4(IV), and α5(IV) chains are expressed in the GBM in patients with normal glomeruli and TBMN. All three chains are missing in affected males with XLAS. A mosaic pattern is present for heterozygous females with XLAS due to X-inactivation. In ARAS, α3(IV), α4(IV), and α5(IV) chains are absent from the glomerulus; however α5(IV) is visible in Bowman's capsule as part of the α5α5α6 network (Reprinted from Kashtan (2005), with permission from Elsevier)

the GBM. However, expression of α5(IV) in Bowman's capsule, distal tubular basement membranes, and collecting duct basement membranes remains positive for α5(IV), due to the normal expression of α5α5α6(IV) trimers. Immunostaining in autosomal dominant AS is normal.

Skin Histopathology

In some situations, a skin biopsy can be considered as an initial diagnostic step. Normal epidermal basement membranes contain the α5α5α6(IV) trimer. Consequently, about 80% of males with XLAS can be diagnosed by skin biopsy on the basis of the absence of α5(IV) expression in EBM. In 60–70% of XLAS females, there is a mosaic, discontinuous expression pattern for α5(IV) by immunostaining. Epidermal basement membrane expression of α5(IV) is normal in patients with autosomal recessive or autosomal dominant AS.

Diagnosis and Differential Diagnosis

Accurate, early diagnosis of AS is important in order to initiate potentially beneficial therapy when appropriate and to identify other family members who may be at risk of kidney disease. Differentiation between AS and other causes of glomerular hematuria can be performed based on careful clinical evaluation, examination of pedigree data, selective application of invasive diagnostic tests such as skin or kidney biopsy, hearing assessment, and genetic testing (Table 2).

In children with familial glomerular hematuria, alternate potential diagnoses include the autosomal dominant *MYH9* disorders (Epstein and Fechtner syndromes, in which thrombocytopenia and large platelets are a constant feature, familial IgA nephropathy, X-linked membranoproliferative glomerulonephritis, and familial hemolytic uremic syndrome) (Bostrom and Freedman 2010; Kiryluk and Novak 2014; Redahan et al. 2014). The presence of autosomal dominant microscopic hematuria in a family with no history of ESKD or hearing loss is suggestive of TBMN (see below), but AS cannot be definitively excluded. In children with no family history of hematuria, AS is still possible since 10–15% of cases are due to spontaneous mutations. Alternately the differential diagnosis may include IgA nephropathy, C3 glomerulopathy, lupus nephritis, active or resolving postinfectious glomerulonephritis, Henoch-Schönlein nephritis, and TBMN. Some of these entities may be diagnosed or suspected based on clinical and laboratory findings; however others can only be confirmed by kidney biopsy.

In a child at risk for AS based on family history, the presence of persistent hematuria is diagnostic. Biopsy or genetic studies are required when clinical and pedigree information cannot rule out AS in a patient with hematuria (Savige et al. 2013). Several options are available for confirming a diagnosis of AS including skin biopsy, kidney biopsy, and genetic testing. Skin biopsy may be utilized as the initial invasive diagnostic procedure in patients suspected of having XLAS because it is less invasive and less expensive than a kidney biopsy. Unfortunately, not all centers offer this procedure and this may limit its utility as a diagnostic test. On skin biopsy, the majority of subjects with XLAS will display abnormal expression of the α5(IV) chain in epidermal basement membranes, as described above. Skin biopsy is normal in individuals with autosomal recessive and autosomal dominant AS and should not be utilized if this diagnosis is suspected. If skin biopsy is not diagnostic, kidney biopsy with type IV collagen immunostaining and careful examination of GBM ultrastructure by electron microscopy can be performed.

Mutation analysis using conventional Sanger sequencing is capable of identifying *COL4A5* mutations in 80%–90% of males with XLAS (Martin et al. 1998). Next-generation sequencing has supplanted Sanger sequencing in recent years and allows for simultaneous evaluation of *COL4A3, COL4A4*, and *COL4A5* mutations (Moriniere et al. 2014; Kovacs et al. 2016). Identification of a specific mutation can provide some prognostic information about the risk of kidney disease progression and risk of associated symptoms such as hearing loss and eye findings in a patient (Jais et al. 2000). Once a new diagnosis of

Table 2 Type IV collagen disorders.

	Gene	Protein	Risk of ESKD	Kidney pathology: IF	Kidney pathology: EM	Extrarenal manifestations
Alport syndrome						
X-linked males	*COL4A5*	α5(IV)	100%	Absent α3α4α5(IV) in GBM in 80%	GBM thinning (early) GBM lamellation (late)	Hearing loss Lenticonus Retinopathy
X-linked females	*COL4A5*	α5(IV)	30% by age 60 years	Mosaic α3α4α5(IV) in GBM in 60–70%	GBM thinning (early) GBM lamellation (late)	Hearing loss Retinopathy
Autosomal recessive	*COL4A3* or *COL4A4* (biallelic)	α3(IV) α4(IV)	100%	Absent α3α4α5(IV) in GBM in majority	GBM thinning (early) GBM lamellation (late)	Hearing loss Lenticonus Retinopathy
Autosomal dominant	*COL4A3* or *COL4A4* (heterozygous)	α3(IV) α4(IV)	50% by 50–70 years	Normal α3α4α5(IV) GBM	GBM thinning (early) GBM lamellation (late)	Hearing loss Retinopathy
Thin basement membrane nephropathy						
Autosomal dominant	*COL4A3* or *COL4A4* (heterozygous)	α3(IV) α4(IV)	0	Normal α3α4α5(IV) GBM	GBM thinning	None
HANAC syndrome						
Autosomal dominant	*COL4A1*	α1(IV)	Not reported	Normal α3α4α5(IV) GBM	Normal GBM thickening and splitting of BM in tubules, Bowman's capsule, and interstitial capillaries	Arterial aneurysms muscle cramps

BM basement membrane, *EM* electron microscopy, *ESKD* end-stage renal disease, *GBM* glomerular basement membrane, *HANAC* hereditary angiopathy with nephropathy, aneurysms, and cramps, *IF* immunofluorescence microscopy

AS is made in a family, all potentially affected family members including females should be screened with a urinalysis to identify those at risk of progressive kidney disease (Savige et al. 2013).

Treatment

The goal of treatment in children and adults with AS is to slow the progression of CKD and to delay the need for dialysis or kidney transplantation. There are no currently approved therapies for AS. Recommendations for treatment are derived from expert consensus, uncontrolled studies, retrospective registry studies, and data from treatment in animal models.

Treatment of mice and dogs with AS with angiotensin-converting enzyme (ACE) inhibition leads to significantly prolonged renal survival (Grodecki et al. 1997; Gross et al. 2003). Uncontrolled studies in pediatric and adult patients with AS have shown that angiotensin blockade can transiently reduce proteinuria (Cohen and Lemann 1996; Proesmans and Van Dyck 2004). In a large multicenter, randomized, double-blind study comparing losartan with placebo or amlodipine in proteinuric children, evaluation of the subpopulation with AS demonstrated a significant reduction in proteinuria in the losartan-treated group over 12 weeks of therapy (Webb et al. 2011). A 3-year extension of this study showed comparable efficacy of either

enalapril or losartan in reducing proteinuria in children with AS (Webb et al. 2013). A retrospective review of Chinese children with AS showed a decline in proteinuria with ACE inhibition over the first 2 years of therapy that was sustained over 5 years of follow-up (Zhang et al. 2016). A report from the European Alport Registry, which included 283 patients followed over 20 years, compared renal outcomes in AS patients initiated on therapy with ACE inhibitors at various timing: microalbuminuria, proteinuria, or in CKD (CKD) stage III–IV (Gross et al. 2012b). Findings from this retrospective review suggested that earlier treatment with ACE inhibitors is more beneficial. They demonstrated a delay in renal replacement therapy by 3 years in the treated CKD group and by 18 years in the treated proteinuric group (Gross et al. 2012b). Similar benefits of ACE inhibition were found in women with XLAS or individuals heterozygous for *COL4A3* or *COL4A4* mutations (Temme et al. 2012b). Side effects of ACE inhibition are rarely reported but include hyperkalemia, cough, and hypotension. Based on these promising retrospective findings, a prospective, double-blind, randomized, placebo-controlled trial is underway in Germany to compare outcomes in children with AS treated with the ACE inhibitor ramipril vs. placebo at an early disease time point (microalbuminuria or isolated hematuria) (Gross et al. 2012a). Prospective trials in AS are challenging due to the rare nature of the disease and slow progression to hard end points such as doubling of serum creatinine or ESKD.

Clinical practice guidelines have been developed to guide treatment of children with AS (Kashtan et al. 2013) (Table 3). Treatment with ACE inhibitors or angiotensin receptor blockers should be offered to all affected individuals, male or female, with AS and overt proteinuria (Kashtan et al. 2013). ACE inhibition should be considered for affected individuals at the microalbuminuria stage if they have either a family history of ESKD at a young age (<30 years) or a known severe *COL4A5* mutation (deletion, splice site, or nonsense mutation). Women of childbearing age, including adolescents, should be carefully counseled about the risks of birth defects while taking ACE inhibitors and risks and benefits of treatment considered prior to initiation. Treatment of hypertension and other manifestations of CKD is similar to children with other etiologies of CKD.

In animal models of AS, several novel strategies have proven effective in prolonging renal survival including TGFβ-1 inhibition (Sayers et al. 1999), chemokine receptor 1 suppression (Ninichuk et al. 2005), administration of bone morphogenic protein-7 (Zeisberg et al. 2003), blockade of matrix metalloproteinases (Zeisberg et al. 2006), anti-microRNA-21 therapy (Gomez et al. 2015), treatment with mycophenolate mofetil (Petrova et al. 2014) or paricalcitol (Rubel et al. 2014), and bone marrow transplantation (Sugimoto et al. 2006; Gross et al. 2009a). Cyclosporine therapy slowed the progression of kidney disease in a dog model of AS; however human studies have demonstrated significant

Table 3 Recommendations for treatment based on urinary findings and anticipated disease course

	Family history of early ESKD (<30 years) or severe[a] COL4A5 mutation		Family history of late ESKD (>30 years) or less severe[b] COL4A5 mutation	
	Males	Females	Males	Females
Hematuria	Intervention prior to onset of microalbuminuria is not recommended at this time	No	No	No
Hematuria + microalbuminuria	Consider intervention	Consider intervention	No	No
Hematuria + proteinuria	Yes	Yes	Yes	Yes

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ESKD end stage renal disease
[a]Deletion, nonsense, or splice site mutation
[b]Missense mutation

nephrotoxicity and adverse effects, and this treatment is no longer recommended (Chen et al. 2003a; Charbit et al. 2007; Massella et al. 2010; Sugimoto et al. 2014). Gene therapy, the transfer of wild-type *COL4A5* genes into glomerular cells to restore the normal composition of the GBM, is an attractive potential therapy for Alport syndrome. Proof of concept studies in mice has demonstrated that restoration of the normal collagen α3α4α5(IV) network in Alport mice slows the progression of kidney disease and prolongs lifespan (Lin et al. 2014). However, application to humans with Alport syndrome is still in development and is limited by the ability to deliver genes to the glomerulus.

Kidney Transplantation

Outcomes following kidney transplantation in patients with AS are generally excellent with graft survival as good or better than other forms of glomerulonephritis (Yilmaz et al. 2015; Temme et al. 2012a). Clinicians involved in transplantation of AS patients must be aware of the two important aspects of the disease. First, the donor selection process must avoid accepting donors who may be at risk for CKD themselves. Second, post-transplant management should provide surveillance for post-transplant anti-GBM nephritis.

As discussed above, women with XLAS are at risk for progressive CKD (Rheault 2012). Nephrectomy in this population may lead to poor outcomes in the donor including hypertension, proteinuria, or more rapid progression of CKD. A report from Germany described five women with XLAS and one ARAS carrier who served as kidney donors (Gross et al. 2009b). One donor had proteinuria prior to transplant and all had microscopic hematuria. Three donors developed new-onset hypertension and two developed new proteinuria, while renal function declined by 25–60% over 2–14 years after donation in four of the donors, highlighting the increased donor risk in this population (Gross et al. 2009b). In addition, receipt of a kidney from a heterozygous carrier may not be optimal for the recipient. A donor kidney from a woman with XLAS may have shorter graft survival than would be expected from a graft with completely normal basement membranes; however this has not been studied.

In males with XLAS and a complete absence of α5(IV) in the GBM, autoantibodies may develop that then cause anti-GBM nephritis after transplant in about 3% of patients (Dehan et al. 1996; Brainwood et al. 1998; Kashtan 2006). Onset is typically in the first year after transplant and presents with hematuria or elevated creatinine. Kidney allograft biopsy with routine immunofluorescence should be performed early in the evaluation of AS patients after transplantation if anti-GBM disease is suspected. Anti-GBM nephritis often results in irreversible graft failure within weeks to months of diagnosis. Treatment with cytotoxic therapy and plasmapheresis have been attempted with little success (Kashtan 2006). The risk of recurrence in subsequent grafts is high. Females with XLAS are at little or no risk of developing anti-GBM nephritis after transplantation to the presence of at least some α5(IV) in the kidney due to X-inactivation. Both males and females with autosomal recessive AS can develop post-transplant anti-GBM nephritis due to antibodies directed against the α3(IV) chain (Brainwood et al. 1998; Kalluri et al. 1995).

Thin Basement Membrane Nephropathy

Epidemiology

The prevalence of thin basement membrane nephropathy (TBMN) is estimated at 1–2% of the general population, making it one of the most common causes of glomerular hematuria (Haas 2006). In children undergoing kidney biopsy for persistent microscopic hematuria without proteinuria, 15–50% are diagnosed with TBMN (Trachtman et al. 1984; Schroder et al. 1990; Piqueras et al. 1998). Classically, families with isolated microscopic hematuria transmitted in an autosomal dominant manner were described as having "benign familial hematuria" (Marks and Drummond 1969; McConville et al. 1966). Kidney biopsies in these individuals are usually

normal except for thin GBMs compared to age- and sex-matched controls (Haas 2006). Over time, it has become clear that these pathological findings are not only seen in benign conditions and can be observed in early AS or women with XLAS who have a risk of progressive CKD. The more descriptive term of "thin basement membrane nephropathy (TBMN)" has gradually supplanted the prior nomenclature to more accurately describe the associated findings and risks. While usually nonprogressive, careful evaluation and follow-up of individuals with TBMN are required to monitor for progressive kidney disease.

Genetics

In discussing the genetics of TBMN, it is important to recall that GBM thinning is a pathological description rather than a distinct, homogeneous entity. The first causative mutation for TBMN was identified in 1996 when Lemmink and colleagues reported a heterozygous *COL4A3* mutation in a family with autosomal dominant hematuria (Lemmink et al. 1996). Since then, a number of heterozygous mutations in *COL4A3* and *COL4A4* (the carrier state for autosomal recessive AS) have been found in association with TBMN (Rana et al. 2005; Nabais Sa et al. 2015). GBM thinning can also be seen in early kidney biopsies in individuals with hemizygous or heterozygous mutations in *COL4A5* (XLAS) or biallelic mutations in *COL4A3* or *COL4A4* (autosomal recessive AS). Approximately 40–50% of families with TBMN will have a mutation in *COL4A3* or *COL4A4* identified or demonstrate linkage to this region. Mutations at other unknown genetic loci may exist, but have not been identified. The factors that influence clinical outcome in individuals with heterozygous mutations in *COL4A3* or *COL4A4* are unknown, but may be related to genotype or the presence of modifier genes. Recently, co-inheritance of podocin variants with heterozygous mutations in *COL4A3* and *COL4A4* was found to be associated with worse renal outcomes (Stefanou et al. 2015).

Clinical Findings

Children with TBMN typically present with persistent microscopic hematuria, although intermittent hematuria or even gross hematuria may be observed. The penetrance of hematuria is only approximately 70% (Savige et al. 2003). TBMN is the most common cause of persistent microscopic hematuria in children and adults and is common in the general population with an estimated prevalence of 1–2% (Tryggvason and Patrakka 2006; Haas 2006). A family history of dominantly inherited hematuria with a negative history of renal failure or hearing loss is typical. Adults with familial hematuria may not be aware that they are affected, and urinalyses on first degree family members may be useful to make the diagnosis in a child with isolated microscopic hematuria (Blumenthal et al. 1988).

Proteinuria is rare in childhood but can be observed in up to 30% of adult patients (Gregory 2005; van Paassen et al. 2004). CKD is observed in <5% of affected adults (Gregory 2005; Auwardt et al. 1999; Nieuwhof et al. 1997; van Paassen et al. 2004). Individuals with progressive CKD and a heterozygous mutation in *COL4A3* or *COL4A4* may be more accurately described as having autosomal dominant AS rather than TBMN. Extrarenal abnormalities, such as hearing loss or ocular defects, are rare and probably not related to the underlying type IV collagen mutation.

Renal Histopathology

Light and routine immunofluorescence microscopy typically is entirely normal. Adult patients with TBMN who have proteinuria, CKD, or hypertension may exhibit premature glomerular obsolescence (Nieuwhof et al. 1997). In contrast to patients with AS, type IV collagen immunostaining is normal (Kashtan et al. 1986; Pettersson et al. 1990). Electron microscopy is required for diagnosis and identifies the characteristic isolated thinning of the GBM with preservation of normal podocyte anatomy (Fig. 2b). Patients with TBMN typically exhibit diffuse thinning of the lamina densa. The

thickness of normal GBM is age and sex dependent (Haas 2006). Both the lamina densa and the GBM increase rapidly in thickness between birth and age 2 years, followed by gradual thickening throughout childhood and adolescence (Vogler et al. 1987). Normal GBM thickness of adult men is greater than that of adult women (Steffes et al. 1983). Because a variety of techniques can be used to measure GBM width, there is no standard definition of "thin" GBM, and local normative values should be taken into consideration. The cutoff value in adults ranges from 250 nm to 330 nm, depending upon the technique (Dische 1992; Tiebosch et al. 1989). For children, the normal range for GBM width is >200–250 nm (250 nm is within 2SD of the mean at age 11) (Schroder et al. 1990; Lang et al. 1990; Milanesi et al. 1984).

Diagnosis and Differential Diagnosis

In a child with persistent isolated microscopic hematuria of glomerular origin, a strong family history of hematuria inherited in an autosomal dominant manner, and a negative family history for renal failure or hearing loss, a presumptive clinical diagnosis of TBMN can be made without need for a kidney biopsy. Genetic testing is not required. If there are atypical findings (no family history of hematuria, presence of non-orthostatic proteinuria or microalbuminuria, elevated creatinine, recurrent gross hematuria, etc.), then a kidney biopsy may be required for diagnosis. IgA nephropathy and AS are alternate diagnoses that may be seen in this clinical scenario.

In the young child with GBM thinning by kidney biopsy and a negative or limited family history, the challenge for the physician is to distinguish nonprogressive TBMN from AS. Audiometry and ophthalmologic examination may be helpful if abnormal, but may not be useful given the usual absence of these abnormalities in young children. Immunostaining for type IV collagen α3(IV), α4(IV), and α5(IV) chains can be particularly helpful in these situations to identify individuals with AS who may be early in their clinical course or women with XLAS. Genetic testing for mutations in all three associated genes (*COL4A3-COL4A5*) is recommended in individuals with TBMN and proteinuria, renal impairment, or when AS cannot be excluded based on family history.

Monitoring and Treatment

Individuals with TBMN should be monitored every 1–2 years for progression of their disease including evaluation for proteinuria, hypertension, and renal impairment and to update the family history. Treatment for children and adults with TBMN is not recommended since the course is typically nonprogressive. The presence of proteinuria should prompt treatment with an ACE inhibitor, similar to patients with AS (Savige et al. 2013; Kashtan et al. 2013).

Hereditary Angiopathy with Nephropathy, Aneurysms, and Cramps (HANAC) Syndrome

Clinical Features and Histopathology

Hereditary angiopathy with nephropathy, aneurysms, and cramps (HANAC) syndrome is a very rare systemic disorder. Kidney involvement in HANAC syndrome is variable and may include isolated microscopic hematuria or cortical and/or medullary cysts (Plaisier et al. 2007; Gale et al. 2016). In reports of kidney biopsy findings in HANAC syndrome, light and immunofluorescence microscopy is normal (Plaisier et al. 2007). By electron microscopy, irregular thickening and splitting of the basement membranes of the tubules, Bowman's capsule, and interstitial capillaries are observed. Electron-lucent areas can also be present. Type IV collagen immunostaining is normal. Progressive CKD can be observed, but generally in individuals after the age of 40–50 years.

Patients with HANAC syndrome present with an angiopathy that affects both small and large vessels leading to retinal tortuosity and retinal hemorrhages, leukoencephalopathy, and intracranial aneurysms (Plaisier et al. 2007). They often have muscle cramps with persistent elevated creatine kinase levels.

Genetics

Mutations in *COL4A1* encode the α1 chain of type IV collagen HANAC syndrome in an autosomal dominant manner (Plaisier et al. 2007). α1(IV) is expressed in the GBM during development and appears to be important for normal podocyte differentiation (Chen et al. 2016). Mutations are localized in the region of the protein that encompasses the major integrin binding site, suggesting that abnormal interactions between cells and the basement membrane may underlie the systemic defects observed in this syndrome (Plaisier et al. 2010). The type of mutation influences the patient phenotype in individuals with *COL4A1* mutations (Chen et al. 2016).

Monitoring and Treatment

No specific treatment is available for individuals with HANAC syndrome, and supportive care is tailored to individual signs and symptoms. Blood pressure, urinalysis, and creatinine should be monitored routinely and hypertension promptly treated to reduce risk of stroke. Ophthalmologic evaluation is recommended at diagnosis and routinely thereafter to monitor for retinal involvement, glaucoma, and cataracts. Brain imaging to assess for asymptomatic cerebral aneurysms should be performed at diagnosis. Genetic counseling is recommended to review risk of disease in other family members and to review reproductive risk if applicable.

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Other Genetic Glomerular Disorders

12

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Abstract

A number of rare glomerular disorders have been identified that cannot easily be categorized along with other glomerular diseases. Knowledge of rare glomerular disorders is important for practicing adult and pediatric nephrologists to ensure early diagnosis, treatment, and identification of possible affected family members. This chapter will review the type III collagen glomerulopathies (nail-patella syndrome and collagenofibrotic glomerulopathy), fibronectin glomerulopathy, lecithin/cholesterol acyltransferase (LCAT) deficiency, *MYH9*-related disorders, and Pierson syndrome.

Keywords

Type III collagen · Nail-patella syndrome · Collagenofibrotic glomerulopathy · Fibronectin glomerulopathy · Pierson syndrome · Epstein syndrome · Fechtner syndrome · Nonmuscle myosin · Microcoria

Nail-Patella Syndrome

Background and Epidemiology

In the kidney, type III collagen is normally found in the blood vessel walls and interstitium, but not in glomeruli (Yoshioka et al. 1989). There are two rare disorders wherein type III collagen accumulates in glomeruli: nail-patella syndrome and collagenofibrotic glomerulopathy (Table 1). Type III collagen can be identified by immunofluorescent microscopy or by electron microscopy (EM). By EM, type III collagen fibrils are long and straight, in parallel array, and have a distinct periodicity of approximately 60 nm. These collagen fibers are typically curved or frayed compared to straight fibers typically observed for type III collagen in the interstitium.

Nail-patella syndrome is a rare autosomal dominant disorder that classically presents with the tetrad of abnormalities in the nails, patellae, and elbows along with the presence of iliac horns. Renal involvement occurs in approximately one third of affected patients and can present as proteinuria with or without hematuria associated with the accumulation of type III collagen in the glomerular basement membrane. The prevalence of nail-patella syndrome is estimated at 1 in 50,000 worldwide; however this may be an underestimate due to undiagnosed individuals with a mild phenotype (Levy and Feingold 2000).

Genetics

Nail-patella syndrome is inherited in an autosomal dominant manner due to mutations in *LMX1B*, LIM homeobox transcription factor 1 beta (Vollrath et al. 1998; Dreyer et al. 1998). The LMX1B protein is involved in pattern formation during limb and kidney development and is expressed in glomerular podocytes beginning at the S-shaped body stage of development (Chen et al. 1998). The pathophysiological consequences of mutations in *LMX1B* are not clear. In mice, loss of Lmx1b expression leads to reduction in GBM expression of the α3 and α4 chains of type IV collagen and the slit diaphragm proteins podocin and CD2AP; however, this is not observed in humans with nail-patella syndrome (Morello et al. 2001; Miner et al. 2002; Rohr et al. 2002; Heidet et al. 2003). LMX1B may play a role

Table 1 Comparison of clinical features of the type III collagen glomerulopathies

	Nail-patella syndrome	Collagenofibrotic glomerulopathy
Inheritance	Autosomal dominant	Unknown
Affected gene	*LMX1B*	Unknown
Nail and skeletal abnormalities	Hypoplastic or dysplastic nails small or absent patellae	None
	Iliac horns	
	Elbow abnormalities	
Nephropathy	Proteinuria ~3–5% risk of ESKD	Proteinuria may be nephrotic range ~50% risk of ESKD
Kidney biopsy: light microscopy	Nonspecific (focal segmental glomerulosclerosis, mild mesangial hypercellularity, or no changes)	Increased mesangial matrix with normal mesangial cellularity
		Thickened capillary walls
Kidney biopsy: electron microscopy	Thickened GBM with "moth-eaten" lamina densa	Lamina densa appears normal (not "moth-eaten")
	Type III collagen fibrils in the lamina densa by phosphotungstic acid stain	Type III collagen fibrils in the mesangium and glomerular capillary walls

ESKD end-stage renal disease, *GBM* glomerular basement membrane

in the maintenance of differentiated podocytes in adult kidneys through effects on actin cytoskeletal organization (Burghardt et al. 2013).

LMX1B consists of three functional domains: two LIM domains and one homeodomain. The homeodomain is highly conserved through evolution and is required for DNA binding and transcriptional regulation. Individuals with mutations in the homeodomain of *LMX1B* are more likely to have renal involvement, although the mechanism of action is unclear (Bongers et al. 2005). Haploinsufficiency, whereby a single functioning copy of a gene is not sufficient to produce enough protein product for normal function, appears to be the mechanism by which heterozygous mutations or deletions in *LMX1B* cause disease, rather than a dominant negative effect (Bongers et al. 2008). Recently, several families with autosomal dominant focal segmental glomerulosclerosis (FSGS) with mutations in *LMX1B* have been described who do not have the classical nail or bony findings. All of these patients had missense mutations in R246, a residue that is important in maintaining the interaction between the homeodomain and DNA (Boyer et al. 2013; Isojima et al. 2014). With increased access to genetic testing worldwide, the incidence is likely to rise and the phenotypic spectrum of *LMX1B* mutations is sure to widen.

Clinical Features

Nail abnormalities are the most common manifestation of nail-patella syndrome and occur in 98% of affected individuals. Nail abnormalities can manifest as anonychia (absence of nails), koilonychia ("spoon nails"), longitudinal striations of the nail, or triangular or absent lunulae, the rounded areas at the base of the nail (Ghoumid et al. 2016). Thumbnails are often the most severely affected and each individual nail is more affected on its ulnar side. Toenails are affected less often than fingernails.

Skeletal abnormalities are the second most common findings in nail-patella syndrome, particularly abnormalities in the patella from which the disease gets its name. Patellae are absent in 9–16% of individuals and hypoplastic in 61–75% (Ghoumid et al. 2016; Sweeney et al. 2003). These findings can cause clinical problems with recurrent subluxation or dislocation, as well as early degenerative arthritis. Elbow dysplasia is also common, affecting 71% of patients, manifesting as loss of elbow extension, radial subluxation, or radial head anomalies (Ghoumid et al. 2016). Iliac horns are considered pathognomonic of nail-patella syndrome but are only found in 78% of patients (Ghoumid et al. 2016). These may be palpable through the skin, but are generally asymptomatic.

Renal involvement in nail-patella syndrome generally presents with proteinuria with or

without hematuria. Proteinuria can be observed at any age from infancy onward and may be intermittent. It may be severe enough to lead to nephrotic syndrome. Twenty-five percent of affected individuals in cross-sectional studies have renal involvement that increases with age (Ghoumid et al. 2016; Sweeney et al. 2003). Three to five percent of patients with nail-patella syndrome progress to end-stage kidney disease (ESKD), and children as young as 8 years have been reported to reach this endpoint (Sweeney et al. 2003; Ghoumid et al. 2016; Leahy 1966). Hypertension is present with advancing CKD; however it does not appear to be a primary manifestation of nail-patella syndrome.

Additional clinical findings include glaucoma in ~20% of affected individuals. This is thought to be due to disruption of normal *LMX1B* gene expression in the anterior portion of the eye that controls differentiation of the trabecular meshwork responsible for draining the aqueous humor. Additional systemic findings with unclear etiology include gastrointestinal symptoms such as constipation or irritable bowel syndrome, reduced sensation to pain and temperature in the hands and feet, Raynaud's phenomenon, and dental problems (Sweeney et al. 2003).

Pathology

Light and immunofluorescent microscopy findings in nail-patella syndrome are nonspecific and may demonstrate FSGS lesions, mild mesangial hypercellularity, or no changes, and EM is required to make the diagnosis. By EM (Fig. 1), glomerular basement membranes (GBMs) are thickened and irregular (Hoyer et al. 1972). With standard lead citrate and uranyl acetate stains, there are multiple lucent areas in the GBM and

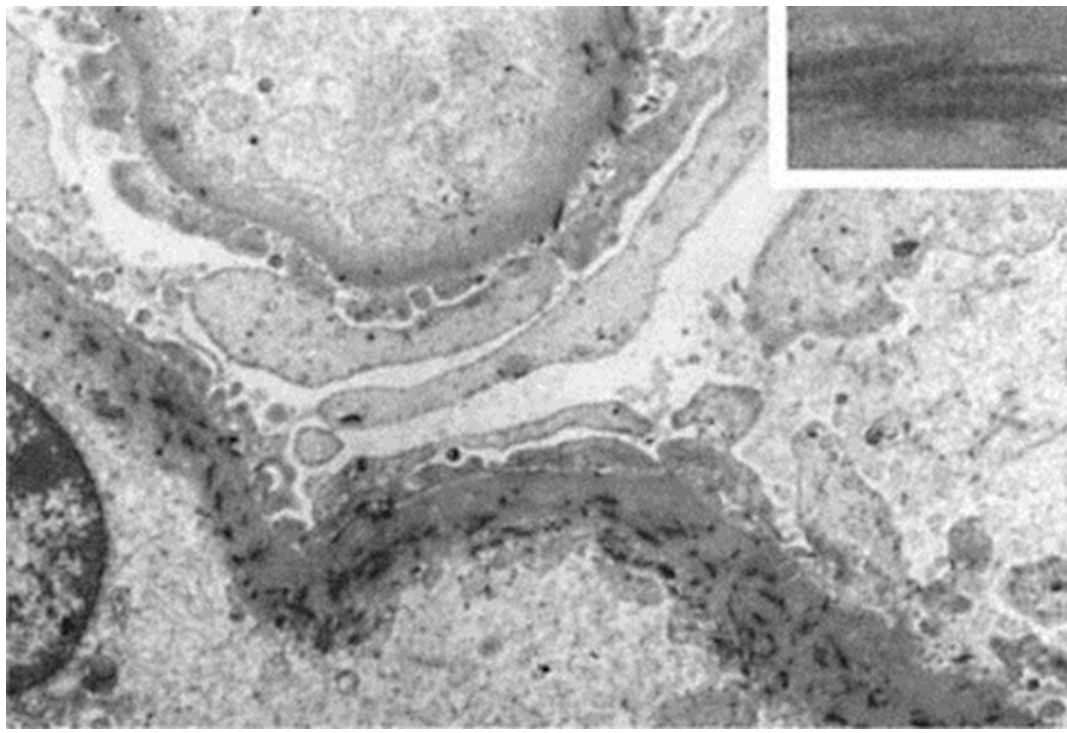

Fig. 1 Nail-patella syndrome. Irregular distribution of fibrillar collagen within the GBM. *Inset* shows the typical periodicity of interstitial collagen (Electron microscopy, Phosphotungstic acid stain 10,500× original magnification, *Inset* 48,000× original magnification) (Used with permission, Pediatric Nephrology, 6th edition, 2009, Springer Publishing Company)

mesangium that have been described as "moth-eaten" appearance. By phosphotungstic acid staining, type III collagen fibrils are readily apparent as collections of straight or curved fibrils of banded collagen with a periodicity of 60 nm within the lamina densa. Type III collagen deposition has been observed in patients with no clinically evident renal disease, and there is no correlation between the extent of GBM changes and patient age, severity of proteinuria, or degree of renal impairment (Hamlington et al. 2001; Knoers et al. 2000). Immunostaining with antibodies against type III collagen demonstrates irregular, discontinuous labeling of the GBM in normal-appearing glomeruli and focally intense staining of sclerotic glomeruli (Heidet et al. 2003). The mechanism behind type III collagen production and deposition in nail-patella syndrome is unclear.

Monitoring and Treatment

Annual monitoring of individuals with nail-patella syndrome should include a urinalysis to detect proteinuria and a blood pressure check. Annual glaucoma screening is also recommended. Potentially affected family members should be offered screening for the presence of the disease. There is no specific therapy for renal disease associated nail-patella syndrome. Kidney transplantation has been carried out successfully, and unlike Alport syndrome, recurrence of renal disease has not been reported. Potential donors should be screened carefully for the presence of this autosomal dominant disorder.

Collagenofibrotic Glomerulopathy (Type III Collagen Glomerulopathy)

Background and Epidemiology

Collagenofibrotic glomerulopathy is a very rare renal disorder first reported in 1979 that is characterized by type III collagen deposition in the glomerulus, no extrarenal findings, and more severe renal dysfunction compared to nail-patella syndrome. Collagenofibrotic glomerulopathy was initially reported from Japan and has been documented primarily in Asian countries; however case reports have demonstrated worldwide distribution (Arakawa 1979). The prevalence of this disorder is unknown but very rare, with fewer than 100 individuals reported in the literature.

Genetics and Clinical Features

The genetic cause of collagenofibrotic glomerulopathy is unknown. While some cases appear to be sporadic, there have also been reports of affected siblings suggesting autosomal recessive inheritance (Gubler et al. 1993). It is also unclear whether collagenofibrotic glomerulopathy represents a primary glomerular disorder or a renal manifestation of a systemic disease. Very elevated serum levels of procollagen type III peptide, a precursor of type III collagen, are found in patients with collagenofibrotic glomerulopathy, suggesting a systemic problem of type III collagen metabolism (Yasuda et al. 1999).

The most common presenting feature of collagenofibrotic glomerulopathy is proteinuria, which may be in the nephrotic range in over 60% of affected individuals (Gubler et al. 1993; Alchi et al. 2007). Individuals can present at any age including infancy; however most cases are in adults (Alchi et al. 2007; Gubler et al. 1993). Hypertension is also common at presentation in approximately 67% of cases. Affected patients develop progressive renal disease with ESKD in up to 50%. There are no associated extrarenal findings including normal nails and skeleton.

Pathology

Light microscopy demonstrates enlarged glomeruli with a lobular appearance. Mesangial matrix is increased with normal mesangial cellularity and may exhibit a nodular appearance. Capillary walls are variably thickened due to the accumulation of eosinophilic material in the subendothelial space. Expanded mesangium and subendothelial capillary deposits stain strongly with the aniline blue

component of trichrome stain. By immunofluorescence microscopy, usual immunoglobulin and complement staining are negative. Abundant presence of collagen type III in the mesangium and glomerular capillary walls can be detected by specific immunostaining. Electron microscopic findings are pathognomonic for this disorder. Banded collagen fibers with a periodicity of 60 nm are present and are typically curved rather than straight. For optimal visualization of banded collagen, special processing with phosphotungstic acid or tannic acid is required. In addition, electron-dense deposits are absent with effacement of podocyte foot processes consistent with the degree of proteinuria. In contrast to nail-patella syndrome, the lamina densa appears normal and does not have a "moth-eaten" appearance (Cohen 2012).

Monitoring and Treatment

There is no specific treatment available for collagenofibrotic glomerulopathy. Interventions should focus on general treatment of chronic kidney disease including management of hypertension and nephrotic edema.

Fibronectin Glomerulopathy

Background and Epidemiology

Fibronectin glomerulopathy (also known as glomerulopathy with fibronectin deposits) is a very rare autosomal dominant renal disorder. The prevalence of fibronectin glomerulopathy is unknown. It has a slight male predominance in reported cases. Fibronectin glomerulopathy is uniquely characterized by massive glomerular deposition of fibronectin, a high molecular weight extracellular matrix glycoprotein. In contrast to collagenofibrotic glomerulopathy above where fibrils are highly organized and 60 nm in diameter, in fibronectin glomerulopathy fibrils are randomly distributed and smaller at 12–16 nm.

Genetics and Clinical Features

Mutations in *FN1*, the gene encoding fibronectin, are present in approximately half of affected families with fibronectin glomerulopathy (Castelletti et al. 2008; Ohtsubo et al. 2016). Fibronectin mutations are present in the heparin-binding domains or the integrin-binding domains and interfere with binding to podocytes and endothelial cells (Castelletti et al. 2008). There appears to be genetic heterogeneity in this disorder. An additional locus on 1q32 was identified that contained a cluster of genes involved in complement regulation; however detailed analysis of this locus was unable to identify a specific causative gene mutation (Vollmer et al. 1998, 2000).

Affected individuals with fibronectin glomerulopathy present with proteinuria, microscopic hematuria, and hypertension usually in the second and third decades of life; however initial presentation at age 3–78 years has been reported (Castelletti et al. 2008; Niimi et al. 2002; Ishimoto et al. 2013). Proteinuria is progressive and nephrotic syndrome present in a subset of individuals. Hypertension is generally severe. Progressive decline in renal function is observed with eventual ESKD. Recurrence after kidney transplant has been reported; however, the mechanism is unknown (Otsuka et al. 2012; Strom et al. 1995). Extrarenal fibronectin deposition has not been reported.

Pathology

Light microscopy demonstrates enlarged glomeruli with mesangial and subendothelial deposits (Fig. 2). The deposits are composed of fibronectin, as determined by specific immunostaining (Castelletti et al. 2008). Fibronectin can be present in plasma as a soluble form or deposited in extracellular matrix as organized fibrils. Glomerular deposits in fibronectin glomerulopathy are primarily derived from soluble fibronectin (Mazzucco et al. 1992). Amyloid staining and Congo red staining are negative.

By electron microscopy, deposits of electron-dense material exhibiting a distinctly granular

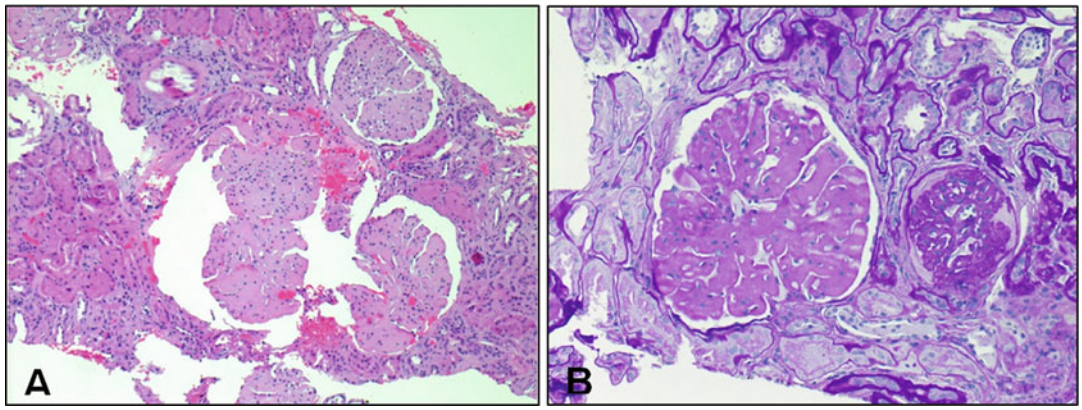

Fig. 2 Fibronectin glomerulopathy. Glomeruli exhibit massive capillary subendothelial and mesangial accumulation of pale eosinophilic, PAS-positive material. Capillary lumens are largely obliterated (**a** H&E stain, 100× original magnification; **b** PAS stain, 200× original magnification)

texture can be seen in the mesangium and subendothelial space (Castelletti et al. 2008). Fibrillary deposits can also be observed with randomly arranged 12–16 nm fibrils (Ishimoto et al. 2013).

Monitoring and Treatment

There are no specific treatments for fibronectin glomerulopathy. Treatment of hypertension and proteinuria should be offered.

Lecithin/Cholesterol Acyltransferase (LCAT) Deficiency

Background and Epidemiology

Lecithin/cholesterol acyltransferase (LCAT) deficiency is a rare autosomal recessive disorder caused by mutations in the *LCAT* gene (Humphries et al. 1988). Less than 100 affected patients have been described in the literature. LCAT is an enzyme that is important in cholesterol metabolism. It is required for esterification, a process by which cholesterol is attached to lipoproteins for transport out of the blood and to the liver. The absence of LCAT activity leads to accumulation of free cholesterol in peripheral tissues.

Clinical Features

The characteristic clinical findings in patients with LCAT deficiency are renal involvement, corneal opacities, and anemia (Hirashio et al. 2014). Affected individuals may have proteinuria presenting in childhood that increases over time or even nephrotic syndrome (Rajpal et al. 2013). This is associated with progressive renal dysfunction that may lead to ESKD in some patients (Borysiewicz et al. 1982). Successful renal transplantation has been reported; however disease recurrence is possible. Corneal opacification is present early in life, however does not appear to affect vision. This appearance is due to accumulation of free cholesterol and phospholipids in the cornea (Winder and Bron 1978). Similarly, erythrocyte membranes accumulate free cholesterol and phospholipids leading to increased hemolysis and shortened erythrocyte life span, clinically evident as anemia. Affected individuals are at increased risk of atherosclerotic events.

Pathology

The characteristic renal pathology findings in patients with LCAT deficiency are due to accumulation of lipids in glomeruli. Expansion of the mesangial matrix is evident along with large

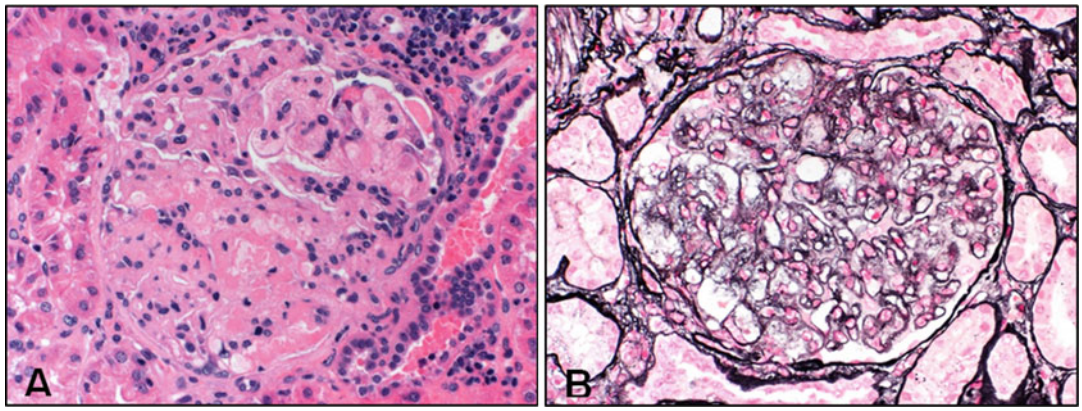

Fig. 3 Lecithin/cholesterol acyl transferase deficiency. Glomeruli demonstrate intracapillary accumulation of foam cells (**a**). Segmental mesangial and capillary deposition of acellular, homogeneous eosinophilic material is also present. Silver stain (**b**) reveals marked vacuolation of glomerular basement membranes and mesangial matrix (**a** H&E stain, 400× original magnification; **b** Periodic acid methenamine silver stain, 400× original magnification)

foam cells filling capillary lumens (Fig. 3). The GBM is typically thickened with lipid deposition, giving a bubbly or honeycombed appearance. Routine immunofluorescence microscopy is normal. By electron microscopy, there are classic findings of lacunae in basement membranes and in the mesangium. Deposition can also be found in Bowman's capsule and the vascular endothelium.

Monitoring and Treatment

Affected individuals with LCAT deficiency should have routine monitoring of kidney function, proteinuria, and blood pressure. Patients should be evaluated by ophthalmology at the time of diagnosis and as recommended thereafter. Finally, evaluation and ongoing management by a preventive cardiologist or lipidologist are recommended. Treatment with cholesterol-lowering drugs or low-fat diet may be beneficial in some patients (Yee et al. 2009). Other case reports have suggested improvements in blood pressure, lipid abnormalities, and proteinuria in patients treated with angiotensin receptor blockers (Aranda et al. 2008).

An early attempt at treatment of LCAT deficiency with plasma infusions demonstrated improvements in triglyceride and cholesterol profiles; however this treatment has not been widely adopted due to the inconvenience and risks associated with recurrent plasma infusions (Murayama et al. 1984). Specific enzyme replacement therapy is a potential treatment for LCAT deficiency, and this therapy is in clinical development. Preclinical studies showed that the addition of recombinant human LCAT to plasma from patients with LCAT deficiency was able to normalize plasma lipoproteins in vitro (Simonelli et al. 2013). Clinical trials are currently ongoing to test this therapy (Shamburek et al. 2016a, b).

MYH9-Related Disorders (Epstein Syndrome, Fechtner Syndrome)

Background and Epidemiology

MYH9-related disorders are rare autosomal dominant disorders caused by mutations in *MYH9*, the gene encoding nonmuscle myosin IIA. The prevalence is unknown but has been reported at 3:1,000,000 in the Italian Registry of MYH9RD. *MYH9*-related disorders have been reported worldwide and are diagnosed equally in men and women. Nonmuscle myosin IIA is an actin-binding protein involved in the generation of chemomechanical forces by the cytoskeleton and is required for normal cell motility, cytokinesis, cell polarization, and maintenance of cell shape

(Vicente-Manzanares et al. 2009). In the podocyte, nonmuscle myosin IIA is a major component of the podocyte actin cytoskeleton (Bondzie et al. 2016). Epstein and Fechtner syndromes, along with May-Hegglin anomaly and Sebastian syndrome, were once thought to be separate disorders; however these were combined under the umbrella term of *MYH9*-related disorders after they were all found to be caused by mutations in the same gene (Seri et al. 2003; Heath et al. 2001).

Clinical Features and Genetics

MYH9-related disorders are highly variable clinically and characterized by progressive renal dysfunction, hematologic abnormalities including large platelets and thrombocytopenia, sensorineural hearing loss, elevated liver enzymes, and cataracts. Renal disease generally presents with microscopic hematuria and proteinuria in approximately 30–70% of individuals with *MYH9* mutations (Singh et al. 2009). Age at diagnosis is variable, but 72% of affected individuals are diagnosed with renal disease prior to the age of 35 years. Progression to ESKD is common for those with renal involvement.

Nonmuscle myosin IIA is required for normal platelet generation and controls platelet size and number. With mutations in *MYH9,* all affected individuals have macrothrombocytopenia that is present from birth. Mean platelet diameter is 4.5 μm in individuals with *MYH9* mutations compared to 2.6 μm in healthy controls (Noris et al. 2014). Thrombocytopenia ranges from mild to severe and may lead to clinical bleeding dysfunction (Pecci et al. 2014). Twenty-eight percent of patients have spontaneous bleeding including epistaxis, gingival bleeding, or menorrhagia. The risk of bleeding strongly correlates with platelet count; however these should be performed manually, as automated counters may not recognize the large platelets (Pecci et al. 2014). Manual review of a blood smear may also detect Döhle-like bodies in the cytoplasm of neutrophils in 42–84% of affected individuals. These Döhle-like bodies are caused by aggregates of *MYH9* mRNA, nonmuscle myosin IIA protein, and ribosomes (Kunishima et al. 2008).

Sensorineural hearing loss may be present in up to 58% of affected families at a mean age of 31 years, although some present in their adolescent years (Pecci et al. 2014). Similar to the risk for renal involvement, patients with mutations in the SH1 domain helix have the highest risk for progressive sensorineural hearing loss. Although the exact mechanism by which mutations in *MYH9* cause hearing loss are unknown, nonmuscle myosin IIA is known to be expressed in several structures of the inner ear important for hearing including the organ of Corti, spiral ligament, and spiral limbus (Mhatre et al. 2004). Cochlear implants have successfully been used to treat hearing loss in this disorder.

Nonmuscle myosin IIA is expressed in hepatocytes, and liver involvement was relatively recently recognized as part of the phenotypic spectrum of *MYH9*-related disorders. Elevated transaminases are found in approximately 50% of individuals with *MYH9*-related disorders, and elevated gamma-glutamyltransferase (GGT) is found in 27% (Pecci et al. 2012). Elevations are generally mild and in the range of 1–3× the upper limit of normal. Despite these findings, liver function does not seem to be impaired.

Cataracts are the least frequent manifestation of *MYH9*-related disorders and are observed in 18% of affected individuals (Pecci et al. 2014).

Genetic testing can provide information about the risk of developing both renal and extrarenal manifestations of *MYH9*-disorders and should be performed for all affected families. The nonmuscle myosin IIA protein structure consists of an N-terminal head or motor domain, a neck region that binds the regulatory light chain, and a α-helical coiled-coil domain that ends in a short nonhelical tail. Mutations affecting the head domain (particularly R702) confer a high risk for early-onset deafness and ESKD with a mean renal survival of approximately 20 years (Pecci et al. 2014). More severe thrombocytopenia is seen in individuals with mutations in the head domain of *MHY9* compared to those with mutations in the tail domain. Other mutations such as R1165 in the coiled-coil domain are associated with high

risk of deafness but low risk of kidney or eye involvement.

Pathology

Renal biopsies are rarely performed in patients with *MYH9*-related disorders due to the bleeding tendency (Sekine et al. 2010; Kopp 2010). Light microscopic findings early in the course of the disease demonstrate mesangial matrix expansion and hypercellularity with minimal tubulointerstitial changes. Biopsies later in the disease course frequently demonstrate lesions of focal segmental glomerulosclerosis. Immunofluorescence microscopy is typically negative. Electron microscopy findings have similarities to those seen in Alport syndrome, and these disorders are often confused due to similar clinical presentations and biopsy findings (Table 2). Early in the disease course, focal foot process effacement is seen in areas of focal thickening of the GBM. At more advanced stages of disease, GBM thickening is more widespread with areas of GBM lamellation. Isolated GBM thinning has also been reported (Naito et al. 1997). Despite the similarities to the appearance of the GBM in Alport syndrome, type IV collagen immunostaining is normal (Naito et al. 1997). The mechanisms by which *MYH9* mutations lead to abnormalities in the GBM are unknown, but suggest that nonmuscle myosin IIA plays a role in GBM assembly, maintenance, and remodeling.

Monitoring and Treatment

Families with a diagnosis of an *MYH9*-related disorder should have a consultation with a genetic counselor or geneticist to review the risk of disease in other family members since this is an autosomal dominant disorder. Affected individuals with *MYH9*-related disorders should have routine monitoring of kidney function, proteinuria, hematologic parameters, liver enzymes, and blood pressure. Ophthalmologic and audiometric examinations should be performed at diagnosis and routinely thereafter to monitor for cataracts and hearing loss.

Treatment for the glomerulopathy of *MYH9*-related disorders is generally supportive. Treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has been reported and is effective in reducing proteinuria

Table 2 Comparison of clinical features of *MYH9*-related disorders and Alport syndrome

	MYH9-related disorders	Alport syndrome
Inheritance	Autosomal dominant	X-linked, autosomal recessive, autosomal dominant
Affected gene	*MYH9*	X-linked: *COL4A5*
		Autosomal: *COL4A3, COL4A4*
Sensorineural hearing loss	Present	Present
Eye abnormalities	Cataract	Anterior lenticonus, maculopathy
Blood abnormalities	Macrothrombocytopenia, Döhle-like bodies	None
Nephropathy	Microscopic hematuria, proteinuria, and progressive renal failure	Microscopic hematuria, proteinuria, and progressive renal failure
Kidney biopsy: immunofluorescence	Normal type IV collagen staining	Absent type IV collagen staining in ~80% of X-linked or autosomal recessive disease
Kidney biopsy: electron microscopy	Early: GBM thinning or focal GBM thickening	Early: GBM thinning
	Late: GBM thickening and lamellation with podocyte effacement	Late: GBM thickening and lamellation with podocyte effacement

GBM glomerular basement membrane

in at least a subset of patients (Pecci et al. 2008; Sekine et al. 2010).

Pierson Syndrome

Background and Epidemiology

Pierson syndrome was first described in 1963 as a combination of eye abnormalities with congenital nephrotic syndrome and ESKD prior to the age of 1 inherited in an autosomal recessive manner (Pierson et al. 1963). In 2004, this disorder was determined to be caused by mutations in *LAMB2* encoding laminin β2 *(*Zenker et al. 2004*)*. The prevalence of Pierson syndrome has been estimated at <1:1,000,000 with a worldwide distribution. Fewer than 100 cases have been reported in the literature (Matejas et al. 2010). Laminins exist as heterotrimers and are a required component of basement membranes. The major laminin in the mature GBM is laminin-521 (laminin α5, laminin β2, and laminin γ1), which is also found in ocular structures and the neuromuscular system (Miner 2012). In the absence of laminin β2, ectopic laminin trimers are present, leading to dysfunction of the basement membrane structure and function.

Genetics and Clinical Features

Mutations in *LAMB2* may also cause isolated congenital nephrotic syndrome although this is a rare association in only 2.5% of affected children (Hinkes et al. 2007). There is a genotype-phenotype correlation in this disorder whereby children with truncating deletions or null alleles generally develop ESKD within the first year of life and have more severe eye findings. Children with missense mutations and residual laminin β2 in the GBM may have isolated renal disease or only minor eye findings initially (Hasselbacher et al. 2006; Kagan et al. 2008). The phenotypic spectrum was widened further in 2012 with the identification of an 11-year-old patient with only nephrotic range proteinuria and normal renal function due to homozygous non-truncating *LAMB2* mutation (Lehnhardt et al. 2012). Pierson syndrome can be diagnosed prenatally via molecular genetic testing. In addition, prenatal findings of increased renal echogenicity, hydrops fetalis, enlarged placenta, oligohydramnios, and anencephaly have been reported (Mark et al. 2006).

Children present with nephrotic range proteinuria and eye abnormalities, often in the neonatal period, and have rapid progression to ESKD. The most common ocular anomaly in children with Pierson syndrome is microcoria (small pupils), although nystagmus, iris abnormalities, retinal detachment, corneal abnormalities, cataracts, and glaucoma have been described (Bredrup et al. 2008). Ocular findings may be different in each of an individual patient's eyes. Classic ophthalmological findings may precede the renal findings and should prompt an evaluation of the urine for protein and genetic testing for *LAMB2* mutations. Importantly, even children with mild ocular abnormalities at presentation may be at risk for serious ocular complications such as retinal detachment, later in their course, and require long-term ophthalmological follow-up.

Children with Pierson syndrome may have neurodevelopmental abnormalities including muscular weakness or hypotonia and global developmental delay; however affected children with normal development have also been described.

Pathology

By light microscopy, diffuse mesangial sclerosis is typically seen. However, glomeruli can variably appear normal or have increased mesangial hypercellularity or focal and segmental sclerosis (Fig. 4) (Choi et al. 2008; Hasselbacher et al. 2006). Electron microscopy demonstrates thinning of the GBM with irregular contours (Choi et al. 2008). Lamellation of the lamina densa or duplication of the lamina dense can been seen along with podocyte foot process effacement.

Laminin β2 knockout mice develop massive proteinuria along with retinal and neuromuscular

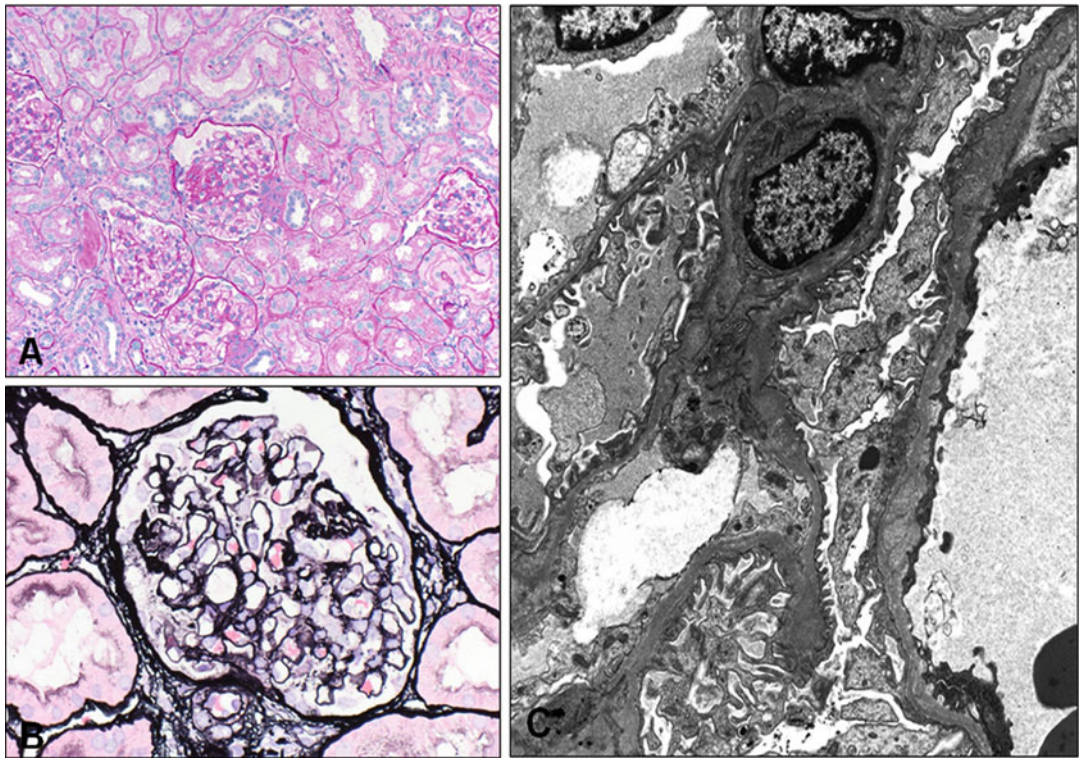

Fig. 4 Pierson syndrome. Glomeruli display mostly normal matrix architecture and cellularity with segmental sclerosis present focally (**a**, center glomerulus). Silver stain (**b**) demonstrates mild segmental matrix alteration consisting of mesangial expansion and capillary basement thickening and wrinkling. Ultrastructural changes are evident in glomerular basement membranes by electron microscopy (**c**) and are characterized by irregular membrane expansion with partial disruption and focal splitting of the lamina densa associated with intramembranous accumulation of granular material (**a** PAS stain, 100× original magnification; **b** Periodic acid methenamine silver stain, 600× original magnification; **c** electron micrograph, 8,000× original magnification)

abnormalities (Jarad et al. 2006). In these mice, massive proteinuria precedes the appearance of podocyte abnormalities, suggesting that the GBM itself contributes to the barrier function of the glomerular capillary wall.

Monitoring and Treatment

No specific treatment is available for renal disease associated with Pierson syndrome. Kidney transplantation is effective, and recurrent nephrotic syndrome has not been described in association with *LAMB2* mutations. Treatment of congenital nephrotic syndrome may require nephrectomy to limit protein loss, similar to patients with congenital nephrotic syndrome due to *NPHS1* (nephrin) mutations; however the more rapid progression to ESKD in patients with Pierson syndrome may limit protein loss and avoid the need for nephrectomy in this condition.

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Lupus Nephritis (Including Antiphospholipid Antibody Syndrome), Adult

13

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that can affect every organ system. The prevalence is higher in people of African, Hispanic, and Asian ancestry. They also tend to have more vital organ involvement than other ethnic or racial groups. In this chapter we describe the most common manifestations including hematologic, cutaneous, neuropsychiatric, gastrointestinal, cardiac, and pulmonary and with the main focus being on renal manifestations. Patient with lupus nephritis (LN) may have a variety of signs and symptoms as their initial presentations ranging from hematuria, nephritic or nephrotic syndrome, and acute kidney injury to an acute thromboembolic event. The diagnosis in some cases can be difficult to make because the patients may have some features of lupus but fall short of meeting the American College of Rheumatology criteria for diagnosis of SLE, others meet the criteria but the pathologic findings are not included in the International Society of Nephrology/Renal Pathology classification of LN. In this chapter we will describe all pathologic types of LN including the atypical types. Treating patients with LN is very complex and should include a comprehensive plan that includes treating SLE, vaccinations, treating the specific type of LN, treating the complications of LN, and treating the complications of

the treatment itself. In this chapter we will describe the comprehensive treatment and the specific treatment for the type of LN. We will also talk about fertility preservation, pregnancy, and antiphospholipid syndrome in patients with LN.

Keywords
Systemic lupus erythematosus (SLE) · Lupus nephritis · Antiphospholipid syndrome (APS) · Lupus podocytopathy · Pregnancy in lupus nephritis

Introduction

Lupus nephritis is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). It affects the kidneys in about 50% of the patients and is associated with considerable risk of progression to end-stage renal disease. The prevalence is higher in people of African, Hispanic, and Asian ancestry. It is characterized by autoantibodies directed against nuclear components, particularly anti-double stranded DNA (dsDNA). The diagnosis in some cases can be difficult because of unusual clinical presentation and/or atypical pathologic findings. The treatment is prolonged, complex, and potentially toxic.

Epidemiology

The incidence and prevalence of systemic lupus erythematosus (SLE) demonstrates that there are ethnic, gender, and geographic differences. SLE is observed more frequently in US blacks, Asians, and Caribbean people and is less frequent among Caucasians (Yap and Chan 2015). The Michigan Lupus Epidemiology and Surveillance Program (MILES) indicates an age-adjusted incidence and prevalence of SLE of 5.5 and 72.8 per 100,000, respectively, with a 2.3-fold higher prevalence in blacks as compared to whites, and a tenfold higher prevalence in women versus men (Somers et al. 2014). Similar results have been reported by the Georgia Lupus Registry (GLR), a Southern USA CDC lupus registry. In that registry, the age-adjusted incidence and prevalence was 5.6 and 73 per 100,000, respectively. The age-adjusted prevalence was more than three times higher in blacks versus whites and more than eight times higher in women versus men. While US blacks have traditionally been considered to have one of the highest incidence and prevalence of SLE, the American Indians and Alaska Native people registry data, obtained from the Indian Health Service (IHS) active clinical population, reveals an age-adjusted incidence and prevalence of SLE of 7.4 and 178 per 100,000, respectively, higher than the US black population as reported in GLR and MILES registries. Geographic differences are also seen. SLE tends to be more common in the urban setting, is more frequent in Europe and Australia, and is not as frequent in Africa (Danchenko and Satia 2006). Those of African and Asian decent in both the US and Europe have the highest rates in their countries.

Pathogenesis

Lupus is the prototypic autoimmune disease, in which there is loss of tolerance to self-antigens. Three genetically determined checkpoints have been described, based upon murine models (Kanta and Mohan 2009):

1. Breach in central tolerance in the adaptive immune system (B and T cells)
2. Peripheral amplification of the autoimmune response by the innate immune system (neutrophils, macrophages, low-density granulocytes)
3. Local processes in the target organ that facilitates end-organ disease (lupus nephritis as the prototypic organ)

Dysregulation of various cell processes have been implicated in the pathogenesis of lupus and lupus nephritis. These include apoptosis, primary and secondary necrosis, NETosis, necroptosis, pyroptosis, and autophagy (Mistry and Kaplan 2016).

All of these have been implicated in the genesis of SLE through multiple proposed mechanisms including increased cell death, decreased scavenging of microparticles with exposed genetic material that would otherwise be isolated from

immune recognition, and most recently through amplification of inflammatory response generated by material derived from neutrophil extracellular traps (NETs) that stimulate plasmacytoid dendritic cells to release interferon alpha, a critical cytokine in lupus pathogenesis (Knight and Kaplan 2012).

Clinical Manifestations

Systemic lupus may affect any organ system in the body. In the Hopkins lupus cohort (Petri 1998), which included 570 patients, 93% females, and 47% African-American, the cumulative manifestations of SLE included in descending order were hematologic (95%), cutaneous (93%), musculoskeletal (91%), renal (78%), neurologic (75%), gastrointestinal (49%), and cardiac (46%).

Hematologic

Hematologic manifestations can be due to the disease or as a result of side effects of medications (iatrogenic). They can be caused by increased peripheral destruction of blood associated with circulating antibodies. The major manifestations include anemia, leukopenia, thrombocytopenia, and antiphospholipid syndrome. While anemia of chronic disease is among the most common hematologic manifestations in patients with SLE (Keeling and Isenberg 1993), hemolytic anemia is part of the required hematologic classification criteria that defines SLE. Other disease-defining hematologic manifestations are leukopenia, lymphopenia, or thrombocytopenia (Hochberg 1997). If the bone marrow is affected, the patients can present with myelofibrosis, aplastic anemia, and pure red cell aplasia. Thrombotic thrombocytopenic purpura (TTP), a thrombotic microangiopathy (TMA), is a life-threatening hematologic syndrome that while not a disease-defining manifestation for SLE, it has been described in SLE in about 1–4% of patients (Fayyaz et al. 2015). TTP should be part of the differential diagnosis of any SLE patient presenting with new onset or worsening thrombocytopenia, hemolytic anemia, and acute renal failure.

Cutaneous

The lupus-specific skin findings can be divided into those specific to SLE and those that are nonspecific. The lupus erythematosus (LE)-specific findings are further classified into acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) cutaneous LE (Stannard and Kahlenberg 2016). They each have their unique characteristic clinical and histopathologic manifestations. The subtypes are further described depending on the extent of skin involvement, morphology, and location. Some examples of lesions noted are malar rash, maculopapular rash, discoid lupus, panniculitis, bullous lesions, vasculitis, mucosal ulcers and alopecia, and photosensitivity. The lesions are commonly found on the face, upper part of the trunk, and extremities.

Neuropsychiatric

There are several subsets of neuropsychiatric syndromes observed in SLE, see Table 1 (Anonymous 1999).

Not included in such description is small fiber neuropathy, which is not apparent on nerve conduction studies, and can be non-length dependent, present as patchy areas of burning pain, and needs

Table 1 Neuropsychiatric syndromes in SLE

Central nervous system	Peripheral nervous system
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy
Cerebrovascular disease	Autonomic disorder
Headache	Mononeuropathy, single/multiplex
Movement disorder (chorea)	Myasthenia gravis
Myelopathy	Neuropathy, cranial
Seizure disorders	Plexopathy
Acute confusional state	Polyneuropathy
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

further testing such as skin biopsy to be diagnosed (Fangtham and Petri 2013).

Gastrointestinal

Except for medication-induced problems, the gastrointestinal (GI) tract is not commonly affected by SLE. Nonsteroidal anti-inflammatory drugs, corticosteroids, and some immunosuppressive medications may lead to GI complications. The following are infrequent gastrointestinal complications in SLE: lupus mesenteric vasculitis (LMV), protein-losing gastroenteropathy (PLGE), intestinal pseudo-obstruction (IPO), and pancreatitis.

Patients with LMV usually present with severe abdominal pain, anorexia, nausea, vomiting, diarrhea, and hematemesis. Patients with PLGE have excessive loss of serum protein from GI tract, and this is clinically the same as patients with nephrotic syndrome, severe edema, and hypoalbuminemia. Other causes must be excluded including hypoalbuminemia from malabsorption, liver disease, or lupus nephritis. Patient with IPO present with features of intestinal obstruction but no identifiable obstructive lesion. Most patients with SLE-related pancreatitis will present with abdominal pain, with radiation to the back (Tian and Zhang 2010).

Cardiovascular

Lupus can affect the heart directly through an inflammatory response at all three cardiac histologic tissues, pericarditis, myocarditis, and (Libman-Sacks) endocarditis or indirectly through an increased risk of atherosclerosis and a higher prevalence of major cardiovascular events. Pericarditis represents the most common direct cardiovascular manifestation (Moder et al. 1999). Myocarditis is uncommon. Coronary artery disease remains the most common cause of mortality in lupus patients, and aggressive primary prevention should be instituted.

Neonatal congenital heart block is a complication that may be seen in the offspring of mothers with lupus who have anti-Ro/SSA and/or anti-La/SSB antibodies (Lateef and Petri 2013).

Pulmonary

Pulmonary manifestations of systemic lupus include pleuritis, acute pneumonitis, pulmonary hemorrhage, interstitial lung disease, thromboembolic disease and pulmonary hypertension, and shrinking lung syndrome.

Renal

Patients usually will present with hematuria and proteinuria depending on the type of renal involvement. Proteinuria can be traced to nephrotic range and hematuria is generally microscopic. Patients with proliferative disease can have significant hematuria with cellular casts with or without elevated creatinine. Hypertension can be present with any class of LN but more severe in patients with severe proliferative disease. Tubular disorders are not common but can be present.

Hematuria

An active urinary sediment is defined as >5 red blood cells and >5 white blood cells per high-power field and/or cellular cast that were not previously present. Improvement is defined as changing from an active urinary sediment to an inactive urinary sediment, defined as <5 red blood cells, <5 white blood cells, and no cellular cast. However, hematuria can be present in mild forms of lupus nephritis such as class II LN, in bladder cancer due to prior exposure of cyclophosphamide, in nephrolithiasis, or cystitis. Hematuria due to bladder cancer is usually frank, intermittent, painless, and present throughout micturition. Initial workup for recurrent hematuria should include renal ultrasound and urine cytology.

Proteinuria

Proteinuria is one of the main indicators of kidney involvement and how the patients are

responding to therapy. It can be assessed with urine protein-to-creatinine (Cr) ratio (uPCR) or with adequate 24-h urine protein excretion. Proteinuria as low as 0.5 g/24 is enough to merit further workup including a renal biopsy (Bertsias et al. 2012). A repeat biopsy after treatment may be helpful to differentiate a decline in renal function with proteinuria as a result of active glomerulonephritis or that of a proteinuria due to sclerosis.

Nephrotic Syndrome

Nephrotic syndrome can be seen in patients with class 5 LN or any other lupus podocytopathy. It is characterized by proteinuria of >3.5 g (1.73 m^2), hypoalbuminemia, edema, hyperlipidemia, and lipiduria.

- Edema

  The exact mechanism is not fully understood. There are two main theories for the mechanism of sodium retention. The undersell hypothesis is that sodium retention is due to a decreased effective circulation volume that is secondary to a decreased effective circulating volume caused by intravascular fluid shifts to the interstitial compartment caused by a decrease in plasma oncotic pressure by hypoalbuminemia. As a result, sodium and water retention ensues. The overfill hypothesis states that sodium retention is caused by an intrinsic defect in the kidney's handling of sodium, causing volume expansion. Activation of the renin-angiotensin-aldosterone system may play a role in some patients with sodium retention but not in all. New evidence suggests that activation of the ENaC channels by atypical filtered proteases may be playing a role in sodium retention in nephrotic syndrome (Ray et al. 2015). The treatment for edema is sodium restriction (2 g sodium per day) and diuretics when needed. The use of albumin and furosemide is controversial but it can be considered in patients that are diuretic resistant (Duffy et al. 2015).
- Hyperlipidemia

  The more severe the proteinuria, the more problems the patient will have with hyperlipidemia. The commonly tested lipids, cholesterol, triglycerides, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) are elevated in nephrotic syndrome. High-density lipoprotein (HDL) levels can be unchanged, reduced, or elevated. These lipid abnormalities contribute to the development and progression of cardiovascular and kidney disease. VLDL and chylomicrons are rich in triglycerides, and they deliver fatty acids to tissues for storage. In nephrotic syndrome there are abnormalities in clearance of VLDL and chylomicrons due to deficiencies of lipoproteins and receptor abnormalities. LDL and total cholesterol also increase due to increased production and impaired clearance of LDL and apoB-100. The treatment of lipid disorders is to treat the cause of nephrotic syndrome first. Statins are effective as well, but the lipid panel should be monitored as hyperlipidemia improves in parallel to the improvement of nephrotic syndrome (Vaziri 2016).
- Hypercoagulable State

  The cause of a hypercoagulable state in nephrotic syndrome is the increase in plasma levels of fibrinogen and coagulations factors V and VIII, urinary loss of antithrombin III, changes in fibrinolytic system, thrombocytosis, and an increase in planet activation and aggregation (Torres et al. 2014). The risk increases when patients are volume depleted with the use of diuretics (Park and Shin 2011). The incidence is 2–5% in children and lower in adults with nephrotic syndrome. The thromboembolic events are more common in patients with membranous nephropathy and more often are venous thrombosis. The renal vein, pulmonary artery, deep veins in the lower extremities, inferior vena cava, and femoral artery are the most commonly affected vessels (Lilova et al. 2000).

  The use of anticoagulation is controversial. It is recommended that patients that previously had a thromboembolic event should be treated if the albumin concentration is <2 g/dl, fibrinogen is >6 g/L, or antithrombin III level is <70% of normal value.

Antiphospholipid Syndrome

Initially described by Hughes in 1983 (Hughes 1983), the antiphospholipid syndrome (APS) is a vasoocclusive disease that can affect the arterial and venous vascular beds, and commonly the microvasculature, which explains its protean clinical manifestations. The syndrome may be primary or secondary, when associated with immune-mediated diseases, such as SLE. Women are more commonly affected, even in the absence of SLE (Cervera and Piette 2002).

Renal involvement in APS encompasses renal artery stenosis, renal vein thrombosis, renal infarction, and thrombotic microangiopathy (Sciascia et al. 2014). The term antiphospholipid nephropathy (APSN) refers to renal damage caused by intrarenal vascular lesions (glomeruli, arterioles, and/or interlobular arteries) in patients with persistent antiphospholipid (aPL) antibodies. It has been described in 32% of patients with SLE, independently and in addition to lupus nephritis. By a multivariate analysis, it has been found to be associated with worse serum creatinine, hypertension, and interstitial fibrosis in patients with systemic lupus (Daugas and Nochy 2002; Nochy et al. 1999).

Clinically, hypertension is a common denominator in the presentation of APSN, associated with various combinations of decreased renal function, hematuria, and usually sub-nephrotic range proteinuria. There are both acute and chronic histopathologic findings in "APSN." When assessing a patient with SLE, worsening kidney function, thrombocytopenia, and hemolytic anemia, especially if the onset is acute, the clinician must consider systemic TMAs, such as TTP and hemolytic uremic syndrome (HUS). When suspected, ADAMTS13 should be drawn, and immediate treatment should be started with plasmapheresis. Catastrophic antiphospholipid syndrome (CAPS) is a severe form of APS. It is characterized by three or more organ involvement in a period of less than 1 week, with histopathologic evidence of microthrombosis. It carries high mortality rate and needs aggressive therapy. Fortunately, it is described in <1% of APS patients (Cervera and Piette 2002).

Management of APSN should include strict blood pressure control, aggressive cardiovascular primary prevention, as well as treatment with anticoagulation when appropriate. When APSN is diagnosed in the setting of prior nonobstetric APS, anticoagulation with warfarin is recommended. The need for anticoagulation is less clear in patients with APSN without prior thrombotic events. In such cases, based on expert opinion, if there is evidence of microthrombi on renal pathology, anticoagulation is usually pursued, but if there are chronic changes rather than acute, the yield of anticoagulation is less clear. There are other drugs that have been on special interest in the management of APS in general, these are hydroxychloroquine, statins, B cell depletion therapy, and most recently sirolimus, since the better understanding of APS and the mTOR pathway.

Diagnosis

SLE has protean manifestations. While classification criteria have been established (American College of Rheumatology 1997), there are no absolute diagnostic criteria for SLE. In clinical practice, the diagnosis is based upon the combination of clinical signs and symptoms involving one or more organ systems along with positive serologic results.

Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus (1997) (Hochberg 1997).

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial fold
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician

(*continued*)

Criterion	Definition
Nonerosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis or pericarditis	Pleuritis-convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleuritic pain or rubbing heard by physician or evidence of pleural effusion Pericarditis documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g per day or > than 3+ if quantitation not performed Cellular casts
Neurologic disorder	Seizures in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance Psychosis in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	Hemolytic anemia Leukopenia- <4,000/mm^3 on ≥2 occasions Lymphopenia-<1,500/mm^3 on ≥2 occasions Thrombocytopenia- <1,000/mm^3 in the absence of offending drugs
Immunologic disorder	Anti-DNA: antibody to native DNA in abnormal titer Anti-SM: the presence of antibody to Sm nuclear antigen Positive finding of antiphospholipid antibodies on: Abnormal serum level of IgG or IgM anticardiolipin antibodies A positive test result for lupus anticoagulant using a standard method A false-positive test results for at least 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test
Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

For the diagnosis of LN, patient should get weight, blood pressure check, renal function, complete blood cell count, and urinalysis with urine sediment on every visit. Antiphospholipid antibodies and lipid profile should be checked at baseline and intermittently. Increase in creatinine with no other reason, reproducible proteinuria ≥0.5 g with or without hematuria, or cellular cast is an indication for renal biopsy (Bertsias et al. 2012).

Pathology

Histopathology of Lupus Nephritis

Renal biopsy is a valuable tool in the diagnosis and management of lupus nephritis because less invasive clinical parameters are comparatively insensitive predictors of the severity of renal involvement. Renal biopsy should be considered in lupus patients who develop hematuria, proteinuria, or elevated serum creatinine to assess for the presence of lupus nephritis and characterize the activity and chronicity of the process.

Light microscopy is used to assess the degree of proliferation and scarring. Immunofluorescence is highly sensitive for detecting immunoglobulin deposition in the kidney. Lupus nephritis is characterized by IgG-dominant or codominant immune deposits, which are often distributed not only in glomeruli but in tubulointerstitial and vascular areas. Often the immunofluorescence profile seen in lupus nephritis is referred to as "full house" showing positive staining for IgG, IgA, IgM, kappa, lambda, C3, and C1q. Electron microscopy is not essential to the diagnosis or classification of lupus nephritis but can be helpful in more precisely demonstrating the location of immune complex deposition. It can also highlight ultrastructural details such as endothelial tubuloreticular inclusions that are commonly seen in lupus nephritis. Electron microscopy is also useful in assessing podocyte injury, which in some cases is out of proportion to immune complex deposition or proliferative activity (see discussion on "Lupus Podocytopathy").

A renal biopsy report should provide the class of lupus nephritis as well as give an indication of the degree of activity and chronicity, specifying the proportion of glomeruli with active proliferative lesions (crescents, necrosis,

and endocapillary proliferation) and sclerosis. The most widely used classification in lupus nephritis is the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification of lupus nephritis published in 2004 (Weening et al. 2004) which is detailed below.

Class I (minimal mesangial lupus nephritis): Light microscopy will show essentially normal glomeruli which should be normocellular, without proliferation. Immunofluorescence will show low levels of immune complex deposition in the mesangium without any significant peripheral glomerular capillary wall deposits. Electron microscopy will show small electron-dense deposits in mesangial areas but none involving peripheral capillaries.

Class II (mesangial proliferative lupus nephritis): Light microscopy shows mesangial proliferation, which is defined as mesangial areas (excluding those near the vascular pole) with over three mesangial cells (Fig. 1). This mesangial proliferation can be focal or diffuse, segmental or global in distribution. No endocapillary proliferation or crescent formation can be present. Immunofluorescence and electron microscopy will demonstrate predominantly mesangial deposits. Occasional small subendothelial or subepithelial deposits may be seen with either immunofluorescence or electron microscopy but these should be sparse. If large subendothelial deposits are identified by immunofluorescence or electron microscopy, even in the absence of endocapillary proliferation or crescent formation, this would warrant the diagnosis of either class III or IV (detailed below).

Class III (focal lupus nephritis) and **class IV** (diffuse lupus nephritis): The lesions that

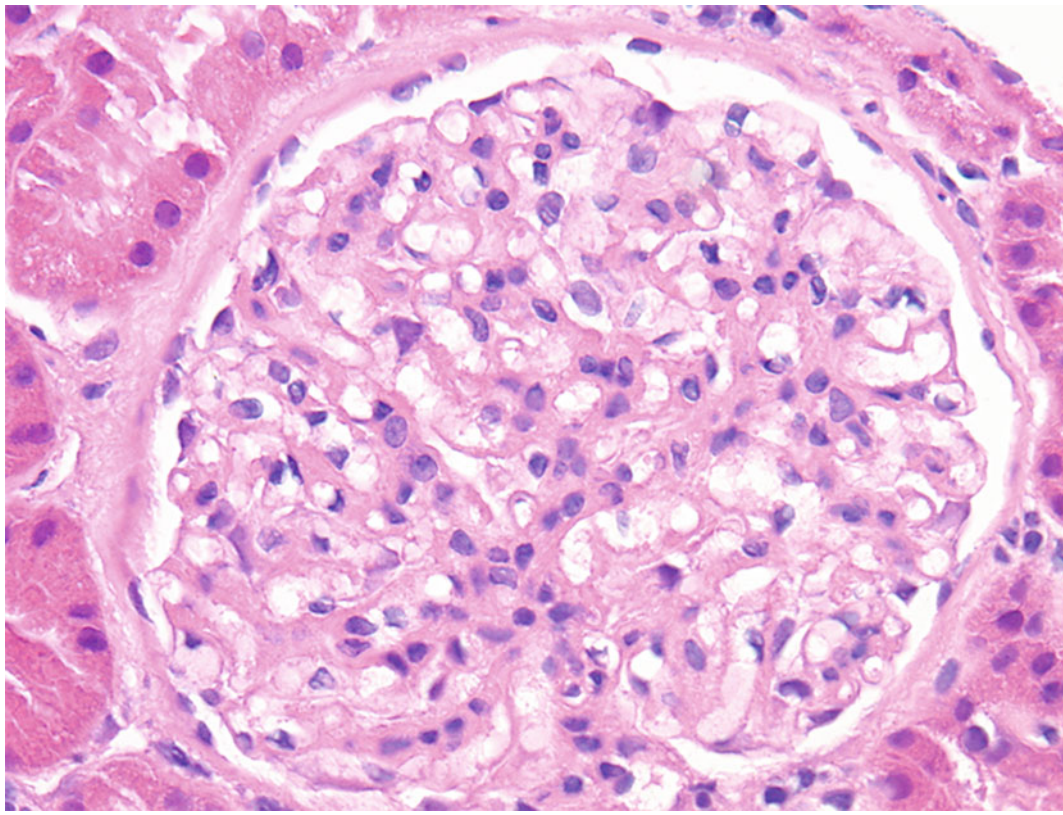

Fig. 1 Mesangial proliferative lupus nephritis. A glomerulus shows patent capillaries but mild mesangial prominence and multiple mesangial areas where over three mesangial cells are present, constituting mesangial proliferation. These findings are typical of what is seen in class II lupus nephritis (H&E, 400× magnification)

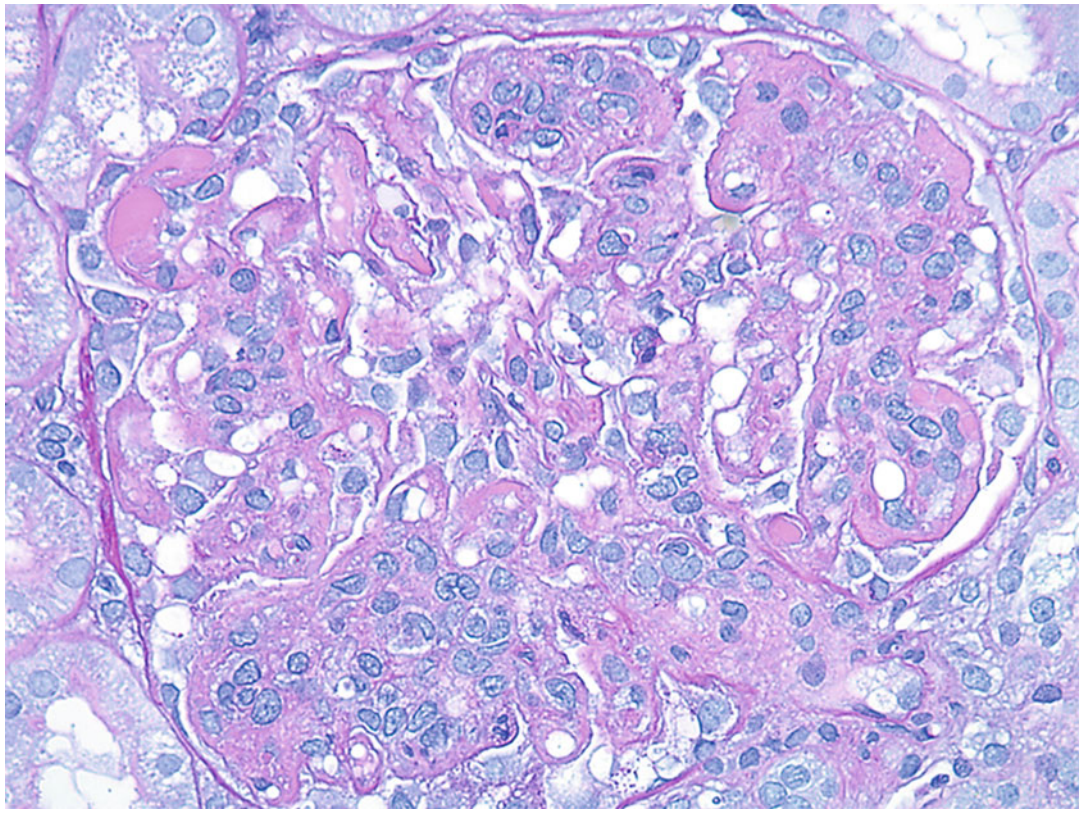

Fig. 2 Endocapillary proliferation and "wire loop" subendothelial deposits. This glomerulus shows occlusion of many glomerular capillaries by proliferating and infiltrating cells. This cellular proliferation is accompanied by abundant subendothelial deposits that have a glassy purple appearance. The presence of either large subendothelial deposits or endocapillary proliferation will merit the diagnosis of either class III or class IV lupus nephritis, depending on the proportion of glomeruli displaying these lesions (Periodic acid Schiff, 400× magnification)

characterize class III and class IV lupus nephritis are similar. The presence of active proliferative lesions including endocapillary proliferation (Fig. 2) and crescent formation (Fig. 3) characterizes these proliferative forms of lupus nephritis. In addition, glomerular scars resulting from old proliferative lesions are included in the assessment of glomerular involvement in proliferative lupus nephritis (Fig. 4). Class III is defined as showing less than 50% glomerular involvement by either proliferative or sclerosing lesions while class IV shows 50% or greater involvement. Class III lupus nephritis should be subdivided into class III (A) which shows only active lesions, class III (A/C) which shows a mixture of both active proliferative lesions and sclerosing lesions, and class III (C) which shows only chronic sclerosing lesions without residual activity. Class IV is similarly divided into A, A/C, and C subgroups but has an additional level of detail specifying whether the glomerular lesions are predominantly segmental (i.e., most lesions show $<50\%$ involvement of the glomerular tuft) or global (i.e., at least half the sampled lesions show 50% or greater involvement of the glomerular tuft). For example, a biopsy classified as lupus nephritis class IV-G (A/C) would contain a mixture of both active proliferative lesions and sclerosing lesions, involving at least 50% of glomeruli in the biopsy, and the majority of these lesions would show "global" involvement ($\geq 50\%$) of the glomerular tuft.

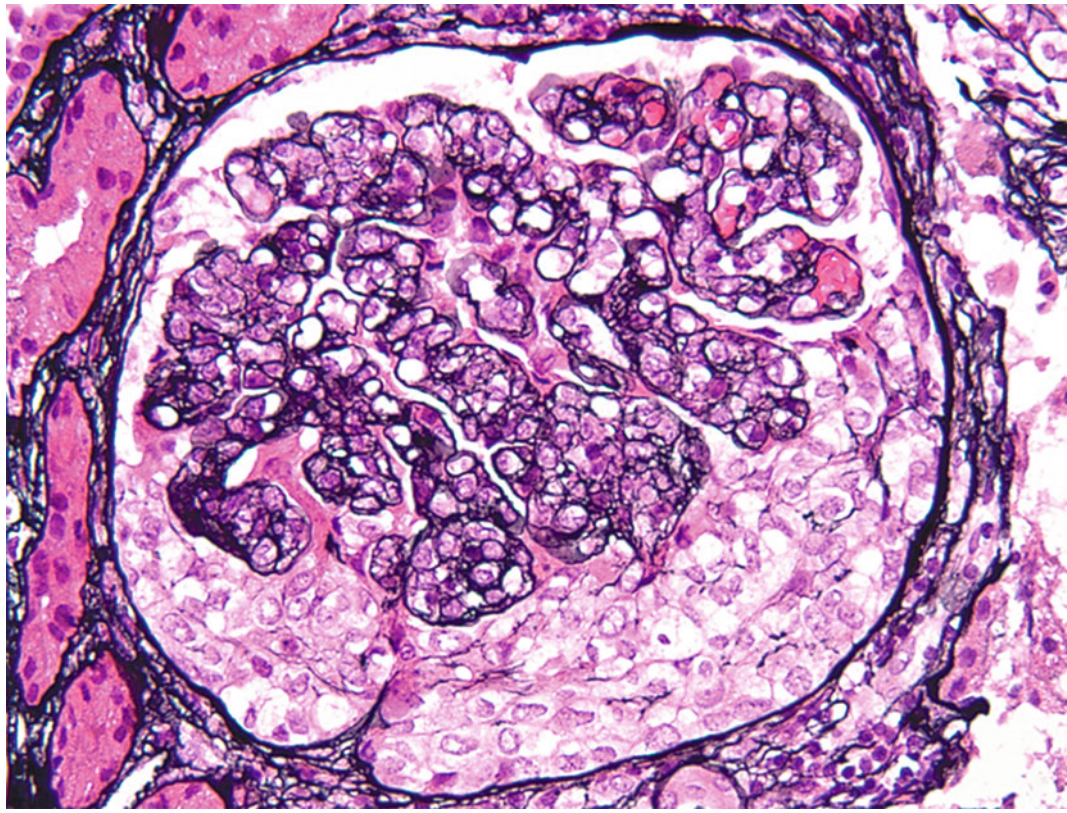

Fig. 3 Cellular crescent and endocapillary proliferation. A glomerulus shows occlusion of glomerular capillaries by cellular proliferation as well as focal rupture of the glomerular basement membrane and cellular crescent formation. Bowman's space is partially filled with proliferating epithelial cells, constituting the cellular crescent. Endocapillary proliferation and crescent formation are both proliferative lesions seen in class III and class IV lupus nephritis (Jones methenamine silver, 400× magnification)

Class V (membranous lupus nephritis): The presence of subepithelial immune deposits characterizes membranous lupus nephritis (Fig. 5). Light microscopy may show glomerular basement membrane spike formation and vacuolization. Immunofluorescence will show granular capillary wall staining, and electron microscopy will show subepithelial deposits usually accompanied by spikes or other remodeling of the glomerular basement membrane and significant podocyte effacement. Mesangial deposits are also frequently seen along with the subepithelial deposits. In pure class V lupus nephritis, these membranous alterations can be either segmentally or globally distributed. Class V lupus nephritis can also be diagnosed in combination with either class III or class IV lupus nephritis. Because occasional subepithelial deposits are often encountered in class III and class IV lupus nephritis, the additional diagnosis of class V is only merited when the membranous changes are diffuse, involving at least half of the glomerular capillary surface area.

Class VI (advanced sclerosing lupus nephritis): Light microscopy will show extensive glomerular scarring with over 90% of glomeruli showing global glomerulosclerosis as well as severe tubulointerstitial scarring. No significant active proliferation (such as cellular crescents or endocapillary proliferation) is present. Immunofluorescence and electron microscopy may show residual immune deposits in glomeruli and the tubulointerstitium. Because of the advanced chronic changes and the lack of activity, class

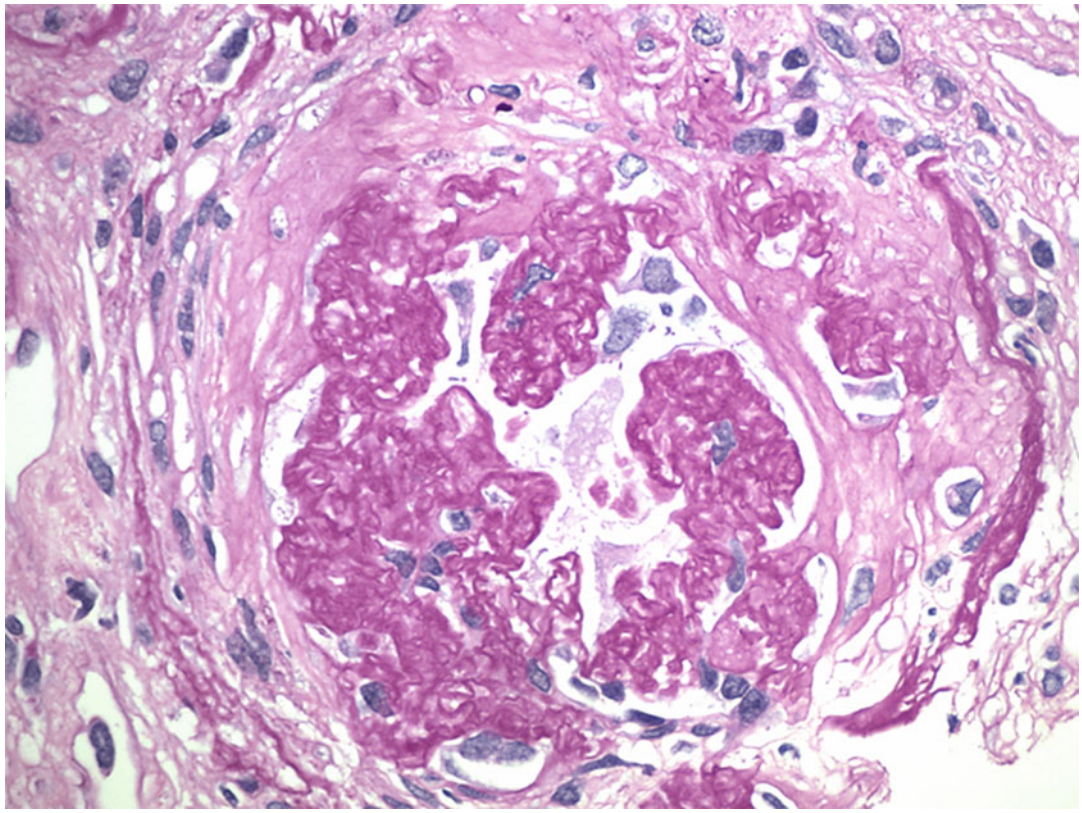

Fig. 4 Glomerular scarring from old proliferative lesions. Class III and Class IV lupus nephritis can show a combination of active proliferative lesions (see Figs. 2 and 3) as well as the chronic sequelae of this proliferation. This sclerotic glomerulus shows evidence of fragmentation of the glomerulus tuft with intervening strands of fibrous tissue, consistent with an old fibrous crescent. Bowman's capsule has also been largely eroded by the prior proliferative activity (Periodic acid Schiff, 400× magnification)

VI lupus nephritis can be difficult to distinguish from other causes of end-stage kidney on morphologic grounds alone.

Histopathology of Antiphospholipid Antibody Syndrome (APS)

APS can cause a broad spectrum of renal injury ranging from overt infarction caused by thrombosis of a major renal artery to acute fibrin thrombosis of glomerular capillaries to chronic fibrotic intimal thickening of arteries. The most common findings are those of narrowing of medium-caliber arteries due to intimal thickening as well as hyalinosis of arterioles. These findings are somewhat nonspecific and can also be encountered in hypertensive nephropathy, but often the intimal sclerosis seen in APS has a more cellular appearance (Fig. 6). Vascular disease that appears to be out of proportion to what might be expected based on the patient's age or blood pressure should prompt evaluation for APS because of the potential for nonspecific histologic findings. Fibrin thrombi ranging from fresh to organized can be encountered in arteries and arterioles. Frequently glomeruli show prominent ischemic wrinkling of glomerular basement membranes when arterioles serving these glomeruli are occluded (Fig. 7). Acute and subacute thrombotic lesions involving glomeruli can also be encountered, and these are

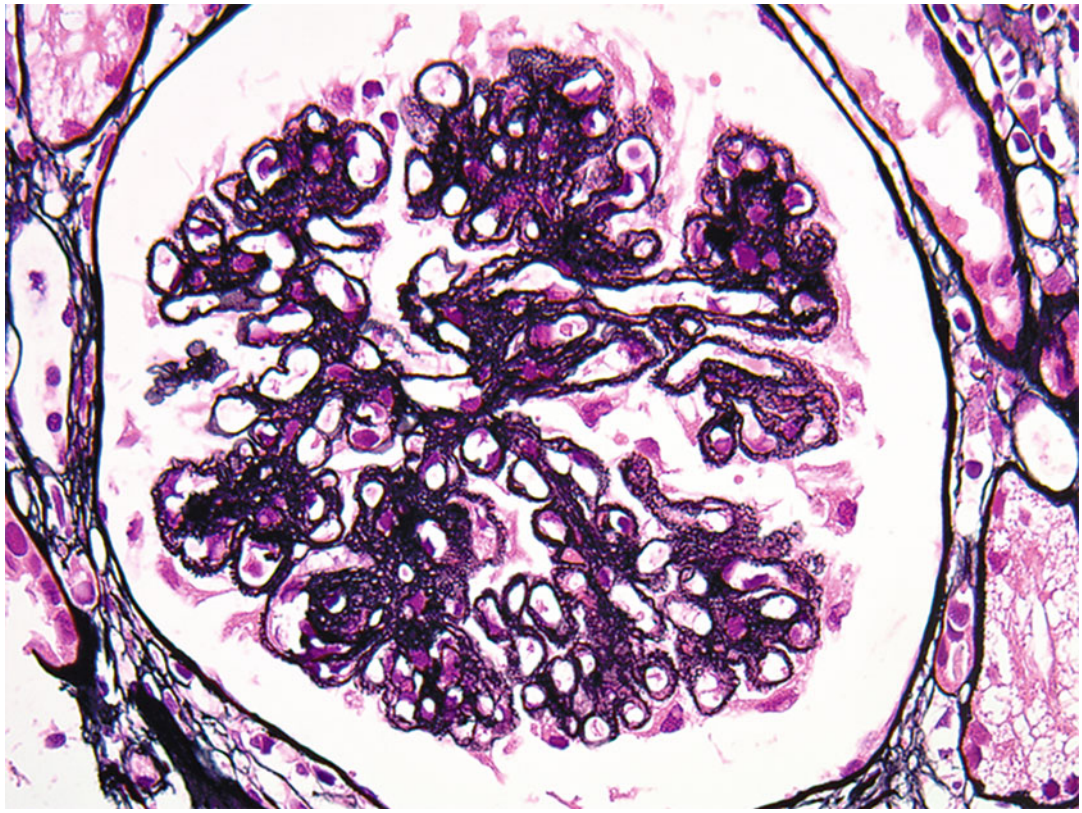

Fig. 5 Membranous lupus nephritis. Class V (membranous) lupus nephritis is characterized by subepithelial immune deposits. The glomerulus pictured shows thickened glomerular basement membranes with prominent vacuolization and glomerular basement membrane spike formation. There is often some mesangial proliferation seen in class V lupus nephritis. If diffuse membranous features are present along with endocapillary proliferation or crescent formation, the diagnosis of class III or IV + V lupus nephritis is appropriate (Jones methenamine silver, 400× magnification)

indistinguishable histologically from what can be seen with HUS and other causes of thrombotic microangiopathy. Glomeruli may contain intracapillary fibrin thrombi and can show prominent endothelial swelling and mesangiolysis (Fig. 8). In the more chronic phase glomerular basement membrane double contours may be prominent. Immunofluorescence will show bright staining for fibrin in areas of fresh thrombosis, but caution must be exercised in the interpretation of fibrin stains, as nonspecific background staining may be prominent. Electron microscopy may highlight intracapillary fibrin tactoids, expansion of the subendothelial zone by electron lucent material, mesangiolysis, or glomerular basement membrane duplication, depending on how acute or chronic the injury is (Fig. 9).

Atypical Types of Lupus Nephritis

Tubulointerstitial Lupus Nephritis

Isolated tubulointerstitial immune complex deposition with minimal or no glomerular involvement is a rare type of lupus nephritis. The mechanism is not fully understood but in experimental models the mechanism is in situ formation of immune complexes following binding of circulating autoantibodies. The pathologic findings will include normal glomeruli and renal vessels. The interstitium

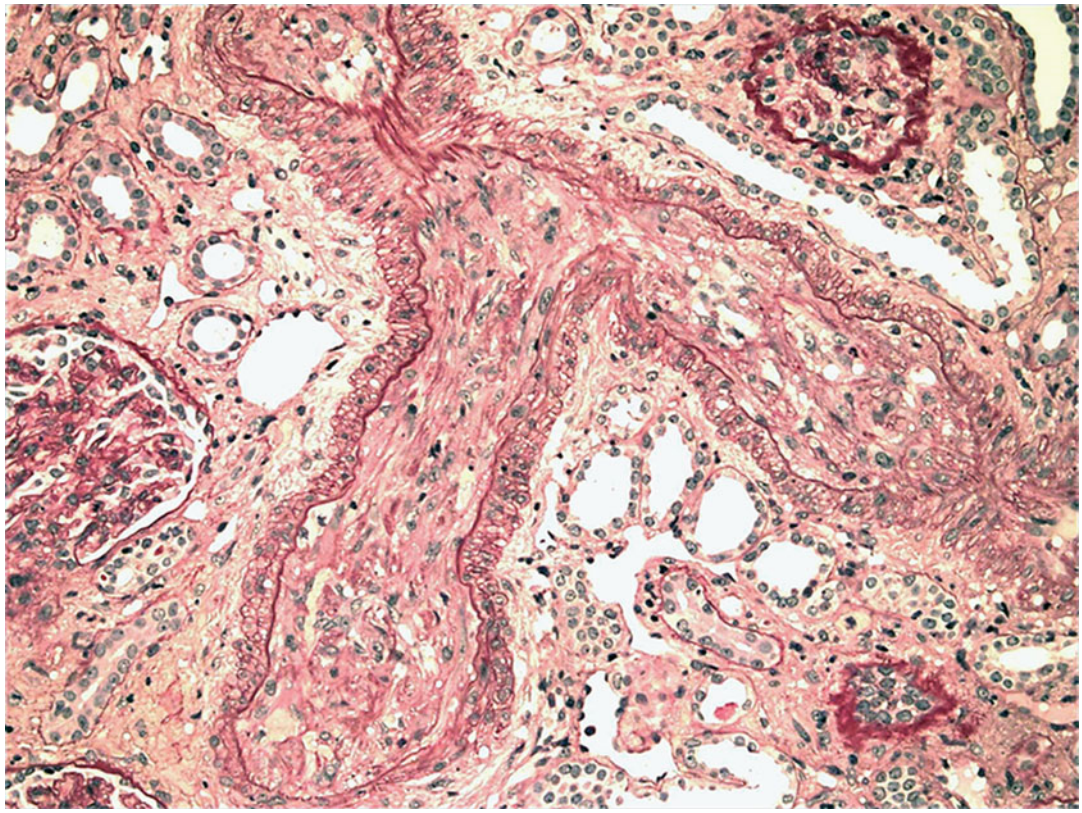

Fig. 6 Intimal sclerosis in antiphospholipid syndrome. A medium caliber artery shows complete occlusion by fibrointimal thickening. This intimal reaction is often more cellular than what is seen with typical hypertensive nephrosclerosis, though these vascular findings are in a spectrum with what can be seen in hypertension. The adjacent glomeruli show prominent ischemic wrinkling of basement membranes and there is increased interstitial fibrosis (Periodic acid Schiff, 100× magnification)

typically shows a prominent lymphoplasmacytic infiltrate and immunofluorescence characteristically reveals either granular or semilinear tubular basement membrane (TBM) staining for IgG, C3, C1q, and sometimes other immunoglobulins. Clinically the patient can present with elevated creatinine, metabolic acidosis, hyperkalemia or hypokalemia, or other signs of tubular dysfunction, non-nephrotic range proteinuria with a relatively normal urinalysis (Ali and Al-Windawi 2013).

Lupus Podocytopathy

Lupus podocytopathy is not included in the International Society of Nephrology/Renal Pathology classification of LN but it is an entity that is increasingly recognized. Lupus podocytopathy should be considered in patients with SLE who present with nephrotic syndrome. These patients have a high incidence of AKI but lack significant hematuria, as opposed to other types of LN. Renal biopsy typically shows findings consistent with MCD or FSGS including diffuse podocyte foot process effacement without significant glomerular proliferation and without subendothelial or subepithelial immune deposits. Mesangial immune deposits and mesangial proliferation do not exclude the diagnosis of lupus podocytopathy. Hu et al. (2016) presented 50 cases of lupus podocytopathy gathered between the years 2000 and 2013. Forty-seven had mesangial immune deposits that were confirmed by immunofluorescence and electron microscopy, 13 had normal finding light microscopy, 28 had mesangial proliferation, and 9 with

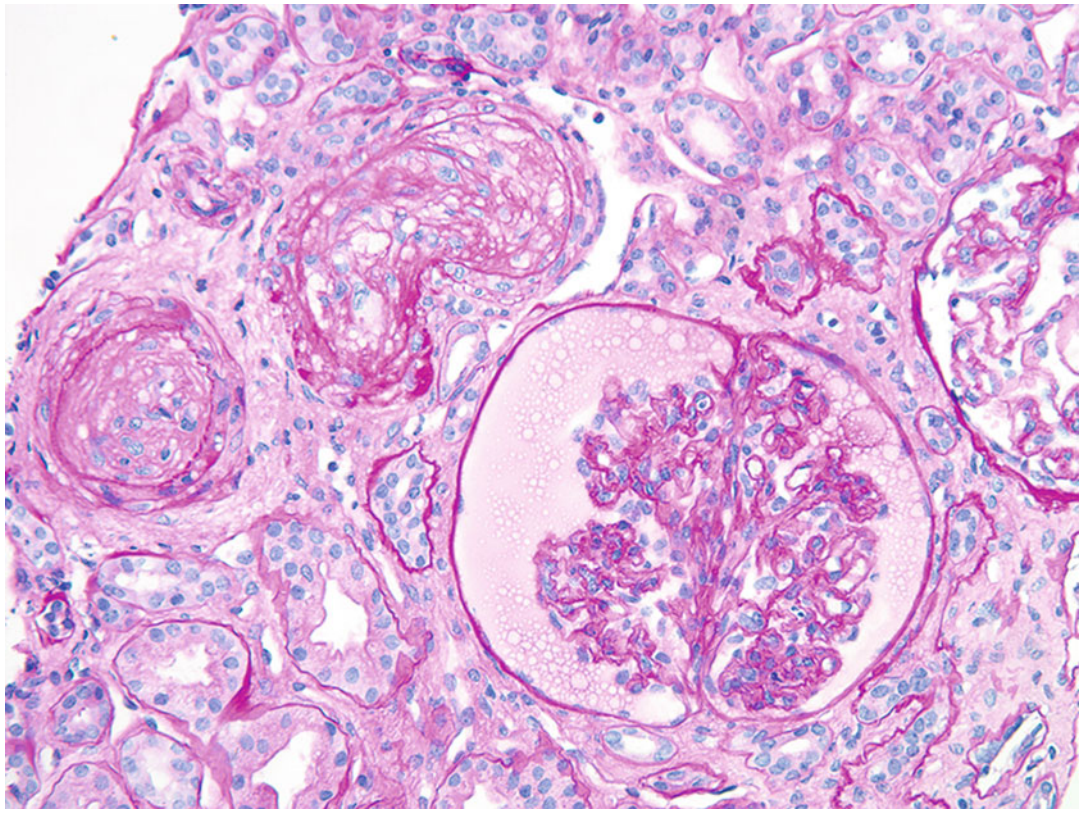

Fig. 7 Arteriolar changes in antiphospholipid syndrome. Smaller arterioles may also show occlusive narrowing which in this case is due to a combination of fibrin, endothelial cell swelling and schistocyted. The glomerulus near these arterioles shows retraction of the glomerular tuft in Bowman's space, consistent with profound ischemia (Periodic acid Schiff, 200× magnification)

FSGS lesions. This has been the largest series of lupus podocytopathy. The authors propose the following criteria for diagnosis of Lupus podocytopathy:

- Clinical diagnosis of SLE by American College of Rheumatology (ACR) and the presence of nephrotic syndrome.
- Light microscopy showing FSGS or normal glomeruli. Mesangial proliferation is permissible but no endocapillary proliferation, necrosis, or crescents should be present.
- Immunofluorescence: Negative glomerular staining or deposits restricted to the mesangium. No subendothelial or subepithelial deposits.
- Electron microscopy: Diffuse foot process effacement (>70%). Immune deposits, if present, should be restricted to the mesangium.

In general patients with lupus podocytopathy require less-aggressive therapy than patients with proliferative LN. Patients with MCD morphology respond better to glucocorticoid therapy alone than those with FSGS.

An aggressive variant of lupus podocytopathy is recognized in patients who show collapsing glomerulopathy on renal biopsy. While rare this variant is described more frequently in female patients with African lineage. Patients respond poorly even with aggressive treatment and frequently progress to ESRD (Salvatore et al. 2012).

Seronegative LN or Renal-Limited LN

As mentioned above the diagnosis of SLE is made when a combination of clinical, laboratory, and pathologic finding is present. About 1–5% of the

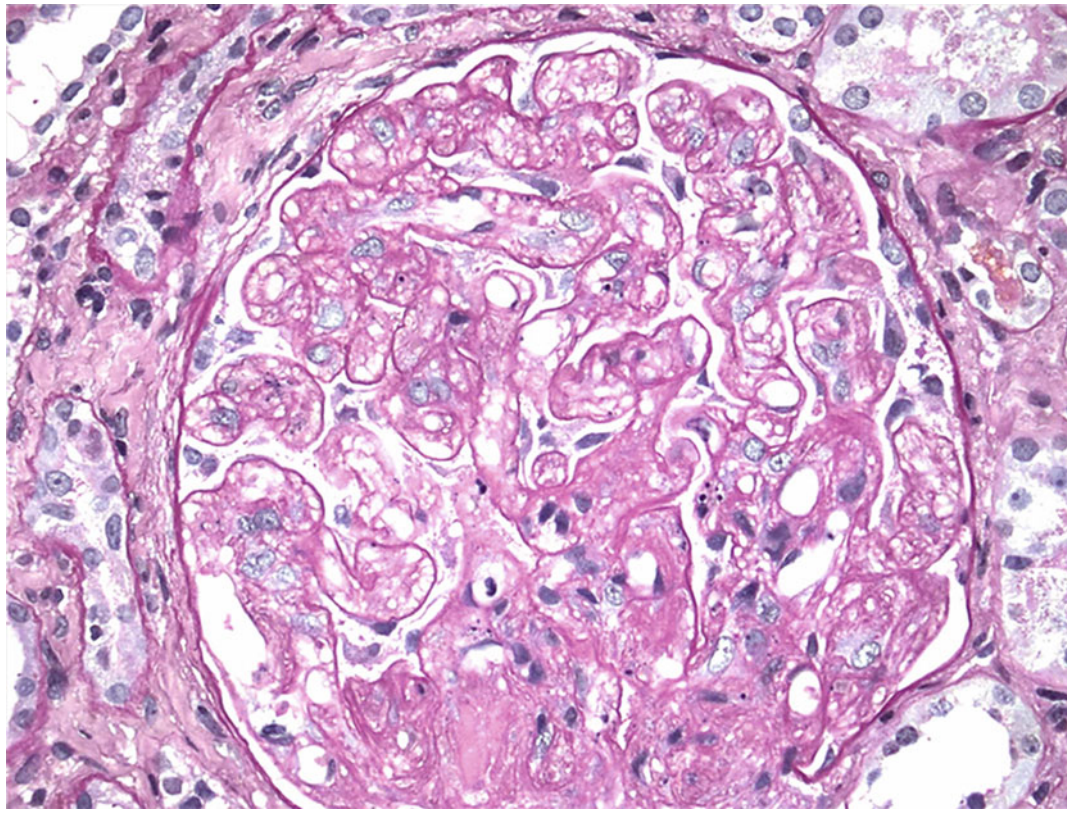

Fig. 8 Glomerular involvement in antiphospholipid syndrome. A glomerulus showing prominent endothelial swelling and extensive loss of mesangial matrix, called mesangiolysis. Focal intracapillary fibrin is also present, best seen at the vascular pole (Periodic acid Schiff, 400× magnification)

patients with SLE will have negative ANA (Kim et al. 2009). Many case reports of SLE with negative serologies but typical histopathologic characteristics of LN have been reported (Pirkle et al. 2013; Huerta et al. 2012; Simmons et al. 2015). The histopathologic features are the same as those found in LN.

The International Society of Nephrology/Renal Pathology classification of LN does not recognize this entity, but it has been described as "lupus-like nephritis," "ANA-negative LN," and "seronegative LN." Some patients exhibit some features of lupus but fall short of meeting ACR criteria for SLE. Others may have negative serologies at the time of renal biopsy but with time develop positive serologic markers. Some patients lack both serologic and systemic signs of SLE. There is no consensus on the diagnosis and treatment for these patients and for that reason they are at high risk of progressing into ESRD. Clinical judgment, prompt treatment, and close monitoring are needed in these patients in order to avoid rapid progression of renal disease.

Treatment

Adjunctive Treatment

Antimalarial Agents

It is the opinion of most experts that patients with LN should be treated with antimalarial agents (hydroxychloroquine) unless otherwise contraindicated, as its use appears to be associated with a lower risk of lupus flares and renal damage (Anonymous 1991; Fessler et al. 2005; Hahn et al.

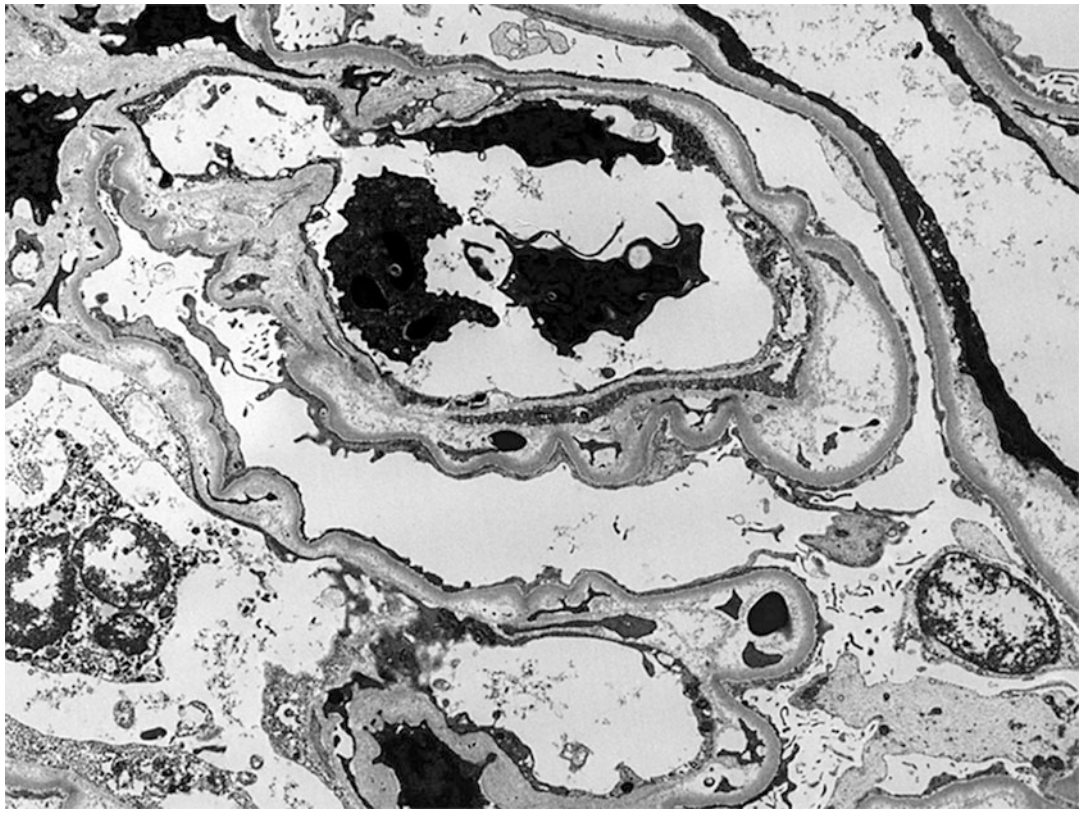

Fig. 9 Ultrastructural findings in antiphospholipid syndrome. Several glomerular capillaries display prominent widening for the subendothelial zone by electron lucent material. The endothelial fenestrations are lost and there is the beginning of a new layer of glomerular basement membrane forming (original magnification ×2900)

2012). It is recommended even during pregnancy. The recommended dose is <6.5 mg/kg/day in patients with normal renal function.

Ocular Toxicity

The side effects of antimalarial agents include keratopathy, ciliary body involvement, lens opacities, and retinopathy. These occur due to duration, cumulative dose, age of patient, and renal or hepatic involvement. Patients should have an annual retinal examination (Bernstein 1983).

Reno-protective Agents

All patients should receive reno-protective agents, unless contraindicated, including angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) for the management of proteinuria and hypertension and statins for the management of hypercholesterolemia (Hahn et al. 2012).

Introduction of Treatment of Lupus Nephritis

Approximately 50% of patients with systemic lupus erythematous (SLE) will develop lupus nephritis (LN), which significantly increases the morbidity and mortality of the disease (Trotter et al. 2016). Historical data about the natural history of severe proliferative LN emphasizes that if left untreated, it will progress to ESRD in less than 2 years (Ginzler et al. 1980).

Current decisions regarding appropriate timing for the initiation of treatment, treatment options, and duration of therapy are largely

guided on the renal biopsy findings, which are characterized based on the 2003 International Society of Nephrology/Renal Pathology Society classification criteria (Weening et al. 2004; Hahn et al. 2012).

Based on the ISN/RPS classification, in general, no immunosuppressive treatment is required for the management of classes I and II LN, as the vast majority of these patients will have a benign long-term course. Immunosuppressive therapy in these patients is usually tailored to the management of other systemic manifestations (Bertsias et al. 2012; Hahn et al. 2012).

Of note, the 2012 KDIGO guidelines for the management of lupus nephritis recommend glucocorticoids (GC) or calcineurin inhibitors (CIN) for the treatment of patients with class II LN associated with significant proteinuria (>3 g/day), as these patients could have associated podocytopathy and usually respond to treatment like patients with minimal-change disease (MCD) (class 2D recommendation) (Beck et al. 2013).

On the other hand, immunosuppressive therapy is indicated for all patients with active proliferative lupus nephritis (classes IIIA and II A/C, IVA and IV A/C, with or without associated class V) given the severe course of these forms of the disease.

Patients with pure membranous LN (MLN, class V) usually have a more benign prognosis and can sometimes be managed without immunosuppressive therapy. However, if they have nephrotic range proteinuria and/or there is deterioration of renal function, immunosuppressive therapy is then warrant, as up to 10% of these patients will progress to ESRD without treatment (Ward and Bargman 2016). If proliferative features are present in association with class V LN, patients are treated as if they would have proliferative disease.

Class VI LN (sclerosis of > = 90% of glomeruli) should not be treated aggressively given its very poor renal prognosis despite treatment. Management of these patients should instead be focused on non-immunosuppressive therapies to slow down the progression of the renal disease and in preparing them for initiation of renal replacement therapy (Bose et al. 2014; Hahn et al. 2012).

Immunosuppressive Therapy

In general, immunosuppressive therapy for LN is divided into an induction and a maintenance phase. The induction phase has the goal to control organ and life-threatening disease and induce remission (either complete or partial). The maintenance phase has the goal to control more indolent disease, preventing relapses and preserving renal function while limiting unwanted complications of medical therapy.

The definitions of complete and partial response are variable. Based on the KDIGO guidelines, 2012, complete response is defined as a return of serum creatinine to baseline and a decline in uPCR to <500 mg/g. Partial response is defined as a stabilization (+/− 25%) or improvement in serum creatinine (sCr) (but not to normal) plus a 50% or more decline in baseline proteinuria. If patient was nephrotic at baseline, a uPCR <3000 mg/g is also required (Beck et al. 2013).

The induction and maintenance phases somehow differ between proliferative and non-proliferative forms of the disease; so in this chapter, the treatment of LN will be divided in the treatment of active proliferative lupus nephritis (ISN/RPS classes IIIa and a/c, IVa and a/c, and III/V, IV/V a, and a/c) and the treatment of pure membranous LN (class V).

Active Proliferative Lupus Nephritis

Cyclophosphamide (CYC) for Induction Therapy of PLN

The standard of care for induction therapy of active PLN involves a combination of glucocorticoids (GC) and either cyclophosphamide (CYC) or mycophenolate mofetil (MMF), usually given for a period of 6 months. These two treatments

have been found to be equally effective for inducing remission.

Cyclophosphamide can be given orally (PO) or intravenously (IV), but current guidelines recommend IV CYC over PO (Beck et al. 2013; Bertsias et al. 2012).

Currently, the most commonly used IV CYC regimens are the modified NIH regimen (or high-dose CYC regimen) and the Euro-Lupus regimen (or low-dose CYC regimen). The modified NIH regimen consists of 6 monthly pulses of IV CYC at a dose of 0.5–1 g/m^2, in conjunction with GC, followed by maintenance, and the Euro-Lupus regimen, consists of 6 biweekly pulses of IV CYC, 500 mg IV each, plus GC, followed by maintenance therapy.

– Background Information on IV Cyclophosphamide for LN

The NIH Trials

The efficacy of the addition of cytotoxic agents to steroid therapy for the management of lupus nephritis was evaluated by the NIH lupus nephritis trials. One of these classic trials (Austin et al. 1986) compared four different immunosuppressive (IS) regimens against high-dose prednisone alone (1 mg/kg) and established the superiority of a combination of pulse IV CYC plus steroids (0.5 mg/kg/day) over oral high-dose prednisone alone for the management of all types of LN. In this study, CYC IV was given at a dose of 0.5–1 g/m^2 every 3 months. All IS regimens were maintained for 18 months after remission or a maximum of 4 years. Of note, the trial excluded patients with a GFR $<$ 20 ml/min/m^2 (Austin et al. 1986).

In a follow-up NIH study, published by Boumpas et al. in 1992, methylprednisolone (MP) was compared against two different regimens of IV CYC in patients with severe LN. Both regimens included monthly infusions of IV CYC (dose as above) for 6 months, but one regimen added quarterly infusions for two additional years. Although both CYC regimens were associated with a lower risk of doubling sCr at follow-up compared with GC alone, only the longer course achieved a significant difference. In addition, the extended course was associated with a significantly lower number of flares than the shorter CYC course (Boumpas et al. 1992).

The Euro-Lupus Trial

Given the concerns for treatment toxicity, mainly ovarian failure, in this group of characteristically young women of childbearing age, and based on retrospective data supporting lower doses and shorter courses of CYC for the treatment of PLN, the Euro-Lupus nephritis study was carried out.

The Euro-Lupus nephritis trial (ELNT) was a multicenter, prospective randomized controlled trial (RTC), which had the goal to test an induction regimen for PLN using low-dose CYC against the current standard of care (the "NIH regimen"). The study included 90 patients who were randomized to either a low-dose CYC regimen (500 mg every 2 weeks for 6 doses) or a high-dose regimen (starting at 0.5 g/m^2 and increase to a maximum of 1500 mg monthly as long as the WBC nadir at 14 days was $>$1500 ml/dl for 6 monthly and 2 quarterly doses).

All patients received methylprednisolone 750 mg IV daily $\times$ 3 days at the initiation of therapy, followed by prednisolone 0.5 g/kg/day (or equivalent dose if other steroid use), except patients with severe disease when a dose of 1 g/kg/day was allowed. Dose was slowly tapered after 4 weeks but patients remained on low dose (5–7.5 mg daily) for at least 30 months.

ELNT used a modified NIH protocol (8 doses of CYC instead of 14 doses of CYC). Cumulative CYC dose in the high CYC group in this trial was 8.5 g +/− 1.9 g; all patients in the low-dose group received a total of 3 g of CYC.

Azathioprine (AZA) was started 2 weeks after the last dose of CYC and continued for at least 30 weeks. The dose was 2 mg/kg/day except for patients with intolerance, which were dosed at 1 mg/kg/day.

After a median follow-up of 40 weeks, there were no significant differences between the two treatment groups even when comparing classes III and IV and whites and nonwhites. There were 50% less severe infections in the low-dose group, but the difference did not achieve statistical significance (Houssiau et al. 2002). Of note, patients in the ELNT were mainly Caucasian and had less severe disease as compared to the NIH trials patients: only 22% had a serum creatinine >1.3 and only 28% had nephrotic syndrome (vs. 62% and 64% in the Boumpas et al. trial).

In a follow-up paper, no significant difference was found in the cumulative probability of ESRD or doubling of serum sCr between the two treatment groups. Additionally, multivariate analysis showed that early response to therapy at 6 months (defined as a decreased in serum creatinine and proteinuria <1 g/24 h) was the best predictor of good long-term renal outcomes (Houssiau et al. 2004).

At 10-year follow-up, death, sustained doubling of serum creatinine and ESRD rates did not differ between the two treatment groups. Noticeably, two thirds of the patients in the low-dose CYC did not receive additional CYC. Of the third that did, the cumulative dose was still significantly lower than in the high-dose CYC group (5.5 g vs. 9.5 g). An early drop in proteinuria remained a good predictor of good renal outcomes (Houssiau et al. 2010b). Of note, death and ESRD rates were significantly lower than in other cohort of LN patients, likely secondary to the fact that did not have significant renal disease activity at baseline and were mainly a Caucasian group.

Oral Cyclophosphamide

Although not considered by many experts, first-line therapy for the induction phase (ACR/EULAR guidelines), oral CYC has also been used successfully for the induction therapy of LN (Mok et al. 2001, 2002; Yee et al. 2004). However, it should be noted that some studies have found it less efficacious than IV CYC (Austin et al. 1986) and PO CYC might be associated with higher cumulative dose and higher risk of toxicity including amenorrhea, infections, and bladder complications (Mok et al. 2001). If oral CYC is used, the EULAR guidelines recommend a dose of 2–2.5 mg/kg/day for a total of 3 months (Bertsias et al. 2012).

Mycophenolate Mofetil (MMF) for Induction Therapy of PLN

MMF is currently considered an equivalent option to CYC for induction therapy of active PLN. MMF dose ranges from 2 to 3 g a day and is continued for 6 months. Although studies have not been done with mycophenolic acid (MPA), it is accepted as an alternative to MMF and if used, the equivalent doses are 1440–2160 mg a day (Hahn et al. 2012).

– Background Information on MMF for PLN

An early study by Chan et al. showed no difference in the rate of remission between the MMF and CYC at 12 months, but patients treated with MMF had a higher chance of relapse at 3 years follow-up (Chan et al. 2000).

In 2009, Appel et al. published the results of the induction phase of the Aspreva Lupus Management Trial (ALMS Trial), which was an opened labeled, two-phase (induction and maintenance), international RCT. In this study 370 patients with LN classes III, IV, and V were randomly assigned to one of the following induction regimens: (1) Oral MMF twice a day, titrated from 0.5 g twice daily in week one, to 1 g twice daily in week two, up to 1.5 g twice daily in week three; (2) monthly pulses of IV CYC, 0.5–1 g/m^2, once a month, following a modified NIH protocol. After the 24 weeks of induction phase, patients who had responded were blindly assigned to either maintenance MMF or AZA. Importantly, the trial included 32 patients with eGFR <30 ml/min/m^2 at baseline. The study found no significant difference between the two treatment groups in achieving reduction of proteinuria and stabilization or improvement in renal function. However, there was a significant difference in the rate of response to MMF in the African-American and mix-race groups. There were no significant differences in

the rate of adverse effects (AEs). There was a tendency to higher withdrawal rates from MMF versus CYC but did not achieve statistical significance. There were more deaths in the MMF group (9 vs. 5), but the difference did not achieve statistical significance (Appel et al. 2009).

Glucocorticoid (GC) Use for Induction Therapy of PLN

The dose of GC that accompany the above regimens is variable, usually involving high or medium daily doses of prednisone (0.5–1 mg/kg/day), with or without methylprednisolone (MP) pulses at the initiation of therapy (sometimes with repeat pulses at a later time), ranging from 500 to 1000 mg each pulse. GC are tapered over 6 months to a low daily dose that usually is continued through the maintenance phase (usually 5–10 mg a day). The ACR task force panel recommends a MP pulse of 500–1000 mg for 1–3 days followed but daily oral GC 0.5–1 mg/kg/day followed by a taper to the minimal dose needed to control disease. However the level of evidence to support these recommendations is low (level C) (Hahn et al. 2012).

– Background Information on GC

GC are potent anti-inflammatory and immunosuppressive medications which has been used for the treatment of severe manifestations of SLE, including LN, since the 1970s, with MP pulses and oral prednisone being the two steroids most widely used during the induction phase of LN. Despite years of use, ideal dose, tapering schedule, and duration of therapy are unclear.

Given the significant toxicities associated with chronic GC use, low-dose and GC-free regimens have been recently evaluated. Doses of methylprednisolone of 500 mg a day for 3–5 days were found to be as effective as doses of 1000 m/day for 3–5 days for the treatment of severe lupus nephritis (Kong et al. 2004; Badsha and Edwards 2003).

A small retrospective study by Ruiz-Irastorza et al. 2014 recently compared a group of patients from the Lupus-Cruces observation cohort to those from a historic cohort (similar to the NIH protocol). The Lupus-Cruces cohort used an induction regimen of methylprednisolone pulses, IV CYC and low-dose prednisone, and the dosing would depend on the stage of LN (not all patients received MS and CYC). The average initial dose of prednisone was 22 mg a day, with an average daily dose at 6 months of 9 mg a day. The historical cohort was treated with CYC 1 g monthly for 6 months, followed by quarterly doses for 2 years, plus prednisone 1 mg/kg/day as starting dose. The average initial dose of prednisone was 49 mg/day and an average daily dose at 6 months 22 mg a day. This study showed higher rates of both partial and complete remission at 6 and 12 months in the low-dose prednisone group. The cumulative CYC dose was lower in the low versus high prednisone groups. Of note, all patients in the low steroids use were also treated with hydroxychloroquine and ACE inhibitors and had lower levels of proteinuria at baseline (Ruiz-Irastorza et al. 2014).

In recent years, rituximab (RTX) has been added to the induction therapy of LN in an attempt to minimize and even avoid prednisone use, with good short-term results. In a recent prospective observational study published by Condon et al. in 2013, 50 patients with classes III, IV, and IV LN were treated with a regimen consisting of rituximab 1 g with methylprednisolone 500 mg IV on days 1 and 15 followed by maintenance MMF (titrated up to a dose of 1500 mg BID), without oral steroids (RITUXILUP protocol). With this regimen, complete or partial remission was achieved by 45/50 patients at a median time of 37 weeks and 52% of patients achieved complete remission at 1 year follow-up. Of note, there was a high rate of relapses (22% by a median follow-up of 65 weeks) (Condon et al. 2013).

Second-Line Therapies for the Induction of PLN

Second-line therapies include calcineurin inhibitors and azathioprine (first line in pregnant patients). For refractory disease, rituximab has

been tried, as well as the addition of plasmapheresis. Most recently, multi-targeted therapy and steroid-free treatments have been tested, with good short-term outcomes in certain cohorts.

– Background Information on Second-Line Therapies for PLN

AZA Versus CYC for Induction Therapy of PLN

AZA was not as effective as IV CYC to induce remission in the classic NIH trial by Austin et al. (Austin et al. 1986).

The Dutch lupus nephritis study, which was the first RTC comparing AZA against CYC for the induction of PLN. At a median follow-up of 5.7 years, doubling of sCr was more frequent in the AZA group but not significantly different. However, relapses and infections, mainly herpes zoster, were more common in the AZA group. The rate of remission, sCr, and proteinuria at last follow-up was not different but authors note that the study lacked sufficient power to notice a difference. The authors concluded that CYC was superior to AZA in preventing relapses of LN and was associated with less frequency of zoster flares (Grootscholten et al. 2006). In a later publication by the same group, CYC was found more effective than AZA to delay the progression of chronic lesions in PLN (Grootscholten et al. 2007). Based on the above, clinical guidelines do not consider AZA first-line therapy for the induction phase of LN (Hahn et al. 2012).

Calcineurin Inhibitors for Induction of PLN

The calcineurin inhibitors, cyclosporine (CsA), and tacrolimus (TAC) have been used for some time as either adjunct or alternative therapies in the management of lupus nephritis, mainly when there is a significant proteinuric component (given the known beneficial effects of this drug in podocytopathies). A retrospective study by Yap et al. (2014) reviewed long-term data on TAC use in LN. In this study, TAC was prescribed as an adjunct therapy on patients with PLN who had failed to decrease proteinuria levels to <2 g/24 h after induction therapy with MMF and steroids or was given as first-line therapy for patients with class VLN (and compared with MMF and steroids). The addition of TAC after 6 months of induction therapy in patient with persistent proteinuria led to 40% additional complete remissions at 12 months and 46.7% at 24 months (Yap et al. 2014).

A recent meta-analysis of the use of CIN for induction and maintenance of LN, reported comparable efficacy of CsA and TAC to CYC and MMF, and CIN were found to be significantly less toxic than CYC (Zhang et al. 2016).

Rituximab

The lupus nephritis assessment with rituximab trial (LUNAR trial) tested the hypothesis that the addition of RTX to MMF and GC would achieve greater induction rates than MMF and GC alone. This study failed to show a superiority of the RTX regimen to achieve a renal response at 52 weeks (Rovin et al. 2012).

Plasma Exchange (PLEX)

Several RTC have evaluated the efficacy of plasma exchange (both alone and with steroids and other immunosuppressant agents) for the management of PLN. A meta-analysis of all available RTC for the management of PLN concluded that PLEX added no benefit to the treatment of LN. Of note, addition of PLEX to cytotoxic regimens was not associated with increased risk of adverse effects (Flanc et al. 2004).

Maintenance Therapy for PLN

Maintenance therapy is indicated in all patients after completion of induction therapy. Lack of

maintenance therapy is associated with worse outcomes, including worsening renal function, ESRD, and even death (Mok et al. 2006). Currently, the two main drugs used for the maintenance phase of PLN are MMF and AZA.

– Background Information of Maintenance Therapy

In 2011, Dooley et al. published the results of the maintenance phase of the ALMS trial. In this phase, MMF (2 g a day) was compared to AZA (2 mg/kg/day) as maintenance therapy of those patients who had achieved response during the induction phase. The trial found that MMF was superior to AZA: there was a lower rate of treatment failure, renal flares, and time-to-rescue therapy in the MMF group (Dooley et al. 2011).

On the other hand, the MAINTAIN nephritis trial, which was a superiority trial which goal was to prove that MMF was associated with less rate of renal flares after induction therapy with the Euro-Lupus regimen, failed to show a significant difference between MMF and AZA as maintenance therapy. However, there was a tendency to fewer relapses in the MMF group. There were significantly more cytopenias with AZA (Houssiau et al. 2010a). A follow-up again did not show superiority of MMF over AZA (Tamirou et al. 2016).

Most recently, the calcineurin inhibitors, cyclosporine and tacrolimus, have emerged as an alternative for the maintenance therapy of LN, with some recent studies showing promising results and adverse effect profile (Lee and Song 2016).

Membranous Lupus Nephritis

Membranous lupus nephritis (MLN) or class V lupus nephritis accounts for 10–20% of lupus nephritis cases and can present alone or in association with a proliferative form. When it is the only finding, the prognosis is typically better than with proliferative lupus nephritis, but there is still a significant number of patients that will develop ESRD (10% at 10 years). It is also associated with increased risk of thrombotic complications (Ward and Bargman 2016).

Treatment of pure MLN includes management of hypertension, edema, and proteinuria, as well as possible complications of the nephrotic syndrome (see section on "Nephrotic Syndrome"). Renin-angiotensin-aldosterone system (RAAS) blockers are first-line agents in the management of hypertension and proteinuria. In patients with severe hypoalbuminemia (< 2.0 g/dl), there is an increase thrombotic risk (mainly if the patient has other risk factors, such as lupus anticoagulant) and prophylactic anticoagulation should be considered (Bertsias et al. 2012).

Guidelines recommend additional treatment with immunosuppressive medications for patients with class V LN with nephrotic syndrome and/or decreased renal function. While the KDIGO guidelines recommend combination of GC with either CYC, MMF, AZA, or CIN. The ACR and EULAR recommend MMF and steroids as first-line therapy (Beck et al. 2013; Bertsias et al. 2012; Hahn et al. 2012). The recommended dose of MMF for MLN is 2–3 g a day.

Although no high-quality evidence exists to guide GC dosing and tapering regimen, most experts and guidelines recommend doses ranging from 0.5 to 1 mg/kg/day, tapered over 6–12 months (Ward and Bargman 2016).

As with proliferative form, use of hydroxychloroquine has been shown to improve outcomes in patients with LMN and should always be included as part of their therapy, unless otherwise contraindicated (Kasitanon et al. 2006).

– Background Information on Treatment for MLN

Evidence of the efficacy of CYC plus GC for the induction of class V LN comes from the initial NIH trial by Austin et al., which included 16 patients (15%) with pure MLN (Austin et al. 1986).

MMF has been shown to be equivalent to CYC for the induction treatment of MLN. In a pooled analysis of patients with class V LN from two RTC (ALMS and US trials), MMF in combination

with high-dose prednisone was associated with similar remission rates in terms of improvement of proteinuria and stabilization of sCr at 24 months than CYC plus high-dose steroids.

Given their intrinsic antiproteinuric effects, calcineurin inhibitors have been used for the management of MLN. A RTC comparing the efficacy of GC monotherapy versus GC plus either 11 months IV CYC or oral CsA showed superiority of the combination therapy over GC alone: 27% versus 60% versus 83%, respectively, achieved either partial or complete remission of proteinuria at 12 months. The difference in remission between IV CYC and oral CsA did not achieve statistical significance, but there was a significantly higher rate of relapses in the CsA group (Austin et al. 2009).

A meta-analysis of studies evaluating treatment for class V showed a significant improvement in outcomes with the addition of an immunosuppressive agent to prednisone, compared with prednisone alone. However, there were no difference between the AZA, CYC, MMF, and CsA groups (Swan et al. 2011).

Mixed MLN and PLN is usually targeted to the treatment of the proliferative form.

Most recently, some investigators tested the hypothesis that multi-target therapy would improve outcomes in patients with combined disease. A recent RTC from China, which included patients with classes III, IV, V, and combination of them, compared a regimen of TAC (2 mg twice a day) plus MMF (500 mg twice a day) with CYC (0.5–0.1 g/m^2) IV monthly for 6 months. Both groups received GC. Significantly more patients in the multi-target therapy group achieved remission (either complete or a combination of partial and complete) at 24 weeks follow-up, as compared to the CYC groups. The higher remission rates in the multi-target therapy group persisted when evaluating patients with pure class IV, pure class V, and a combination of classes IV and V (although in this last group the difference did not achieve statistical significance). The incidence of adverse events was similar in both groups, including serious adverse events (Liu et al. 2015).

In the previously mentioned study by Condon et al. that evaluated the effectiveness of treating lupus nephritis with RTX and MMF but no oral GC, 44% of patients had pure MLN (50% with nephrotic syndrome). Of the patients with class V and nephrotic syndrome, 18% achieved complete remission at 6 months and 36% at 1 year. Of the total group of MLN patients, 32% achieved complete remission at 6 months and 23% partial remission, and by 12 months, 38% and 24% achieved complete and partial remission, respectively (Condon et al. 2013).

It is important to keep in consideration that resolution of proteinuria is time dependent. Immune deposits reabsorption and resolution of glomerular basement membrane abnormalities usually lag behind the cessation of the immune activity. In cases of persistent significant proteinuria after induction, consideration to a repeat renal biopsy should be made before continuing with high-intensity immunosuppression (Ward and Bargman 2016).

Maintenance Therapy of MLN

Once remission has been obtained, maintenance therapy can be done with MMF, CIN, or AZA. A recent meta-analysis by Lee and Song, comparing the efficacy and safety of TAC, MMF, AZA, and CYC for the maintenance phase of LN and which included several patients with pure class V LN, showed no significant difference between the drugs in terms of efficacy (Lee and Song 2016).

The optimal duration of maintenance therapy for all classes of LN is unknown but should be at least 1 year, but many experts and guidelines recommend 3–4 years (Beck et al. 2013; Bertsias et al. 2012; Hahn et al. 2012).

Resistant Disease

Clinical guidelines recommend changing immunosuppressive regimen if there is no response by 6 months or if there is worsening by 3 months. In the case of PLN, if the patient was initially treated with CYC, recommendation is to attempt

remission with MMF and vice versa. Another option is to add or change to rituximab. Multi-targeted therapies as noted above can also be considered.

In cases of treatment failure, consideration should be made to repeat a renal biopsy to rule out transformation to a different type of LN (e.g., from pure class V to class V plus a proliferative form) and to rule out significant fibrosis (that would warrant decreasing and not increasing IS).

Non-adherence to treatment is a well-recognized cause of treatment failure in lupus. Medication adverse effects are one of the reasons for it. The possibility of non-adherence should be always considered in the cases of patients which are not responding to therapy (Masood et al. 2009).

Follow-Up

Patients with active LN should be monitored every 2–4 weeks and diagnosis or after a flare for about 4 months and lifelong every 3–6 months. If they have active LN, each clinic visit should include weight, blood pressure, evaluation or proteinuria and urine sediment, renal function test, serum complements C3 and C4, anti-dsDNA antibody levels and complete blood cell count. A repeat biopsy should be considered in patients that are worsening or are refractory to IS (failure to decrease proteinuria by $\geq$50%, persistent proteinuria $>$1 year or worsening renal function) or at relapse. This will help differentiate between a change and progression of histologic class and assess for chronicity and activity and for prognosis or to diagnose other pathologies (Bertsias et al. 2012).

Vaccines

Per CDC guidelines all patients with systemic lupus should receive the inactivated influenza virus vaccine once per year.

All adults aged $\geq$19 years with immunocompromised conditions, in this case, systemic lupus on immunosuppression, should receive:

If have not received 13-valent pneumococcal conjugate vaccine (PCV 13) or 23-valent pneumococcal polysaccharide vaccine (PPSV23)	Administer PCV13 followed by PPSV23 at least 8 weeks after PCV13. Administer a second dose of PPSV23 at least 5 years after the first dose of PPSV23
If have not received PCV13 but have received one dose of PPSV23	Administer PCV13 at least 1 year after the PPSV23. Second dose of PPSV23 should be given 8 weeks after PCV 13 and at least 5 years after the first dose of PPS23
If have not received PCV 13 but have received two doses of PPSV23	PCV 13 at least 1 year after the most recent PPSV23
If have received PCV13 but not PPSV23	Administer PPSV23 at least 8 weeks after PCV13
If have received PCV13 and one dose of PPSV23	Administer a second dose of PPSV23 at least 8 weeks after PCV13 and at least 5 years after the first dose of PPSV23

As a general rule, immunocompromised hosts like systemic lupus patients should not receive live vaccines such as measles, mumps, rubella, BCG, and zoster vaccine. Having said that, given that compared to the general population, patients with systemic lupus have higher rates of herpes zoster and at a lower age (Yun et al. 2016) and for that reason, zoster vaccine may be considered in patients with controlled disease and not severely immunosuppressed.

Human papilloma virus vaccine is recommended on females younger than 25 years old.

Renal Transplant in Lupus Nephritis

Renal insolvent of SLE occurs in about 50% of the patients and approximately 5–22% will progress to ESRD (Burgos et al. 2009). In most patients the disease activity will diminish as they approach ESRD. For many patients the next option will be renal transplant. As with other ESRD patients, the survival is better than those that are treated with hemodialysis or peritoneal dialysis. The transplant outcomes are similar to those other causes of ESRD (Golebiewska et al. 2016). Comparing transplant outcomes across subtypes of

GN in the US from the US Renal Data System. The average age of transplant in patients with LN was 38 years, and they were the most highly sensitized to human leukocyte antigens when compared to other patients with GN. Patients have lower mortality than patients with diabetic nephropathy but higher than patients with ADPKD (O'Shaughnessy et al. 2016).

Leading cause of death was infection and not SLE. Antiphospholipid antibody syndrome (APAS) continues to be a leading cause of adverse outcomes in graft survival. APAS occurs in about 15% of patients with SLE. These patients are at high risk for thromboembolic events or thrombotic microangiopathy and if they do not receive anticoagulation before or with their kidney transplant they will have 100% incidence of graft thrombosis and failure (Vaidya et al. 2000; Golebiewska et al. 2016). Recurrence on LN in kidney allograft is about 11–30% and when present it does not influence graft survival because the recurrence is usually mild and nonproliferative type (Bunnapradist et al. 2006; Burgos et al. 2009). This is likely due to chronic immunosuppression for renal transplant. Patients receiving MMF have better diseased donor graft survival rates (Bunnapradist et al. 2006). Patients with African-American ethnicity have worse outcomes.

Prophylaxis

Pneumocystis Jiroveci Pneumonia (PCP)

Most of the literature of pneumocystis jiroveci pneumonia (referred here as PCP) comes from the HIV, hematologic malignancies, and solid organ transplant patients. The rheumatic disease with the highest reported occurrence of PCP pneumonia is granulomatosis with polyangiitis with 89 cases per 10,000 hospitalizations per year, followed by 65 in polyarteritis nodosa, 27 in patients with inflammatory myopathy, 12 in those with systemic lupus, 8 with scleroderma, and 2 in those with rheumatoid arthritis (Ward and Donald 1999). Cellular immune deficiency and systemic steroids have been considered major risk factors. When focusing on systemic lupus erythematosus patients, higher disease activity, and higher dose of systemic steroids, renal involvement and lower lymphocyte count as well as lower CD4+ count have been described as risk factors of PCP (Lertnawapan et al. 2009). Data from Mayo Clinic of 116 non-HIV patients, reported that as high as 25% of patients who developed PCP pneumonia were treated with prednisone with a dose as low as 16 mg daily and for 8 weeks or less duration of therapy (Yale and Limper 1996). For PCP prophylaxis in the non-HIV patient, it is reasonable to recommended prophylaxis in patients treated with 20 mg or more of prednisone for longer than 2–3 weeks (Fishman 2001).

For primary prophylaxis, first choice in non-sulfa-allergic patients is trimethoprim-sulfamethoxazole (TMP-SM) single-strength daily or double-strength three times per week (usually prescribed on Mondays, Wednesdays, and Fridays). Special attention should be given to potassium levels, and the clinician should be vigilant regarding bone marrow suppression. When given to patients with renal impairment, the clinician should keep in mind that TMP-SM decreases creatinine secretion and that after starting it, creatinine may be elevated, without representing true worsening of kidney function due to the underlying disease, in this case systemic lupus. Alternative to TMP-SM, include dapsone 100 mg daily (check glucose-6-phosphate dehydrogenase deficiency prior to starting it), monthly 300 mg of inhaled pentamidine (may cause bronchospasm), or atovaquone 1500 mg PO daily (to be given with high-fat meals for enhanced absorption) (Thomas and Limper 2004; Rodriguez and Fishman 2004).

Osteoporosis

Patients with SLE are at an increased risk of osteoporosis. Multiple factors appear to contribute to this risk, including limited exercise capacity, chronic inflammation, (medication induced) gonadal dysfunction, and renal disease. Patients with lupus nephritis are at further increased risk

given their secondary hyperparathyroidism and vitamin D deficiency. In addition these patients are recurrently on glucocorticoids, and they are the most common cause of drug-induced osteoporosis (McIlwain 2003). The following osteoporosis risk factors should be considered when assessing bone health in a patient with SLE: low body mass index, parental history of hip fracture, tobacco use, ≥3 alcoholic drinks per day, and declining central bone mineral density measurements that exceeds the least significant change (Grossman and Gordon 2010).

When risk stratifying patient on systemic steroids, we follow the 2010 American College of Rheumatology (ACR) steroid-induced osteoporosis guidelines. The ACR risk stratifies patients based on FRAX score, which is applicable to men and women older than 40 years and calculates the risk of major osteoporotic fracture in 10 years. Based on FRAX, there are three groups: low risk (<10% for 10-year major osteoporotic fracture), medium risk (10–20% for 10-year major osteoporotic fracture), and high risk (>20% for 10-year major osteoporotic fracture). Antiresorptive therapy is recommended for postmenopausal women and men older than 50 years old receiving glucocorticoid therapy who are high and medium risk; pharmacological treatment is not recommended for patients who are low risk based on FRAX and who will be taking prednisone <7.5 mg/day. For premenopausal women and men <50 years old, the ACR panel concluded that they could make recommendations only for those with prior fragility fracture who were clearly at a higher risk for additional fracture. For women of childbearing potential, drugs with shorter half-lives were recommended, and for those of non-childbearing potential, the recommendations were similar to those for postmenopausal women and for men >50 years old; however, the anticipated duration of glucocorticoids required to trigger therapy was 3 months (Grossman and Gordon 2010).

When choosing an antiresorptive (bisphosphonates or denosumab) or anabolic (teriparatide) agent for patients with lupus or lupus nephritis on corticosteroid treatment, we identify two groups: patients with GFR >30 and those with GFR <30. Based on expert opinion, we recommend bisphosphonates or teriparatide for patients that meet criteria for therapy and have GFR >30. It should be noted that patients with chronic kidney disease and secondary hyperparathyroidism should not be treated with anabolic agents such as teriparatide. For patients with GFR <30, we favor denosumab over bisphosphonates given the need of dose adjustment and lack of safety data on bisphosphonates in patients with advanced CKD. When starting denosumab, the clinician must ensure that the patient has adequate serum calcium and vitamin D levels and that calcium intake is sufficient to avoid denosumab-associated hypocalcemia.

Gastrointestinal

Gastrointestinal mucosal disruption by the use of high-dose corticosteroids alone is a controversial subject. There are some positive and other negative studies. The exact mechanism is not fully understood but several proposed mechanisms have been described: inhibition of synthesis of gastric mucus, enhancement of gastrin cell and parietal cell hyperplasia with augmented acid secretion, and suppression of arachidonic acid metabolism and prostaglandin synthesis (Luo et al. 2002). The potential gastrointestinal tract consequences are gastritis, ulcers, and even bleeding. The complications are enhanced with concomitant use of NSAIDs (Gabriel et al. 1991).

The use of proton pump inhibitors (PPIs) has been associated with increased risk of clostridium difficile infections, hypomagnesemia, acute kidney injury, chronic kidney disease, and pneumonia. Therefore, the patient that needs to receive PPI prophylaxis should be chosen carefully. Risks and benefits should be taken into account.

Varicella Zoster Virus

Varicella-zoster virus (VZV) remains latent in trigeminal and dorsal root gangly. Reactivation

increases as cell-mediated immunity declines. In the case of patients with lupus, the use of immunosuppression can cause it to reactivate. The incidence of VZV reactivation in patients being treated for LN is unknown. The most common manifestation is cutaneous herpes zoster, which presents as a painful vesicular rash involving one or two adjacent dermatomes. Disseminated VZV can also occur, and it is diagnosed when more than two dermatomes or two non-contiguous dermatomes are present. In rare occasions invasive complications of CNS and other organs can be present (Zuckerman and Limaye 2013).

Physician should consider antiviral prophylaxis during the period of intense immunosuppression on patients that have a history of VZV. Routine use of antiviral prophylaxis can increase the risk of nephrotoxicity; therefore prophylaxis is not recommended on patients with no prior history of herpes simplex virus infection or HSV IgG negative. The following regimens can be used:

Acyclovir 400–800 mg PO BID
Valacyclovir 500 mg PO BID
Famciclovir 500 mg PO BID

Lupus Nephritis and Pregnancy

Lupus is often seen in women of childbearing age. Women with active SLE, including lupus nephritis, are at increased risk for maternal and fetal complications. In general, pregnancy in this population should be limited to those who have relatively inactive or well-controlled disease (with minimal major organ involvement). Thus, discussion of and attention to effective methods of contraception are an important consideration. When assessing appropriateness to conceive, it is not advisable to proceed with conceiving (Lateef and Petri 2013) if the following complications are present:

- Severe pulmonary hypertension (systolic pulmonary artery pressure > 50 mmHg)
- Severe restrictive lung disease (FVC < 1 L)
- Advanced renal insufficiency (creatinine > 2.8 mg/dL)
- Advanced heart failure
- Previous severe preeclampsia or HELLP despite therapy

The success of term pregnancy is related to the activity of disease in the 6 months prior to conception. If the disease has been active within the past 6 months, pregnancy is not advisable; if the disease has been in remission or relatively inactive, the patient can plan for pregnancy. Several of the mediations used to treat SLE are contraindicated immediately before and during pregnancy, including methotrexate, leflunomide, cyclophosphamide, mycophenolate mofetil, warfarin (relative), and antihypertensives of the angiotensin-converting enzyme inhibitor and angiotensin receptor blockers. Several medications may be used during this time, including azathioprine, hydroxychloroquine, and corticosteroids. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, tacrolimus, and biologic agents (e.g., belimumab, rituximab) may be used cautiously but are not well studied. Patients should continue hydroxychloroquine throughout their pregnancy and start aspirin for preeclampsia prophylaxis. Additional therapy, such as anticoagulation, will be determined by the presence of antiphospholipid syndrome (APS) or positive lupus anticoagulant without clinical or obstetric APS.

Relevant serology should be reviewed with the potential mother, including antibodies to anti-Ro/SSA and/or anti-La/SSB as 1.7% of pregnant women positive for these antibodies have a baby with autoimmune congenital heart block (CHB). The risk increases to 16% for mothers who have had previous CHB-affected pregnancies. Echocardiography is recommended each week from weeks 16 to 26 and biweekly thereafter.

Lupus nephritis during pregnancy merits special attention, as it increases the risk of adverse maternal and fetal outcomes, such as preeclampsia, fetal loss, preterm delivery, and intrauterine growth restriction. When assessing renal function during pregnancy, it is important to recall the following physiologic changes that occur during pregnancy (Kattah and Garovic 2015):

- Glomerular filtration rate increases by 50% and creatinine clearance increases by 30%.
- A creatinine of 0.9–1 mg/dl may be significantly abnormal.
- Urine protein excretion increases from normal nonpregnant levels of 60–90 mg/24 h to 180–250 mg/24 h.
- The protein-creatinine ratio has not been validated specifically for the evaluation of proteinuria in patients with lupus nephritis during pregnancy.

Lupus nephritis during pregnancy is more likely to present in patients who have had previous renal involvement. The diagnosis of a lupus flare during pregnancy is difficult because pregnancy-induced thrombocytopenia, proteinuria, and palmar and facial erythema can also occur during pregnancy without lupus. Proteinuria from SLE can be distinguished from proteinuria from preeclampsia, if the patient has other signs of SLE, such as rising levels of anti-dsDNA antibody, low complement, and RBC's or urinary casts (6 Creasy and Resin's Maternal-Fetal Medicine principles and practice, Seventh edition, 64, 1092–1099). Nevertheless, it can be challenging to differentiate preeclampsia from lupus nephritis. The risks and benefits of renal biopsy, which has more complications in this population, may need to be considered.

Lupus nephritis often results in CKD even if the patient achieves remission. Pregnancy in CKD is associated with adverse outcomes in both the fetus and the mother. Fetal survival and pregnancy complications in women with CKD stages 3 to 5 remain high but have improved. Studies have shown that there will be irreversible loss of renal function in 30–50% in women with moderate to severe CKD (creatinine >1.4 mg/dL or estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2) after a pregnancy and that one third of patients with advanced CKD (creatinine >2.0 mg/dL or eGFR <30 ml/min/1.73m^2) that become pregnant will require renal replacement therapy within 1 year of delivery (HALL). This also needs to be taken into consideration when counseling the patients in childbearing age that wish to become pregnant.

Fertility Preservation

Patients, males and females, treated with cyclophosphamide are at risk for infertility because of the gonadotoxic effect of the drug. The mechanism is unknown. Meistrich et al. monitored sperm counts and noted that high doses of cyclophosphamide can produce permanent azoospermia. The recovery of normospermia was dose dependent. Patients receiving less than 7.5 g/m^2 demonstrated recovery. Fertility preservation method in males is sperm banking. It is recommended that two samples 24–48 h apart are stored before the treatment starts (Schover et al. 2002). Other methods include microsurgical epididymal aspiration, electro-ejaculation, or testicular biopsy. For patients with low sperm count after cyclophosphamide therapy can use intrauterine insemination (IUI) or in vitro fertilization (IVF) using intracytoplasmic sperm injection (ICSI) (Hsiao et al. 2011). Male patient should be referred to sperm banks.

For females ovarian toxicity is age and dose dependent. Women younger than 32 years old and those that receive lower cumulative dose have lower incidence of ovarian failure. Ioannidis et al. studied 67 premenopausal women receiving IV cyclophosphamide and found that half the women receiving 8 g/m^2 will have sustained amenorrhea and 90% of those receiving 12 g/m^2 had serious toxicity. They recommend limiting the cumulative dose to less than 8 g/m^2 for older women that want to protect their reproductive function. Most studies focus on sustained amenorrhea but not having amenorrhea does not mean the patient is still fertile. Poor egg quality and premature ovarian failure can still be percent despite menstruation. Long-term follow-up studies are needed that are focus on live births of patients that received cyclophosphamide and not on the presence of amenorrhea.

Methods used on females focus on decreasing ovarian blood flow and metabolic activity and preventing ovulation. GnRH agonist has been use for this purpose. It initially increases plasma levels of gonadotropins. They remain elevated for 1–2 weeks of GnRH agonist therapy and then decrease resulting in low levels of LH, FSH, and

estrogen. Therapy with GnRH agonist should be given 1–2 weeks before cyclophosphamide therapy to make sure the ovarian function is suppressed entirely (Dooley and Nair 2008). The majority of human studies one GnRHa and fertility preservation are observational. The results are controversial. Some have shown positive results while others have not (Mersereau and Dooley 2010).

The most common side effects of GnRHa are hot flashes, decreased libido, emotional lability, headaches, and decreased breast size, vaginal dryness, and increase risk of thrombosis in patients that are already high risk. The effects last 4–12 weeks after stopping the drug (Dooley and Nair 2008).

Female patient should be referred to reproductive endocrinology and infertility specialist for workup and recommendations about fertility preservation.

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14 Lupus Nephritis (Including Antiphospholipid Antibody Syndrome), Pediatric

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Contents

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Abstract

Childhood-onset systemic lupus erythematosus (cSLE) has been defined as a subset of SLE with onset prior to 18 years of age. Around 15% of SLE patients present with nephritis before this age, and debatably these patients have a greater genetic component to their disease etiology, a more systemic involvement, and a more severe disease course. Patients develop their loss of tolerance to self at an earlier time than patients with adult-onset SLE, or at least their loss of tolerance progresses sooner to immune complex deposition and tissue injury. In this chapter, we review the joint approach of pediatric nephrologists and rheumatologists towards patients with cSLE and nephritis. We address the areas where evidence exists and the areas where we must rely on expert opinion or evidence based on primarily adult studies. Fortunately, 5- and 10-year mortality is lower than in adult-onset lupus nephritis, and patient and renal survival has improved over the years. However, relapses during the transition from adolescence to adulthood are common and cardiovascular and infectious complications are frequent in long-term survivors.

Keywords

Child · Pediatric · Lupus · SLE · Immune complex · Complement · Autoantibody · Autoimmune · Rheumatology

Introduction

The prevalence of SLE in the USA is 70–90 per 100,000 individuals. Up to 20% of cases of systemic lupus erythematosus are diagnosed during childhood (i.e., disease onset prior to age 18 years). In the literature, there has been variability in age cutoffs used to define childhood-onset SLE (cSLE), ranging from 14- to 21-years (Silva et al. 2012). This variability combined with the racial and ethnic differences in the epidemiology of SLE are likely to explain the differences in prevalence rates of cSLE reported in different studies.

Between 40% and 70% of cSLE patients will develop lupus nephritis (LN) during their disease course (Livingston et al. 2011; Hiraki et al. 2012; Ambrose et al. 2016). LN is a common cause of glomerular disease in children. A meta-analysis shows a 10–30% higher prevalence of LN in cSLE than in adult-onset SLE (Livingston et al. 2011). Compared to LN in adult-onset SLE (aSLE), LN in cSLE tends to present earlier after SLE diagnosis and behaves more aggressively (Brunner et al. 2008; Ambrose et al. 2016). Moreover, children with SLE and LN have a unique set of issues (i.e., growth, school performance, social pressures) that need to be taken into account for optimal management of their kidney disease.

Genetics

Genetics of cSLE

Childhood-onset SLE is thought to differ from aSLE in part because of the influence that genetic polymorphisms play in the development of disease at an earlier age. Numerous genome-wide-association and linkage studies in SLE have generated a large list of potential disease genes with associated polymorphisms that partially explain genetic risk in different races and ethnicities (Harley et al. 2008; Gateva et al. 2009; Sanchez et al. 2011; Yang et al. 2013). Researchers are now attempting to integrate these polymorphisms into immune system biology and the pathogenic mediators involved in the development of SLE. Immune system subphenotypes such as type I interferon responses and autoantibody production have been linked to several genetic polymorphisms (Kariuki et al. 2010; Salloum et al. 2010).

Several strains of mice have been studied as spontaneous models for the development of SLE. Six disease genes with known function have also been liked to models of murine lupus (*HLA-DR2, HLA-DR3, STAT4, IRAK1, IL10,* and *ITGAM*). These genes encode the proteins for histocompatibility leukocyte antigens DR2 and DR3, signal transducer and activator of transcription 4 (Stat4), interleukin-1 receptor-associated kinase 1(Irak-1), interleukin 10, and the integrin alpha M subunit (Itgam) of macrophage-1 antigen (Mac-1) or complement receptor 3 (CR3).

Identical twin concordance rates for SLE range between 30% and 50% (Block et al. 1975; Deapen et al. 1992), and first-degree relatives of lupus patients have an approximately 20-fold increased risk of SLE as compared with the general population (Alarcon-Segovia et al. 2005). The disease risk for siblings of affected individuals is 20- to 30-fold higher than that for the general population (Block et al. 1975). The variants identified so far only explain around 20% of disease heritability (So et al. 2011). The missing heritability is thought to come from complex interactions between environment and genetics, as well as from disrupted epigenetic regulation of gene expression.

Genetics of LN

A number of gene variants have also been linked to development of LN in patients with SLE. Deleterious variations in at least 16 genes have been associated with nephritis in SLE patients (Table 1) (Musone et al. 2008; Taylor et al. 2008; Liu et al. 2009; Niederer et al. 2010; Taylor et al. 2011; Lin et al. 2012; Zhou et al. 2012; Dang et al. 2014). Reduced Fc-receptor gene copy number has also been associated with increased risk of developing SLE and LN (Yuan et al. 2015). Other genes are associated with prognosis: Apolipoprotein L1 (APOL1) risk variants are more common in African American populations and are strongly associated with the development of end-stage kidney disease (ESKD) in African American SLE patients (Freedman et al. 2014).

Immune complex glomerulonephritis (GN) occurs spontaneously in numerous genetically modified mouse strains. Homozygous deficiency of complement factors C1q (Botto et al. 1998) and C4 (Einav et al. 2002), inhibitory Fc-receptors (Fukuyama et al. 2004), nuclear factor kappa-B inhibitor TNFAIP3 (Kool et al. 2011), and cyclin-dependent kinase inhibitor $p27^{Kip1}$ (Opha-scharoensuk et al. 1998) are a few well-described

Table 1 Disease genes associated with nephritis in systemic lupus erythematosus

Gene	Protein	Gene	Protein
ACE	Angiotensin converting enzyme	ITGAM	Integrin alpha M (Mac1, CR3)[a]
APOL1	Apolipoprotein L1	KLK	Kallikrein
BLK	B-lymphoid tyrosine kinase	MYH9	Myosin heavy chain 9
FCGR2A	Fc-gamma receptor 2A	STAT4	Signal transducer and activator of transcription
FCGR3	Fc-gamma receptor 3	TLR9	Toll-like receptor 9
HLA-DRB1	Histocompatibility leukocyte antigen DRB1	TNFAIP3	Tumor necrosis factor alpha-induced protein 3
IKZF1	Ikaros family zinc finger protein 1	TNFSF4	Tumor necrosis factor superfamily member 4
IRF5	Interferon regulatory factor 5	TNIP3	TNFAIP3-interacting protein 3

[a]Integrin alpha M forms one subunit of both Mac1 (macrophage-1 antigen) and CR3 (complement receptor 3)

models. In addition, congenic animals have been used to link genotype to the phenotype of GN in autoimmunity-prone strains. Examples include the Bxs1 and Bxs3 loci from the BXSB mouse strain (Haywood et al. 2004); the Adnz1, Sle1d, and Sle2b loci from the NZM2410 strain (Morel et al. 2001; Waters et al. 2004; Li et al. 2005); and the Mag locus from the MRL/lpr strain (Ichii et al. 2008). Positional cloning of the genetic variation at these loci will aid in the elucidation of pathogenic mechanisms for LN in patients with cSLE. For example, the genetic variant mapped to the Sle2b has been identified as a function mutation in a type I interferon (Li et al. 2005).

Pathophysiology

Loss of Tolerance

SLE is a systemic autoimmune disease characterized by loss of tolerance to numerous self-antigens. No one unifying inciting event has been identified. Sex hormones (Rubtsova et al. 2015), viral infection (Getts et al. 2013), diet (Strickland et al. 2013), drugs (Cornacchia et al. 1988), ultraviolet irradiation (Barbhaiya and Costenbader 2014), gut microbiota (Markle et al. 2013), and other environmental factors might play an important role in the disease process, either additively or by interacting with each other and with genetic factors.

The production of autoantibodies appears to have numerous different causes. Many patients with SLE demonstrate defective clearance of cell debris, which appears to trigger autoimmune responses against large intracellular antigens (chromatin, nucleosomes, DNA, RNA, and ribonuclear proteins) that would otherwise evade immune responses. Defects in the classical pathway of complement (such as C1q), DNase enzymes, and phagocyte receptors (such as those encoded by FCGR2B, FCGR3, and ITGAM) all contribute to an increased exposure to apoptotic cell debris.

The type-I interferon pathway has also proven to be pathogenic in many patients with SLE. Administration of recombinant human interferon to treat viral infections and malignancies has resulted in de novo cases of lupus, and disease improved with cessation of therapy (Niewold and Swedler 2005). The disease gene TLR9 encodes an intracellular receptor for nucleic acids (Toll-like receptor 9). TLR9 activation leads to production of type-I interferons as part of the innate immune response (Leadbetter et al. 2002). The interferon and TLR pathways are not only thought to be involved in loss of tolerance to nucleic acids. Polymorphisms of IRF5 (interferon regulatory factor 5), IKZF1 (Ikaros family zinc finger protein 1), and STAT4 are all linked to development of immune complex GN and their encoded proteins all mediate type-I interferon signaling in inflammatory cells as well as resident kidney cells (Dang et al. 2014). Defects in other disease genes that regulate another innate immune response, the nuclear factor kappa-B pathway (TNFAIP3, TNIP3, encoding

tumor necrosis factor alpha-induced protein 3, and TNFAIP3-interacting protein 3) also predispose to development of autoimmune nephritis (Musone et al. 2008; Caster et al. 2013).

The loss of tolerance to self-antigens is also caused in other patients by abnormalities in lymphocytes. The risk variant for PTPN22 (Protein tyrosine phosphatase, nonreceptor type 22) produces a mutant signaling protein that leads to a failure to eliminate autoreactive B cells (Menard et al. 2011). Reduced expression of BLK (B-lymphoid tyrosine kinase, another B-cell signaling molecule) promotes nephritogenic lymphocyte generation in mice prone to lupus (Samuelson et al. 2014). BAFF (B-cell activating factor) promotes the humoral immune responses that then sustain autoantibody production (Boneparth and Davidson 2012).

Immune System in Nephritis

Tissue damage in multiple organs requires more than just autoantibody generation. Although testing for antinuclear antibodies (ANA) has a low false-negative rate, it is very nonspecific, and many individuals can test positive for ANA without developing any manifestations of SLE. There are numerous assays that can subdivide ANA, and anti-double stranded DNA antibody titers loosely associate with LN activity. Experimentally, anti-dsDNA and anti-nucleosome antibodies can deposit in the kidney and cause proteinuria (Vlahakos et al. 1992; Kalaaji et al. 2007; Krishnan et al. 2012). Besides ANA, autoantibodies against alpha-actinin, alpha-enolase, annexin A1, and vimentin in the kidney associate with GN (Mostoslavsky et al. 2001; Deocharan et al. 2002; Kinloch et al. 2014; Bruschi et al. 2014). Anti-C1q antibodies occur at higher titers in patients with LN and colocalize with complement deposits in the glomeruli of patients with nephritis (Moroni et al. 2001; Trouw et al. 2004). However, experimentally and clinically, immune complex deposition in the kidney can be detected in the absence of histopathology or renal disease.

Aside from genetic susceptibility, it is also not clear why only certain children with SLE develop LN. CC-chemokine ligand 2/monocyte chemoattractant protein-1 (CCL2/MCP-1) is involved early in the GN process (Tesch et al. 1999), and tumor necrosis factor is involved at onset of proteinuria (Bethunaickan et al. 2012). Type-I interferons cause direct injury to cells in the glomerulus (Migliorini et al. 2013). Genetic polymorphisms in the KLK (kallikrein) locus associated with decreased concentrations in the kidney also associate with the development of nephritis in patients with SLE, and agonists of the kallikrein pathway are protective in animal models of immune complex GN (Liu et al. 2009).

Numerous inflammatory cells play a role in LN. Patients with cSLE have increased numbers of the low-density granulocyte subset of neutrophils (Midgley and Beresford 2016). The production of neutrophil extracellular traps has been shown to be important in the pathogenesis (Villanueva et al. 2011; Lood et al. 2016). Neutrophil and endothelial cell microparticles contribute to immune complex formation and localize to glomerular immune deposits (Nielsen et al. 2015; Dieker et al. 2016). Resident and infiltrating macrophage (Bergtold et al. 2006; Sahu et al. 2014), dendritic cells (Tucci et al. 2008; Sahu et al. 2014), and basophils (Charles et al. 2010) participate in inflammation and subsequent development of renal fibrosis.

Cellular infiltrates in LN are common and are composed of phagocytes and B and T lymphocytes (Chang et al. 2011). Lymphocyte infiltrates in subtypes of T cells, including cytotoxic CD8 cells (Winchester et al. 2012), type 17 T-helper CD4 cells (Shah et al. 2010), follicular helper CD4 cells (Simpson et al. 2010), and CD3 + CD4–CD8–"double negative" T cells (Crispin et al. 2008), have all been implicated in the pathogenesis of LN. The disease gene encoding tumor necrosis factor superfamily member 4 (TNFSF4, a coreceptor on T cells) influences differentiation into these pro-inflammatory subtypes. These effector T cells, together with numerous soluble mediators, elicit chronic inflammation within glomerular and tubulointerstitial sites in the kidneys. Dysregulation or regulatory T cells or resistance of effector T cells to these suppressor cells also likely

contributes to tissue injury (Venigalla et al. 2008; Vargas-Rojas et al. 2008).

Resident Kidney Cells in Nephritis

Immune complexes formed in patients with SLE can bind directly to glomerular mesangial (Santiago et al. 1989) and endothelial cells (Suwanichkul and Wenderfer 2013). In mesangial cells, binding to Fc-receptors causes complex internalization, cellular proliferation, and release of inflammatory cytokines (Gomez-Guerrero et al. 1994; Radeke et al. 2002; Suwanichkul and Wenderfer 2013). Moreover, mesangial cells produce more extracellular matrix after treatment with anti-dsDNA antibodies (Zhang et al. 2012). Anti-dsDNA antibodies also bind to annexin II on mesangial cells with functional responses (Yung et al. 2010).

In diseased tissue, both activated glomerular endothelial cells and damaged podocytes release endothelin-1 that amplifies glomerular injury by causing mitochondrial stress (Daehn et al. 2014). Loss of renal VEGF-A (vascular endothelial growth factor A) characterizes LN both in human disease and mouse models and distinguishes it from other forms of chronic kidney disease (Berthier et al. 2012). Other vascular disturbances in LN include hypoxemia (Shi et al. 2017), a decrease in the ratio of proangiogenic angiopoietin 1 (ANG-1) to antiangiogenic ANG-2 (Kumpers et al. 2009), and alterations in levels of endothelial nitric oxide synthase (Gilkeson et al. 2013). These changes also occur in the peritubular capillaries and contribute to chronic interstitial disease and renal fibrosis. Therefore, the parenchymal cells of the glomerulus play a significant role in the acute and chronic manifestations of LN.

Pathology

Kidney biopsy remains the gold standard for diagnosis of LN in cSLE. In children, as in adults, the procedure is performed percutaneously under sedation with ultrasound guidance. Kidney biopsy requires the involvement of several medical teams and prolonged observation post procedure and is a source of emotional distress for the family and the child. Typically, two tissue cores are obtained via 16 or 18 gauge needles. The increased availability of procedural imaging and automated needles has reduced adverse events. Registry studies provide evidence for the relative safety of performing kidney biopsies in children: 2% children developed gross hematuria and bleeding only requires blood transfusion or surgery in 0.1% (Tondel et al. 2012).

As in aSLE, either the World Health Organization classification, developed in the 1970s, or the revised classification of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (Weening et al. 2004) is used to interpret kidney biopsy findings. The prevalence for each class of LN is similar in cSLE and aSLE (Boneparth and Ilowite 2014). The utility of distinguishing between histological classes of LN, such as proliferative and membranous, and between segmental and global forms of proliferative LN is supported by studies of cSLE (Hagelberg et al. 2002; Zappitelli et al. 2004; Rianthavorn and Buddhasri 2015; Marks et al. 2007).

Active lesions are amenable to immunosuppressant therapy, while chronic lesions represent nonreversible damage (Austin et al. 1983), often requiring supportive therapy instead. Activity index (AI) and chronicity index (CI) quantify mainly glomerular injury, and tubulointerstitial activity index (TIAI) quantifies extraglomerular kidney disease (Hill et al. 2000). As in adults, risk factors for poor outcome in cSLE include AI $\geq$7, CI $\geq$ 4, and TIAI >5 (Zappitelli et al. 2008; Brunner et al. 2016).

Practice patterns for initial and repeat kidney biopsy have been published for cSLE. There is more disparity among either nephrologists or rheumatologists than between the two specialties (Wenderfer et al. 2015). Most specialists use the indications for initial kidney biopsy developed by the American College of Rheumatology, whereas others use more inclusive indications and fewer only recommend biopsy when the diagnosis of cSLE is unclear.

Clinical Presentation

History

Renal disease occurs in 50–75% of all cSLE patients and mostly within the first 2 years of diagnosis in children and adolescents (Levy and Kamphuis 2012). LN is more common in males and in non-White populations (Alarcon et al. 2002; Bernatsky et al. 2006). Initial manifestations of renal disease range from minimal proteinuria and microscopic hematuria to nephrotic-range proteinuria, urinary casts, hypertension, peripheral edema, renal insufficiency, or, in severe cases, renal failure.

Patients with LN typically present with fatigue, general malaise, chest pain, or edema. The clinical presentation for active LN can be similar even within different subclasses of LN. Many patients will complain of lower extremity swelling; however, in milder disease, patients will have no symptoms at all. Thus, it is important to ask about other signs of active lupus during the clinic visit including mouth sores, hair loss, photosensitive skin rashes, joint pain and swelling, color changes of the fingers consistent with Raynaud phenomenon, chest pain (especially with reclining), and fever. SLE can typically be distinguished from other causes of GN by its extrarenal manifestations. When a cSLE patient has these active symptoms, they are at increased risk of developing active disease in their kidneys.

Physical Examination

Examination of children with LN typically reveals lower extremity swelling/pitting edema or with other exam findings for active SLE such as a worsening malar rash, digital angiitis, alopecia, fever, and arthritis. The distribution of the rash usually allows distinction from Henoch Schoenlein purpura. Serositis can mimic the findings of other forms of pulmonary renal syndrome, such as Goodpasture or ANCA vasculitis. Since the physical exam may be normal in patients with mild disease, it is extremely important to screen for disease activity by urinalysis at every visit and to regularly quantify urinary protein excretion by either random protein/creatinine ratio or timed urine collection. Many patients will also present with new or worsening hypertension. If the patient complains of gross hematuria, it should raise the suspicion for other causes such as renal thrombosis, thrombotic microangiopathy, or a clotting deficiency (Eberhard et al. 1994).

Laboratory Evaluation

Complement

Complement testing is an important laboratory test utilized to help in the diagnosis of SLE as well as in monitoring disease activity. Normal complement levels, specifically C3 and C4, are reassuring that LN is quiescent; however, in patients that have membranous LN, complement levels can be normal. C3 and C4 levels can be followed over time to help assess whether a patient is responding to treatment. Many lupus patients have a C4 null allele and cannot achieve C4 levels in the normal range. C2 and C1q should be checked if there is any concern for a genetic complement deficiency. C1q antibodies have been demonstrated to inhibit the interactions of C1q with IgG and CRP, suggesting their contribution to functional C1q deficiency as well as to defective clearance of apoptotic materials and ICs as observed in many patients with SLE and LN. Also, in animal models, studies clearly implicate complement activation, particularly of the alternative pathway, in glomerular injury (Bao et al. 2002; Wenderfer et al. 2007; Sekine et al. 2011).

ANA (Anti-DNA, Smith and RNP Antibodies)

Antinuclear antibodies (ANA) are present in more than 99% of children with SLE (Hochberg 1997). However, not all children with a positive ANA have lupus, as a positive ANA test can be associated with other autoimmune diseases, infectious causes, and certain drug exposures.

Conversely, anti-dsDNA antibodies have a high specificity for SLE. In proliferative LN, levels of anti-C1q Ab and anti-dsDNA Ab have been shown to be significantly higher in more active LN than less active LN. Both antibodies had a positive correlation with SLEDAI score and proteinuria and a negative correlation with C3 reduction (El-Hewala et al. 2011). However, in membranous LN, patients may present without other clinical or serologic manifestations of lupus. Thus, a clinician should not be dissuaded from the diagnosis of MLN in a young woman who has heavy proteinuria, lacks anti-dsDNA antibodies, and has normal complement levels (Beck and Salant 2009).

Anti-Smith (Sm) antibodies are detectable in approximately 5–30% of SLE patients. They are more prevalent in blacks and have a high specificity for SLE. Anti-RNP antibodies are detectable in 25–47% of SLE patients; high titers of anti-RNP antibodies, usually without the presence of Sm antibodies, are diagnostic of mixed connective tissue disorder (i.e., patients with Raynaud phenomenon and milder renal involvement). Due to the close localization of the epitopes for these autoantibodies on small nuclear ribonucleoprotein antigens (especially U1snRNP), anti-RNP and Smith antibodies frequently occur together. Smith antibodies with or without anti-RNP antibodies are associated with the severity and activity of renal involvement (Migliorini et al. 2005). The measurement of anti-Smith and anti-RNP antibodies is more important in the diagnosis of SLE than in the follow-up of patients.

Antiphospholipid Antibodies and Lupus Anticoagulant

Antiphospholipid antibodies are antibodies directed negative charged phospholipids. The most important antiphospholipid antibodies for identifying patients at risk for immune-mediated thrombosis are anticardiolipin antibodies, anti-β_2 glycoprotein antibodies, and the lupus anticoagulant. Persistent positivity of these antibodies (verified on at least two occasions 12 weeks apart) puts a patient at risk for thrombosis and specifically microangiopathic antiphospholipid associated syndromes. Antiphospholipid antibodies have a variety of procoagulant effects, including the activation of platelets, activation of monocytes, and activation of endothelium. They also impede downregulation of thrombosis via impairment of activated protein C. They activate complement, leading to activation of the endothelium and neutrophils that accumulate in the tissue, thus promoting local inflammation (Ieko et al. 1999).

Approximately 50–60% of all cases of antiphospholipid syndrome in pediatric populations are associated with underlying autoimmune disease (Berkun et al. 2006; Avcin et al. 2008; Zamora-Ustaran et al. 2012).

Manifestations of antiphospholipid syndrome in the kidney include vascular occlusion, thrombotic glomerular microangiopathy, and hypertension. Antiphospholipid syndrome-associated nephropathy is used to describe thrombotic microangiopathy that involves both arterioles and glomerular capillaries that cause hypertension, acute renal failure, proteinuria, and poor renal function (Tektonidou et al. 2004; D'Cruz 2005; Cheunsuchon et al. 2007). The term microangiopathic antiphospholipid-associated syndrome is used to describe patients with antiphospholipids and clinical features of thrombotic microangiopathy (hemolytic syndromes such as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura). The symptoms may at first be subtle, starting with malaise, fever, headache, and sometimes diarrhea. As the condition progresses, clots (thrombi) form within blood vessels and platelets are consumed. Red blood cells passing the microscopic clots are subjected to shear stress which damages their membranes, leading to rupture of red blood cells within blood vessels, which in turn leads to anemia and schistocyte formation. Treatment includes immunosuppressive treatment and plasmapheresis.

Proliferative LN

Proliferative lupus nephritis (PLN) commonly refers to either class III or class IV LN, which have often been combined in adult therapeutic

trials. The prevalence of PLN in cSLE is between 50% and 80% (Cameron 1994; Sorof et al. 1998; Hiraki et al. 2008; Pereira et al. 2011). Differences in biopsy practices as well as ethnic and racial admixture account for this variability. Proliferative lesions can be defined as segmental or global glomerular hypercellularity in a mesangial, endocapillary, or mesangiocapillary pattern. These lesions are usually accompanied by positive immunostaining of capillary loops for immunoglobulins and complement components, and extensive subendothelial electron dense deposits. Class IV LN has also been referred to as diffuse proliferative glomerulonephritis (DPGN).

There are no established noninvasive biomarkers that distinguish between class III and class IV LN. Both can present with abnormalities in the urine sediment (dysmorphic erythrocytes, red blood cell casts), with or without large amounts of proteinuria and nephrotic syndrome. Both can present with acute kidney injury or rapidly progress to chronic kidney failure. It is unclear whether development of class III or IV nephritis represents different disease mechanisms, or simply a spectrum of severity of proliferative injury.

Initial Therapy

Untreated PLN is associated with a high rate of morbidity and mortality and ESKD. Drug trials to date have focused on proliferative LN for this reason (Table 2). In the early 1970s, the NIH established cyclophosphamide and high-dose IV solumedrol as the treatment of choice for proliferative LN (Austin et al. 1986). This became known as the NIH regimen. In another landmark aSLE study (Euro-Lupus Nephritis Trial), low-dose cyclophosphamide compared favorably with the high-dose, longer-duration NIH regimen (Houssiau et al. 2002; Houssiau et al. 2010b).

Although children under 18 years old have traditionally been excluded from enrollment in these therapeutic trials of aSLE, pediatric physicians rely on the evidence from these studies to guide their decisions for treating cSLE. Although no evidence for the Euro-lupus protocol exists for cSLE patients with PLN, studies in adults of all races and ethnicities have confirmed efficacy with fewer side effects. Therefore, it has been used for select "low risk" patients with PLN in some centers. Given that studies in aSLE have demonstrated equivalent results for induction therapy using mycophenolate mofetil either alone (Appel et al. 2009) or in combination with tacrolimus (Liu et al. 2015), many pediatric centers have started using these agents in cSLE

Table 2 Summary of adult studies[a]

Induction Therapy	
NIH (Austin et al. 1986)	Fewer relapses and improved 3–5 years renal survival with monthly IV CYC (0.5–1 g/m^2/dose) × 6 doses as add on therapy, compared to corticosteroids alone
Euro-lupus Trial (Houssiau et al. 2002, 2010b)	Low-dose IV CYC (0.5 g/dose q14d × 6 doses) compared favorably with the high-dose, longer-duration NIH regimen
ALMS (Appel et al. 2009)	MMF and IV CYC had similar rates of remission African Americans and Hispanics responded better to CYC
LUNAR (Rovin et al. 2012)	RTX as add-on therapy demonstrated no benefit in renal outcomes
Multi-target Trial (Liu et al. 2015)	TAC + MMF together were more effective than IV CYC in achieving complete remission by 24 weeks, with comparable side effect rates
Maintenance Therapy	
MAINTAIN (Houssiau et al. 2010a; Tamirou et al. 2015)	MMF and AZA were similar efficacy for long-term maintenance in rates of relapse, disease activity, and kidney function with lower rates of anemia and leukopenia in the MMF group
ALMS (Dooley et al. 2011)	MMF was superior to AZA in maintaining long-term remission

[a]Abbreviations: *AZA* azathioprine, *CYC* cyclophosphamide, *MMF* mycophenolate mofetil, *RTX* rituximab, *TAC* tacrolimus

as well. Retrospective studies of mycophenolate in cSLE have confirmed its efficacy as an induction agent (Lau et al. 2008; Falcini et al. 2009). Mycophenolate is prescribed 600 mg/m2/dose twice daily (maximum 3000 mg total daily dosage).

Other immunosuppressive agents with some evidence for efficacy in cSLE and PLN include: azathioprine, tacrolimus, and cyclosporine. These agents are usually continued at least until a sustained response has been achieved. Retrospective data in children showed a favorable response to azathioprine and prednisone compared to cyclophosphamide and prednisone for induction therapy of PLN (Silverman and Lang 1997). Azathioprine is prescribed 1–2.5 mg/kg/dose once daily (maximum 250 mg total daily dosage). A multicenter, randomized controlled study of 81 subjects as young as 14 years of age with PLN in China suggests comparable renal response rates (90%) and superior complete response rates (52%) using tacrolimus plus prednisone versus IV cyclophosphamide plus prednisone (82% and 39%) (Chen et al. 2011). Adverse events were less frequent (gastrointestinal, leukopenia) with tacrolimus. The starting tacrolimus dosage is 0.05–0.1 mg/kg twice daily, then adjusted to target pre-dose blood levels of 4–10 ng/ml. A prospective randomized trial showed comparable outcomes between cyclosporin and cyclophosphamide in children (Fu et al. 1998). Cyclosporin is prescribed 3–5 mg/kg/dose twice daily, then dose adjusted to target pre-dose blood levels of 50–100 ng/ml. Retrospective data in children support the efficacy of sequential induction therapy with mycophenolate followed by a calcineurin inhibitor for PLN (Aragon et al. 2016).

Despite prospective clinical trials failing to show benefit for use of B-cell depleting agents in aSLE (Table 2), there are numerous observational studies reporting efficacy for refractory disease using rituximab as an add-on therapy for use in both aSLE and cSLE (Pereira et al. 2011; Willems et al. 2006; Lehman et al. 2014; Watson et al. 2015; Tambralli et al. 2015). Review of 26 reports and 300 patients treated with RTX demonstrated combined complete and partial remission in 87% of patients with LN (Weidenbusch et al. 2013). A UK pediatric cohort study (25 patients with LN, 38 courses) showed improved disease activity (Watson et al. 2015). The safety of rituximab use for pediatric autoimmune diseases has been assessed in a single center study of 104 patients (including 50 with cSLE) and the rate of infections requiring hospitalization was 9.1% (Tambralli et al. 2015).

Since conducting large-scale clinical trials in cSLE has not been feasible due to small population size and lack of funding, reduction of clinical practice variability through the development of consensus treatment plans (CTPs) is an alternative approach that provides for future comparison of outcomes and standardization of therapy. In 2012, the Childhood Arthritis Rheumatology Research Alliance developed CTPs for induction therapy of an initial episode of proliferative LN in cSLE (Mina et al. 2012). The CTPs use either mycophenolate or cyclophosphamide for the initial 6 month induction period, combined with one of three corticosteroid strategies: primarily oral, primarily intravenous (IV), and mixed oral/IV based on practitioner preference (Fig. 1). Patients receiving cyclophosphamide are also given MESNA to decrease the risk of hemorrhagic cystitis. Cell counts are typically checked 10 days following the cyclophosphamide infusion to determine the leukocyte nadir. If patient is severely neutropenic, the dose of cyclophosphamide should be adjusted. Dose adjustments are also necessary in patients with renal failure.

Maintenance Therapy

Maintenance therapy continues to be based on the adult studies that support the use of azathioprine and mycophenolate for long-term maintenance (Table 2). The MAINTAIN trial reported good efficacy for either azathioprine or mycophenolate for maintenance therapy of LN in aSLE (Houssiau et al. 2010a; Tamirou et al. 2015). There is evidence for mycophenolate as maintenance therapy in cSLE as well (Kizawa et al. 2014). It is also important to note that hydroxychloroquine has been shown to reduce the rates of flare in SLE, incidence of renal disease and improves renal outcomes in adult studies (Fessler et al. 2005; Barber

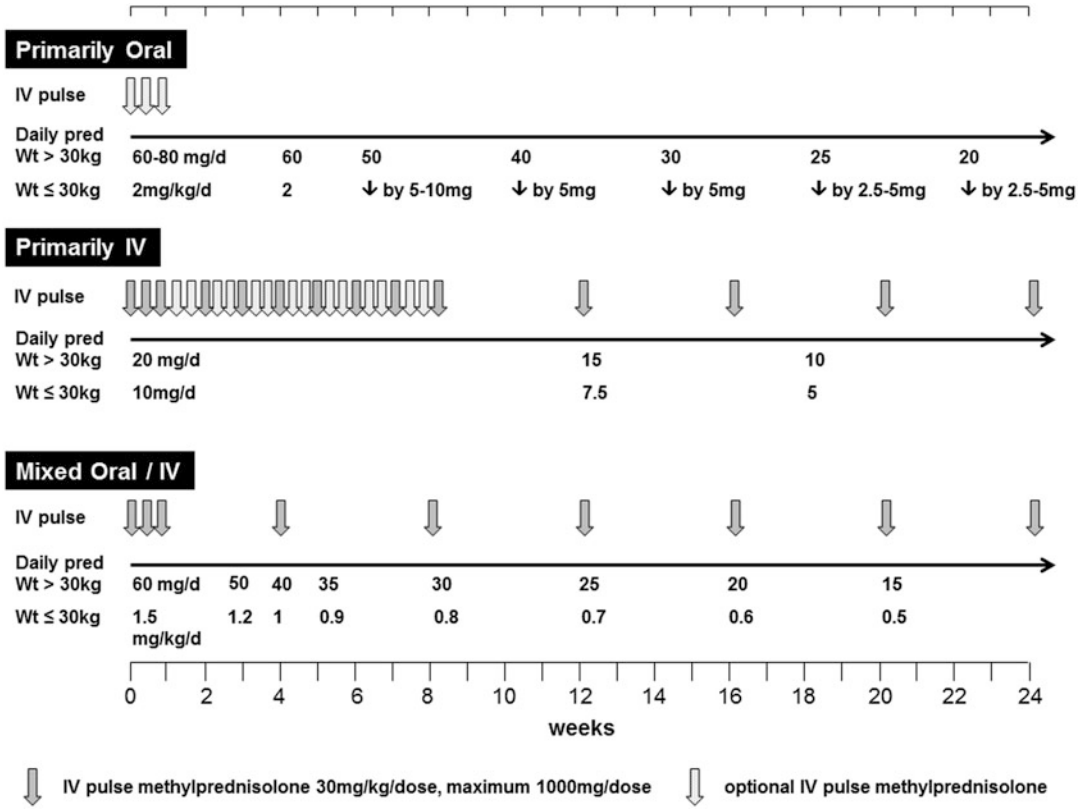

Fig. 1 Consensus treatment plans for corticosteroid dosing for the induction therapy of an initial episode of proliferative LN in cSLE, as developed by the Childhood Arthritis Rheumatology Research Alliance (Mina et al. 2012). The choice of strategy is based on practitioner preference.

et al. 2006; Kasitanon et al. 2006; Pons-Estel et al. 2009; Shinjo et al. 2010; Siso et al. 2008). ACE inhibitors have also demonstrated benefit in reducing proteinuria and preserving renal function (Duran-Barragan et al. 2008; Kanda et al. 2005; Kitamura et al. 2009; Kunz et al. 2008; Tse et al. 2005).

Refractory Therapy

Despite significant advances in the treatment of LN, one third of patients are still refractory to conventional therapy (Lau et al. 2008; Falcini et al. 2009). These patients continue to have an active urine sediment and deterioration of renal function. A repeat kidney biopsy can be highly informative in this group of patients. Although a class switch from proliferative to pure nonproliferative class is not common, an increase in activity index may justify more aggressive immunosuppression (Daleboudt et al. 2009). An improvement in histopathology may be reassuring. A large increase in chronicity index is a poor prognostic marker, and together with low activity index predicts progressive decline in renal function regardless of therapy. In this situation, aggressive immunosuppression would no longer be warranted. Finally, the presence of pauci-immune vasculitis or thrombotic microangiopathy on repeat biopsy may guide alternative therapies.

Common treatment approaches for refractory LN include switching from mycophenolate to cyclophosphamide or vice versa, or adding rituximab. Another alternative approach has been to add a calcineurin inhibitor to therapy with mycophenolate. The use of novel agents for the treatment of refractory LN is currently being

explored. If fibrin thrombi are noted on repeat biopsy and antiphospholipid antibodies are detected, addition of anticoagulation may be beneficial (Khamashta et al. 1995).

Definitions for Response

The definitions listed in Table 3 were adapted through consensus and based on aSLE studies.

Table 3 Definitions of renal outcomes in patients with cSLE and lupus nephritis[a]

Outcome measure	Definition
Core renal parameters	Proteinuria (spot uPCR)
	Renal function (creatinine clearance, serum creatinine, or cystatin C)
	Urine sediment (urine WBC, RBC, or casts)
Renal response definitions	
Substantial response (complete remission)	Inactive urine sediment (<5 WBC and <5 RBCs/hpf, no casts)
	Urine protein to creatinine (UPC) ratio < 0.2
	Normal renal function (Schwartz GFR > 90 mL/min/1.73 m^2)
Moderate response	At least 50% improvement in two of three core renal parameters (max uPCR ≤1.0) without clinically relevant worsening of the remaining core parameter
Mild response	30–50% improvement in two of three core renal parameters without clinically relevant worsening of the remaining core parameter
No response	Patients who do not qualify for any improvement as above

uPCR urine protein/creatinine ratio, *GFR* glomerular filtration rate, *hpf* high powered field
[a]Adapted from (Mina et al. 2012)

Membranous LN

The prevalence of pure class V LN in cSLE is between 10% and 25% (Cameron 1994; Sorof et al. 1998; Nathanson et al. 2006; Hiraki et al. 2008; Pereira et al. 2011, 2017). Membranous lesions can be defined as segmental or global thickening of glomerular basement membranes, often with spikes noted on silver stain, positive immunostaining of capillary loops for immunoglobulins and complement components, and electron dense deposits in an epimembranous or subepithelial location. The kidney biopsy findings resemble primary membranous nephropathy (Southwest Pediatric Nephrology Study Group 1986) but can usually be distinguished by the presence of tubuloreticular inclusions and/or immunostaining for C1q. Membranous lupus nephritis (MLN) can be the initial presenting feature in cSLE: cases have been reported of children initially diagnosed with membranous nephropathy who then become ANA positive and then years later develop other manifestations of SLE (Kallen et al. 1977). Membranous lesions can coexist in a cSLE patient with proliferative lesions (so-called mixed class LN).

There are no established noninvasive biomarkers that distinguish between PLN and MLN. It is more common to see cSLE patients with pure MLN in the absence of either hypocomplementemia or positive anti-dsDNA antibodies. It is also more common to see nephrotic syndrome associated with a normal urine sediment. However, without a kidney biopsy many cSLE patients with MLN cannot be distinguished clinically from those with PLN.

Initial Therapy

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that patients with pure MLN, normal renal function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressive therapy as dictated by the extrarenal manifestations of systemic lupus (Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group 2012). However, patients with MLN and persistent proteinuria >3.5 g/day may require additional immunosuppression specifically targeting the nephritis.

Initial dosing of oral corticosteroids is similar to that of PLN (1.5–2 mg/kg/day oral, maximum

total daily dosage 80 mg) (Mina et al. 2012), but IV pulse steroid therapy is often unnecessary (Nathanson et al. 2006; Wong et al. 2009; Hugle et al. 2014; Pereira et al. 2017). Monitoring for iatrogenic effects of initial therapy should mirror those discussed for therapy of PLN. The optimal approach to mixed membranous and proliferative LN is uncertain but tends to resemble that of pure DPGN (Boneparth and Ilowite 2014).

Several immunosuppressive agents have been utilized as initial therapy for MLN (Swan et al. 2011). Management decisions are guided by studies in aSLE. There are fewer clinical trials for pure MLN, but data is available from trials that included both PLN and MLN patients. Response rates are summarized in Table 4, but investigators concluded that adverse event rates, flares, and survival data were likely biased by underreporting. The combination of corticosteroids and additional immunosuppressant therapies is more effective than steroids alone in patients with nephrotic syndrome at baseline.

Mycophenolate mofetil is currently the most commonly used agent for therapy of MLN. Mycophenolate may indeed be more effective for MLN than for PLN (Buratti et al. 2001). Small single center cohort studies have described experience with mycophenolate, azathioprine, and cyclophosphamide (Hagelberg et al. 2002; Nathanson et al. 2006; Cramer et al. 2007; Lau et al. 2007; Wong et al. 2009; Hugle et al. 2014). Mycophenolate (prescribed 600 mg/m2/dose twice daily, maximum 3000 mg total daily dosage) or azathioprine (1–2.5 mg/kg/dose once daily, maximum 250 mg total daily dosage) is usually continued at least until a sustained response has been achieved. Cyclophosphamide has been used orally (1.5–2 mg/kg/day) or intravenously (0.5–1 g/m^2/dose monthly) for 3–6 months, adjusting dose for leukopenia or renal insufficiency. Chlorambucil is prescribed orally for 3 months (0.1–0.2 mg/kg/dose once daily). Calcineurin inhibitor (cyclosporine A, starting dosage 3–5 mg/kg/dose twice daily adjusted to target pre-dose blood levels of 50–100 ng/ml; tacrolimus, starting dosage 0.05–0.1 mg/kg/dose twice daily to target pre-dose blood levels of 4–10 ng/ml) use is based on experience treating isolated nephrotic syndrome and membranous nephropathy in patients without lupus.

The role of antiproteinuric therapy in addition to immunosuppression has not been directly studied. ACE inhibitors or angiotensin-II receptor blockers are considered first line agents for cSLE patients with HTN, unless contraindicated due to hyperkalemia, acute kidney injury, or angioedema. Due to the risk for birth defects or "ACE-fetopathy," females of childbearing age should be counseled to stop taking these medications as soon as they learn that they might be pregnant (Bullo et al. 2012).

Table 4 Remission rates in adults with pure membranous lupus nephritis

Agent[a]	Trials	Subjects	CR	PR	NR	Flare	SAE	Deaths
Total	34	495	198	163	132	53	79	15
			40%	33%	27%	>11%[b]	>16%[b]	>3%[b]
Steroids only	7	136	43%	15%	42%	40%	23%	5%
MMF	9	97	41%	41%	18%	19%	19%	1%
MMF + CYC	1	2	50%	0%	50%	50%	0%	50%
CYC	7	87	46%	38%	28%	10%	39%	6%
Chlorambucil	1	11	64%	36%	0%	9%	NR	0%
AZA	1	38	63%	21%	16%	16%	50%	0%
CsA + AZA	1	10	40%	30%	30%	20%	10%	0%
CsA	2	35	51%	40%	9%	43%	9%	0%
TAC	1	18	39%	44%	17%	NR	1	0%

AZA azathioprine, *CsA* cyclosporine, *CYC* cyclophosphamide, *MMF* mycophenolate mofetil, *TAC* tacrolimus
[a]Adapted from (Swan et al. 2011)
[b]Not reported in all studies

Maintenance Therapy

After completion of initial therapy, relapse is common unless patients remain on maintenance immunosuppression. Steroid sparing strategies have been used similar to the maintenance therapy of PLN (antimalarials combined with either mycophenolate or azathioprine) (Tsakonas et al. 1998; Tamirou et al. 2015). Hydroxychloroquine is dosed once daily 5–6 mg/kg (maximum daily dosage 400 mg) and requires monitoring for retinal complications with annual examinations by an ophthalmologist. Repeat biopsy has not been reported as a means of monitoring the optimal time to start or stop maintenance immunosuppression for MLN. ACE inhibitors or angiotensin-II receptor blockers should be continued in patients with hypertension or proteinuria considered to be secondary to renal scarring.

Refractory Therapy

There is no consensus on how to define refractory disease in patients with pure MLN and no evidence to guide the therapy in adults or children. Since it can take 2–3 years for proteinuria to fully respond to initial therapy, refractory therapy should be reserved in this setting for children who (1) develop progressive renal failure on therapy or (2) have ongoing edema from nephrotic syndrome after 3–6 months of initial therapy. Options include switching immunosuppressive agents or "add-on" therapy with either IV rituximab (750 mg/m^2/dose, maximum 1000 mg/dose, on two separate occasions approximately 14 days apart, or 4 weekly doses of 375 mg/m^2/dose, maximum 500 mg/dose), intravenous immunoglobulin (IVIg, high dose of 2000 mg/kg divided over 2–5 days, or low dose of 85 mg/kg/day on alternate days, for a total of three doses repeated quarterly), or corticosteroid pulses (Contis et al. 2016; Levy et al. 2000; Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group 2012).

Definitions for Response

Outcomes are usually better for pure MLN than for proliferative or mixed class LN (Boneparth et al. 2016). Rates of complete renal response vary by geographic location and ethnicity but tend to take years of immunosuppressive therapy (Nathanson et al. 2006).

Although definitions of response also differ from study to study, five core renal parameters are typically considered: (1) proteinuria, (2) hypoalbuminemia, (3) edema, (4) renal function, and (5) urine sediment. Repeat kidney biopsy studies rarely show complete resolution of membranous lesions. A proposed set of definitions for response, based on the Childhood Arthritis Rheumatology Research Alliance definitions for proliferative LN in cSLE (Mina et al. 2012), has recently been announced and is awaiting validation (Table 5) (*in preparation*).

Nonclassifiable LN

Some patients with SLE develop renal disease that is not primarily caused by immune complex deposition. Although unclear how these patients should best be managed, it is likely that the different pathogenesis portends a different approach to pharmacotherapy.

Lupus Podocytopathy

Podocytopathy in SLE has been reported in 1% of aSLE patients with renal involvement (Kraft et al. 2005; Hu et al. 2016). Patients present with nephrotic syndrome. There are either minimal changes on histology or focal segmental glomerulosclerosis (FSGS), with >50% podocyte foot process effacement on electron microscopy. The glomerulosclerosis can resemble collapsing glomerulopathy (see ▶ Chap. 9, "Focal Segmental Glomerulosclerosis, Adult"). Some have argued that lupus podocytopathy can coexist with immune complex GN (Bomback and Markowitz 2016), but it is unclear whether

Table 5 Definitions of renal outcomes in patients with cSLE and pure class V membranous lupus nephritis[a]

Outcome measure	Definition
Core renal parameters	Proteinuria (spot uPCR)
	Hypoalbuminemia
	Edema/nephrotic syndrome
	Renal function (creatinine clearance or serum creatinine)
	Urine sediment (urine WBC, RBC, or casts)
Renal response definitions	
Substantial response (complete remission)	Inactive urine sediment (<5 WBC and <5 RBCs/hpf, no casts)
	uPCR <0.2
	No hypoalbuminemia
	No edema
	Normal renal function (Schwartz GFR > 90 mL/min/1.73 m^2)
Moderate response[b]	At least 50% improvement in uPCR (max ≤1.0)
	No hypoalbuminemia
	No edema
	At least 50% improvement or normalization of one other core renal parameter without clinically relevant worsening of the remaining parameter
Mild response[b]	30–50% improvement in uPCR
	At least 30% improvement in hypoalbuminemia
	No nephrotic syndrome
	No clinically relevant worsening of the remaining core parameters
No response	Patients who do not qualify for any improvement as above

uPCR urine protein/creatinine ratio, *GFR* glomerular filtration rate, *hpf* high powered field

[a]Adapted from (Mina et al. 2012). Abbreviations: uPCR, urine protein/creatinine ratio, GFR, glomerular filtration rate, hpf = high powered field

[b]If other four baseline renal parameters were normal, improvement in proteinuria ALONE is sufficient to meet criteria

podocytopathy changes the prognosis of classifiable LN.

The presence of mesangial proliferation and/or mesangial deposits does not seem to alter response rates in this disease subgroup. The response to steroids was inconsistent in patients with FSGS lesions, but isolated lupus podocytopathy with minimal change histology tends to respond well to therapy with corticosteroids in 4 weeks (Hu et al. 2015). Overall response rates are nearly 95% at 12 weeks with complete response in 75% (Kraft et al. 2005; Hu et al. 2016). Collapsing glomerulopathy associates with AKI and poor renal prognosis (Nasr et al. 2014). As with podocytopathies in patients without SLE, relapse rates are high (55% in one study) (Hu et al. 2016).

Pauci-Immune LN

Segmental necrotizing GN has been described in SLE patients with class III-like (Schwartz et al. 1983; Nasr et al. 2008) and class V-like LN (Marshall et al. 1997) except that there was a paucity of immunostaining for immunoglobulin or complement and a paucity of electron dense deposits. Some of these patient may get diagnosed as class IV-S based on the ISN/RPS criteria (Hill et al. 2005). Pauci-immune LN has also been reported in children (Sawai et al. 1995). These patients are less likely to have associated hypocomplementemia or detectable dsDNA antibody titers and more likely to present with AKI (termed rapidly progressive glomerulonephritis, RPGN, see ▶ Chap. 5, "Overview of the Current Approach to Glomerular Disease Classification"). Antineutrophil cytoplasmic antibodies (ANCA) are not specific for pauci-immune LN (Ho et al. 2000) but may be pathogenic and/or a marker for disease activity in these patients. Crescentic glomeruli are commonly seen.

The estimated prevalence of this SLE/ANCA vasculitis overlap syndrome is 2% of all LN patients. Remission has been reported in 50% of patients (Jarrot et al. 2016) and renal and patient survival is worse than for pure class IV DPGN (Grishman and Venkataseshan 1988; Sawai et al. 1995). Cyclophosphamide and corticosteroids were used in most cohort studies (Nasr et al. 2008; Jarrot et al. 2016), but it has been suggested

that more favorable responses might come with treatment following guidelines for renal vasculitis than for LN (Hill et al. 2005).

Differential Diagnosis of GN with Full House IF

There has long been debate about whether isolated immune complex renal disease with full house immunofluorescence should be considered a form of SLE, either in the presence or absence of positive ANA (termed seronegative LN). Children with negative ANA test results and immune complex GN have been reported (Enriquez et al. 1988; Gianviti et al. 1999; Baskin et al. 2007; Caltik et al. 2013; Ruggiero et al. 2016). Theoretically, a patient with ANA might test negatively if the immune complex kidney is severe and all autoantibodies are entrapped by immune complexes or absorbed by the kidney. Alternatively, high grade proteinuria causing hypogammaglobulinemia might cause a false negative ANA assay. Some have been reported to develop a delayed SLE with time, but clearly their renal disease predated their development of significant amounts of autoantibodies.

C1q nephropathy differs from LN due to an absence of significant IgA and IgM (and often C3 and C4) staining on immunofluorescence. For a diagnosis of C1q nephropathy, the C1q staining should be dominant (i.e., at least one point greater on the 4-point semiquantitative scale used by renal pathologists) and no tubuloreticular inclusions should be present (Sharman et al. 2004). Similarly, IgA and Henoch Schoenlein nephropathy can mimic LN but should be diagnosed only when the IgA staining is dominant (and usually C1q staining is absent). The differential diagnosis also includes membranoproliferative glomerulonephritis (MPGN) associated with infected shunts (Smet et al. 2001) or chronic infections such as hepatitis B or C or HIV have also been reported to cause full house immunofluorescence (Jennette and Hipp 1985).

The outcome of patients with seronegative full house nephropathy who do not progress to development of SLE is reportedly better in children (Ruggiero et al. 2016) than in adults (Huerta et al. 2011). Response rates of 90% (with complete response rates of 75%) after 3 years have been reported in children (Ruggiero et al. 2016). Relapse rate is 18%, and recurrences were limited to the first 4 years following diagnosis, allowing consideration of immunosuppression withdrawal after remission is achieved. At 10 years, the probability of chronic kidney disease progression was 5%.

Lupus Nephritis Relapses

Relapses are common in cSLE patients who respond to therapy. The rate of renal flares due to SLE is 25–50% on therapy (Wu et al. 2013; Hugle et al. 2014; Aragon et al. 2016). Relapses can be either proteinuric or nephritic, and histologic class switch is possible at time of relapse. Childhood Arthritis Rheumatology Research Alliance has proposed pediatric specific definitions for cSLE (Mina et al. 2012) based on the definitions for aSLE by the American College of Rheumatology (Liang et al. 2006) and the European League Against Rheumatism (Gordon et al. 2009).

Definition of Nephritic Flare

A renal relapse is considered to be nephritis when there is an increase or recurrence of "activity" in a patient's urinary sediment, with or without a concomitant increase in proteinuria. Ideally, the urine sediment analysis should be performed by the provider looking at a spun fresh urine specimen. The reappearance or increased number of cellular casts or the reappearance of increased proportion of dysmorphic erythrocytes constitutes increased activity on urine sediment analysis. The American College of Rheumatology and the Childhood Arthritis Rheumatology Research Alliance have both endorsed the finding of increased hematuria by urinalysis (automated urine microscopic evaluation in the laboratory) as a reasonable surrogate when performance of urine sediment analysis by a trained individual is not possible (Liang et al. 2006; Mina et al. 2012). An elevation in creatinine is not required in cSLE for a renal relapse to

predict renal survival (Gibson et al. 2009), and this requirement is not included in the definition of nephritic flare in cSLE patients.

Definition of Proteinuric Flare

A renal relapse is considered to be proteinuric when there is a persistent increase in proteinuria in the absence of an elevated creatinine or active urine sediment. Proteinuria can be quantified by either timed urine collection or spot urine protein-creatinine ratio (uPCR). Values >0.5 mg/mg on a uPCR after achieving complete response or a doubling of uPCR with values >1.0 mg/mg after achieving a partial response would constitute a significant change in disease activity.

Repeat Kidney Biopsy

Nephritic flares often warrant repeat biopsy to evaluate for proliferative LN, especially when accompanied by an elevation in serum creatinine. Proteinuric flares are usually managed with an increase in the dose of either corticosteroids or maintenance immunosuppression, and a repeat biopsy is rarely necessary.

Management

The treatment of renal flares is not evidence based and must be individualized for each patient. The coexistence of extrarenal involvement must also be taken into account. In a patient who flares upon weaning of immunosuppression, returning to the dose that last controlled disease may be the best initial strategy. Determination of a patient's adherence to their medication regimen at the time of flare is crucial. Sometimes restarting the subscribed medication dosages in a nonadherent patient is sufficient for treating the flare.

Treatment of nephritic flares more often requires a change in immunosuppressive medication or a repeat course of induction therapy. Due to concerns over cumulative dosage effects, shortened courses of cyclophosphamide (3 months instead of 6 months) have been used to treat relapses of proliferative LN. For the same reason, mycophenolate is often used for induction therapy for relapses even if cyclophosphamide was effective initially. For patients with a nephritic flare on mycophenolate maintenance therapy, the dose is escalated up to 3 g/day. Alternatively, rituximab has also been used with success as an add-on therapy for these patients. There is no consensus on the dosing of corticosteroids for treating flares, but the oral dose is usually increased and often accompanied by a 3 day IV pulse with or without a course of weekly IV steroid pulses.

Treatment of proteinuric flares depends upon the severity of the proteinuria. An increase in proteinuria without nephrotic syndrome will often respond to an increase in oral steroids without the need for IV pulses. IV corticosteroids and/or additional immunosuppression are usually required for proteinuria severe enough to cause nephrotic syndrome. For patients with pure membranous LN with a more severe proteinuric flare, repeating the initial therapy is usually attempted. Alternatively, rituximab has been used with success.

Weaning Immunosuppression

There is a dearth of evidence for when and under what circumstances immunosuppression can be weaned or discontinued in LN. An ongoing study in aSLE sponsored by National Institute of Allergy and Infectious Diseases seeks to describe the effect of withdrawal from mycophenolate on risk of clinically significant disease reactivation in quiescent SLE patients who have been on long-term mycophenolate therapy. The primary outcome is time to reactivation of disease. Many pediatric physicians do wean immunosuppression over time especially corticosteroids. In some settings, prednisone can be weaned over months or years while on other immunosuppression intended to be steroid-sparing (such as mycophenolate, azathioprine). There is no consensus on whether or how quickly steroid sparing agents should be weaned or discontinued. Unless contraindicated, hydroxychloroquine is hardly ever discontinued in a patient with cSLE.

Outcomes

Patient Survival

Outcomes in pediatric LN have improved since the 1980s (Table 6). A retrospective study reported improvement in 5-year pediatric patient survival from 83% to 91% and renal survival from 52% to 88% over the past three decades. Predictors of poor renal outcome include nephrotic range proteinuria at time of diagnosis, African American race, apolipoprotein L1 genetic risk alleles, low GFR, lack of response to treatment in the first 6 months, high chronicity on renal biopsy, and high degree of chronic tubulointerstitial disease.

School Performance

Cognitive impairment in children and adolescents with SLE can affect intelligence, academic achievement, arithmetic, reading comprehension, learning, visual memory, and complex problem solving ability (Moorthy et al. 2010). Patients self-report difficulty with schoolwork, problems with memory and concentration, and disappointment with regard to their school attendance and performance. Eighty-three percent of cSLE patients feel they would have done better in school had they not have developed SLE (Moorthy et al. 2010). Patients receiving medications by IV infusion miss more school days compared with those on only oral medications, and a greater number of missed school days correlated significantly with increased disease activity. Activities related to caring for cSLE clearly impose a burden on children's academic performance and should be considered in all clinical trials designed to treat cSLE.

Growth and Puberty

Clinicians who care for children with any chronic glomerular disease, including LN, recognize that the disease and its therapy (in particular the use of corticosteroids) can lead to significant changes in growth and may ultimately lead to a decreased final height (Hiraki et al. 2007). Most patients with LN will be on prolonged courses of

Table 6 Patient outcomes of lupus nephritis in cSLE over the past 50 years[a]

Date of diagnosis	Country	SLE patient survival	LN patient survival[b]	Reference
1945–1967	USA	28% 5-yr	–	Hagge et al. (1967)
1959–1966	USA	56% 5-yr	23% 10-yr	Meislin and Rothfield (1968)
1948–1980	England	76% 10-yr	–	Caeiro (1981)
1958–1974	USA	86% 10-yr	73–87% 10-yr	Fish et al. (1977)
1970–1983	USA	–	28% 10-yr	McCurdy et al. (1992)
1958–1980	USA	85% 10-yr	69% 9-yr	Glidden et al. (1983)
1965–1999	USA	–	86% 10-yr	Vyas et al. (2002)
1965–1992	USA	–	68% 10-yr	Baqi et al. (1996)
1984–1991	Canada	–	94% 10-yr	Hagelberg et al. (2002)
1983–2001	Serbia	–	98% 5-yr	Bogdanovic et al. (2004)
1985–2007	Thailand	64% 10-yr	–	Vachvanichsanong et al. (2011)
1984–2013	Croatia	–	91% 5-yr	Batinic et al. (2015)
1990s	USA	91% 5-yr	–	Hersh et al. (2010)
1990–2010	USA	–	94% 5-yr	Pereira et al. (2011)
1999–2011	Taiwan	–	87% 10-yr	Lee (2013)
1991–2013	India	–	59% 10-yr	Wu et al. (2013)
1995–2013	Singapore	–	100% 9-yr	Aragon et al. (2016)
2000–2010	Hungary	95% 7-yr	–	Tarr et al. (2015)

[a]Outcomes should be considered best case scenarios, since each study had subjects lost to follow-up
[b]Range provided because publication compares outcomes of different classes of lupus nephritis (LN)

corticosteroids. Children with lupus are at increased risk for delayed skeletal growth, short stature, and fractures later in life.

Growth failure in cSLE is defined as the presence of any two of the following: (1) height less than third percentile for age, (2) growth velocity over 6 months less than third percentile for age, and (3) crossing at least two percentiles on the growth chart (Gutierrez-Suarez et al. 2006). In a study of the Pediatric Rheumatology International Trials Organization, growth failure occurred in 8% of cSLE patients within 1 year and 25% of patients after 5 years (Gutierrez-Suarez et al. 2006). Although poor growth is a significant side effect of active disease and/or its therapy in cSLE, other studies provide evidence to suggest a potential for catch-up growth once disease is better controlled and corticosteroids can be weaned.

Delayed puberty is also a concern in patients with cSLE (Gutierrez-Suarez et al. 2006). It is difficult to measure whether this is related to a constitutional delay or a delay secondary to disease with impairment of the hypothalamic-pituitary axis. Fortunately, this is a short-term morbidity. However, bone mineral density increases 40% during puberty and peak bone mass is typically reached at age 18 years.

Several studies have demonstrated that a high percentage of children with cSLE have vitamin D deficiency or insufficiency (Robinson et al. 2014; Casella et al. 2012) (Stagi et al. 2014). Urinary losses of 25(OH)D and vitamin D binding protein in patients with LN and proteinuria only exacerbate vitamin deficiency. Corticosteroids may have a regulatory effect on vitamin D metabolism which can additionally aggravate bone turnover. The best method to monitoring vitamin D status is to measure the circulating level of 25(OH)D. The Institute of Medicine has defined vitamin D deficiency in children as a level of <20 ng/mL (Ross et al. 2011). Vitamin D insufficiency is 21–29 ng/mL, vitamin D sufficiency is >30 ng/mL, levels between 40 and 60 ng/mL are ideal, and levels up to 100 ng/mL are safe. Although the benefit of supplementation remains debated, several pediatric specialists treat with daily calcium and vitamin D supplements. Optimal bone health also includes participation in daily weight-bearing and aerobic exercise.

It is important that patients have regular bone mineral density screenings by dual x-ray absorptiometry (DEXA scan). In a Norwegian study of cSLE, the lumbar spine is the most seriously affected skeletal site, followed by the femoral neck (Lilleby et al. 2005). The cumulative dose of corticosteroids was shown to be an important explanatory variable. Patients with cSLE have an increased fracture risk, and decreased bone density in the spine 6 months after starting immunosuppression was a significant risk factor (Rodd et al. 2012).

Ovarian Suppression

The risk of amenorrhea and infertility remain a concern for patients receiving cyclophosphamide. In a 1993 study of women with SLE under <40 years of age, the risk of sustained amenorrhea after treatment with a long course (≥ 15 doses) of cyclophosphamide was greater than a shorter course (7 doses). The risk was less in patients aged <25 years than in those ≥ 31 years (17% vs. 100% after long course, 0% vs. 25% after short course). Although use of the Euro-lupus protocol for dosing cyclophosphamide might be expected to reduce ovarian toxicity, there is insufficient data to evaluate this possibility.

Concurrent use of gonadotropin-releasing hormone analog (GnRH-a) treatment with cyclophosphamide may provide ovarian protection by suppressing ovulation. Conflicting results regarding their efficacy have been reported (Dooley and Nair 2008; Gajjar et al. 2015). Monthly depot leuprolide injections were effective against the development of premature ovarian failure (Somers et al. 2005). Another GnRH-a (triptorelin) has been used safely for the protection of ovaries during cyclophosphamide therapy in cSLE (Brunner et al. 2015). Ovarian preservation is also an option for adolescents who have achieved menarche and spontaneous ovulation, but is not an option in younger premenarchal patients.

Male Infertility

There is active proliferation of Sertoli and Leydig cells in the testes even before puberty and thus

azoospermia has been reported in boys treated with cyclophosphamide. Dose-dependent declines in sperm production were demonstrated in patients within 4 months of starting treatment (Meistrich et al. 1992). Despite having normal sperm counts prior to treatment, all patients were azoospermic after 12 months of treatment. Recovery of sperm counts is dose dependent (Meistrich et al. 1992). Sperm banking is a well-established, effective, and accepted practice for collecting and storing male gametocytes in adolescent patients who are at Tanner III stage of development or greater (Lee et al. 2006; Gajjar et al. 2015).

Pregnancy in cSLE

The onset of SLE typically occurs during childbearing years. Thus, it is important to discuss issues related to reproductive health including the risks of pregnancy. The rate of pregnancy loss has decreased from 43% to 17% in recent years (Clark CA et al., 2005). However, pregnancy still carries a high risk of complications. Disease activity may worsen during the pregnancy. A multidisciplinary team including rheumatology and a high-risk maternal fetal specialist is important in managing patients with SLE who become pregnant especially in patients with LN. It is more difficult to diagnose and treat pregnancy complications and disease flares as many of the features of both entities can overlap. Increased fetal loss, especially in the presence of antiphospholipid antibodies, preterm births, intrauterine growth retardation, and neonatal syndromes including congenital heart block continue to be major issues (Lateef and Petri 2013). Close monitoring of these patients with judicious use of appropriate medications is essential to achieve good outcomes.

Thrombosis

Thrombosis is more likely to occur with the existence of hereditary and acquired thrombotic factors. Venous thrombosis is the most common vascular occlusive event seen, occurring in up to 60% of children with antiphospholipid syndrome (Avcin et al. 2008). A variety of venous thrombosis events can occur including deep vein thrombosis in the upper and lower extremities, cerebral sinus vein thrombosis, portal venous thrombosis, and superficial vein thrombosis.

Cardiovascular Disease

It has been assumed based on findings in aSLE that the cSLE population would similarly be at increased risk of cardiovascular disease. Patients with cSLE carry an increased burden of both traditional and nontraditional risk factors. Twenty percent of patients have hypertension and a third of those have target organ damage, as measured by sonographic left ventricular hypertrophy (Sozeri et al. 2013). There is evidence of dyslipidemia and insulin resistance (Boros et al. 2011). However, the greater plasticity of vessels in childhood may be protective against cardiovascular injury.

When compared to children without lupus, cSLE patients develop both vascular damage, as measured by increases in carotid intima media thickness (Schanberg et al. 2009; Sozeri et al. 2013; Quinlan et al. 2015) and increased arterial stiffness, as measured by pulse wave velocity (Boros et al. 2011; El Gamal et al. 2013; Sozeri et al. 2013). Progression of carotid intima media thickening occurs faster in cSLE than in other high risk populations, including those with familial hypercholesterolemia (Schanberg et al. 2009). Unfortunately, in the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial, children had no meaningful improvement in carotid intima media thickness when treated with statins (Schanberg et al. 2009). Risk factors for vascular damage in cSLE include increasing age, minority status, higher body mass index (BMI), male sex, increased creatinine clearance, higher lipoprotein(a) level, proteinuria, azathioprine, and prednisolone treatment. In multivariate analysis, moderate doses of prednisolone were associated with decreased carotid intima media thickness, while high and low doses were associated with increased carotid intima media thickness. There is no significant correlation with physical activity or disease activity, and the association with disease

duration has been inconsistent between studies (Schanberg et al. 2009; Quinlan et al. 2015). The pulse wave velocity of the proximal aorta correlated with disease activity (El Gamal et al. 2013). Flow mediated dilatation and myocardial perfusion were normal in cSLE (Boros et al. 2011).

Hypertension

Elevated blood pressure is commonly found in patients with cSLE with or without renal involvement. Even in cSLE patients with prehypertension, ambulatory blood pressure monitoring has revealed an increased prevalence of attenuated nocturnal dipping and nocturnal hypertension (Campbell et al. 2015). It may be caused by sodium retention and fluid overload, excess activation of the renin–angiotensin system, or a functional nitric oxide deficiency. Corticosteroids contribute by overstimulation of the mineralocorticoid receptor, exacerbating sodium retention in the kidney, and subsequently fluid retention. Autoantibodies or autoimmune lymphocytes targeting the vasculature could also play a direct role. Patients with serologically active disease are significantly more likely to be hypertensive when compared to those with inactive disease and controls (Lozovoy et al. 2014).

Since hypertension is a proven risk factor for cardiovascular disease, all patients with cSLE should have their blood pressure checked, regardless of the presence of LN and should receive appropriate therapy to achieve both systolic and diastolic blood pressures below the goal 90th percentile for height, age, and gender (National High BP Education Program Working Group on High BP in Children and Adolescents 2004). ACE inhibitors or angiotensin-II receptor blockers should be used in patients with hypertension and abnormal proteinuria unless contraindicated. Diuretics can treat the sodium retention, especially in patients on high dose corticosteroids, but should be used judiciously in cSLE patients with nephrotic syndrome, to avoid the risk of intravascular volume contraction.

Hyperlipidemia

Lipoprotein profiles and HDL function is altered in SLE (McMahon et al. 2009; Santos et al. 2010; Volkmann et al. 2010; McMahon et al. 2011). In cSLE as in aSLE, active disease is associated with three findings: (1) hypertriglyceridemia, (2) elevated very low density lipoprotein levels, and (3) reduced HDL levels (Ilowite et al. 1988; Gonzalez-Juanatey et al. 2008). Corticosteroid therapy further increases total cholesterol, lipoprotein, and triglyceride levels, whereas hydroxychloroquine usage is associated with lower LDL levels (Ettinger et al. 1987; Boros et al. 2011).

Under chronic inflammatory conditions, HDL dysfunction actively contributes to atherosclerosis (McMahon et al. 2009; Norata et al. 2012). HDL normally prevents the oxidation of LDL and its uptake by monocytes, thus preventing the formation of foam cells, one of the important steps in atherogenesis. The major protein in the HDL particle, apolipoprotein A-1, exerts antioxidant and anti-inflammatory properties. It blocks the contact-mediated activation of monocytes by T cells. Antibodies to HDL and apolipoprotein A-1 have been found in 8–32% of individuals with SLE, and they have been shown to be higher in those with persistently active disease (Dinu et al. 1998; O'Neill et al. 2010). Dysfunctional HDL is unable to prevent the oxidation of LDL and instead increases oxidation. Therefore, HDL can be considered pro-oxidant and pro-inflammatory in cSLE.

HMG-CoA reductase inhibitors (statins) can both reduce cholesterol and inflammation. Their anti-inflammatory effects include upregulation of nitric oxide synthesis, attenuation of reactive oxygen generation, monocyte and endothelial cell adhesion, inflammatory cytokine production, tissue factor expression, and proliferation of macrophage and T lymphocytes (Waehre et al. 2004). In animal models of lupus, treatment with statins alone attenuated renal disease (Lawman et al. 2004; Woo et al. 2010). While the use of statins is effective in reducing C-reactive protein levels and slowing the progression of atherosclerosis in some aSLE cohorts (Plazak et al. 2011; Mok et al. 2011), large clinical trials in adults (Petri et al. 2011) and children (Schanberg et al. 2012) have failed to show any appreciable benefit to treatment with statins in SLE. In cSLE, reduced progression

of carotid intima media thickening could only be shown in a subgroup of pubertal patients with higher C-reactive protein levels (Ardoin et al. 2014). However, the cSLE trial excluded patients with renal insufficiency or active nephrotic syndrome.

Whether hypercholesterolemia should be treated at all with pharmacologic therapy in children age 8 to 18 years is controversial. The potential benefits of statin use must be weighed with the concerns about its effects on myelination and the risk of statin-induced rhabdomyolysis. An expert panel has published guidelines on pediatric cardiovascular risk reduction which has been endorsed by the National Heart Lung and Blood Institute (NHLBI 2011). Additional guidelines specifically recommend against the use of statins or ezetimbe in children with chronic kidney disease, endorsing instead implementation of therapeutic lifestyle changes to manage hypercholesterolemia and hypertriglyceridemia (KDIGO Working Group 2013). The guidelines do not address use in patients with cSLE with or without nephritis, so decision to prescribe should be made on a case-by-case basis.

Renal Survival

Although renal outcomes differ based on ethnicity, race, and socioeconomic status, all have greatly improved over the past several decades (Table 7). Prior to corticosteroid therapy, progression to ESKD was seen in over half of patients (Hagge et al. 1967; Meislin and Rothfield 1968). Outcomes greatly improved by 1990 in both children (Fish et al. 1977; Glidden et al. 1983; McCurdy et al. 1992; Baqi et al. 1996; Vyas et al. 2002; Bogdanovic et al. 2004; Vachvanichsanong et al. 2011; Pereira et al. 2011; Batinić et al. 2015) and adults (Tektonidou et al. 2016) with SLE and PLN (90% 10-year renal survival), but have been unchanged over the past two decades (Vachvanichsanong et al. 2011; Pereira et al. 2011; Wu et al. 2013; Batinić et al. 2015; Singh et al. 2015; Tarr et al. 2015; Tektonidou et al. 2016;

Table 7 Improvement in renal survival of lupus nephritis in cSLE[a]

Proliferative lupus nephritis				
Date of diagnosis	Country	5-year renal survival	10-year renal survival	Reference
1970–1983	USA	–	60%	McCurdy et al. (1992)
1965–1999	USA	–	45%	Vyas et al. (2002)
1965–1992	USA	–	30%	Baqi et al. (1996)
1984–1991	Canada	–	85%	Hagelberg et al. (2002)
1983–2001	Serbia	89%		Bogdanovic et al. (2004)
1985–2007	Thailand	93%		Vachvanichsanong et al. (2011)
1984–2013	Croatia	87%		Batinic et al. (2015)
1990–2010	USA	90%		Pereira et al. (2011)
1999–2011	Taiwan		89%	Lee et al. (2013)
1991–2013	India		78%	Wu et al. (2013)
1995–2013	Singapore	94%		Aragon et al. (2016)
2000–2010	Hungary	94%		Tarr et al. (2015)
Membranous lupus nephritis				
1985–1997	USA	95%		Sorof et al. (1998)
1990–2005	USA	92%		Lau et al. (2008)
2002–2005	France	100%		Nathanson et al. (2006)
1991–2003	USA	75%		Cramer et al. (2007)
1990–2003	China	92%		Wong et al. (2009)
1984–2008	Canada	100%		Hugle et al. (2014)
1990–2010	USA	97%		Pereira et al. (2017)

[a]Outcomes should be considered best case scenarios, since each study had subjects lost to follow-up

Aragon et al. 2016). The management change associated temporally with the largest improvement in renal survival was the addition of maintenance immunosuppression after induction therapy (Pereira et al. 2011).

Despite immunosuppression, only 55% of cSLE patients with PLN (class III and IV) achieve renal remission (Askenazi et al. 2007; Lee et al. 2007; Rianthavorn and Buddhasri 2015). However, 90% of cSLE patients with pure membranous LN in cSLE achieve renal remission and 76% can maintain remission on low-dose oral corticosteroids (Sorof et al. 1998; Nathanson et al. 2006; Lau et al. 2007; Wong et al. 2009; Hugle et al. 2014). In addition to class IV DPGN, risk factors for progression of renal failure include male gender, black race, apolipoprotein L1 risk alleles, hypertension, nephrotic syndrome, antiphospholipid antibodies, high glomerular staining for monocyte chemoattractant protein-1, chronicity on biopsy, poor response to induction therapy, and occurrence of nephritic renal flare (Marks et al. 2007; Lee et al. 2007; Gibson et al. 2009; Freedman et al. 2014).

Management of ESKD in cSLE

The mortality rate on dialysis (22% at 5 years) is similar to that reported for other causes of pediatric-onset ESKD (Hiraki et al. 2011). However, mortality from SLE with ESKD is almost double among African Americans/blacks compared to Caucasians/whites (Hiraki et al. 2011; Nee et al. 2015). Patients with SLE have similar outcomes on chronic dialysis with either hemodialysis or peritoneal dialysis (Goo et al. 2004; Nossent et al. 1990; Siu et al. 2005; Weng et al. 2009; Kang et al. 2011; Chang et al. 2013). Due to concerns for peritonitis, some centers prefer hemodialysis for patients on high-dose immunosuppression (Kang et al. 2011). Peritoneal dialysis may be preferable in patients with antiphospholipid antibody syndrome due to the possibility of hemodialysis access failure from thrombosis (Shafi and Gupta 2007).

The 10-year survival rate for SLE patients with ESKD is better for those taking prednisone and hydroxychloroquine than corticosteroids alone, and outcome of dialysis is worst for patients on no immunosuppressive medication (Broder et al. 2011). Whereas azathioprine and cyclophosphamide are cleared with hemodialysis, the dialytic clearance of other immunosuppressive drugs is minimal (Maroz and Segal 2013). Cyclophosphamide dose is usually reduced 50% and given 1 day before the next hemodialysis session (Aronoff et al. 2007). As opposed to patients with oliguric AKI, there is no need for intravenous fluids or bladder irrigation for anuric ESKD patients who receive IV cyclophosphamide. Unfortunately, there is no data on clearance of immunosuppressive agents during peritoneal dialysis.

Patients should continue to be followed by their rheumatologist after declaration of ESKD, as extrarenal flares are common (Bruce et al. 1999). SLE patients on dialysis who continued to have two or more regular follow-up visits with rheumatology annually had improved longevity and were more likely to receive effective immunosuppressive therapy (Broder et al. 2011).

Management of cSLE Patients Post Kidney Transplantation

One third of cSLE patients with LN and ESKD receive a kidney transplant within 5 years. Based on data from the US Renal Data System (USRDS) from 1995 to 2006, 51% were African American and 24% Hispanic (Hiraki et al. 2011). There were significantly fewer kidney transplants among adolescents (as opposed to younger children), African American and Hispanic children, and those with Medicaid (as opposed to private insurance). Moreover, children in the northeast and west (vs. south) are more likely to be offered a kidney transplant (Hiraki et al. 2011).

Serological markers of disease activity (complement C3 and C4 levels, dsDNA antibodies) are even less accurate measures of disease activity during the posttransplantation period. While glomerular immune complex deposition is seen on half of surveillance biopsies, recurrent nephritis is very low: less than 3% of patients had symptomatic disease (Contreras et al. 2010). Overall, graft survival and infection-related complications are

comparable between transplantation patients with LN-associated ESKD and allograft recipients with ESKD because of other causes (Contreras et al. 2010; Hiraki et al. 2011). Only 7% of graft failures are attributable to recurrent LN. However, if a patient has recurrent nephritis, they have a four-fold increased risk for graft failure (Contreras et al. 2010).

A history of antiphospholipid syndrome is associated with reduced 10-year graft survival. To a lesser degree, the presence of antiphospholipid antibodies in SLE patients is also a risk for early graft failure. Anticoagulation with warfarin or low molecular weight heparin is usually provided to reduce the risk of graft thrombosis, but does not improve graft survival (Vaidya 2012). For most cSLE patients, overall survival posttransplant is comparable to that of children who receive a kidney transplant for other causes (Bartosh et al. 2001).

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PLA_2R- and THSD7A-Associated Primary Membranous Nephropathy

15

Stephanie Toth-Manikowski and Laurence H. Beck Jr.

Contents

Abstract

Primary membranous nephropathy (MN) is an organ-specific autoimmune disease and is a common cause of nephrotic syndrome in adults. As opposed to primary focal segmental glomerulosclerosis or minimal change disease, which appear to be caused by as yet unidentified circulating permeability factors, primary MN is caused by antibodies directed against target antigens located on the glomerular podocyte. The accumulation of antigen-autoantibody immune complexes at the base of the podocyte and subsequent activation of the complement system are responsible for

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podocyte injury and damage to the glomerular filtration barrier, which gives rise to massive proteinuria and other features of the nephrotic syndrome. Two podocyte proteins that serve as autoantigens in MN have been identified in the past decade: the M-type phospholipase A_2 receptor (PLA_2R) and thrombospondin type-1 domain-containing 7A (THSD7A). There is evidence of antibodies to PLA_2R in up to 80% of all cases of primary MN. The identification of these antigens and their corresponding autoantibodies has allowed better precision in the diagnosis and monitoring of disease activity in primary MN. Although one-third of cases of primary MN may undergo a spontaneous remission, in other cases, treatment with immunosuppressive agents is necessary to stop the autoimmune process and to prevent complications of sustained proteinuria and decline in renal function. Nonetheless, a proportion of patients do progress to end-stage kidney disease, and many later undergo kidney transplantation. Persistence or reemergence of the circulating autoantibodies may lead to recurrent MN in the allograft, so careful monitoring is advised in this setting.

Keywords

Membranous nephropathy · PLA_2R (phospholipase A_2 receptor) · THSD7A (thrombospondin type-1 domain-containing 7A) · Autoantibody · Autoantigen · Autoimmunity · Biomarker · Nephrotic syndrome

Introduction

Membranous nephropathy is an antibody-mediated, immune complex disease that affects the filtration barrier of the glomerulus and leads to the loss of abnormally high amounts of protein into the urine. Its pathophysiology is explained by the gradual accumulation of immune complexes (containing antibody, antigen, and complement components) at the basal surface of the podocyte, also known as the visceral epithelial cell of the glomerulus. The complement system is activated by the locally deposited immune complexes and leads to cellular injury with loss of the normal slit diaphragm structure, causing the loss of massive amounts of protein into the urine which in turn leads to the nephrotic syndrome, defined by the pentad of tissue edema, proteinuria, hypoalbuminemia, hyperlipidemia, and lipiduria. Whereas secondary forms of MN may be caused by circulating immune complexes and/or extrinsic antigens that may become planted in a subepithelial position, primary MN is caused by autoantibodies that form against intrinsic proteins of the podocyte and lead to the in situ formation of immune complexes. The recent identification of two autoantigens in MN – the M-type phospholipase A_2 receptor (PLA_2R) and thrombospondin type 1 domain-containing 7A (THSD7A) – is rapidly changing the way that we diagnose, monitor, and treat this disease and will be the subject of this chapter.

Prevalence and Epidemiology

Although membranous nephropathy (MN) is relatively rare disease with an annual incidence of approximately 1 per 100,000 persons (Maisonneuve et al. 2000; McGrogan et al. 2011), it is the most common cause of nephrotic syndrome amongst Caucasian adults without diabetes. MN occurs in individuals of all races and has been described in most parts of the world. In adults, primary MN has a 2:1 male-to-female predominance and a peak incidence in the fifth and sixth decades of life.

Several points about terminology should be introduced up front. Membranous nephropathy does not represent a single disease but rather a common histopathologic pattern (see "Histopathology" below) that shares a common feature of immune complexes that form between the podocyte and the glomerular basement membrane (GBM) ultimately leading to a thickening of the GBM. Several other names for MN are used in the literature, including *membranous glomerulopathy* or *membranous glomerulonephritis*. Since the

lesion of MN is typically not marked by an infiltration of inflammatory cells, we discourage the use of the term membranous "glomerulonephritis." MN has been historically divided into an *idiopathic* form (meaning that the exact etiology was unknown) and cases that were *secondary* to systemic disease processes such as infections, other autoimmune disorders, cancers, or toxins. Although the term *idiopathic membranous nephropathy* is still widely used, many authors are encouraging the abandonment of this term and using *primary MN* instead. The recent discovery of antibodies to the M-type phospholipase A_2 receptor 1 (PLA$_2$R) and thrombospondin type-1 domain-containing 7A (THSD7A) proteins have established MN as a disease caused by kidney-specific antibodies which subsequently helped elucidate its pathogenesis. These cases are now known as primary MN and represent approximately 80% of all MN diagnoses in developed nations (Francis et al. 2016). The term idiopathic MN should nowadays be reserved for those cases of MN with no evidence of autoantibodies to PLA$_2$R or THSD7A, with no evidence of a secondary cause.

Twenty-five percent of all MN is felt to be secondary in nature (see ▶ Chap. 23, "Secondary Membranous Glomerulonephritis"). Well-established secondary causes are those in which a close association with MN appears time and time again, such as class V ("membranous") lupus nephritis that occurs in the setting of systemic lupus erythematosus, or MN that occurs secondary to infection with hepatitis B virus, or after the use of nonsteroidal anti-inflammatory agents. Certain solid malignancies have been associated as a secondary cause of MN. However, long lists of secondary "causes" have been published (KDIGO 2012), and in many cases, it is not known whether there is causation or merely association of two rare disorders or exposures. Close temporal association with the exposure, as well as improvement and disappearance of the MN with treatment of the disease/exposure can be suggestive of causality. For example, remission of MN after surgical excision of a malignancy might suggest a causal nature, which would be strengthened by relapse of the MN associated with recurrence of the tumor. However, this at times controversial association has been addressed in several publications (Beck 2010; Brueggemeyer and Ramirez 1987; Burstein et al. 1993), and coincidental occurrence of a common cancer with membranous nephropathy in an aging male-predominant population cannot be ignored.

Primary MN is classically thought of as a disease of adulthood because the prevalence of MN amongst childhood cases of nephrotic syndrome is felt to range only between 1% and 5% (Ayalon and Beck 2015; KDIGO 2012; Menon and Valentini 2010). Compared to adults, the incidence in children is 0.1 per 100,000 (Ayalon and Beck 2015; McGrogan et al. 2011) although this figure is likely an underestimation for a few reasons. First, childhood nephrotic syndrome is typically treated empirically with corticosteroids, with biopsies reserved for those who do not respond. As MN can be a steroid-responsive disease in children, it is impossible to know what percentage of the steroid-responsive and thus unbiopsied cases were due to MN. Second, "children" are defined as any person between the ages of 0 and 18. When one looks closely at studies involving biopsy-proven MN in children, the incidence of primary MN rises from as low as 1–3% in children aged 1–12 years to 18.5–22% in adolescents aged 13–18 years (Ayalon and Beck 2015; Hogg et al. 1993; Mubarak et al. 2012) suggesting that the incidence of primary MN rises as children enter adolescence. Hence, the lower prevalence of primary MN in "children" as a whole is in part skewed by inclusion of a greater proportion of young children in these studies (Ayalon and Beck 2015; Mubarak et al. 2012). There is a male-to-female predominance of 1.6:1 in childhood MN, similar to that in adults (Chen et al. 2007). In children, secondary MN is more common and may even account for the majority of MN diagnoses.

Natural History and Clinical Features

MN is one of the major causes of nephrotic syndrome in adults. Unlike primary focal segmental glomerulosclerosis (FSGS) and minimal change

disease, which tend to have a more explosive presentation of the nephrotic syndrome, the weight gain and edema that occur as a result of MN tend to be more insidious in onset. It is likely that the underlying pathophysiological process has been going on for months before an individual patient presents to clinical attention. Upwards of 80% of patients present with the full nephrotic syndrome consisting of nephrotic-range proteinuria >3.5 g/day, hypoalbuminemia, hyperlipidemia, and edema. The remainder of patients generally present with sub-nephrotic-range proteinuria of ≤3.5 g/day, although the amount of proteinuria may increase with follow-up. Hypertension may be present in one-third of patients. Despite the degree of proteinuria, a majority of patients (71.3% in one study) have preserved renal function upon presentation, as defined by an eGFR >60 mL/min/1.73 m^2 (Polanco et al. 2010). The urine sediment often shows features of lipiduria, with oval fat bodies, fatty casts, and occasional cholesterol crystals. Microscopic hematuria and/or granular casts can occasionally be seen as well.

Overall, MN has a variable clinical course, which makes prognostication and choice of therapy difficult for any given patient. The natural course of MN has been described by the rule of thirds: one-third of patients have complete and spontaneous remission of their proteinuria, another third achieve partial remission but has persistent sub-nephrotic-range proteinuria, and the final third have persistent nephrotic-range proteinuria and go on to develop end-stage kidney disease (ESKD).

A notable recent description of the natural history of primary MN comes from the Spanish Group for the Study of Glomerular Disease (GLOSEN) study (Polanco et al. 2010). Prior to this study, it was known that some patients would undergo spontaneous remission; however, clinicians did not have an understanding of who these patients might be and what types of long-term outcomes to expect in patients with primary MN. The GLOSEN study retrospectively evaluated 328 patients with nephrotic-range proteinuria and biopsy-proven MN (Polanco et al. 2010). Of these patients, almost one-third developed a spontaneous remission, either complete or partial, which most often occurred within 2 years of diagnosis. Predictors of remission included female gender, lower baseline serum creatinine or proteinuria, ≥50% decline in proteinuria within the first year of follow-up, and treatment with either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). Importantly, one of every five patients with high levels (>12 g/d) of proteinuria underwent spontaneous remission suggesting that the degree of proteinuria did not necessarily portend outcome; additionally, these patients thereafter had excellent renal outcome and overall survival (Polanco et al. 2010). Another study found that patients with sub-nephrotic-range proteinuria and biopsy-proven MN had an excellent prognosis and that their decline in renal function averaged less than 1 mL/min/year (Hladunewich et al. 2009).

It is important to realize that MN may recur as a relapse at any point after successful treatment (or spontaneous remission) of the initial episode. Relapses occur in up to 25% of cases, often years after the first episode (Jha et al. 2007) although some studies show lower rates, especially after a spontaneous remission (Polanco et al. 2010). Triggers for such relapses are not known. Relapses that occur soon after the cessation of treatment (e.g., with calcineurin inhibitors) are more likely to represent incompletely treated disease rather than a new and distinct immunological event. In the same manner, relapses occur less often after complete remission than after partial remissions (Kanigicherla et al. 2016). Cumulative rates of relapse depend on length of follow-up, and one study showed a relapse rate of 19% at 5 years, 29% at 10 years, and as many as 40% by 15 years of follow-up (Kanigicherla et al. 2016).

As we have learned in the past decade from studying the autoantibodies that cause primary MN (see below), many aspects of the natural history of MN can be better understood by considering the pathophysiology of the disease (Fig. 1). While the humoral immune system is actively producing antibodies that target the podocyte and lead to larger and more subepithelial immune deposits,

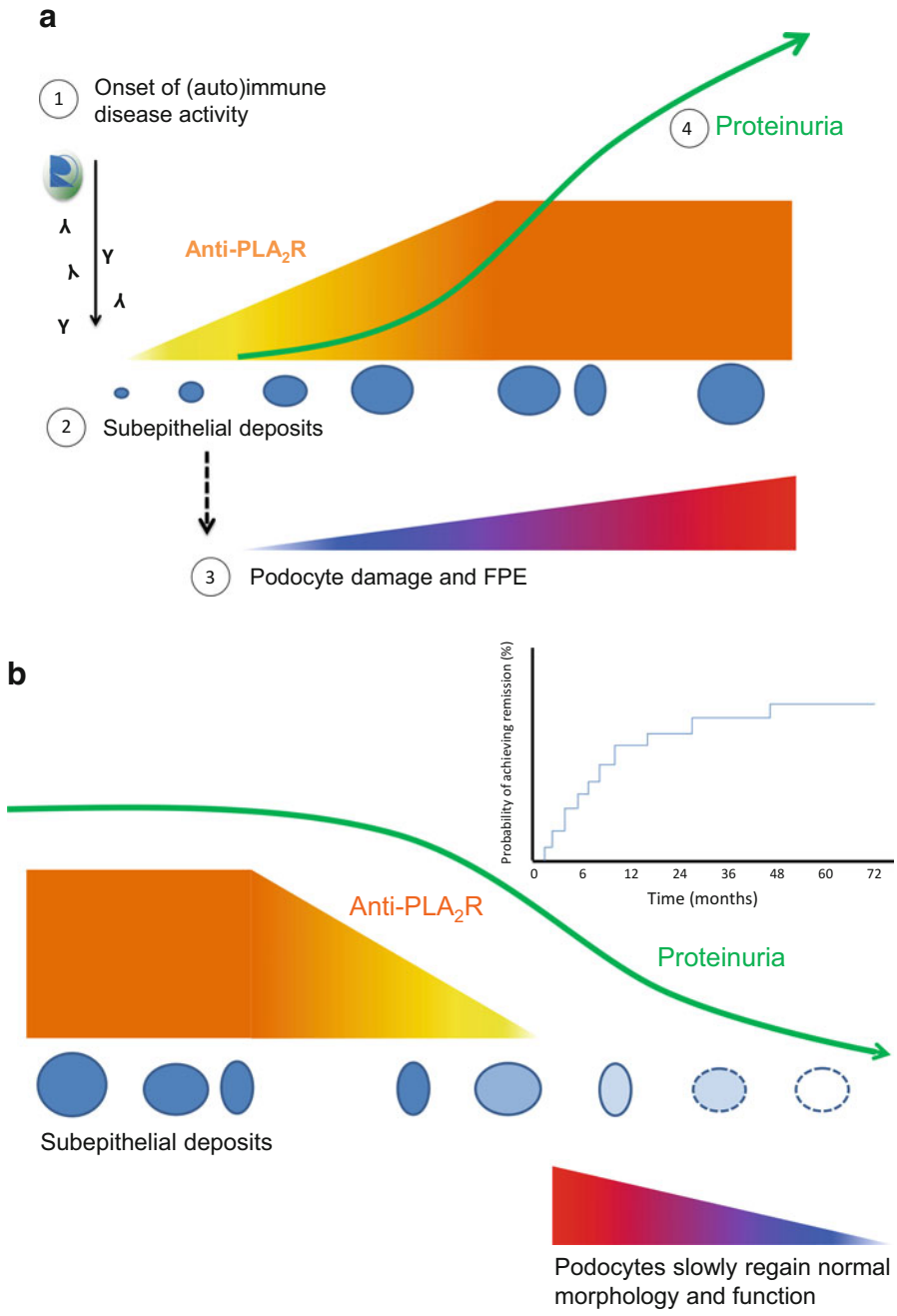

Fig. 1 (**a**) An illustration depicting the onset of immunologic disease, as represented by serum anti-PLA_2R levels, and the corresponding pathologic and clinical stages of disease as demonstrated by subepithelial deposits and proteinuria, respectively. As the production of anti-PLA_2R antibodies rises, immune complexes are deposited in the subepithelial layer within the capillary walls. Because the kidney acts as a "sink" for the initial circulating antibodies, subepithelial deposits are present before circulating anti-PLA_2R antibodies can be measured in the serum. As plasma cells continue to produce anti-PLA_2R antibodies, both the size of the immune complex deposits and the circulating mass of anti-PLA_2R antibodies increases. This ultimately results in damage to the podocytes, foot process effacement (FPE), and the onset of proteinuria. Because the rise of circulating anti-PLA_2R antibodies precedes proteinuria, they can be used to measure disease activity well before proteinuria. (**b**) An illustration depicting the

proteinuria will persist and perhaps increase. At some point, either spontaneously or with immunosuppressive treatment, the autoantibodies will decline and ultimately disappear from the circulation. Only at this point will the subepithelial deposits stop enlarging and serving as the cause of podocyte cell injury. However, this immunological remission does not lead to an immediate change in proteinuria. Only with time, as the deposits are resorbed and the glomerular filtration barrier can slowly reform does the proteinuria similarly decline. Thus, longstanding, highly active disease with a high degree of proteinuria may take months if not years to achieve a partial remission (<3.5 g/d) and even longer to achieve a complete remission (<0.3 g/d). If there has been interim parenchymal damage (secondary FSGS, tubular atrophy, interstitial fibrosis) from longstanding disease or treatment with nephrotoxic calcineurin inhibitors, it is possible that some degree of proteinuria may remain indefinitely, independent of the resolved primary glomerular pathology. This lag between immunological and clinical course, as well as the fact that not all patients may be able to ultimately achieve a complete remission, complicate studies of the natural history of MN.

Before the advent of modern day therapy, those with nephrotic syndrome succumbed to recurrent infections and ultimately died from these infections (Jones 1957). Although this no longer occurs in the modern world, patients still go on to develop edema and hyperlipidemia, and up to 7% of patients will suffer a venous thromboembolic event (VTE) (Lionaki et al. 2012). The risk of VTE increases with the severity of the nephrotic syndrome, with a threshold for increased risk marked by a serum albumin level <2.8 g/dl. Deep vein thrombosis, renal vein thrombosis, and pulmonary embolism are all potential venous thromboembolic events in MN. More recently, there has been an appreciation that other (arterial) cardiovascular events are also increased in MN, both in the initial phase of disease as well as later in the disease course (Lee et al. 2016). Progression to Stage 5 CKD, in the setting of either never achieving remission or due to disease relapse, is associated with a higher risk of cardiovascular death (Kanigicherla et al. 2016).

Children with MN exhibit a similar clinical picture to adults although there are some differences. More often than not, children present with hematuria (69%), and they are less likely (38%) to have edema or nephrotic-range proteinuria on presentation (Chen et al. 2007). Their renal function is almost always normal upon presentation, and their long-term outcomes are considered better when compared to adults. With treatment, remission rates are upwards of 75% (Valentini et al. 2009) which may in part explain why so few children progress to ESKD (Cameron 1990). Children also tend to have more of a relapsing and remitting course that responds to therapy (Cameron 1990). Importantly, as mentioned earlier, children often develop MN as a result of a secondary cause or agent. Thus, it is imperative to conduct a thorough workup for secondary causes prior to initiating steroids or potentially cytotoxic therapy, which might otherwise be avoided.

Target Antigens in Membranous Nephropathy

In the 1950s, Walter Heymann developed an experimental animal model for MN that is still being used today (Heymann et al. 1959). This model, known as Heymann nephritis, provided the crucial first step toward understanding how MN causes disease in humans. In his rat model, Heymann actively immunized Lewis rats with a fraction of renal tubular brush border

Fig. 1 (continued) resolution of immunologic disease followed by improvement in clinical disease. As circulating anti-PLA_2R antibody levels decline, fewer immune complexes are deposited in the subepithelium. Over time and with complete disease remission, the subepithelial deposits disappear altogether allowing podocytes to heal and regain their normal morphology and function. As already noted in (**a**), the decrease in circulating anti-PLA_2R levels precedes the decline in proteinuria and can serve as an earlier marker for disease remission (either partial or complete)

membrane known as Fx1A. After a few weeks, the rats developed clinical and pathologic features of MN that were nearly identical to those in humans. At that time, it was believed that antibodies to the antigenic Fx1A fraction formed circulating immune complexes (CIC) that deposited in the subepithelial space of the GBM and subsequently led to MN. A passive model, in which antibodies were raised in a sheep to the Fx1A fraction and then injected into the rat, also produced disease albeit with a much more rapid onset. It was still assumed that the passively transferred antibodies were reacting with native antigen to form CIC that lodged in the glomerulus in a subepithelial position. It was not until two groups independently studied the phenomenon in an ex vivo perfused rat kidney system that an alternative to CIC was proposed. When these isolated rat kidneys were perfused ex vivo with anti-Fx1A in a system that did not allow any recirculation of potential CIC, small subepithelial deposits and other histopathological features of MN were nonetheless formed (Couser et al. 1978; VanDamme et al. 1978). These important experiments essentially refuted the CIC model and instead suggested that there was an intrinsic antigen within the glomerular filtration barrier and that antibodies were targeting it in situ to form the subepithelial deposits.

The major antigen present in the tubular brush border fraction Fx1A as well as in the rat glomerulus was ultimately identified as the large membrane glycoprotein megalin (Kerjaschki and Farquhar 1982; Makker and Singh 1984). Subsequent studies could induce a Heymann nephritis-like picture with antibodies raised against megalin alone (Yamazaki et al. 1998), confirming it as the major antigenic determinant. Megalin, an endocytic receptor largely known for its role in low molecular weight protein uptake by the tubular brush border, shares some features with the other podocyte antigens that would be later found to be the targets in human disease. It is a transmembrane protein with a large, multi-domain extracellular region, expressed at the basal surface of the podocyte.

While the discovery of megalin was the first important step to understanding that MN could be caused by an intrinsic antigen located within the podocytes of Lewis rats, it also posed a new problem: megalin was neither expressed in the subepithelial deposits of patients with MN nor was there any evidence of anti-megalin antibodies in their serum. Thus began the search for the human equivalent of megalin.

The first major breakthrough occurred in 2002 when Debiec and colleagues described a baby boy with oliguria and massive proteinuria (Debiec et al. 2002). A kidney biopsy revealed pathology consistent with MN. Since the infant was too young to have formed antibodies of his own, it was postulated that the mother had passed antibodies to her fetus in utero which then led to his proteinuria at birth. A comprehensive investigation revealed that both mother and the neonate possessed antibodies to neutral endopeptidase (NEP), a protein found in human podocytes. The mother was genetically deficient for this protein (which explained why she herself had not developed the nephrotic syndrome despite high titers of circulating anti-NEP antibody) and had been previously sensitized to NEP during a prior miscarriage. These anti-NEP alloantibodies were transferred to her fetus upon her subsequent pregnancy and targeted NEP on the fetal podocytes, which was present by virtue of the paternal gene. Fortunately for the infant, the maternal antibodies existed only transiently in his circulatory system, and upon their elimination, his nephrotic syndrome resolved. This case served as the first proof of concept that an intrinsic podocyte antigen could serve as the target for the formation of in situ immune complexes in humans. Several other cases of anti-NEP fetomaternal alloimmune MN have been described by these European investigators (Debiec et al. 2004; Vivarelli et al. 2015).

It was not until 2009, 50 years after Walter Heymann's description of his experimental model of MN, that the first major autoantigen in human MN was identified (Beck et al. 2009). Many laboratories in the field had been using patient serum as a source of autoantibodies to probe mixtures of glomerular proteins by Western blotting, but no consistent signals had previously been found. The standard technique for Western blot involves denaturing the protein with heat and

reducing agents prior to gel electrophoresis, to eliminate higher order secondary and tertiary structures. When Beck and colleagues left disulfide bonds intact by omitting the reducing agent from the standard gel electrophoresis loading buffer, sera from MN patients, but not from controls, consistently recognized a high molecular weight 185 kDa band that had never been noted before. Partial purification and mass spectrometric analysis ultimately identified the antigenic band as the M-type phospholipase A_2 receptor (PLA_2R), and antibodies to this protein localized to the podocyte in normal human kidney. The autoantibodies to PLA_2R seemed to recognize a conformation-specific epitope or epitopes within the molecule that was dependent on the presence of disulfide bonds, thereby explaining why previous attempts to identify the protein using the standard Western blot technique had not detected this band (Truong and Seshan 2015).

In this landmark study, sera from 70% of patients with primary MN recognized both native (isolated from human glomeruli) and recombinant PLA_2R by Western blot, whereas no sera from healthy controls, patients with secondary causes of MN, or other glomerular or autoimmune diseases were reactive with PLA_2R (Beck et al. 2009). Moreover, only IgG eluted from biopsies from patients with primary MN recognized PLA_2R. The circulating anti-PLA_2R autoantibodies were predominantly of the IgG4 subclass, although smaller amounts of the other subclasses were present. Co-localization of the PLA_2R antigen and IgG4 was specific to cases of PLA_2R-associated primary MN. These initial findings were quite suggestive that the major antigen had been found. Confirmatory studies in other international cohorts (Debiec and Ronco 2011; Hoxha et al. 2012; Oh et al. 2013; Qin et al. 2011) were to follow, in addition to a genome-wide association study that implicated the gene for the antigen PLA_2R1 was genetically linked to the disease (Stanescu et al. 2011).

Studies in the following years would suggest that 80% of all patients with primary MN had PLA_2R-associated primary MN (defined by the presence of circulating anti-PLA_2R autoantibodies and/or a positive tissue stain for the PLA_2R antigen within immune deposits on kidney biopsy). What then was the target antigen in the remaining 20%? There were early hints of a non-PLA_2R-associated antigen associated with MN. An elderly patient with longstanding prostate cancer developed MN with deposits enriched for IgG4, blurring categorization of his disease as secondary or primary. Serum from this patient recognized another high molecular weight band in glomerular extracts that was clearly distinct from PLA_2R (Beck 2010). Over the years, similar cases accrued – some with apparent idiopathic disease, but others with known malignancy – and a similar approach to that described above was used to identify this second potential antigen.

An international collaborative effort identified this second antigen as a protein known as thrombospondin type-1 domain-containing 7A (Tomas et al. 2014). The prevalence of antibodies to THSD7A is much less than that of anti-PLA_2R, being detected in approximately 10% of those MN patients who were seronegative for anti-PLA_2R, and representing only 3–5% of all cases of primary MN. Similar to PLA_2R, THSD7A was shown to be present on human podocytes (Godel et al. 2015; Tomas et al. 2014) in the native state. In disease (but only in THSD7A-associated cases), human IgG4 could be shown to co-localize with the antigen THSD7A within immune deposits. IgG eluted from the biopsies of these cases recognized THSD7A but not PLA_2R. Similar to the case with PLA_2R, human autoantibodies only recognized the protein on Western blot when disulfide bonds were left intact.

Several interesting features have emerged since the first description of THSD7A as the second autoantigen in MN. First, there have been two reported cases (Larsen et al. 2016) in which an individual patient harbors circulating antibodies to both PLA_2R and THSD7A. The true prevalence of such dual positive cases is not fully known at this point but appears to be rare since no other dual positive cases were found in another study (Hoxha et al. 2016a). Second, there seems to be an association with malignancy for THSD7A-associated MN, more so than would be expected by chance. On two occasions, in a patient with THSD7A-associated MN, a contemporaneous malignancy

(or a recurrence thereof) was found that exhibited polysomy for chromosome 7 and overexpressed THSD7A (Hoxha et al. 2016a, b). The follicular dendritic cells of the draining lymph node were also shown to have taken up THSD7A, most likely from the tumor, and thus, this may have been the mechanism by which tolerance was breached, and the antigen was effectively presented to the host immune system. The implications of these findings are far from clear but may suggest that a patient who is found to have THSD7A-associated MN needs a comprehensive evaluation for occult malignancy.

NEP, PLA_2R, and THSD7A are all examples of intrinsic, podocyte-expressed antigens that incite a humoral immune response and cause the in situ deposition of antibody-antigen immune complexes. There is also evidence that the humoral immune response may spread to target other molecules expressed by the podocyte. One study showed that, although anti-PLA_2R antibodies were the most prevalent in a cohort of Italian patients with MN, a proportion of patients also had circulating antibodies to alpha-enolase, Mn-type superoxide dismutase, aldose reductase, and neutral endopeptidase (Murtas et al. 2012). Several of these proteins are intracellular proteins and are expressed at relatively low levels by the healthy podocyte. The authors of this study provide evidence that they are induced by injury and expressed at the cell surface, thus becoming neoepitopes. It is hypothesized that these additional antigenic targets may worsen and/or sustain disease, although clinical evidence for this is limited, and longitudinal studies looking at these autoantibodies are needed. A recent study shows that antibodies to alpha-enolase are found in a large proportion of patients with primary, PLA_2R-associated disease, but the antigen itself was not found in the deposits (as opposed to PLA_2R, which was detected) (Kimura et al. 2016).

Genetics

Shortly after the discovery of PLA_2R and the report that anti-PLA_2R autoantibodies were conformation sensitive (i.e., that anti-PLA_2R no longer recognized the protein when disulfide bonds were absent), several groups searched for a genetic mutation that might predispose individuals to primary MN. Initially, interest focused on the possibility that single nucleotide polymorphisms (SNPs) within the *PLA2R1* gene might explain the target antigen's conformational dependence and be the underlying cause of primary MN (Kim et al. 2010; Liu et al. 2010). Several nonsynonymous SNPs (i.e., those coding for an alternative amino acid) were found to have a statistically significant association with MN as opposed to non-disease controls. In an unbiased, genome-wide association study (GWAS) approach, two SNPs, one within the *PLA2R1* gene on chromosome 2 and another within the *HLA-DQA1* gene on chromosome 6, were found to be independently associated with primary MN in a combined European (and thus Caucasian) cohort from England, France, and the Netherlands (Stanescu et al. 2011). More importantly, those homozygous for both risk alleles were 80 times more likely to have MN than controls. The most significant SNP found by GWAS was intronic; however, it was in strong linkage disequilibrium with a nearby nonsynonymous SNP, still keeping alive the possibility of a conformational mutation that predisposed to MN. Coenen and colleagues directly addressed the possibility by performing sequencing of all 30 *PLA2R1* exons and splice sites in 95 patients with idiopathic MN, most of whom were known to have PLA_2R-associated disease (Coenen et al. 2013). Their conclusion was that there were no specific coding mutations that associated with disease; patients could still have the native "consensus" PLA_2R sequence and still develop disease. Since these initial findings, it has become increasingly clear that no single genetic mutation confers primary MN upon an individual. Instead, disease likely occurs in a trigger-and-target model, similar to what has been described in other autoimmune conditions. In the case of primary MN, the "trigger," a genetic variation within the HLA locus (HLA-DQA1) may confer susceptibility to autoimmune disease. The "target," a SNP mutation within the *PLA2R1* gene, might lead to a subtle conformational change in the antigenic protein that allows it to better fit in the

HLA class II molecule peptide-binding groove and thus be presented more efficiently to the immune system. These two occurrences, in addition to other environmental "hits" (such as molecular mimicry due to infection with an organism that expresses an epitope similar to that in PLA_2R) that may accumulate throughout a person's lifetime, are likely what increase a person's risk for primary MN with increasing age (Salant 2013).

The identification of a class II MHC molecule and a target antigen as important loci in a GWAS screen is not unique to MN. A subset of ANCA vasculitis has also recently been mapped to the HLA-DP locus as well as to *SERPINA1* and to *PRTN3*, the gene for the autoantigen proteinase 3 (Lyons et al. 2012). It is likely that genetic information from the antigen (e.g., the exact amino acid sequence and proteolytic cleavage sites, promoter and enhancer regions that regulate expression level which may in turn affect stability and quality control of synthesis), as well as from the precise genetically inherited class II MHC molecule that would best be able to present the antigen, would both contribute to genetic risk. Risk has been mapped to specific amino acids within the peptide-binding groove of MHC class II molecules for type I diabetes mellitus and rheumatoid arthritis (Han et al. 2014; Hu et al. 2015), and similar work is being done for primary MN by investigators in Beijing, China. Such work points to a close interaction between the peptide-binding groove of the inherited class II MHC molecule and the antigen itself.

Pathogenesis

MN in all its forms is marked by the presence of subepithelial immune deposits, but how do these deposits lead to the severe podocyte injury and foot process effacement that is typical of the disease? A wealth of studies in the Heymann nephritis model suggest that complement mediated cytotoxicity is a major mediator of podocyte cell injury. Whereas the complement-fixing gamma1 fraction of anti-Fx1a can cause experimental MN in the passive Heymann nephritis model, administration of the non-complement-fixing gamma2 fraction does not cause proteinuria, despite formation of subepithelial deposits (Salant et al. 1980). In a similar manner, depletion of complement components with cobra venom factor, or using rats depleted of one of the terminal complement components (C6), the deposits form in the appropriate location but fail to induce cellular injury (Baker et al. 1989; Salant et al. 1980).

In this paradigm, immune complexes of antigen and complement-fixing antibodies locally activate the complement system in the subepithelial space, via the classical complement pathway (CP). Given the absence of inflammatory cell recruitment to the glomerulus, seen both in Heymann nephritis and in human MN, it is assumed that the liberation of the anaphylatoxins C3a and C5a occurs far enough away from the capillary lumen to be inconsequential. However, the generation of C5b, fueled by an ongoing influx of complement components from the glomerular capillary blood supply, leads to the assembly of the terminal complement factors C5b-9 to form the membrane attack complex. The insertion of C5b-9 into nearby lipid bilayers (i.e., the basal surface of the podocyte foot process) leads to calcium influx into the podocyte and the activation of many maladaptive intracellular signaling pathways. The precise mechanisms that have been identified in in vivo and in vitro studies in Heymann nephritis are beyond the scope of this review, but the interested reader can find excellent reviews of this topic (Cybulsky et al. 2005; Ma et al. 2013). The ongoing sublethal injury to the podocyte results in a more dedifferentiated state with retraction of the foot processes and loss of slit diaphragms. The protein-rich plasma that has filtered through the GBM is no longer restricted by slit diaphragm and instead flows between podocyte cell-cell junctions and causes nonselective loss of proteins into the urine.

Many findings in human disease also support a major role for complement. Complement factor 3 (C3) is invariably present within immune deposits. Although most renal pathologists do not stain for complement factor 4 (C4), it also tends to be present within immune deposits (Espinosa-Hernandez et al. 2012; Kusunoki et al. 1989; Val-Bernal et al. 2011). Several studies have stained for the C5b-9

MAC and shown that it is present in the vicinity of deposits, as well as in the urine of patients with MN. But why is there a relative absence of C1q, one of the initiating components of the classical pathway, in primary MN? As previously mentioned, the predominant circulating forms of both anti-PLA_2R and anti-THSD7A are IgG4, and IgG4 is the predominant subclass found within immune deposits of primary MN. Yet IgG4 is felt to be an inhibitory, non-complement-fixing IgG subclass. The precise role of IgG4 in terms of complement-mediated injury and/or other mechanisms of cytotoxicity is unresolved and is the subject of ongoing investigation.

Although secondary forms of MN, whose deposits are rich in complement-fixing IgG1 or IgG3 subclasses, may more easily activate the classical pathway and explain the presence of C1q in these forms, the precise pathway by which complement is activated in primary MN remains unresolved. Several hypotheses have been generated. The first implicates the classical pathway (CP), at least in the early phases of disease. If one uses the Ehrenreich-Churg stage of deposits as a marker of disease duration, it can be shown that early disease (with Stage I deposits) tends to have a relatively increased ratio of IgG1 to IgG4, as well as more C1q than is seen in more established disease (Huang et al. 2013). This might suggest that IgG1 can activate the CP in early disease, which may be attenuated or sustained at a low level by the alternative pathway (AP) later in disease when the deposits shift to more IgG4. A second hypothesis is that IgG4 itself, perhaps due to age- or disease-associated changes in terminal sugar residues on glycans attached to the IgG4 molecule, can directly activate the lectin pathway (LP) of complement activation (Ma et al. 2013). An intriguing recent case series looks at this possibility. Several patients with PLA_2R-associated primary MN were shown to be genetically deficient in mannan-binding lectin (MBL), the initiator of the LP (Bally et al. 2016). While these patients still had disease that was clinically similar to those retaining MBL function, the notable difference in their biopsies was an absence of complement factor 4 (C4). This would suggest that the C4 that is usually seen in the immune deposits (Espinosa-Hernandez et al. 2012; Kusunoki et al. 1989; Val-Bernal et al. 2011) is generated not by the C1qrs complex of the CP but rather as a result of the MBL/MASP complex of the LP. However, the presence of disease in the MBL-deficient patients, without C1q (a specific marker of the CP) or C4 (a marker of both the CP and LP) suggests that in some cases, the AP alone may be sufficient to cause disease (Bally et al. 2016). Further studies relating ratios of autoantibody subclasses to the particular complement activation pathways are necessary, in hopes that the complement activation system can be therapeutically targeted in the future.

It is essential to appreciate that the resolution phase of MN is slow and protracted. This is in stark contrast to minimal change disease, which in response to corticosteroid therapy and as yet undefined changes to soluble immune factors, the podocyte morphology can rapidly become reestablished, slit diaphragms reformed, and proteinuria completely eliminated within days. Following immunological remission in MN, the immune deposits may stop growing in size, but they remain in place for months to years (Ruggenenti et al. 2008), significantly altering the structure of the GBM. The resolution of proteinuria is gradual, as evidenced by the cumulative increase in partial and then complete remissions that occur years out after spontaneous remission or after immunosuppressive treatment.

Histopathology

Recall that the term "membranous nephropathy" represents only a general histopathological descriptor. Many features may be common to both primary and secondary forms of disease, while others may be more suggestive of primary or secondary MN. Pathognomonic for MN are the subepithelial immune deposits, most apparent by immunofluorescence as a fine granular peripheral capillary loop staining pattern (Fig. 2), and on electron microscopy as homogeneous, electron-dense deposits that separate the podocyte from the GBM (Fig. 3).

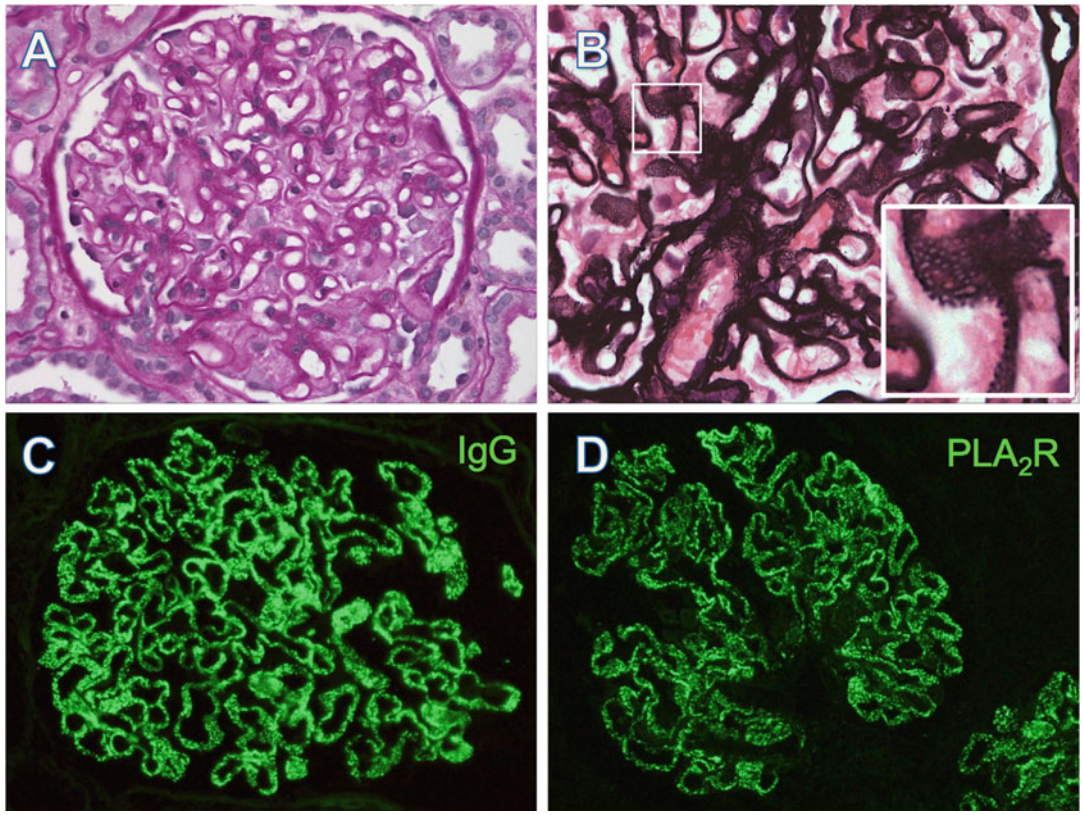

Fig. 2 *Representative pathologic images in primary membranous nephropathy.* (**a**) Periodic acid-Schiff (PAS) staining reveals extensive thickening of the GBM in the capillary loops, with normal cellularity; original image 40×. (**b**) The methenamine silver (Jones) stain highlights extracellular matrix material as black. Immune deposits, which do not stain with silver, appear as defects ("craters" or "pits") in the GBM (see *inset*). New matrix laid down between the deposits can be seen as "spikes" (*inset*). Original image 60×. (**c**) Immunofluorescence (IF) stain for IgG reveals the pathognomonic fine granular staining of the peripheral capillary loops; original image 20×. (**d**) IF staining for the PLA_2R antigen demonstrates a similar fine granular capillary loop staining pattern to that which is seen with IgG and C3 (not shown); original image 20× (All images courtesy of Dr. Joel Henderson, Boston University School of Medicine)

In the early stages of MN, the glomerulus may appear entirely normal on light microscopy. There are no inflammatory infiltrates and no thickening of the GBM. As immune complexes accumulate and grow in size, the podocyte secretes extra matrix material such that the GBM expands and grows around the immune deposits. With time, the capillary loops appear thickened and more prominent; it is this uniform thickening of the GBM, often assessed by periodic acid-Schiff (PAS) staining that gives MN its name (Fig. 2a). While the immune complexes are not well highlighted by the light microscopic PAS or hematoxylin-eosin (H&E) stains, the silver methenamine ("Jones") stain highlights GBM material but does not stain the immune complexes, allowing for visualization of the GBM spikes that have formed between and around the deposits (Fig. 2b and inset). In more tangential sections of the GBM in a case of advanced MN, pits or craters (representing the unstained deposits) may be readily evident amongst the more heavily silver stained GBM material. Inflammatory or proliferative features such as increased cellularity, presence of inflammatory cells, or mesangial proliferation are absent in MN.

Immunofluorescence (IF) microscopy offers the ability to stain the immune deposits for any

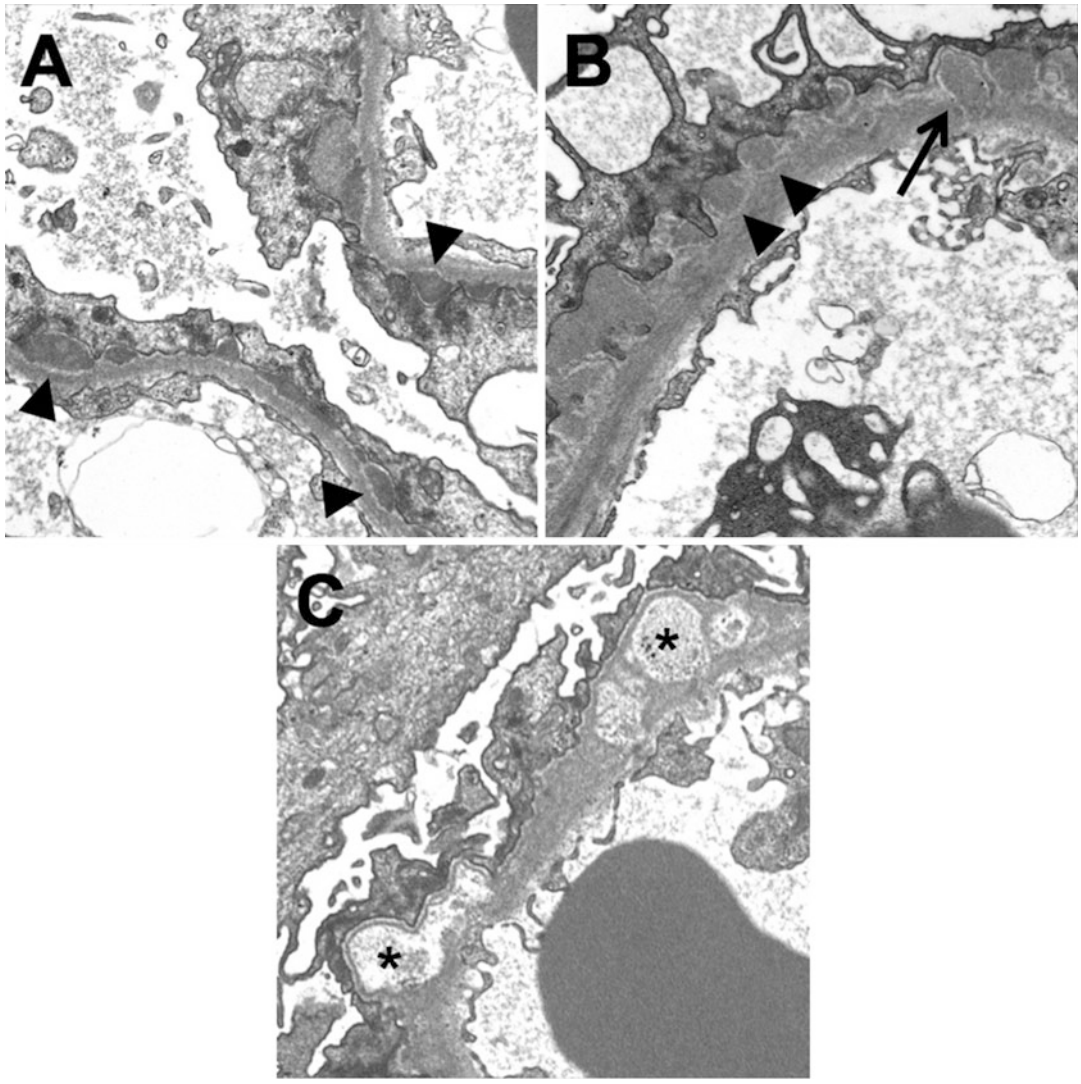

Fig. 3 *Examples of the Ehrenreich-Churg electron microscopic stages of membranous nephropathy.* All images show evidence of current or prior immune deposits on the subepithelial side of the glomerular basement membrane, directly beneath the basal surface of the podocyte. (**a**) Electron-dense Ehrenreich-Churg Stage I deposits (*arrowheads*) form beneath the podocyte but do not yet have evidence of any deposition of additional matrix material around them. (**b**) Stage II deposits (*double arrowheads*) show evidence of matrix material deposited between the immune deposits. This extra matrix material corresponds to the "spikes" seen on silver stain (Fig. 2b). Stage III deposits (*arrow*) are completely surrounded by extracellular matrix. Note the thin layer of matrix immediately below the podocyte that has surrounded the deposit. (**c**) Stage IV deposits (*asterisks*) are electron-lucent and represent deposits from previous disease that have been partially or completely resorbed. They can coexist with more active deposits if the disease has relapsed soon after a previous episode of disease (Images courtesy of Dr. Joel Henderson, Boston University School of Medicine)

molecular constituent that may lie within. Using the traditional stains, IF microscopy demonstrates diffuse staining of the immune deposits with IgG (see Fig. 2c), C3 complement, and kappa and lambda light chains of roughly equal intensity. Significant IgA, IgM, or C1q in the deposits is uncommon in primary MN, although mild mesangial staining for IgM is not uncommon.

The pathognomonic pattern is a granular or beaded appearance along the peripheral capillary walls that, depending on the size and multitude of immune complexes, can almost appear linear. Although not commonly used as a reagent in native biopsies, C4d is becoming another marker that can reliably be used to differentiate MN from other nephrotic diseases (Espinosa-Hernandez et al. 2012; Hui et al. 2014; Kusunoki et al. 1989; Val-Bernal et al. 2011). In many cases, C4d will mirror the staining pattern for C3. Exceptions include cases of MN in patients with a genetic deficiency of mannan-binding lectin (MBL), in which case C4 staining is notably reduced (Bally et al. 2016). Staining with IgA, IgM, or C1q complement should be absent in primary MN and if present, should prompt evaluation of secondary MN or a separate cause altogether. With the identification of the two autoantigens in primary MN, more and more renal pathologists are also including a stain for PLA_2R and/or THSD7A (Fig. 2d). Finding of either antigen within the deposits (co-localized with IgG and complement) as opposed to its usual location in the normal glomerulus can define a case as either PLA_2R- or THSD7A-associated MN. There are also several centers that routinely stain MN biopsies for the individual IgG subclasses. As noted above, IgG4 is the predominant IgG subclass in primary MN, and subepithelial deposits will stain accordingly, although IgG1 positivity may also be seen early in the disease course.

The predominant electron microscopic feature in MN are the multiple electron-dense deposits, representative of the immune complex deposits, that form in the subepithelial space just adjacent to the cell membrane of the foot process or basal surface of the podocyte. With time, surrounding these immune complex deposits will be the "spikes" of GBM material that are laid down around the deposits. The Ehrenreich-Churg staging system is often used to describe the degree of GBM reaction around the deposits (see Fig. 3). In Stage I, the subepithelial dense deposits are small and there is no surrounding GBM reaction. In Stage II, there is early GBM reaction up the sides of the now medium-sized subepithelial dense deposits which gives rise to the "spike" appearance on EM. At this point, there is also effacement of the podocyte foot processes. Stage III is notable for subepithelial dense deposits that have been completely surrounded by the GBM (also called "intramembranous"). At this point, the capillary walls appear diffusely thickened. In Stage IV, the deposits, usually fully surrounded by GBM, have started to be resorbed, leaving more electron-lucent areas in their place. Other commonly noted features on EM, although not specific for MN, are those of podocyte injury: widespread effacement of the foot processes with near-complete loss of slit diaphragms, as well as innumerable thin membrane extensions on the apical surface of the cell ("microvillous change") and vacuolization of the podocyte.

Despite the common findings of IgG and C3 in a peripheral capillary loop pattern by IF and the presence of electron-dense subepithelial deposits by EM, there are important pathologic distinctions between primary and secondary MN (see Table 1). By LM, any mesangial or endocapillary proliferative features should raise suspicion for a secondary cause of MN, particularly associated with an autoimmune disease. There has also been a suggestion that the presence of >8 infiltrating inflammatory cells per glomerulus is a sign of malignancy-associated MN (Lefaucheur et al. 2006), although this finding has not been since validated. The presence of all five components usually tested by IF (IgG, IgA, IgM, C3, and C1q) has been called a "full-house" staining pattern, and its presence is suggestive of a systemic autoimmune disease such as lupus. As mentioned above, although staining for the four IgG subclasses is not routine practice, it is used by several renal pathology centers to provide added information as to the presence of primary or secondary disease. While a predominance (or codominance) of the IgG4 subclass within the immune deposits is suggestive of primary disease (Doi et al. 1984; Kuroki et al. 2002), dominance of IgG1, IgG2, or IgG3 may often suggest secondary disease, especially class V lupus nephritis or malignancy-associated MN (Noël et al. 1988; Ohtani et al. 2004; Qu et al. 2012). The caveat is that very early primary and/or PLA_2R-associated MN may be associated with predominance of the IgG1 subclass (Huang et al. 2013).

Table 1 Histopathologic features of Primary versus Secondary Membranous Nephropathy

	Primary	Secondary
Light microscopy	Thickened capillary walls	Thickened capillary walls
	GBM thickening with "spikes"	GBM thickening with "spikes"
	Absence of proliferative features	Proliferative features Mesangial proliferation Endocapillary proliferation
Immunofluorescence	Diffuse and granular staining of capillary walls	Diffuse and granular staining of capillary walls
	(+) IgG staining with IgG4 predominance	(+) IgG1, IgG2, and IgG3 predominance
	(+) C3, kappa and lambda light chain staining	(+) C3, kappa and lambda light chain staining
	Minimal IgM, IgA, C1q staining	(+) IgM, IgA, or C1q staining
Electron microscopy	Multiple electron-dense subepithelial immune deposits separated by GBM "spikes"	Subepithelial deposits, plus: Mesangial deposits Subendothelial deposits
	Podocyte foot process effacement	Podocyte foot process effacement

EM can also provide a number of clues that would point towards a secondary etiology of MN. The electron-dense deposits of primary MN are typically subepithelial, paramesangial (at the junction where the capillary loop reflects away from the mesangium), or – if the disease has been ongoing for some time – intramembranous. The presence of subendothelial or true mesangial deposits is quite suggestive of a secondary etiology, and a systemic autoimmune disease (e.g., lupus) with circulating immune complexes should be considered. The presence of tubuloreticular inclusions in glomerular capillary endothelial cells is a sign of the interferon gamma response and can be seen in lupus and with viral etiologies of MN.

Diagnosis

The diagnosis of MN should be considered in any individual, regardless of age, who presents with the subacute development of edema and proteinuria. Although many patients will have nephrotic-range proteinuria at diagnosis, those caught earlier (or significantly later) in the disease course may be sub-nephrotic. We should also point out that with prolonged severe nephrotic syndrome, serum albumin and total protein levels may be so low that "nephrotic" (e.g., >3.5 g/d) levels of proteinuria may no longer be attainable. Although MN is not limited to any particular age group or race, the development of nephrotic syndrome in a Caucasian male in his 50s, without other systemic disease, would be typical of a diagnosis of MN. The presence of renal vein thrombosis caused by otherwise unexplained nephrotic syndrome should also raise the question of MN.

Traditionally, the diagnosis of MN was made histologically by kidney biopsy and involved exclusion of secondary causes of MN. With the discovery of circulating antibodies to PLA_2R and/or THSD7A, some have raised the question of whether serological testing alone is sufficient for the diagnosis (Hofstra and Wetzels 2014). A serological diagnosis of MN may be important in situations in which the risk of kidney biopsy is particularly high, such as when a patient with nephrotic syndrome has already been placed on anticoagulation for a VTE or in the patient with a solitary kidney. The 2012 KDIGO Clinical Practice Guidelines on Glomerulonephritis (KDIGO 2012) comment on the clinical potential of using anti-PLA_2R antibodies to diagnose primary MN; however, they were published shortly after the discovery of PLA_2R target antigen and only months after the first

commercial anti-PLA_2R antibodies became available. In other words, there was insufficient scientific mass to purport their use in clinical guidelines.

Since that time, numerous studies have confirmed both the sensitivity and specificity of anti-PLA_2R antibodies in diagnosing primary MN. A meta-analysis of 2,212 patients determined that the sensitivity and specificity of testing with serum anti-PLA_2R antibodies was 78% and 99%, respectively (Du et al. 2014). While the higher specificity sacrifices sensitivity, it reduces the likelihood of false positive testing. It should also be noted that the sensitivity of testing is never expected to be much above 80%, since this number reflects the proportion of primary MN that is PLA_2R associated. It is important to note that there are certain clinical instances where patients with secondary MN test positive for anti-PLA_2R. While these instances are certainly the exception, it has been noted in patients with hepatitis B and C infection, sarcoidosis, and certain neoplasms (Dong et al. 2016; Knehtl et al. 2011; Larsen et al. 2013; Nawaz et al. 2013; Svobodova et al. 2012; Xie et al. 2015). Recall however that there is no practical way to distinguish a coincidental association from causation and that many of these anti-PLA_2R positive cases may truly have primary disease in coincidental association with other positive serologies or infection. From a clinical perspective, it is most important to keep in mind that anti-PLA_2R antibody tests have never been positive amongst patients with other types of proteinuric kidney disease. In other words, if a patient with the nephrotic syndrome tests positive for anti-PLA_2R antibodies, the clinical diagnosis is MN and is most likely primary.

It should be noted that there are at least three circumstances in which a patient might test negative for circulating anti-PLA_2R antibodies despite a biopsy-confirmed diagnosis of MN. The first would be in cases in which the target antigen is a protein other than PLA_2R (THSD7A-associated disease, truly idiopathic primary MN, or secondary MN). Other serological tests, such as anti-THSD7A when commercially available, ANA, or viral serologies, may be helpful in this situation. The other situations relate to the relationship between immunological and clinical course of PLA_2R-associated MN. At the very onset of disease, circulating anti-PLA_2R antibodies may be so low that they are undetectable using current assays (Ramachandran et al. 2015; van de Logt et al. 2015). In this instance, the low levels of autoantibodies produced by the humoral immune system are quickly adsorbed by the abundant PLA_2R protein in the glomerulus, such that only negligible amounts of antibody are left in the serum. The second situation in which anti-PLA_2R may not be detected despite the presence of proteinuria is a more common situation. This occurs when circulating autoantibodies have already declined and disappeared (immunologic remission) but before proteinuria has resolved.

For many of the reasons mentioned above, kidney biopsy still plays an important role in the diagnosis of primary MN. In addition to diagnosis, the kidney biopsy can provide important information about the extent of chronic damage that may already be present and thus can help to guide therapy. In cases of biopsy-proven MN, staining the tissue for PLA_2R or THSD7A can help subclassify the type of MN, even when circulating antibodies are not detectable. Nevertheless, given that validated anti-PLA_2R antibodies are now commercially available, perhaps fewer patients will require an invasive procedure to confirm diagnosis. We anticipate that the next set of guidelines on MN will more confidently address the use of antibody testing in diagnosis.

Management and Treatment

Initial management and definitive treatment is necessary to lower levels of proteinuria and reduce immediate risks from the nephrotic state and longer term risk of declining renal function. The definitive treatment of primary versus secondary MN differs. Treatment of secondary MN is theoretically simple as it involves either removal of the causative agent (toxins, malignancy) or treatment of the underlying systemic process (infections, systemic autoimmune disease). This is more thoroughly discussed in

▶ Chap. 23, "Secondary Membranous Glomerulonephritis." In primary disease, the target antigen is a normal component of the podocyte, so treatment needs to be directed at controlling or stopping the autoimmune process. The general treatment strategy for primary MN is summarized below. For a more comprehensive review on the nuances of treatment, we direct readers to several excellent recent reviews on the topic (Chen et al. 2014; Hofstra et al. 2013; KDIGO 2012; Waldman and Austin 2012).

There are several considerations in terms of treatment. The ultimate goal is to have the patient enter an immunologic remission, either spontaneously or induced by immunosuppression. Historically, it was difficult to predict who might attain a spontaneous remission, so a "wait-and-see" period is often instituted; during which, the patient is treated with optimized doses of conservative therapy (see below). A more immediate goal is to lower the amount of daily proteinuria to a level that does not pose excessive risk of renal deterioration.

To date, only one validated algorithm exists that can be used to assess risk of renal decline in patients with primary MN (Cattran et al. 1997; Pei et al. 1992). The predictive model takes into account the creatinine clearance (CrCl) at diagnosis, the rate of change of CrCl over 6 months, and time-averaged proteinuria over 6 months. The model correctly identifies risk of progression in 85–90% of patients and categorizes patients into low-, medium-, or high-risk groups for disease progression. Those considered low risk for progression have a normal CrCl at diagnosis, stable renal function over the first 6 months, and proteinuria <4 g/d; long-term renal outcome in these patients is excellent. Patients at medium risk for progression also present with normal CrCl and have stable renal function over the first 6 months; however, they average between 4 and 8 g/d proteinuria. These patients were 50–55% likely to progress to CKD within the first 10 years of diagnosis. The group at highest risk for progression had proteinuria of >8 g/d and regardless of their renal function, had a 65–80% probability of progressing to advanced CKD over 10 years.

Supported by the above findings, the KDIGO GN Guidelines recommend delaying treatment in low-risk patients for a minimum of 6 months to observe for spontaneous remission. In those with >4 g/d proteinuria, a partial remission (defined by a 24 h urine protein amount of <3.5 g *and* a $\geq 50\%$ decrease in proteinuria from the peak value) confers substantial risk reduction, although complete remission (defined by a 24 h urine protein amount of <0.3 g) is preferred. As the decline in proteinuria is gradual, many patients will enter a partial remission before proceeding to a complete remission months to years later. The reason management focuses on reducing proteinuria is simple: patients who undergo treatment-induced or spontaneous remission have excellent long-term outcomes and a decreased risk of mortality and progression to ESKD (McQuarrie et al. 2012; Polanco et al. 2010).

This risk prediction model explains why KDIGO recommends an observation period of 6 months (as long as the patient has stable renal function and no severe consequences of the nephrotic syndrome); during which, supportive therapy should be optimized. Supportive therapy during these initial 6 months after diagnosis involves initiating either an ACEI or an ARB for the antiproteinuric effect. Surprisingly, there is little data to support this recommendation despite its widespread use. In fact, their use may lead to acute kidney injury in those with severe proteinuria so caution is advised with its initiation in this cohort (Hofstra et al. 2013). However, given their renal-protective record in other proteinuric diseases, they remain a mainstay of therapy in MN as demonstrated by the GISEN group (1997).

Patients with overt hypertension should start antihypertensive therapy, ideally with an ACEI or an ARB as noted above, but supplemented as needed with diuretics and/or other agents. Blood pressure should be targeted to 125/75. Further management includes sodium-restriction and diuretic therapy if edema persists. Hyperlipidemia in patients with persistent proteinuria is treated with a statin to reduce cardiovascular risk. This may be particularly important given the elevated risk of cardiovascular events noted in recent studies (Kanigicherla et al. 2016; Lee et al. 2016). As noted earlier, there is a 7% risk of a VTE in primary MN (Lionaki et al. 2012). Hypoalbuminemia was the

most significant independent predictor of VTE in patients with MN (clinical practice differs on this issue worldwide); an albumin level <2.8 g/dL carried the greatest risk (Lionaki). Anticoagulation is not routinely started in this patient population as the benefits of anticoagulation must be weighed against the risk of a significant bleed while at the same time taking into account the individual's risk factors, e.g., immobility, prior VTEs, a family history of VTE, low serum albumin level, or anticipated steroid initiation (Lee et al. 2014). Clearly, a patient who presents acutely with a VTE should receive anticoagulation at least until the nephrotic state resolves.

Patients presenting with sub-nephrotic-range proteinuria may ultimately progress to nephrotic-range proteinuria. These patients need to be monitored regularly and managed in accordance with the KDIGO chronic kidney disease (CKD) guidelines (Hofstra et al. 2013; KDIGO 2012).

Patients with proteinuria >4 g/d that remains >50% of the initial baseline value after 6 months of monitoring, severe symptoms of the nephrotic syndrome, or a rise in serum creatinine ≥30% within 6–12 months of diagnosis require initiation of immunosuppressant therapy (KDIGO 2012). The recommended initial choice of therapy is a 6-month course of oral and intravenous corticosteroids alternating with an oral alkylating agent (Ponticelli et al. 1984). This regimen is known colloquially as the "Ponticelli regimen." Although both cyclophosphamide and chlorambucil effectively preserve renal function and induce remission (Jha et al. 2007; Ponticelli et al. 1989, 1995), cyclophosphamide is the preferred agent given its reduced side effect profile (Ponticelli et al. 1998). Because time to remission is variable and cumulative doses of cyclophosphamide are associated with an increased risk of malignancy and infertility (Chen et al. 2014; van den Brand et al. 2014), clinicians are encouraged to resume supportive management for a minimum of 6 months following treatment with an alkylating agent unless kidney function is rapidly deteriorating (KDIGO GN). Adverse events are not insignificant (Chen et al. 2014). Consideration needs to be given to renal function in the elderly, prior treatment with alkylating agents, risk factors for bladder cancer, gonadal suppression, and potential complications from infection. Studies have shown that use of cyclophosphamide for the treatment of MN does increase the risk for future malignancies (van den Brand et al. 2014). Immunosuppression should be withheld from patients with active infection in most circumstances.

The benchmark for treatment efficacy was established by the landmark publications by Ponticelli and colleagues. In the initial study, 62 patients with normal renal function and nephrotic syndrome due to biopsy-proven MN were randomized to receive both steroids and chlorambucil in an alternating, monthly fashion or to a control group that received supportive care only. Recipients of the intervention achieved a higher rate of complete or partial remissions compared to controls, and whereas the intervention group maintained normal renal function after 2 years of follow-up, the control group experienced a significant decline (Ponticelli et al. 1984). A follow-up study of this cohort revealed that remission rates remained statistically significant between the two groups 10 years later, with 83% of treated patients having achieved remission versus only 38% in the control group (Ponticelli et al. 1995). Additionally, the intervention was associated with less nephrotic syndrome, a slower decline in renal function, and a lower likelihood of developing ESKD (8% in the treatment arm vs. 40% in the control arm) than with supportive care alone (Ponticelli et al. 1995). These differential rates of progressing to ESKD at 10 years were confirmed independently through studies in an Indian cohort of MN patients treated with a modified Ponticelli regimen (Jha et al. 2007). The findings using chlorambucil were later replicated by the Ponticelli group in a similar population using cyclophosphamide instead of chlorambucil, with long-term follow-up analysis again demonstrating higher rates of remission and dialysis-free survival in the cyclophosphamide group compared to controls (Ponticelli et al. 1998). As a result, and for the reasons noted above, cyclophosphamide became the alkylating agent of choice in the treatment of MN. It should be noted that although dialysis-free survival

10 years after receiving an alkylating agent was approximately 90%, it was ≥60% in the control groups. This once again sheds some light on the difficult decision facing physicians when it comes to the treatment of MN. Initiating all comers with MN on cyclophosphamide would unnecessarily expose many to a toxic medication they may not need. Again, this underscores the importance of careful consideration prior to the initiation of any immunosuppressant medication.

The KDIGO Glomerulonephritis Guidelines offer calcineurin inhibitors (CNI) as an alternative first-line immunosuppressive agent for MN patients who cannot tolerate or refuse treatment with alkylating agents (KDIGO 2012). The two calcineurin inhibitors (CNIs) used to treat MN are cyclosporine (often with low-dose oral corticosteroids) and tacrolimus, which has been given as monotherapy. The few, mostly uncontrolled, trials evaluating CNIs demonstrated effectiveness in inducing remission (Alexopoulos et al. 2006; Cattran et al. 1995, 2001,; Praga et al. 2007); however, they were associated with an increased risk of relapse upon CNI withdrawal (Caro et al. 2015). In one randomized controlled trial that compared tacrolimus plus steroids to oral cyclophosphamide plus steroids, rates of remission and relapse were comparable (Chen et al. 2010). However, long-term data of the effect of CNIs on renal endpoints are lacking when compared to alkylating agents. For this reason, KDIGO recommends their use as an alternative to alkylating agents in patients who cannot tolerate the latter treatment option. Their recommended use is for a minimum of 6 months and no more than 12 months, and dosing is based on regular monitoring drug levels with the aim of achieving therapeutic but not nephrotoxic levels. The mechanisms of action of CNI may explain the often rapid induction of partial remission, but the high relapse rate if treatment is not given for a sufficient duration. In one study, remissions increased from 60–78% to 84% at 6, 12, and 18 months, respectively However, 44% relapsed following treatment, often during or shortly after tapering off the CNI (Caro et al. 2015). Having achieved only a partial remission (vs. complete remission) or a short duration of taper were independently associated with relapse by multivariate analysis. CNI are known to have an acute vasoconstrictive effect (which adds to their potential to induce hypertension or cause a chronic ischemic nephropathy) that is likely responsible for their acute lowering of proteinuria. CNIs have also been shown to have a direct antiproteinuric effect on the podocyte, by stabilizing the cytoskeleton (Faul et al. 2008). However, as opposed to alkylating agents and rituximab (see next section), both of which have direct B cell effects and can acutely cause a decrease in autoantibody levels, CNI target T cells, so the effect on B cells and antibody production is indirect, likely through T regulatory cells.

Rituximab is a chimeric anti-CD20 monoclonal antibody that has already been used in observational studies for over a decade for the treatment of MN. However, since no head-to-head randomized controlled trial has been published to date comparing it to the recommended therapies above, it is not endorsed as first-line therapy by the KDIGO guidelines. Given that B cells play a critical role in the pathogenesis of MN, both as precursors of antibody-producing cells and antigen-presenting cells (Cravedi et al. 2014), it seems logical that targeted B cell therapy should play a more definitive role in the care of patients with primary MN. In fact, multiple cohort studies have demonstrated that rituximab decreases proteinuria and induces remission (Fervenza et al. 2008, 2010; Remuzzi et al. 2002; Ruggenenti et al. 2012) with one study attaining 80% remission 2 years after treatment (Fervenza et al. 2010). Remission rates were similar in patients that had previously failed other immunosuppressive regimens (Ruggenenti et al. 2012). Immunologic remission, that is a disappearance in anti-PLA_2R antibodies, occurred in nearly 70% of patients treated with rituximab (Beck et al. 2011). Importantly, relapse rates in the above studies were low. A recent randomized trial of rituximab added to optimal supportive therapy showed improvements at 6 months in albumin and reduction in anti-PLA_2R in the immunosuppressive treatment (rituximab arm) vs. control. In the observational follow-up period, rituximab treatment was independently associated with achieving remission (Dahan et al. 2016). Lastly, while rituximab is

certainly not an innocuous drug, it has a much better safety profile than either of the alkylating agents. The results of the Membranous Nephropathy Trial of Rituximab (MENTOR), the first randomized controlled trial comparing rituximab to cyclosporine, are eagerly anticipated as this study will provide clinicians with long-term data on remission outcomes, relapse rates, immunologic remission, and quality-of-life markers (Fervenza et al. 2015). Preliminary results, presented as an oral abstract, indicate that rituximab is non-inferior to cyclosporine in achieving remission in patients with membranous nephropathy, and is also associated with fewer relapses. The final results of the MENTOR study are still pending as of the publication of this chapter. Another ongoing trial (STARMEN) is comparing rituximab given at day 180 after 6 months of tacrolimus and prior to a 3-month taper with the Ponticelli regimen (Rojas-Rivera et al. 2015).

There have been several small studies investigating the use of the antimetabolite purine analog mycophenolate mofetil (MMF) as an immunosuppressive agent for primary MN. In initial studies, MMF with steroids was as effective as alkylating agents with steroids at improving renal function in primary MN patients at high risk for progression to CKD (Branten et al. 2007; Chan et al. 2007; Senthil Nayagam et al. 2008). However, they were associated with higher rates of disease relapse and are not recommended for use by KDIGO (Hofstra et al. 2013; KDIGO 2012). Monotherapy with MMF is not effective; if MMF is to be tried as a second-line agent, it should be used in conjunction with corticosteroids.

Adrenocorticotropic hormone (ACTH) was used decades ago for treatment of the nephrotic syndrome (in fact, it is the only FDA-approved immunosuppressive treatment for this purpose), and several more recent observational studies show evidence for an effect in MN. Its mechanism of action seems to be more than merely stimulating corticosteroid secretion from the adrenal gland, especially as it is well known that corticosteroid monotherapy for MN is ineffective. Smaller peptide fragments of the 39 amino acid ACTH molecule (such as the 13 amino acid peptide alpha-melanocyte-stimulating hormone) are known to have immunomodulatory properties and may underlie the action of MSH (Gong 2014). There are also reports of a direct action of ACTH and/or its proteolytic fragments on podocytes. A European trial using a synthetic 24 amino acid analog of ACTH (not available in the USA) showed comparable efficacy to the Ponticelli regimen in a small randomized controlled trial of primary MN (Ponticelli et al. 2006). Several observational studies with the purified ACTH product available in the USA showed evidence of a beneficial effect in reducing proteinuria and inducing remission when used as salvage therapy in patients that had previously failed other immunosuppressive regimens (Bomback et al. 2012). Longer-term data on relapse rates and other renal endpoints are lacking. A recent study also shows evidence of clinical and immunological efficacy in treatment-naïve patients (Hladunewich et al. 2014). Due to a very significant cost with limited data about efficacy, ACTH is not recommended as a first-line agent but could be tried for refractory MN, as its mechanism of action may be different from other more standard agents.

Despite the number of distinct immunosuppressive options available for the treatment of primary MN, there are patients that fail to respond to one or more therapies. Failure to achieve remission with adequate doses and duration of one regimen should prompt switching to an agent of another class. For those patients with severe nephrotic syndrome refractory to conventional treatments, one group has shown success of a salvage regimen involving plasma exchange, intravenous immunoglobulin (IVIG) and rituximab, with 9 of 10 of these high-risk patients achieving partial remission (Muller-Deile et al. 2015). There is a case report of a single patient "refractory" to 6 months of ACE inhibition and corticosteroids who responded to a single dose of the proteasome inhibitor bortezomib (Hartono et al. 2014). Future therapeutic agents in primary MN should target the conformation-dependent epitope of PLA_2R as this would effectively prevent immune complex formation altogether. Alternatively, complement

antagonists disrupting the formation of MAC and its subsequent damage of the podocyte membrane may also play a role in future therapies.

Role of PLA_2R in Management

The field of MN is currently in transition, as nephrologists and investigators learn how to apply the knowledge about the autoantibody and autoantigen biomarkers to diagnosis and monitoring. Therapeutic trials and clinical recommendations have been based entirely on clinical parameters (largely proteinuria-based) in terms of achieving remission. Although limited evidence about anti-PLA_2R levels and their association with clinical activity was present at the time of the 2012 KDIGO Glomerulonephritis Guidelines, the body of data was insufficient at that time to recommend their routine use. In the intervening years, the level of evidence has rapidly increased, to the point where the ongoing trials in MN have all incorporated measurement of anti-PLA_2R (Dahan et al. 2016; Fervenza et al. 2015; Rojas-Rivera et al. 2015).

It has been known for some time that anti-PLA_2R antibody levels correlate with clinical status as defined by proteinuria, being readily detectable at the time of clinically evident nephrotic syndrome, or at relapse of disease, but being absent in remission (Hofstra et al. 2011). Such designations are "snapshots" in the temporal course of disease and oversimplify the dynamic relationship between circulating autoantibody levels and clinical parameters. This lag time between and dissociation of changes in antibodies and changes in proteinuria was also known relatively early (Beck et al. 2011; Beck and Salant 2010) (see Fig. 1). Early studies were mixed about whether levels of anti-PLA_2R associated with the amount of proteinuria, with some studies finding a positive correlation (Hofstra et al. 2011, 2012), but others not. This is understandable: if a cohort is composed of patients all within the same phase of disease (i.e., at the onset of disease with increasing levels of proteinuria), then titer and proteinuria may show a positive correlation. If the cohort is more heterogeneous, with patients both at the onset of disease and also entering remission, the same level of proteinuria may be associated with very different anti-PLA_2R titers (which would also have different trajectories).

Although serial measurements of circulating autoantibodies would be optimal, some studies have had success in showing that baseline levels are associated with clinical outcome. In an overall population of primary MN, low baseline levels at study entry have been associated with subsequent remission (Hofstra et al. 2012; Timmermans et al. 2015). This is hypothetically due to the fact that due to the slow onset of initial disease and a relatively late clinical discovery of symptoms, investigators are not likely to find many patients in early disease (when low levels might herald a longer duration of disease). In fact there are only scattered case reports of patients with unmeasurable circulating levels of anti-PLA_2R that go on to "seroconvert" later in the disease process (Ramachandran et al. 2015; van de Logt et al. 2015). Another subpopulation of primary MN patients that might be more expected to have early disease are those with sub-nephrotic proteinuria. In these sub-nephrotic patients, those with higher levels of anti-PLA_2R seropositivity had faster onset of nephrotic proteinuria than those who were anti-PLA_2R negative and conceptually could have been closer to the end of their disease course (Hoxha et al. 2014a).

Alternatively, low anti-PLA_2R levels may reflect resolving disease and thus may herald spontaneous remission. In several studies, patients who experienced spontaneous remission had significantly lower baseline levels of anti-PLA_2R antibody than those who did not. The importance of these findings is clear when one considers that immunosuppressive treatment might be avoided in patients with a higher likelihood of spontaneous disease remission. The opposite finding also holds true; those with higher anti-PLA_2R levels were less likely to have spontaneous remission of their disease and were more likely to experience a decline in their renal function during follow-up (Hofstra et al. 2012; Hoxha et al. 2014b; Kanigicherla et al. 2013). Application of these studies suggests that patients with

higher titers of anti-PLA_2R might be less likely to experience spontaneous remission of their disease and may thus benefit from treatment initiation. As a result of these studies, PLA_2R antibody levels are now known to be an independent risk factor for achieving remission as defined by proteinuria (Hoxha et al. 2014b). Two studies looking at treatment of MN with rituximab have also shown that low-to-moderate levels of anti-PLA_2R are independently associated with attainment of remission (Dahan et al. 2016; Ruggenenti et al. 2015).

A single measurement of anti-PLA_2R (or anti-THSD7A) is not as informative as serial measurements, which can assess whether the circulating autoantibodies are increasing, stable, or declining. Note that a negative level in the presence of positive tissue stain may also require serial testing, due to the rare findings of patients who seroconvert from negative to positive in very early disease. Decreasing autoantibody levels, either spontaneously or in response to treatment, are strongly associated with a subsequent remission (Bech et al. 2014; Beck et al. 2011; Hoxha et al. 2014b; Medrano et al. 2015; Radice et al. 2016; Ruggenenti et al. 2015). Therefore, if a patient is noted to have spontaneously falling titers during while only receiving supportive (non-immunosuppressive) therapy, it may be worthwhile to follow closely and not initiate immunosuppression, which carries its own inherent risks.

Perhaps just as important is assessment of anti-PLA_2R levels at the completion of immunosuppressive therapy. Seroconversion from anti-PLA_2R positive to negative at the end of treatment was associated with a good chance of remaining in remission over a follow-up course of 5 years (Bech et al. 2014). On the other hand, in this study, all of the patients who were still anti-PLA_2R positive at the end of immunosuppressive treatment relapsed within several years. Less than a 50% reduction in anti-PLA_2R at 6 months following rituximab was associated with no response to treatment (Ruggenenti et al. 2015), and reemergence (or an increase in titer for those whose autoantibody levels did not completely disappear) was associated with a rapid clinical relapse.

All of these findings argue that anti-PLA_2R is in fact part of the pathogenic process and is closely associated with immunologic disease activity. The studies noted above make a strong case for incorporating anti-PLA_2R antibody levels into disease management, and several experts in the field have suggested this. Future predictive models should take anti-PLA_2R levels into account. The importance of this finding cannot be stressed enough. If trending anti-PLA_2R levels can predict which patients will undergo spontaneous remission and which will progress to nephrotic-range proteinuria, immunosuppressive therapies can be individualized and potentially avoided altogether in certain patients. In addition, despite recommended lengths of treatment (e.g., the 6-month Ponticelli regimen and less certain duration for calcineurin inhibitors), future nephrologists may extend (or shorten) treatment durations based on the timing of a definitive disappearance of circulating autoantibodies. More studies need to be performed with the more recently described anti-THSD7A antibodies before similar conclusions can be applied to this subgroup of patients.

The awareness that multiple epitopes in PLA_2R may be variably targeted in disease has offered another potential avenue by which to assess prognosis, although such assays are still only research based. There is evidence that having antibodies to all three epitopes in PLA_2R (contained within the N-terminal cysteine-rich domain and in the first and seventh C-type lectin-like domains) is associated with a more severe disease course and that more such patients have reached ESKD on last follow-up (Seitz-Polski et al. 2016). Another study shows that many patients with "standard" anti-PLA_2R recognize both the human and rabbit PLA_2R protein by ELISA. Some patients recognize human, rabbit, and mouse PLA_2R, and these patients also are associated with worse outcome (Seitz-Polski et al. 2015). While the epitope in the cysteine-rich region is felt to be the initial, immunodominant epitope (Fresquet et al. 2015; Kao et al. 2015), it may not be sufficient to induce severe disease (Seitz-Polski et al. 2016). Only with epitope spreading to other regions of the molecule is the disease fully active, similar to what had been shown in the experimental rat model.

Disease Recurrence After Transplant

In those patients who develop ESKD from primary MN and later undergo kidney transplantation, recurrent MN is a distinct possibility. Recurrence of primary MN is estimated to occur anywhere between 10% and 45% in renal allografts. The wide range in recurrence estimates is due to inter-institution variability with regard to posttransplant protocol biopsies (Cosyns et al. 1998; Dabade et al. 2008; El-Zoghby et al. 2009; Moroni et al. 2010). Centers that perform early protocol biopsies find more cases in the subclinical phase.

Disease pathogenesis is felt to be the same, with circulating anti-PLA_2R antibodies targeting the antigen present on podocytes of the allograft. As opposed to the situation in native kidneys, when the immunologic onset of disease is never captured, recurrent MN in the allograft represents an excellent opportunity to follow disease course in its earliest stages. This is due to the fact that in many cases, the kidney allograft is transplanted into a recipient in whom circulating anti-PLA_2R antibodies still persist. Therefore, the new donor allograft is immediately the target of these circulating antibodies. In one case, deposits that contained both IgG and the PLA_2R antigen were detected within 6 days of transplantation (Blosser et al. 2012). Because IF is more sensitive at detecting the early deposits than EM, the situation may arise where IgG- and C3-positive deposits in a granular peripheral capillary loop pattern are detected prior to any evidence of immune deposits by EM. These deposits have been called "Stage 0" by Rodriguez and colleagues (Rodriguez et al. 2012). With persistence of circulating autoantibodies, the deposits continue to grow in size, leading to increasing levels of proteinuria and clinically evident disease (Rodriguez et al. 2012).

Several case reports and larger cohort studies have addressed the significance of positive serology for anti-PLA_2R at the time of transplantation (Debiec et al. 2011; Gupta et al. 2016; Kattah et al. 2015; Quintana et al. 2015; Seitz-Polski et al. 2014; Stahl et al. 2010). In general, positive and negative predictive values are poor. A patient negative for anti-PLA_2R at the time of transplantation may be in immunologic remission (this would be more certain if that patient were known to have had PLA_2R-associated disease) or may have other unmeasured circulating antibodies (to THSD7A or other as yet unidentified antigens) that could lead to rapid recurrence. In addition, just as in native disease, we do not know what causes the reemergence of autoantibodies at times of relapse. Even though a patient may be negative for anti-PLA_2R immediately prior to transplantation, the immune system could "turn on" again months or years after transplantation. Separate arguments are necessary for why documented anti-PLA_2R at transplantation are not always associated with recurrence. In many cases with high levels of autoantibody, an early recurrence is in fact detected. However, with lower starting levels, the transplant immunosuppression (e.g., corticosteroids, calcineurin inhibitor, and mycophenolate) may be sufficient to induce immunological remission. In these cases, small Stage 0 deposits may start to form immediately after transplantation, but the decline and disappearance of circulating antibodies within weeks to months never leads to clinical disease.

When anti-PLA_2R or other autoantibodies do persist in spite of transplant immunosuppression, proteinuria tends to increase from sub-nephrotic to nephrotic levels. Sustained levels of heavy proteinuria are associated with progressive loss of renal function and thus should be treated. Most transplant nephrologists would use rituximab in this situation, and there is observational data that this adjunctive immunosuppressive agent is efficacious in this setting (Grupper et al. 2015). Although there is a concern for recurrent disease, which could potentially lead to worsened outcomes after transplantation, positive serologies prior to transplantation are not a contraindication to transplantation. With close follow-up of proteinuria and anti-PLA_2R, it can be determined if transplant immunosuppression alone will be sufficient for "treatment" or whether rituximab will be necessary. In patients who have had severe, rapidly progressive disease in their native kidney or first transplant, consideration could be given to treating with rituximab prior to transplantation. As a whole, these studies suggest that

posttransplant monitoring of anti-PLA_2R antibody titers may help predict disease relapse.

Conclusions

Primary MN is the most common cause of nephrotic syndrome in nondiabetic Caucasian adults and can affect patients of all races, genders, and age, starting in adolescence. In recent years, it has become evident that primary MN is a renal-specific autoimmune disease that occurs as a result of autoantibodies targeting the antigens PLA_2R and THSD7A, which are intrinsic podocyte proteins. Activation of the complement cascade causes sublethal injury to the podocyte resulting in proteinuria and the nephrotic syndrome. The natural course of disease is variable, with a third of patients going on to develop spontaneous remission and third going on to develop ESKD. Treatment is generally reserved for patients with worsening nephrotic syndrome or renal function and is targeted at reducing proteinuria as this leads to decreased morbidity and mortality. While RAAS blockade and alkylating agents are the mainstays of therapy in those necessitating treatment, rituximab has potential to become a first-line agent given its known efficacy and superior side effect profile. Lastly, anti-PLA_2R antibodies are now commercially available and known to predict aspects of disease such as remission and relapse. We anticipate that they will become incorporated into routine management and outcome prediction models in the future.

Cross-References

► Secondary Membranous Glomerulonephritis

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ANCA-Associated Vasculitis, Adult

16

Patrick H. Nachman and Shannon L. Murphy

Contents

Abstract

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis is a pauci-immune systemic small vessel vasculitis. ANCA are autoantibodies directed toward an antigen found in neutrophils, either myeloperoxidase (MPO) or proteinase 3 (PR3). ANCA are pathogenic and cause disease by activating neutrophils, which damage blood vessels. ANCA vasculitis may affect various organs and is associated with glomerulonephritis in most patients. The disease can be classified into one of a few phenotypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). However, recent evidence has shown that the ANCA antigen specificity (i.e., MPO- or PR3-ANCA) may be more important in characterizing the disease than the pathologic phenotype (MPA, GPA, or EGPA).

ANCA vasculitis is organ- and life-threatening in many cases, but with early and appropriate therapy, patients can remit. Therapies including corticosteroids, cyclophosphamide, rituximab, and plasmapheresis are

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effective in inducing a remission in the vast majority of patients. However, relapse is unfortunately common and the existing options for both induction and maintenance therapy are associated with risks for substantial adverse effects. The risks of continued immunosuppression with maintenance therapy must be weighed against the risk of relapsed disease, and there is currently no clear answer regarding the optimal duration of immunotherapy. Although our understanding of this disease has come a long way in a relatively short time, there is still much work to be done in understanding the pathophysiology of disease and identifying better treatment options.

Keywords
ANCA vasculitis · Pauci-immune necrotizing glomerulonephritis · Microscopic polyangiitis · Granulomatosis with polyangiitis · Eosinophilic granulomatosis with polyangiitis · Rapidly progressive glomerulonephritis · Systemic vasculitis · Pulmonary-renal syndrome

Nomenclature/Classification

ANCA vasculitis is a small vessel vasculitis, predominantly affecting venules, capillaries, arterioles, and small arteries (though medium caliber arteries and veins can be affected). The disease is pauci-immune, meaning that it is characterized by the paucity or absence of immunoglobulin deposits when tissue is examined by immunofluorescence microscopy.

ANCA vasculitis may present with a wide range of possible organ involvement and clinical manifestations. Small vessel vasculitides have been grouped into several clinicopathologic phenotypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). These different vasculitides were classified by the Chapel Hill Consensus Conference (Jennette et al. 1994), with revised nomenclature presented following a 2012 conference (Jennette et al. 2013). See Table 1 for definitions. This nomenclature is typically used for patients with systemic vasculitis; if the kidney is the only organ involved, the disease is often referred to as renal-limited pauci-immune necrotizing GN.

GPA and EGPA differ from MPA by the pathologic finding of granulomatous inflammation. GPA is characterized by necrotizing granulomatous inflammation and usually involves the upper and lower respiratory tracts, though necrotizing GN is frequently seen as well. EGPA also involves granulomatous inflammation and is notable for the presence of eosinophil-rich inflammation, as well as its association with asthma and peripheral eosinophilia. Renal involvement is less common in EGPA than in MPA or GPA. Necrotizing GN and pulmonary capillaritis with associated alveolar hemorrhage are common to all disease phenotypes. The pulmonary involvement in GPA may also present with nodules and cavities (corresponding to the granulomatous inflammation) instead of infiltrates representing alveolar hemorrhage. Granulomata are rarely seen on renal biopsy. As such, MPA and GPA can generally not be distinguished based on the kidney biopsy examination.

The ANCA serotype is not a criterion for classification of the disease phenotype between GPA, MPA, or EGPA. The majority of patients with GPA have circulating PR3-ANCA, whereas the majority of patients with MPA and renal limited disease have MPO-ANCA. It is important to note that approximately 10–15% of patients with pauci-immune small vessel vasculitis are ANCA-negative (Shah et al. 2016; Jennette 2003). Recent data suggests that ANCA antibodies are not detected in some "ANCA-negative" patients because the target epitope of MPO is bound to serum ceruloplasmin, thus masked from detection of the ANCA autoantibody using the routine clinical ANCA test (Roth et al. 2013). Only about 40% of patients with EGPA have circulating ANCA, usually MPO-ANCA, and ANCA is more commonly detected in patients who have GN.

Table 1 Definitions for small vessel vasculitis adopted by the 2012 International Consensus Conference on the Nomenclature of Vasculitis (CHCC2012)

CHCC2012 name	CHCC2012 definition
Small vessel vasculitis	Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules, medium arteries and veins may be affected
ANCA-associated vasculitis (AAV)	Necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels, (i.e., capillaries, venules, arterioles, and small arteries), associated with MPO ANCA or PR3 ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCA-negative
Microscopic polyangiitis (MPA)	Necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent
Granulomatosis with polyangiitis (GPA) (Wegener's)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common
Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present

MPO, myeloperoxidase; PR3, proteinase 3

Increasingly, though, evidence supports the use of ANCA serotype as more meaningful and useful in classifying disease. In many cases, it is difficult to accurately classify a patient's disease as MPA versus GPA because of the similarities and overlap in the clinical features. In addition, recent studies have demonstrated different genetic associations for MPO- and PR3-ANCA associated disease (Lyons et al. 2012; Cao et al. 2011). Furthermore, antibody serotype, rather than disease phenotype, is useful in stratifying a patient's risk of relapse. PR3-ANCA-positive patients are almost twice as likely to relapse as those with MPO-ANCA (Lionaki et al. 2012; Hogan et al. 2005; Pagnoux et al. 2008a). Within each ANCA serotype group, patients with GPA, MPA, and kidney-limited disease had a similar probability of relapse-free survival. As a result of these findings, there is a growing interest in classifying small vessel vasculitis based on the ANCA serotype (MPO-ANCA vs. PR3-ANCA vasculitis) rather than the traditional disease phenotype.

Demographics/Epidemiology

ANCA vasculitis has a peak incidence in older adults in their 50s and 60s, but is not uncommon in older patients. The mean age at biopsy in a cohort of over 300 patients with this disease was 56 years old (Jennette 2003). ANCA vasculitis can affect children and young adults, but it is

relatively infrequent. It occurs at similar rates in males and females.

ANCA vasculitis is seen primarily in Caucasians. The proportion of African Americans with disease varies depending upon the population from which a sample or cohort is drawn. In one cohort of 350 patients, African Americans comprised 9% of patients with ANCA vasculitis (compared with approximately 27% of the population) (Hogan et al. 2005). In other cohorts, the percentage of patients with ANCA vasculitis who were black was much lower, but these are often drawn from areas with a smaller prevalence of blacks in the general population.

There are unfortunately little data on the incidence of ANCA vasculitis. One study done in the UK, using a hospital-based population drawn from a population of over 400,000 in a relatively isolated coastal area from 1988 to 1994, reported an annual incidence of 8.5/million for GPA, 2.4/million for MPA, and 2.4/million for EGPA (Watts et al. 1995). Another study out of the UK reported the incidence of pauci-immune RPGN at 3.9/million; this was calculated from a population of 2.5 million over 10 years (Hedger et al. 2000). However, this did not include patients that had systemic vasculitis without renal manifestations or with more indolent renal involvement, and thus likely underestimates the true incidence of ANCA vasculitis. These numbers can help give an idea of incidence, but accurate estimates are hard to obtain. Another study estimated the prevalences of MPA, GPA, and EGPA from a multiethnic population near Paris, France to be 25, 24, and 11 cases, respectively, per one million adults (Mahr et al. 2004).

The majority of rapidly progressive glomerulonephritis (RPGN) cases are due to pauci-immune glomerulonephritis, and this proportion increases with age – in patients over 60 years old, about 80% of crescentic GN cases are due to pauci-immune disease (Jennette 2003). Of note, ANCA vasculitis is about 10 times more common than anti-glomerular basement (GBM) disease, which also causes an RPGN. About a third of patients with anti-GBM disease also have circulating ANCA, usually MPO-ANCA, in addition to anti-GBM antibodies. Conversely, a much smaller proportion of patients with ANCA-vasculitis also have anti-GBM antibodies. Clinically, these double-positive patients exhibit the severe glomerulonephritis and relatively poor prognosis associated with anti-GBM disease, and the extrarenal and extrapulmonary organ involvement, and high rate of relapse associated with ANCA-vasculitis.

Pathophysiology

The major pathogenic mediator in ANCA vasculitis appears to be the ANCA itself. ANCA are autoantibodies directed toward MPO or PR3 antigens found in neutrophils and monocytes. These autoantibodies are not typically detected in healthy patients. The inciting event(s) for ANCA formation are not clear, but as with other autoimmune diseases, potential risk factors or triggers include infectious, environmental, and genetic etiologies. In order to develop disease, in addition to the presence of ANCA, MPO or PR3 antigens (normally intracellular) must become localized to the cell surface of neutrophils and monocytes and interact with ANCA. This causes neutrophil activation and degranulation, which leads to inflammatory injury and direct damage to endothelial cells and small vessel walls.

Possible explanations for how these autoantigens localize from intracellular granules of neutrophils and monocytes to the cell surface in certain individuals include an increase in TNF and/or cytokines due to an inflammatory process (such as infection), a genetic increase in membrane expression of autoantigens, or loss of epigenetic silencing of the autoantigens (Falk and Jennette 2010). Different etiologies may be implicated in different patients.

The mechanism(s) involved in granulomatous forms of vasculitis are less clear, but it has been proposed that extravascular neutrophils and interstitial ANCA interact to cause necrotizing inflammation and subsequent granuloma formation (Jennette and Falk 2014).

A mouse model has provided in vivo evidence for the pathogenic role of anti-MPO ANCA. Splenocytes from MPO knockout mice immunized with mouse MPO were injected into mice that lacked functional B- and T-cells. These mice developed pauci-immune vasculitis with necrotizing and crescentic GN as well as pulmonary capillaritis with

hemorrhage. In another experiment, those mice (lacking functioning B- and T-cells) were injected with anti-MPO IgG and again developed the same pauci-immune GN (Xiao et al. 2002). These results strongly support a direct role for anti-MPO antibodies in the pathogenesis of pauci-immune vasculitis. A modification of this mouse model has brought to attention a previously unsuspected role of complement activation in anti-MPO-mediated vasculitis through activation of the alternative pathway but not the classical or lectin binding pathways. C6 deficient mice were not protected from anti-MPO mediated disease, suggesting that the C5b-9 membrane attack complex formation is not essential in the pathogenetic pathway (Xiao et al. 2007).

More recently, an animal model for PR3 was developed. Splenocytes from mice immunized with PR3 were transferred into immunodeficient (severe combined immunodeficiency) mice; the immunodeficient mice developed vasculitis with necrotizing GN. Disease did not develop in similar immunodeficient mice receiving splenocytes from mice that were not immunized against PR3 (Primo et al. 2010). This provides evidence for a pathogenic role of PR3 autoantibodies in pauci-immune vasculitis. There are to date no established animal models reproducing granulomatous inflammation with ANCA.

ANCA can sometimes be found in asymptomatic patients at low titers. These ANCA appear to differ from the ANCA found in patients with disease in a few important ways, however, including their avidity for the autoantigen as well as the number of epitopes within the antigen that they have affinity for.

Although some of the mechanisms have yet to be fully elucidated, the accumulated data support a pathogenic role for ANCA. Continued research on the mechanisms of disease, including both humoral and cellular pathways, will be important to identify new therapeutic targets.

Pathology

The characteristic lesion of ANCA vasculitis in the kidney is a crescentic and necrotizing GN which has limited or no deposition of immunoreactants on immunofluorescence (IF). The lesions occur in a focal segmental and sometimes global pattern. On light microscopy, it is indistinguishable from anti-GBM disease.

Crescents are formed by rupture of the glomerular basement membrane, with subsequent exudation of plasma and inflammatory cells into Bowman's space. Fibrinoid necrosis occurs when plasma coagulation factors interact with tissue factor and other prothrombotic materials in Bowman's space, forming fibrin. With more severe injury, disruption of Bowman's capsule can also be seen.

Crescents can be more cellular or fibrous depending upon the chronicity of the injury. Within the first week they start to evolve, as cellular elements disappear and collagen is synthesized. Cellular crescents indicate a more recent injury, whereas fibrous crescents and glomerulosclerosis are seen with more time after the acute insult. A mix of cellular (acute) and fibrous (chronic) crescents can be seen in some patients denoting the possibility of previous waves of active glomerulonephritis alongside recent relapsed/active disease. In patients who have a more subacute and less fulminant course, biopsy may reveal mostly glomerulosclerosis and interstitial fibrosis and tubular atrophy, due to repeated episodes of injury over time.

About 90% of patients with GN due to ANCA vasculitis have crescents at biopsy, and half have crescents in more than 50% of the sampled glomeruli (Jennette 2003). Crescentic GN can be due to anti-GBM disease, immune-complex GN, or pauci-immune GN. Anti-GBM disease and pauci-immune GN are indistinguishable on light microscopy. These groups are differentiated by findings on IF; pauci-immune GN by definition has little or no staining on IF. Faint staining with C3 or immunoglobulins can sometimes be seen and is due to these molecules becoming trapped within crescents.

Periglomerular inflammation can be seen, though generally in glomeruli in which there has been rupture of Bowman's capsule. Of note, periglomerular granulomatous changes may be present and are not specific for any type of ANCA, but if granulomatous features involve the interstitium or vessels, this is more consistent with GPA or EGPA.

Electron microscopy in these patients shows few or no immune-complex type electron-dense

deposits. In affected glomeruli, breaks in the GBM as well as subendothelial or intraluminal fibrin can be seen.

Clinical Presentation and Features

ANCA vasculitis is a systemic disease which can affect small vessels throughout the body, and thus has a wide range of presenting symptoms or features depending on which organs/vascular beds are involved. Manifestations vary with the ANCA serotype (MPO- vs. PR3-ANCA), with certain manifestations being associated more with one serotype or the other (Fig. 1). In addition to symptoms associated with specific organ involvement (e.g., renal, pulmonary, sinus, gastrointestinal, skin, etc.), nonspecific systemic symptoms are common, including fever, fatigue, malaise, arthralgias, myalgias, and anorexia/weight loss.

Most patients have renal involvement due to vasculitis of the glomerular capillaries. This presents with worsening GFR, hematuria, and proteinuria. It can occur as an RPGN or, less commonly, with a more indolent course. As with any nephritic syndrome, new or worsened hypertension is common. Disease can be limited to the kidneys, without any other evidence of systemic vasculitis.

The upper and lower respiratory tracts can be involved, especially in GPA. Pulmonary manifestations include cough (productive or nonproductive), shortness of breath, or pleuritic pain. Alveolar hemorrhage due to capillaritis presents with radiographic infiltrates with or without hemoptysis. Findings on imaging include nodules, cavitary lesions, infiltrates, or interstitial disease. Because the hemorrhage is alveolar rather than bronchial in origin, the hemoptysis may be a relatively late event, and its absence does not exclude the possibility of pulmonary hemorrhage. Some patients, in spite of infiltrates or other pulmonary involvement, have few or no symptoms.

Upper respiratory involvement includes sinusitis, rhinitis, and subglottic stenosis. Symptoms of rhinitis may precede other symptoms and diagnosis

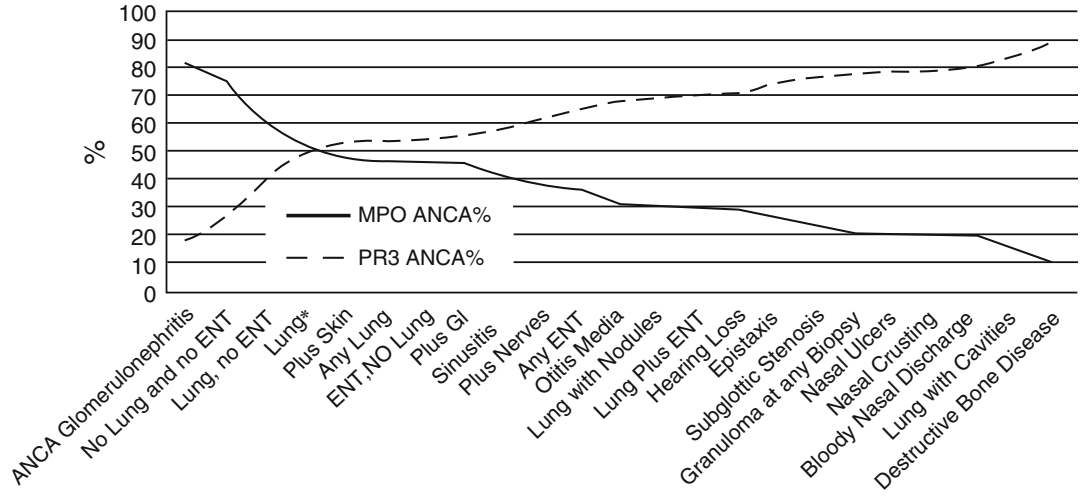

Fig. 1 Frequency of PR3- and MPO-ANCA specificity by a variety of clinical phenotypes (organ groupings are not mutually exclusive). No lung and no ENT: Vasculitis in any organ except the lungs and the ENT system. Lung, no ENT: Vasculitis localized in the lungs but not in the ENT system. Lung*: Vasculitis localized in the lungs without indicative markers (nodules or cavities) or histological proof (granulomas) of granulomatous inflammation. Plus gastrointestinal (GI): Vasculitis localized at any organ plus involvement of the gastrointestinal tract. Plus skin: Vasculitis localized at any organ plus dermal involvement. Plus nerves: Vasculitis localized at any organ plus involvement of the nerves. Any lung: Any type of pulmonary vasculitis such as pulmonary hemorrhage, infiltrates, nodules, cavities, granulomas, or respiratory arrest. ENT, no lung: Vasculitis localized at the ENT system but not in the lungs. Any ENT: Any type of vasculitic manifestation of the ENT system. Lung with nodules: Vasculitis localized at the lungs with radiographic proof of nodules. Lung plus ENT: Any type of pulmonary vasculitis plus any type of vasculitic manifestation of the ENT system (Lionaki et al. 2012)

by years. Patients with sinus disease often report bloody or purulent nasal drainage, nasal crusting, or epistaxis. Imaging of the sinuses can demonstrate opacification or air-fluid levels, polyps and nodules, or bony erosion. Over time, ongoing vasculitis can lead to collapse of the nasal septum causing a saddle-nose deformity. Infection is a frequent complication in patients with sinus involvement, and this can be difficult to differentiate from vasculitic disease activity. Subglottic stenosis can be a very serious complication, and in some patients is severe enough to require tracheostomy. Although often asymptomatic, especially early, this can cause hoarseness, cough, or stridor.

In addition to upper airway and sinus symptoms, ocular and otic manifestations are also seen. A wide variety of ophthalmologic manifestations are described, including uveitis, conjunctivitis, episcleritis, and optic nerve vasculitis. Proptosis can occur in patients with granulomatous disease, due to retroorbital pseudotumors. These can involve extraocular muscles or cause vision loss due to optic nerve ischemia and are often poorly responsive to treatment (Hoffman et al. 1992). Ear involvement includes tinnitus, otitis media (due to eustachian tube obstruction), or hearing loss (conductive or sensorineural).

Dermatologic involvement is seen in about half of patients, including a purpuric rash or cutaneous nodules or ulcers. The lower extremities are the most common site of involvement. Neurologic involvement is seen in a minority of patients. When present, it most frequently presents as mononeuritis multiplex, though CNS symptoms, including cranial neuropathies, are possible.

Most patients have some joint symptoms, which can include arthralgias, and rarely, arthritis. Arthralgias frequently present as migratory joint pain, without associated clinical signs of joint inflammation. Arthritis is rare, but may affect the large joints and is nondeforming; when arthrocentesis is performed, the fluid is nondiagnostic.

Gastrointestinal manifestations are uncommon. These include mesenteric ischemia leading to hematochezia or melena and pain. Involvement of the pancreas or liver can occur, presenting as pancreatitis or transaminitis.

It is important to note that patients with ANCA vasculitis are at significantly increased risk of venous thromboembolism (VTE). Reported rates have been higher than that in patients with lupus, and similar to that in patients with a history of recurrent VTE (Merkel et al. 2005; Springer and Villa-Forte 2013). One study reported VTE in 12% of ANCA vasculitis patients, with the incidence significantly higher during active disease (Stassen et al. 2008). Thus, having a high index of suspicion for this when caring for these patients is important to ensure timely diagnosis and treatment if and when it occurs.

Diagnosis

There are no published or widely adopted diagnostic criteria for ANCA vasculitis. The diagnosis is a clinicopathologic one based on the clinical history and exam, laboratory data, and tissue biopsy.

The first step in diagnosis is to obtain a thorough history. Though ANCA vasculitis is a rare disease, prognosis depends upon early treatment, and thus the diagnosis must be considered and workup undertaken early in patients with signs/symptoms of disease. Specifically, in patients with an RPGN, or AKI with hematuria and proteinuria (evidence of a glomerular etiology), this must be included in the differential. As ANCA vasculitis is a systemic disease, which can often have extrarenal manifestations, the history and review of systems are crucial. Patients will often report a history of intermittent symptoms such as cough/dyspnea, rhinitis or sinus symptoms, arthralgias, rash, or fatigue/malaise. Though these are nonspecific symptoms, the relapsing-remitting course (in some cases, over years) as well as the constellation of symptoms (especially in a patient with evidence of renal involvement, such as renal insufficiency, hematuria, or proteinuria) should prompt consideration of this disease.

The diagnosis of ANCA vasculitis is unfortunately often quite delayed. One study reported a median time from first symptoms to diagnosis of 4.7 months, and a mean of 15 months – with the time depending in part upon the severity or clinical course as well as whether the patient had renal or pulmonary involvement, as these are more common and well-recognized manifestations of

ANCA disease (Hoffman et al. 1992). Patients may be evaluated by several physicians before the diagnosis is established. One study looking at pathways from first symptoms of disease to diagnosis found that 62% of patients experienced a delay in diagnosis. These delays were attributable to physicians not making the diagnosis or referral to a nephrologist as well as patients not seeking care (Poulton et al. 2013).

In any patient with hematuria and/or proteinuria, microscopic urine examination is an important part of the workup. In patients with pauci-immune glomerulonephritis, urine microscopic evaluation will reveal dysmorphic hematuria and sometimes red blood cell casts.

ANCA serologies should be ordered in any patient for whom this disease is suspected or considered in the differential. Indirect immunofluorescence (IIF) distinguishes between the two major types of ANCA based on the pattern of staining on alcohol-fixed neutrophils – cytoplasmic (C-ANCA) or perinuclear (P-ANCA). Antigen-specific enzyme linked immunosorbent assays (ELISA) have since been developed and detect the autoantibodies to MPO or PR3 directly. These direct immunoassays have better specificity – 90% and above compared to 70% and above for IF – though specificity is highest using both IIF and direct ELISA (Lim et al. 1999). Patients with a positive ANA can have a false positive P-ANCA by IIFM. In such cases, a positive antigen-specific ELISA test is necessary for a diagnosis of MPO- or PR3-ANCA associated disease.

As mentioned previously, approximately 10–20% of patients with pauci-immune glomerulonephritis are ANCA-negative. Thus, a negative ANCA test does not rule out the diagnosis of pauci-immune small vessel vasculitis or glomerulonephritis in a patient presenting with the correct clinical constellation of signs and symptoms or pathologic findings on biopsy.

Of note, while ANCA serologies are an important part of the diagnostic workup, titers do not correlate with disease activity in many cases, and should not be used for treatment decisions. It appears that in some patients, disease flares are preceded by a rise in titer; however, in these patients, there is a variable and often significant interval between the rise in titer and clinical relapse, and in other patients, there may be no association (Boomsma et al. 2000). A systematic review found that studies addressing this question had significant methodologic limitations and heterogeneity and were thus not able to draw any conclusions regarding the value of ANCA testing/titer in monitoring patients for relapse (Birck et al. 2006).

Other laboratory tests should be undertaken in a patient suspected to have a glomerular lesion. Although not diagnostic, these can be helpful in supporting a diagnosis of ANCA-vasculitis or excluding other diagnoses. Proteinuria can range from subnephrotic to nephrotic. Inflammatory markers (ESR, CRP) are usually elevated in the setting of active disease, reflecting the ongoing systemic inflammation. A normocytic anemia and/or thrombocytosis are common. Leukopenia and thrombocytopenia are rarely seen (Fauci et al. 1983). Rheumatoid factor can be positive in approximately one third of patients (Seo and Stone 2004). Complement levels are almost always normal in patients with ANCA vasculitis. Severe hypocomplementemia should prompt consideration of another process.

Ultimately, in patients with ANCA-associated pauci-immune GN, a biopsy is nearly always necessary to make the diagnosis, though in rare cases this can be delayed or deferred. Renal biopsy is important to establish the diagnosis of pauci-immune GN, especially in the 10–20% of patients who are ANCA-negative, as well as to evaluate the degree of activity and scarring for prognostic purposes. As such, a renal biopsy is not always absolutely necessary for a diagnosis of ANCA vasculitis. In the presence of clinical signs of glomerulonephritis, RPGN, pulmonary nodules, cavities, or alveolar hemorrhage, the positive predictive value of an ANCA test is close to 90% (Falk et al. 1996), and a kidney or lung biopsy is not absolutely necessary to establish diagnosis. In such cases, treatment should not be delayed until a biopsy result is available, especially in the case of rapidly progressive or organ- or life-threatening disease. Additionally, in a patient with severe renal failure who may be at high risk of bleeding due to uremic platelets, proceeding with steroids and plasmapheresis and delaying biopsy until

after the patient has started dialysis may be a better option. This question should be addressed on a case-by-case basis with careful consideration of the risks and benefits, but given the potential adverse effects of therapy, confirming the diagnosis as well as histopathologic activity or chronicity is usually advisable.

In patients with other systemic symptoms suggestive of ANCA disease, but without evidence of renal involvement (normal renal function, no activity on urine sediment), biopsy of the involved/affected tissue may be pursued, though the risks and diagnostic yield must be weighed for each patient. While biopsy may reveal vasculitis, it is not always diagnostic and it is not uncommon (especially in skin or sinus tissue) to see nonspecific changes such as acute and chronic inflammation. Other disease processes can look very similar to and coexist with ANCA disease, so a broad differential diagnosis and careful workup is essential. For example, in patients with known GPA with sinus involvement, either infection or relapsing inflammation (or both) can present similarly with purulent nasal drainage, epistaxis, fever/malaise, opacification of sinuses on imaging, etc. Working with an otolaryngologist who has experience with ANCA vasculitis can be very helpful when caring for these patients.

A number of drugs have been identified as being associated with ANCA disease. One of the most important common causes of drug-induced ANCA vasculitis that has become increasingly prevalent is levamisole. Levamisole is an antihelminthic agent, which has been taken off the market due to toxicity but is used to cut cocaine, with approximately 75% of cocaine in the USA containing levamisole. Patients with ANCA due to levamisole-adulterated cocaine are often found to have high titers of both MPO- and PR3-ANCA, a pattern rarely seen outside of this setting. These patients may also have other autoantibodies and severe hypocomplementemia. Clinically, they frequently present with severe large eschared skin lesions. In addition a number of prescription medications which have been associated with ANCA vasculitis, most notably minocycline, hydralazine, and propylthiouracil (PTU) (Pendergraft and Niles 2014). Hydralazine-associated ANCA-vasculitis may also present with a double positive MPO- and PR3- ANCA vasculitis, whereas PTU exposure is usually associated with MPO-ANCA. A thoughtful medication history and a low threshold for recreational drug testing are important in any patient diagnosed with ANCA, as withdrawal of the offending/implicated medication is an essential component of treatment.

Therapy

Treatment of ANCA vasculitis has progressed a great deal over the past decades. Before the use of cyclophosphamide and corticosteroids, small vessel vasculitis was fatal within 1–2 years in the majority of patients (Fauci et al. 1983). Survival time and mortality rates improved somewhat with the use of corticosteroids. However, the use of cyclophosphamide markedly improved remission rates to about 80% and decreased the rate of relapse about threefold (Fauci et al. 1983; Nachman et al. 1996; De Groot et al. 2001).

Today, the mainstays of induction therapy include corticosteroids, cyclophosphamide and/or rituximab, as well as plasmapheresis for patients with pulmonary hemorrhage and/or severe renal disease.

Early therapy is extremely important in ANCA vasculitis as the disease can be organ- and life-threatening, and quickly decreasing the inflammation is necessary to minimize further damage. Chronic renal insufficiency is one of the most serious complications of this disease. The necrotizing and crescentic inflammation seen in the kidneys rapidly evolves into a more chronic lesion. The neutrophil-rich infiltrates are replaced by monocytes and macrophages within days, and collagen deposition and scarring can be seen within 1–2 weeks (Jennette and Falk 2014). The earlier the inflammation is treated and stopped, the less damage and scarring, and the more renal function a patient is likely to recover. Pulmonary involvement, especially DAH, may be quickly fatal if untreated, and thus should be treated as a medical emergency. As described previously, the most important step is making the diagnosis quickly, but also necessary is coordination of

care to ensure urgent implementation of appropriate therapies in a patient with rapidly progressive or severe disease.

The purported goal of early high dose corticosteroids therapy is to quickly decrease the ongoing necrotizing inflammation characteristic of ANCA vasculitis. Oral prednisone is typically started at 1 mg/kg/day (or equivalent) with a usual maximum dose of 60 mg daily. Induction with pulse intravenous methylprednisolone was introduced in the late 1970s and was then associated with improved response to therapy and survival (Cole et al. 1976; Bolton and Couser 1979). However, its routine use was never formally tested in a controlled trial and remains a matter of regional tradition rather than evidence based. Its use is recommended in cases of severe disease (e.g., RPGN or alveolar hemorrhage), when access to immunotherapy with cyclophosphamide or rituximab is not readily available. When used, pulse methylprednisolone is usually given as 7 mg/kg/day for 3 consecutive days. Oral corticosteroids should be tapered down over 3–4 months and may be discontinued completely after 4–5 months. Treatment with corticosteroids is however insufficient, and the addition of cyclophosphamide or rituximab should be instituted as soon as possible.

Treatment with cyclophosphamide may be given as a daily oral regimen (generally 2 mg/kg/day, adjusted for age, renal function and WBC count) or as a regimen of intravenous pulses at monthly intervals (usually starting at 0.5–0.75 g/m^2 body surface area and increased to 1 g/m^2 body surface area based on the nadir WBC count >3000 cells/mL). A regimen utilizing IV pulses corresponds to a cumulative dose that is a third to a half of the cumulative dose of cyclophosphamide given as a daily oral regimen (for a same duration of treatment). This difference in total dose is of import as some of the risk of malignancy associated with cyclophosphamide is related to the cumulative exposure (Knight et al. 2004; Westman et al. 1998; Faurschou et al. 2007).

The question of oral versus intravenous cyclophosphamide was addressed in the Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis (CYCLOPS) trial. This randomized controlled trial (RCT) which assigned 149 patients newly diagnosed with ANCA vasculitis with renal involvement to either pulse intravenous (IV) cyclophosphamide or daily oral cyclophosphamide, as well as a standardized regime of corticosteroids. This study found similar rates of remission and time to remission in the IV and oral cyclophosphamide groups (De Groot et al. 2009). The IV-treated group had a lower rate of leukopenia, but the rates of serious infection were similar between the two groups (De Groot et al. 2009; Harper et al. 2012). Over a median follow-up of 4.3 years, the IV cyclophosphamide group experienced a higher rate of relapse than the daily oral group; however, there was no significant difference in mortality or renal function as last follow-up between the groups (Harper et al. 2012). Given the association between the risk of malignancy and the cumulative dose of cyclophosphamide, the intravenous regimen is the currently favored approach when available.

Early cyclophosphamide protocols typically continued the drug for 12 months. The Cyclophosphamide versus Azathioprine for Remission in generalized vasculitis (CYCAZAREM) RCT tested the hypothesis that cyclophosphamide treatment could be discontinued and switched to a less toxic maintenance treatment with azathioprine after the patient attained a complete remission. Patients with a new diagnosis of ANCA vasculitis were treated with oral cyclophosphamide and prednisolone until they achieved remission (a minimum of 3 months) then were randomized to receive either continued oral cyclophosphamide for a total of 12 months or switched to azathioprine (2 mg/kg/day). All patients were maintained on azathioprine after 12 months from treatment start for an additional 12 months. There was no significant difference in the relapse rate between those that continued cyclophosphamide and those that were switched to daily azathioprine. There was also no difference in the rate of severe adverse events during the remission phase (Jayne et al. 2003). Thus, a prolonged course of cyclophosphamide is not necessary and azathioprine can safely be used for maintenance therapy after a patient reaches remission with cyclophosphamide.

Although cyclophosphamide was cornerstone of induction therapy for many years, rituximab

has recently emerged as an alternative in the treatment of patients with ANCA vasculitis. The Rituximab versus cyclophosphamide for ANCA-associated vasculitis (RAVE) trial compared cyclophosphamide to rituximab for induction therapy. The RAVE trial randomized 197 patients with either new or relapsed disease to either four weekly doses of rituximab (375 mg/m^2 body surface area) or daily oral cyclophosphamide for induction therapy. After attaining remission, patients in the cyclophosphamide group were switched to azathioprine, whereas those randomized to rituximab received no further immunosuppression. This RCT demonstrated that treatment with rituximab was noninferior to cyclophosphamide (Stone et al. 2010). It is important to note that patients with pulmonary hemorrhage and/or severe renal failure (defined as serum creatinine greater than 4 mg/dL) were excluded from this trial; thus, the efficacy of rituximab in these patients is not known. Interestingly, in a sub group analysis of patients treated for disease relapse, rituximab therapy was associated with a statistically significant higher rate of remission than cyclophosphamide.

The rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXIVAS) trial was an RCT comparing rituximab plus a reduced dose of cyclophosphamide ($N = 33$ patients) to standard dose cyclophosphamide ($N = 11$). Patients with newly diagnosed ANCA vasculitis with renal involvement were given either four weekly doses of rituximab plus two pulses of IV cyclophosphamide or three to six monthly pulses of IV cyclophosphamide followed by azathioprine. There was no significant difference between the groups in the rates of remission or serious adverse events (Jones et al. 2010).

Methotrexate was evaluated as a possible alternative to cyclophosphamide for induction therapy in patients with mild disease. The nonrenal Wegener's granulomatosis treated alternatively with methotrexate (NORAM) trial randomized patients to either oral cyclophosphamide or oral methotrexate, along with oral prednisolone. Although methotrexate was not found to be inferior to cyclophosphamide with regards to remission rate at 6 months, the time to remission was shorter in patients receiving cyclophosphamide, as compared to methotrexate. Importantly, patients were excluded if they had significant renal dysfunction (Cr >1.7, RBC casts in urine, or proteinuria >1 g/day) or other organ- or life-threatening disease (De Groot et al. 2005). Therefore, methotrexate is not a favored option for induction therapy. Because of the risk of toxicity, methotrexate should not be used in patients with renal dysfunction.

The role of plasmapheresis in the management of patients with ANCA vasculitis remains under investigation. The methylprednisolone versus plasma exchange (MEPEX) trial randomized 137 patients with newly diagnosed ANCA vasculitis with severe renal disease (defined as Cr >5.7 mg/dL at presentation) to receive a course of seven plasma exchanges versus IV methylprednisolone, in addition to standard therapy with oral cyclophosphamide and oral prednisolone. Dialysis-free survival at 3 months (69% of plasmapheresis vs. 49% of methylprednisolone group, 95% CI for the difference 18–35%; $P = 0.02$) and 12 months was significantly higher in the plasma exchange group than the methylprednisolone group. Patient survival and rate of adverse events were not significantly different between the two groups (Jayne et al. 2007). The outcomes of the patients enrolled in the MEPEX trial were analyzed in a follow-up study (Walsh et al. 2013). Over a median duration of 3.95 years, the hazard ratio for plasmapheresis compared to pulse methylprednisolone for death or ESRD was 0.81 (95% CI, 0.53–1.23). Treatment with plasmapheresis was associated with a lower risk of ESRD which did not reach statistical significance. The role of plasmapheresis as an adjunctive therapy in ANCA vasculitis, notably for patients with less severe degrees of renal disease, is being evaluated in an ongoing large RCT (plasma exchange and glucocorticoids for treatment of anti-neutrophil cytoplasm antibody (ANCA) – associated vasculitis (PEXIVAS) Clinicaltrials.gov NCT00987389). Preliminary results, presented recently in abstract format, indicate that plasmapharesis did not improve the primary endpoint of death or ESRD. However, until the peer-reviewed results of this larger trial are available, plasmapheresis is

recommended for patients presenting with severe or rapidly progressive renal disease. Although not formally evaluated in an RCT, retrospective case series have also led to the routine use of adjunctive plasmapheresis in the treatment of patients with diffuse alveolar hemorrhage due to ANCA vasculitis (Klemmer et al. 2003).

In summary, induction therapy should consist of corticosteroids in addition to either cyclophosphamide or rituximab. Cyclophosphamide should be continued for 1–2 months after remission is achieved. Adjunctive plasmapheresis is recommended in patients presenting with severe renal failure or diffuse pulmonary hemorrhage.

Resistance to therapy, defined as disease progression despite initiation of induction therapy with corticosteroids and cyclophosphamide or rituximab or failure to achieve remission within 6 months of treatment, is uncommon. Patient who fail to respond to standard induction therapy may be treated by the addition of other agent (i.e., rituximab if initially treated with cyclophosphamide, or cyclophosphamide if initially treated with rituximab) or the addition of plasmapheresis.

After achieving remission with induction therapy, patients are switched to a regimen of maintenance therapy. The data pertaining to the choice of maintenance therapy derives largely from studies using corticosteroids and cyclophosphamide for induction therapy.

Several clinical trials have provided some guidance regarding options for maintenance. Azathioprine is an effective option, as demonstrated in the CYCAZAREM trial (described above) (Jayne et al. 2003).

Azathioprine was compared to methotrexate in 126 patients who had achieved remission with IV cyclophosphamide and corticosteroids in the azathioprine or methotrexate maintenance for ANCA-associated vasculitis (WEGENT) trial. This RCT, which was designed to compare the incidence of adverse events between the two treatments to test the relative safety, revealed no significant difference in the number of patients that relapsed or in the number of adverse events. It was noted that the majority of patients who did relapse did so after discontinuation of the maintenance therapy (Pagnoux et al. 2008b). Therefore, this study demonstrated no advantage of methotrexate over azathioprine. Because of the increased risk of toxicity, methotrexate should be avoided in patients with decreased renal function.

The maintenance of remission using rituximab in systemic ANCA-associated vasculitis (MAINRITSAN) randomized controlled trial evaluated the use of rituximab for maintenance therapy, comparing it to azathioprine. In this study, 115 patients who had attained a complete remission with cyclophosphamide and corticosteroid induction were treated with rituximab (2 doses 2 weeks apart, followed by one 500 mg dose every 6 months with the last dose at 18 months) or daily azathioprine until 22 months. A significantly higher relapse rate was seen in the azathioprine group, whereas the rates of adverse events were similar between the two treatment groups (Guillevin et al. 2014). However, a few important issues with this trial are noteworthy. Patients with MPA (versus GPA) and those with MPO-ANCA (versus PR3-ANCA) comprised a minority of those included, so it is unclear if there were adequate numbers to generalize the findings to patients with MPO-ANCA. While the overall results of this trial support the use of rituximab for maintenance therapy, further studies are necessary to fully define its optimal use for maintenance therapy. A follow-up study of maintenance of remission using rituximab in systemic ANCA-associated vasculitis 2 (MAINRITSAN 2) is currently ongoing and compares a regimen of scheduled infusions of rituximab (500 mg every 6 months), to a regimen whereby dosing of rituximab is determined based on CD19+ B lymphocyte count and ANCA titer (clinicaltrials.gov NCT01731561). In addition another study of maintenance therapy with rituximab, the rituximab vasculitis maintenance study (RITAZAREM), is also ongoing whereby patients with relapsing disease receive induction therapy with rituximab and are thereafter randomized to maintenance therapy with either rituximab (1000 mg IV every 4 months) or azathioprine (clinicaltrials.gov NCT01697267).

Maintenance therapy with mycophenolate mofetil (MMF) was evaluated in the international mycophenolate mofetil protocol to reduce outbreaks of vasculitides (IMPROVE) trial in which

156 patients with a new diagnosis of ANCA vasculitis received induction therapy with cyclophosphamide and corticosteroids and were then randomized to daily oral MMF or azathioprine. The relapse rate was higher in the mycophenolate group than in the azathioprine group (HR for mycophenolate 1.69; 95% confidence interval, 1.06–2.70; $P = 0.03$) (Hiemstra et al. 2010). Thus MMF is not currently favored for maintenance therapy unless other agents (azathioprine, rituximab, methotrexate) are contraindicated or not tolerated.

The optimal duration of maintenance therapy is currently unknown, as there is currently limited evidence-based data to guide this decision. In an RCT, 131 patients with C-ANCA vasculitis who received a standardized induction treatment with oral cyclophosphamide and corticosteroids. Patients who became C-ANCA negative at remission received standard maintenance therapy. Patients who remained C-ANCA positive at the time of remission were randomized to standard ($N = 24$) or extended ($N = 21$) maintenance with azathioprine. Standard maintenance treatment was carried on for 1 year after diagnosis followed by a taper by 25 mg every 3 months. Extended azathioprine maintenance therapy was continued for 4 years after diagnosis and tapered thereafter. At 4 years after diagnosis, the relapse free survival of patients was similar across all three groups of patients (Sanders et al. 2016). This study therefore did not demonstrate a benefit of prolonged maintenance immunosuppression with azathioprine. It is not possible to extrapolate from this study as to the optimal duration of maintenance therapy with other agents such as rituximab. This study also did not confirm previous reports that a persistently positive C-ANCA at the time of clinical remission was associated with an increased risk of subsequent relapse.

As reviewed above, patients in the RAVE trial who were randomized to the rituximab group did not receive additional maintenance therapy. The timing and choice of maintenance therapy after rituximab is therefore still under investigation. In clinical practice, patients who receive induction treatment with rituximab are frequently continued on maintenance therapy after reaching a complete remission.

Common practice consists of continuing maintenance therapy for 12 months after remission is attained. Patients who remain in complete clinical remission after a year may be tapered off their maintenance therapy and followed with careful observation. There are no data on whether maintenance immunosuppression should be tapered down progressively rather than discontinued. Likewise, the length of low-dose maintenance corticosteroid therapy remains a matter of tradition rather than evidence based. A retrospective cohort analysis revealed no significant benefit in terms patient or relapse-free survival, but an increased risk of treatment related complications with maintaining daily corticosteroids beyond 6 months (McGregor et al. 2012). On the other hand, a study-level analysis seems to suggest lower rates of relapse in cohorts or studies wherein daily corticosteroids were continued long term.

Choice of treatment for a relapse depends upon the severity and manifestations as well as whether the patient was on maintenance therapy at the time of relapse. In patients who have already received cyclophosphamide in the past, rituximab is preferred choice of therapy at the time of relapse in order to limit the cumulative exposure to cyclophosphamide. If the relapse is mild, switching to an alternative maintenance agent or increasing the intensity of the maintenance regimen are also options. If a patient remained in remission on maintenance therapy and relapsed after it was discontinued, restarting the same agent is reasonable.

Prognosis/Outcome

The prognosis of patients with ANCA vasculitis has been analyzed in a number of cohort studies. A number of prognostic factors has been described based on retrospective analysis of cohort studies and clinical trials. In the early acute phase of the disease, the presence of diffuse pulmonary hemorrhage is recognized as a major risk factor for death. In that setting, the level of serum creatinine at the time treatment is initiated is the most important predictor of renal recovery.

However, even patients with very low-renal function (estimated GFR < 15 ml/min/1.73 m^2) at presentation can recover significant renal function. The likelihood of ESRD is predicted by the response to treatment in the first 4 months. A study of patients with severe kidney failure at presentation showed that only 5% of patients who were still dialysis dependent after 4 months subsequently recovered renal function. Histopathologic chronicity index score and baseline eGFR (greater than or less than 10 ml/min/1.73 m^2) were both associated with the likelihood of treatment response by 4 months. However, even among patients with the highest chronicity index score and lowest eGFR, 14% of those treated with cyclophosphamide and corticosteroids had a response to treatment (defined as survival off dialysis without active vasculitis at 4 months) (Lee et al. 2014). Therefore, based on these findings, there is no threshold of renal function or pathological findings which should preclude treatment. However, if a patient remains dialysis-dependent at 4 months, in the absence of extrarenal manifestation of disease, the risks of continued immunosuppressive therapy likely outweigh the potential benefits.

Although induction therapy is usually effective at getting patients into remission – about 80–85% of patients will achieve remission after treatment with cyclophosphamide – relapse is common (De Groot et al. 2009). Relapse can occur months to years after achieving remission. Reported numbers vary, depending in part upon the population included and follow-up time, but relapse occurs in roughly 40–50% of patients that initially achieve remission, within several years of achieving remission (Hogan et al. 2005; De Groot et al. 2001; Hoffman et al. 1992; Westman et al. 1998). Factors predicting an increased risk of relapse include PR3 ANCA positivity (HR 1.66–1.77), lung involvement (HR 1.56–1.68), and upper airway involvement (HR 1.58) (Hogan et al. 2005; Pagnoux et al. 2008a). It has been suggested that persistent PR3-ANCA positivity is associated with an increased risk of relapse, but, as noted above, a more recent study found no evidence of this association (Sanders et al. 2016).

The question of whether to use maintenance therapy for all patients and how long to continue is a challenging one as this has not been answered with the existing data. These decisions must weigh the risk of continued immunosuppressive therapy with the risk of relapse. Serious infection is a major risk and cause of mortality in these patients, but relapsed disease remains a source of substantial morbidity and mortality as well. There is a great degree of heterogeneity in patients' courses, with some patients relapsing frequently, and others entering long periods of remission off of all immunosuppressive therapy. However, even though risk factors for relapse have been identified, these are as yet insufficient to confidently predict an individual patient's course. Thus, the decision should be an individualized one taking into account a patient's unique clinical history and risk factors, and consistent regular follow-up remains an important part of the long-term management of patients with ANCA vasculitis.

Unlike patients with anti-GBM disease alone who typically have a severe renal failure at presentation but a very low frequency of relapse, patients who have concurrent anti-GBM and ANCA disease, tend to have a relapsing course similar to that of patients with vasculitis.

The outcomes of patients with ANCA vasculitis have evolved over time as therapy has evolved. As mentioned previously, mortality was very high without treatment but has improved substantially with most patients achieving remission with induction therapy. Consequently, mortality due to disease has decreased dramatically, as has the overall mortality rate. However, the major cause of mortality has shifted from active vasculitis to infections and other adverse events of treatment (Little et al. 2010; Harper 2013). A review of 1 year outcomes in a group of 524 patients from clinical trials reported a 1-year mortality of 11.1%, with 59% of these deaths due to adverse events from therapy (infection the most common), and only 14% from active disease (Little et al. 2010). In addition to declining mortality rates, rates of end-stage renal disease (ESRD) have decreased over time with improvements in therapy as well (Rhee et al. 2016).

In patients who undergo renal transplant, disease can recur in the transplanted kidney in about 17% of patients. The presence of detectable ANCA at the time of transplant does not appear

to correlate with the risk of recurrence (Nachman et al. 1999). More recently, a study of 12 ANCA vasculitis patients transplanted while in remission reported that six experienced a relapse post-transplant but achieved remission after immunosuppression was increased (except for one reported to be noncompliant who suffered rejection) (Geetha et al. 2017). Though the relapse rate in this group was higher, the numbers were small.

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ANCA-Associated Vasculitis, Pediatric

17

Keisha Gibson and Dorey Glenn

Contents

Abstract

Antineutrophil cytoplasmic autoantibody (ANCA)-driven vasculitis is associated with high morbidity in children and adolescents. Albeit rare, the disease warrants efficient diagnosis and aggressive treatment as more than half of these children experience irreversible organ damage and in particular chronic kidney disease. Distinct clinical phenotypes of this form of vasculitis exist, and the classification and definitions of these phenotypes have evolved over the decades. As new insights into the pathophysiology of ANCA-associated vasculitis grow, new potential therapies are slowly emerging.

Keywords

ANCA · Vasculitis · Small-vessel vasculitis · Granulomatosis with polyangiitis · Microscopic polyangiitis · Eosinophilic polyangiitis · Pauci-immune glomerulonephritis

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Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-driven vasculitis is a small-vessel vasculitis associated with high morbidity and mortality. Fortunately and unfortunately, it is extremely rare in childhood. Indolent symptoms, which alone can be common in childhood, often smolder for months to years before the diagnosis becomes evident and significant damage has occurred (Morishita et al. 2017; Sacri et al. 2015; Iudici et al. 2018). Multiple organs are often affected, but rare variants where only the kidneys are affected (pauci-immune glomerulonephritis) exist. In 1994, the now routinely used Chapel Hill nomenclature provided names and definitions for the vaculitidies. This classification system is primarily based upon the size of affected vessels (Jennette 2013). In 2005, the European League Against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PReS) developed the first pediatric-specific classification of vasculitis (Ozen et al. 2006). This classification system, similar to the Chapel Hill nomenclature systems, is primarily based upon the size of affected vessels but also the presence or absence of granulomas.

Definitions

Systemic vasculitis is often classified upon the size of affected vessels. Unlike diseases such as Takayasu's vasculitis, which affects large caliber vessels, or Kawasaki and polyarteritis nodosa, which affect medium-sized vessels, Henoch-Schönlein purpura (HSP) and the ANCA-associated vasculitis affect small caliber vessels.

Several clinical phenotypes exist under the umbrella of ANCA-associated vasculitis. The Chapel Hill Consensus Conference in 1994 established the historical nomenclature, Wegener's granulomatosis, microscopic polyangiitis, and Churg Strauss syndrome to distinguish these subgroups. Due to inconsistent usage of terminology, the omission of diagnostic criteria in addition to clinical features, the absence of data identifying prognostic significance in the terminology, and finally the concern of an eponym derived from the name of a disgraced historical figure (Dr. Wegener), another International Consensus Conference convened in 2012 to revise the nomenclature system. Broadly, this conference introduced several new terms that better defined the pathological features of vasculitis subtypes and included categories for previously omitted or unidentified vaculitidies and secondary forms of vasculitis. In regard to small-vessel vasculitis, the term immunoglobulin A vasculitis was proposed to replace the historical term, HSP. Under the ANCA vaculitidies, the terms granulomatosis with polyangiitis and eosinophilic granulomatosis were proposed to replace the old eponyms, Wegener's granulomatosis and Churg Strauss syndrome, respectively. In 2005, the vasculitis working group of the Pediatric Rheumatology European Society (PRES), supported by the European League Against Rheumatism (EULAR), proposed new pediatric-specific classification criteria for GPA, which were validated in 2008. Under these pediatric-specific guidelines, children classified as "Wegener's granulomatosis" had to meet three of six set criteria: abnormal urinalysis, granulomatous inflammation on biopsy, nasal sinus inflammation, subglottic/tracheal/or endobronchial stenosis, abnormal chest radiography or CT, or PR3-ANCA/c-ANCA staining. There were no classification criteria proposed beyond that of the Chapel Hill Consensus for microscopic polyangiitis.

Epidemiology

The incidence of ANCA vasculitis in children is largely unknown. Recent pediatric GPA cohorts have reported incidence rates between 0.03 and 3.2 per 100,000 children per year. Other cohorts have reported incidence rates as high as 6.93 cases per million children per year (Cabral et al. 2009; Calatroni et al. 2017). ANCA vasculitis is more common in males than females in adults but in children occurs more commonly in females than males. Although commonly unreported, Black and Hispanic children represent less than 5% of reported cases of ANCA vasculitis (Morishita et al. 2017).

Specific environmental exposures have been implicated in both increased incidence of ANCA

vasculitis and relapsing disease. Individuals who are at high risk for silica dust exposure (farmers and dental workers) have been found to have as much of 1.9–4.4 higher odds for the development of ANCA vasculitis (Hogan et al. 2001; Gomez-Puerta et al. 2013). There may be a protective immunomodulatory effect of ambient UV radiation in the development of GPA and EGPA (Gatenby et al. 2009). A few medications such as PTU and levamisole-adulterated cocaine have been associated with increased incidence of ANCA vasculitis and relapsing disease (Slot et al. 2005; McGrath et al. 2011). However, data investigating levamisole to treat frequently relapsing nephrotic syndrome did not demonstrate an association with ANCA vasculitis (Gruppen et al. 2018). Chronic staphylococcal carriage is associated with a high rate of relapse in patients with GPA and has been documented from onset in up to 63% of patients diagnosed with GPA (Salmela et al. 2017; Popa et al. 2002).

Disease Subtypes

Granulomatosis with Polyangiitis (GPA)

Necrotizing granulomatous inflammation involving the upper and lower respiratory tract and necrotizing vasculitis predominantly affecting small- to medium-sized vessels are hallmark features in patients with GPA. The median age of diagnosis in childhood-onset disease is 14 years (Cabral et al. 2016). Constitutional symptoms such as fever, malaise, and weight loss are present in 90% of children at diagnosis. Pulmonary manifestations including pulmonary hemorrhage, nodules, infiltrates, pleurisy, oxygen dependency, and respiratory failure may be present in up to 80% of children. Eighty percent of patients have upper respiratory disease that may include oral or nasal ulcerations, nasal septum perforation (with subsequent saddle nose deformity), recurrent epistaxis, sinusitis, mastoiditis, hearing loss, and subglottic stenosis. Renal involvement is common and may include hematuria, proteinuria, glomerulonephritis, and kidney failure in up to 75% of children. The renal disease is classically necrotizing and pauci-immune on biopsy. Ninety percent of patients with GPA are ANCA positive, and 80–90% of those patients are cytoplasmic ANCA (c-ANCA)/pr3 positive. Biopsy of inflamed tissue is helpful to confirm the diagnosis (Fig. 1).

Microscopic Polyangiitis (MPA)

Patients with MPA are characterized by necrotizing vasculitis with few or no immune deposits that affect small- and less frequently medium-sized vessels. There is less demographic data about children with MPA compared to GPA. A recent multicenter North American Cohort compared 48 patients with MPA to 183 patients with GPA

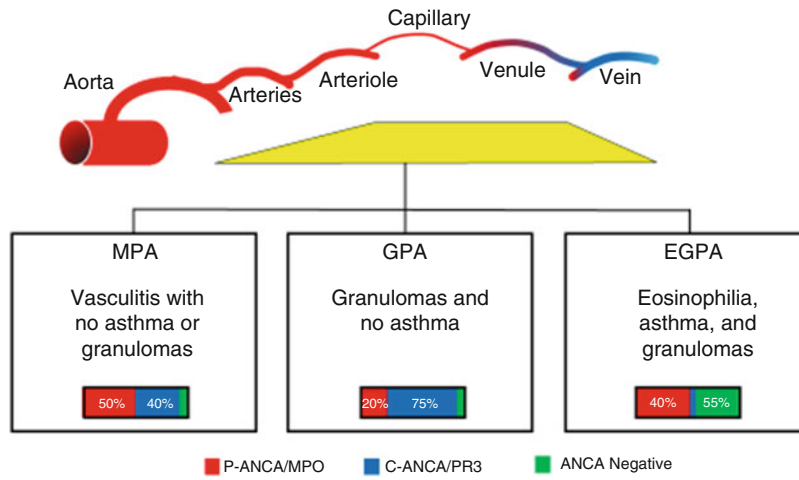

Fig. 1 Spectrum of ANCA-associated vasculitis

and found that children with MPA tended to present earlier (12 vs. 14 years of age) (Cabral et al. 2016). Similar to GPA, constitutional symptoms such as fever, malaise, and weight loss are present in 80–90% of children with MPA. While upper airway disease (subglottic stenosis, sinusitis, nasal septal changes, etc.) is virtually absent in patients with MPA, it is important to recognize that pulmonary involvement is not infrequent. Pulmonary involvement has been reported in up to 40% of children with MPA with up to 20% having frank alveolar hemorrhage. Patients with MPA almost globally display renal involvement with classic findings of glomerulonephritis (Cabral et al. 2016; Iudici et al. 2016). A French meta-analysis revealed that almost 95% of children with MPA had renal involvement at presentation compared to only 65% of children with GPA (Iudici et al. 2016). Renal histopathology is indistinguishable from that found in GPA. P-ANCA staining pattern with specificity to MPO (myeloperoxidase) is found in 80–90% of patients with MPA.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Eosinophil-rich and necrotizing granulomatous inflammation that commonly involves the respiratory tract and necrotizing vasculitis affecting small to medium vessels characterize patients with EGPA. Asthma and eosinophilia are common manifestations in these patients. Renal involvement is uncommon in this population. P-ANCA staining pattern is noted in up to 35–40% of cases, but over half of these patients test ANCA negative.

Pauci-immune "Crescentic" Glomerulonephritis (PICG)

The term pauci-immune glomerulonephritis represents intricate and overlapping "spectrum" of disease processes. About 10% of the cases in the pathologic continuum of PICG are ANCA negative despite similar clinical features and renal biopsy findings as compared to ANCA-positive cases. In addition, although pauci-immune necrotizing GN typically occurs in association with involvement of other organs in both GPA and MPA, some patients present with a renal-limited, ANCA-positive vasculitis.

Diagnosis

In 1982, antibodies directed against neutrophil cytoplasmic antigens were first described in patients with pauci-immune glomerulonephritis (Davies et al. 1982; Jennette and Falk 1997). There are two types of antineutrophil cytoplasmic antibody (ANCA) assays that are currently in wide use: indirect immunofluorescence assay, using alcohol-fixed buffy coat leukocytes, and enzyme-linked immunosorbent assay (ELISA), using purified specific antigens. Of these two techniques, the immunofluorescence assay is more sensitive, and the ELISA is more specific. The optimal approach to clinical testing for ANCA is therefore to screen with immunofluorescence assays, if available, and to confirm all positive results with ELISAs directed against the vasculitis-specific target antigens. However, since ANCA testing is not standardized, the sensitivity and specificity will vary with the laboratory; there are also no reference values for normal. With the c-ANCA pattern, the staining is diffuse throughout the cytoplasm. In most cases, antibodies directed against PR3 cause this pattern, but MPO-ANCA can occasionally be responsible. The perinuclear or P-ANCA pattern results from a staining pattern around the nucleus, which represents an artifact of ethanol fixation. With ethanol fixation of the neutrophil substrate, positively charged granule constituents rearrange themselves around the negatively charged nuclear membrane, leading to perinuclear fluorescence. Among vasculitis patients, the antibody responsible for this pattern is usually directed against MPO (and only occasionally PR3). Atypical ANCA patterns may be observed on immunofluorescence testing in patients with immune-mediated conditions other than systemic vasculitis (e.g., connective tissue disorders, inflammatory bowel disease, and autoimmune hepatitis). These

atypical ANCA patterns may be confused with P-ANCA patterns. However, ELISA is negative in such cases.

Pathophysiology

There is increasing evidence that ANCA may play a primary role in the development of necrotizing small-vessel vasculitis. The pathogenicity of ANCA has been demonstrated in mice by immunizing MPO knockout mice with MPO antibodies. In this model, anti-MPO antibodies and a necrotizing crescentic glomerulonephritis developed (Xiao et al. 2002). An interesting case report describes the recovery of MPO-ANCA in the cord blood of a neonate who developed pulmonary hemorrhage and renal disease and mother who at that the time had preeclampsia, low MPO titers, and a history of MPO vasculitis (Bansal and Tobin 2004). In vitro studies have demonstrated that ANCA can stimulate neutrophils to produce reactive oxygen species and lytic enzymes. However, before this can occur, pro-inflammatory cytokines [tumor necrosis factor-alpha (TNF-α), interleukin (IL) 1, and IL 18] must prime the neutrophils, leading to upregulation of neutrophil adhesion molecules (CD11b) and translocation of PR3/MPO antigens to the neutrophil surface membrane. Subsequent interaction between ANCA and the relevant ANCA antigen activates the neutrophil, causing increased vessel wall adherence and transmigration. The ensuing ANCA-mediated activation results in neutrophil degranulation and release of reactive oxygen species, resulting in vasculitis. Neutrophil extracellular traps (NETs) may play a role in the development of autoimmune diseases like ANCA vasculitis. NETs are extracellular fibers extending from neutrophils that are composed of decondensed chromatin threads laced with cytoplasmic proteins (Soderberg et al. 2015; Sangaletti et al. 2012). Neutrophils from AAV patients are more prone to release NETs spontaneously than neutrophils from healthy blood donors. NETs contain pro-inflammatory proteins and are thought to contribute to vessel inflammation directly by damaging endothelial cells and by activating the complement system and indirectly by acting as a link between the innate and adaptive immune systems through the generation of PR3- and MPO-ANCA. The activation and release of these NETs or NETosis have also been shown to be induced by ANCAs contributing to relapsing disease. This activation of neutrophils has also been found to lead to the release of properdin and factor B that both activate the alternative complement pathway. Activation of the complement pathway leads to the generation of C5a which then amplifies the inflammatory response via increased neutrophil recruitment, priming, and ANCA-mediated activation (van Timmeren and Heeringa 2012). Increased plasma levels of C5a have been found in patients with active ANCA vasculitis (Gou et al. 2013).

Growing data has substantiated the antigenic specificity of MPO, and PR3-ANCA are in fact genetically distinct. Both groups of antibodies appear to associate with different class II HLA genes (HLA-DQ for MPO and HLA-DP for PR3). PR3-ANCA also has been found to be associated with genes encoding for PR3 (PRTN3) and α1-antitrypsin (SERPINA1) (Alberici et al. 2014; Lyons et al. 2012).

Treatment

ANCA-associated vasculitis carried a nearly 100% mortality rate until cyclophosphamide and glucocorticoids were found to be efficacious by Dr. Fauci and colleagues in the late 1970s (Fauci et al. 1979). Treatment approaches in children with ANCA-associated vasculitis have relied heavily on conclusions drawn from adult studies. The CYCLOPS study aimed to answer whether pulse cyclophosphamide was superior to daily oral cyclophosphamide for the induction of remission of newly diagnosed ANCA patients. CYCLOPS randomized 149 adult patients with newly diagnosed ANCA vasculitis to pulse cyclophosphamide or daily oral cyclophosphamide (de Groot et al. 2009; Harper et al. 2012). Both groups received corticosteroids and azathioprine. Despite its lower cumulative cyclophosphamide dose, pulse cyclophosphamide resulted in similar

rates of remission as daily oral cyclophosphamide. Pulse cyclophosphamide was associated with a significantly lower risk of leukopenia but a nonsignificant trend toward higher risk of relapse. In 2012, the authors published follow-up results (median 4.3 years), showing a higher relapse in the pulse cyclophosphamide group than the daily oral group (39.5% vs. 20.8%; $P = 0.029$) with mean follow-up of 4.3 years (Harper et al. 2012). Despite an increased risk of relapse, there was no significant difference in renal function at last follow-up or end-stage renal disease (ESRD) between the two study arms. Ten (13%) pulse patients and eight (11%) daily oral patients developed ESRD. Eighty-three (42 pulse and 41 daily oral) patients did not have ESRD and had data on renal function available at last visit; in these patients, there was no difference in median creatinine at last follow-up (pulse limb, 117 (89–185) μmol/l; daily oral arm, 117 (105–144) μmol/l; p = 0.92).

There are almost no controlled clinical trials to guide therapy of pediatric patients with AAV, and most treatments are based on extrapolation from adult studies. High-dose corticosteroids and cyclophosphamide for at least 3 to 6 months are considered the gold standard of treatment with significant organ involvement of their ANCA vasculitis. Pediatricians face the added challenge of caring for a frequently relapsing disease in a population expected to have many life-years of disease in front of them. Due to the cumulative dose-dependent toxicity of cyclophosphamide, the need for less toxic therapies is paramount.

Whether cyclophosphamide can be further reduced or avoided completely by the use of rituximab was addressed in two randomized, controlled trials in adult patients. In the Randomized Trial of Rituximab *Versus* Cyclophosphamide for ANCA-Associated Renal Vasculitis (RITUXVAS) trial, 44 patients with newly diagnosed ANCA vasculitis were randomly assigned 3:1 either to rituximab plus cyclophosphamide or to cyclophosphamide alone (Jones et al. 2010). Rituximab for the treatment of Wegener granulomatosis and microscopic polyangiitis (Rituximab for ANCA-Associated Vasculitis [RAVE] trial) was a multicenter, double-blind, randomized, placebo-controlled trial of 197 patients to assess the noninferiority of rituximab plus corticosteroids *versus* cyclophosphamide plus corticosteroids in patients with new-onset and relapsing disease. In both trials, rituximab was shown noninferior to cyclophosphamide (Jones et al. 2015). In the RITUXVAS, remissions were common (approximately 90%), whereas in the RAVE trial, the remission rate was much lower (64%). Complicating the generalizability of the RAVE trial is exclusion of patients with alveolar hemorrhage requiring intubation and renal failure. These data support an important role for rituximab in the treatment of patients with ANCA vasculitis, but there is still insufficient evidence to support its role as solitary induction therapy along with corticosteroids in the setting of advanced renal presentations or pulmonary hemorrhage. Guidelines established by KDIGO and the EULAR-ERA-EDTA recommend rituximab be considered for treatment in patients (including children) who are not responding to conventional therapies (glucocorticoids and cyclophosphamide), have relapsing disease, or have a contraindication to conventional therapies (Radhakrishnan and Cattran 2012; Guerry et al. 2012). A recent report on the children hospitalized in the United States with ANCA-associated vasculitis revealed that pediatric subspecialists are moving toward rituximab as initial therapy, but controlled studies with long-term follow-up are not available to help us understand the efficacy and safety of this drug in this population (James et al. 2017). The contemporary, multicenter inception cohort registry for childhood vasculitis (ARChiVe) reported the outcomes in 48 children with MPA and 183 children with GPA. In this cohort, 76% were treated with both corticosteroids and either oral or intravenous cyclophosphamide, and 12% received rituximab as initial therapy (Cabral et al. 2016).

Notably in the aforementioned pediatric study, plasma exchange (PLEX) was employed as part of initial therapy in 21% of these children as an adjunctive initial therapy. The role of PLEX in patients with advanced renal disease and pulmonary hemorrhage has remained controversial mainly due to the lack of consensus on what

defines "severe" renal involvement and concern for removal of coagulation factors in patients with pulmonary hemorrhage. ANCAs have been shown to be pathogenic, and thus there removal as part of the therapy for the most severely affected patients makes intuitive sense. A series in 2003 demonstrated the survival of 19 of 20 patients with pulmonary hemorrhage (45% requiring mechanical ventilation) on presentation (Klemmer et al. 2003). There are several non-randomized, controlled studies and case series that indicated a renal recovery rate of 75% in PLEX-treated patients presenting with creatinine greater than 5.8 mg/dL (>500 μmol/L) (Pusey et al. 1991; Jayne et al. 2007; Walsh et al. 2013). The 2012 KDIGO guidelines recommend the addition of PLEX for patients requiring dialysis or with rapidly increasing serum creatinine (1C), patients with diffuse pulmonary hemorrhage (2C), and patients with an overlap syndrome of ANCA vasculitis and anti-glomerular basement membrane glomerulonephritis (2D) (Radhakrishnan and Cattran 2012). Again, there are no reported data in children.

Outcomes

ANCA vasculitis is associated with significant organ damage, particularly renal, and 50% of patients can be expected to have a disease relapse. Of the children who develop the classical pauci-immune necrotizing crescentic glomerulonephritis (ANCA GN), 30–40% will progress to chronic kidney disease (CKD), and up to 34% may progress to end-stage renal disease (ESRD). Hattori et al. reported 80% renal survival at 1 year and 75% renal survival at 39 months in 31 children with ANCA-associated GN who presented in a 7-year period from all of their hospitals associated with the Japanese Society for Pediatric Nephrology (Hattori et al. 2001). Among 66 children reported in a multicenter French cohort, renal survival was 74, 70, and 59% at 1, 5, and 10 years, respectively. These lower survival rates were measured despite almost 90% of children experiencing remission status after induction therapy (Sacri et al. 2015). Relapsing disease has been described as a contributor to poor renal survival in patients with ANCA-associated vasculitis. Iudici et al. reported relapses in 33% of their MPA, 50% in those with EGPA, and 83% in those with GPA who had experienced remission status following induction therapy in a cohort of 33 children (Iudici et al. 2018). Across four cohort studies of children with ANCA vasculitis, relapses were reported in anywhere from 25 to 50% of the patients (Iudici et al. 2015, 2016; Hattori et al. 2001; Basu et al. 2015). End-stage kidney disease across these cohorts ranges from 22 to 34% and of even greater concern anywhere from 5 to 9% of study cohort reported deaths.

As with any cause of ESKD, transplantation is the renal replacement therapy of choice for patients with ESKD due to ANCA GN. Graft survival rates in adult patients with ESKD due to ANCA GN range from 77 to 100% at 5 years. Transplant data in children is limited to mostly case reports, but one recent review reported preserved graft function in six of seven children with ANCA GN who received kidney transplant. There were no episodes of recurrent disease, and the one graft that was lost was due to medication nonadherence (Noone et al. 2017). Recurrent ANCA GN has been reported in anywhere from 3 to 50% in small single-center studies. A pooled analysis of 127 patients with ESKD due to ANCA however revealed a relapse rate of 17.3% with average time to relapse of 30.9 months (Nachman et al. 1999). While it is generally recommended that patients with ESKD from ANCA GN experience 1 year of remission from active ANCA disease prior to transplantation, the need for absent circulating antibodies to MPO and PR3 is not supported by data (Radhakrishnan and Cattran 2012; Nachman et al. 1999; Goceroglu et al. 2016). The presence of circulating antibodies correlates poorly with active disease, and thus the use of tools such as the Birmingham Vasculitis Activity Score and the Pediatric Vasculitis Activity Score may be more helpful in determining quiescent disease (Dolezalova et al. 2013; Mukhtyar et al. 2009).

Future Directions

Exciting insights into the pathophysiology of ANCA vasculitis are emerging every year. Despite this expanding knowledge, there has been little advancement in the development of biomarkers that can guide clinicians when to wean immunosuppression in a patient who has experienced several years of disease remission. We know very little about how the emerging data regarding NETosis, epigenetic influences, and other factors in autoimmunity are impacted by age – an important factor when considering this disease in children. Given the toxicities of standard therapies such as steroids and cyclophosphamide, novel therapies such as drugs blocking the C5a receptor to modulate complement activity in ANCA are currently in trials. Clinical trials assessing the efficacy and safety of potential treatments have consistently excluded patients under 18 years of age. The pediatric community must advocate the inclusion of our young patient population in these studies to insure continued improvement in patient outcomes and survival as our knowledge of the rare disease expands.

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Anti-glomerular Basement Membrane Disease

18

Corinne Benchimol

Contents

Abstract

Anti-GBM antibody disease is a rare autoimmune disorder characterized by circulating autoantibodies directed against specific antigenic targets within the glomerular and alveolar basement membranes. It is extremely uncommon in children, and typically presents with acute renal failure caused by a rapidly progressive glomerulonephritis that is commonly associated with crescentic changes.

Keywords

ANCA: Antineutrophil cytoplasm antibodies · Alpha-3(IV) NC1: Alpha-3 chain of type IV collagen · ELISA: Enzyme-linked immunosorbent assay · HLA: Human leukocyte antigen

Introduction

Anti-GBM antibody disease is a rare autoimmune disorder characterized by circulating autoantibodies directed against specific antigenic targets within the glomerular and alveolar basement membranes. It is extremely uncommon in children, and typically presents with acute renal failure caused by a rapidly progressive glomerulonephritis that is commonly associated with crescentic changes. The disease may present with glomerulonephritis alone but is often accompanied with potentially life-threatening pulmonary hemorrhage. Goodpasture's syndrome is a clinical term often used in those patients that have rapidly progressing glomerulonephritis (RPGN) and

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pulmonary hemorrhage while Goodpasture's disease describes patients with RPGN with or without pulmonary hemorrhage associated with proven anti-GBM antibodies.

Epidemiology

The incidence of anti-GBM disease is rare and is estimated to occur in one case per million populations per year (Bolton 1996). Anti-GBM glomerulonephritis accounts for 20% of all cases of rapidly progressive glomerulonephritis in adults and for less than 10% of such cases in children (Bolton 1984; McLeish et al. 1978). In adults, anti-GBM disease is responsible for approximately 5% of all cases of glomerulonephritis and is diagnosed in 1–2% of renal biopsy specimens (Bolton 1984, 1996; Wilson and Dixon 1973). It occurs more commonly in Caucasians than in black people with an age of distribution that tends to be bimodal; older children and young adults (20–30 years) and adults (60–70 years). The prevalence is higher in men in the younger age group and women in the older age group (Hudson et al. 2003). The older patients tend to have isolated glomerulonephritis while the younger patients tend to present with the full Goodpasture's syndrome that includes pulmonary hemorrhage (Savage et al. 1986; Levy et al. 2001). Anti-GBM disease is rare in children with limited published data in this age group. The US Renal Data System (USRDS) reports that 0.5% (40/8228) between 2004 and 2008 and 0.8% (54/7713) between 2009 and 2013 were attributable to Goodpasture's syndrome, presumably anti-GBM disease. The disease can present all-year round, but a greater number of cases are diagnosed during spring and summer. Some localized outbreaks have been associated with infection.

Pathogenesis

The disorder was named after Dr. Ernest Goodpasture, a pathologist, who identified the syndrome in 1919 during an influenza pandemic when he reported his findings on a patient who died from pulmonary hemorrhage and renal failure (Goodpasture 1919). In the 1950s, Stanton and Tange used the term "Goodpasture's syndrome" to describe a series of patients with pulmonary-renal syndrome. Krakow and Greenspoon later identified the glomerular basement membrane as the antigen. In 1967, Lerner, Glassock, and Dixon showed that taking the antibody from kidneys of patients with Goodpasture's disease produced the glomerulonephritis in animals thereby showing that an autoantibody itself can cause the disease. Hudson and coworkers identified the noncollagenous (NC1) domain of the alpha-3 chain of type IV collagen (alpha-3 (IV)NC1) as the Goodpasture autoantigen. The cDNA for the alpha-3(IV) chain was cloned and identified to the q35-37 region of the long arm of chromosome 2 (Morrison et al. 1991; Turner et al. 1992). Anti-GBM nephritis is characterized by circulating autoantibodies directed against an antigen in the glomerular or alveolar membrane. The inciting stimulus is unknown but both genetic and environmental factors have been implicated in the pathogenesis of anti-GBM nephritis. In most patients, the principal target antigen of the anti-GBM antibodies is a 28-kd monomeric subunit present within the noncollagenous domain (NC1) of the alpha-3 chain of type IV collagen. Collagen IV is a family of six alpha-chains (alpha-1 through alpha-6) where the alpha-3NC1 monomer is assembled into the collagen IV network through the association of the alpha-3, alpha-4, and alpha-5 chains to form a triple helical promoter. The Goodpasture antigen is usually hidden from immune surveillance through interactions with other noncollagenous domains of the triple helical promoter alpha-345NC1. A perturbation of the quaternary structure of the alpha-345NC1 hexamer induces a pathogenic conformational change in the alpha-3NC1 subunit, exposing it to the immune system which in turn elicits an autoimmune response. In Goodpasture's disease, the autoantibodies require hexamer dissociation to unmask hidden epitopes (Lerner et al. 1967). Two conformational epitopes of anti-GBM antibodies, named EA and EB, have been identified at residues 17–31 and 127–141 of the alpha-3(IV)

NC1 (Netzer et al. 1999; Hellmark et al. 1999). Although most of the antibody activity is directed to the alpha-3(IV)NC1 domain of type IV collagen, antibody may be also directed against other alpha chains and other constituents of the GBM. Both alpha-5NC1 and alpha-3NC1 autoantibodies are frequently present in the kidneys and lungs of patients with Goodpasture's disease (Johnansson et al. 1993; Kefalides et al. 1993; Matsukura et al. 1993). The anti-GBM antibodies bind to a conformation-dependent epitope encompassing the EA region in the alpha-5NC1 monomer and EA and EB in the alpha-3NC1 monomer. Anti-GBM antibodies are almost exclusively of the immunoglobulin G (IgG) isotype generally of the IgG1 and IgG4 subclasses, although IgM and rare IgA-mediated cases have been described (Savage et al. 1986; Border et al. 1979; Fervenza et al. 1999). Linear IgG deposition along the GBM by direct immunofluorescence of kidney biopsy defines the disease. When the autoantibodies bind to their reactive epitopes in the basement membranes, they activate the complement cascade, causing tissue injury. This is considered a classic type II reaction in the Gell and Coombs classification of antigen-antibody reactions. The mechanism of injury in anti-GBM nephritis is complex. Once complement is activated by the binding of anti-GBM antibodies to the GBM, the filtration barrier, and Bowman's capsule is disrupted causing proteinuria. Complement cascade activation causes polymorphonuclear leukocytes, antigens, and monocytes to infiltrate the glomeruli. Fibrinogen leaks into Bowman space and breaks down fibrin by prothombinase enzyme, which is associated with active monocytes. These monocytes generate crescents in the glomeruli. Furthermore, interleukin-1 may attract fibroblasts from renal interstitium which enhance crescent formation (Couser 1988; Fox and Swann 2001). In addition to the role of T cells in B cell activation and the production of anti-GBM antibodies, they are also directly involved in tissue injury. Migration of macrophages and neutrophils into the kidney is induced by CD4+ and CD8+ T-cells (Wu et al. 2002). The participation of antibody and associated pathways in triggering an inflammatory response alone cannot fully explain many aspects of the pathways in experimental and human glomerulonephritis. T cell-mediated cellular immunity has long been suspected as potentially the most important mediator of glomerulonephritis with increasing evidence for the importance of cell-mediated immunity in the initiation and maintenance of Goodpasture's disease (Wu et al. 2001). In experimental models and human studies, both humoral and cellular mechanisms have been demonstrated to be involved in disease pathogenesis. Studies demonstrate that in the absence of B cells and immunoglobulin, cell-mediated processes are capable of inducing renal injury in experimental autoimmune Goodpasture's disease induced by the same antigen responsible for human anti-GBM glomerulonephritis. Regulatory T cells (CD4+ CD25+) seem to play a role in the regulation of the autoimmune response and reduce the severity of glomerular lesions seen in murine anti-GBM glomerulonephritis (Salama et al. 2003; Salama et al. 2001). Passive transfer studies showed that sera from mice with glomerulonephritis containing autologous antibodies can induce proteinuria. Therefore, both cell-mediated processes and humoral mechanisms induce injury in anti-GBM glomerulonephritis (Salama et al. 2001; Dean et al. 2005). If left untreated, the inflammatory reaction in the glomerulus will produce proteinuria which will lead to development of tubular epithelium damage, interstitial nephritis, and subsequent fibrosis. Although the alpha-3(IV) collagen is also found in a number of other specialized basement membranes throughout the body such as the choroid plexus in the brain, uveal tract, thymus, and the cochlea, all patients with anti-GBM antibodies develop glomerulonephritis, 40% develop pulmonary hemorrhage, and very few to none develop other organ involvement.

Clinical Presentation

Most patients initially present with hematuria, erythrocyte casts, proteinuria (less than 3 g every 24 h), pallor, elevated serum creatinine, and oliguria indicative of progressive renal

insufficiency. This presentation is similar to other forms of rapidly progressive glomerulonephritis and is often diagnosed late because of the vague symptomology early on. Systemic features such as fatigue, weakness, loss of appetite, and flu-like symptoms may be present but fever, weight loss, arthralgia, and myalgia are usually absent. Significant hypertension is usually not a feature of the disease. Pulmonary hemorrhage which affects about 40% of patients is manifested as blood streaked sputum to massive, fatal pulmonary hemorrhage. Hemoptysis is generally episodic, and occasionally it is so extreme that it floods the lungs and produces asphyxia and possibly death. Patients often complain of shortness of breath and cough. Chest radiographs will show the appearance of alveolar shadowing with sparing of the upper fields suggestive of lung hemorrhage. More sensitive and clinically valuable test of lung function is the diffusing capacity of the lungs to carbon monoxide (DLCO, also known as transfer factor for carbon monoxide or TLCO) which is designed to reflect properties of the alveolar-capillary membrane, specifically the ease with which oxygen moves from inhaled air to the red blood cells in the pulmonary capillaries. This is increased in lung hemorrhage secondary to the presence of hemoglobin in the alveoli (Donaghy and Rees 1983). Evaluation of lung involvement with imaging studies such as computed tomography or magnetic resonance is not necessary for the diagnosis. Making prompt diagnosis of pulmonary hemorrhage is imperative as it is the primary cause of early death in anti-GBM disease. In adults, pulmonary hemorrhage occurs in smokers, can follow pulmonary infections, or be associated with pulmonary injury. In children, this association is not clear.

Renal involvement can occur in isolation or in association with pulmonary hemorrhage. It can range from normal to rapidly decreasing over a few weeks or months (Bailey et al. 1981; Zimmerman et al. 1979). Progressive renal failure leading to oliguria is a poor prognostic sign. Early diagnosis and intervention correlate with improved outcome (Merkel et al. 1994; Shah and Hugghins 2002). There have been reports of individuals with anti-GBM disease and normal renal function (Savage et al. 1986; Ang et al. 1998). The histological abnormalities are not as marked in patients with normal renal function as in those with renal impairments. These patients have the potential to progress rapidly but have a good prognosis when treated aggressively.

In common with other autoimmune disorders, there is mounting evidence that genetic factors affect the susceptibility to anti-GBM antibody disease with a strong association with the inheritance of human leukocyte antigen (HLA) class II genes. In the regulation of immune responses, the HLA-DR and HLA-DQ class II molecules primarily function to bind and present peptides derived from extracellular proteins to CD4+ cells. Serological typing studies in patients with anti-GBM disease have shown an increased incidence of DR alleles with strong positive associations with HLA-DR15 and DR4 alleles and negative associations with DR7 and DR1 (Phelps and Rees 1999).

About 5–10% of patients with Alport's syndrome, who undergo transplantation, develop anti-GBM nephritis. Alport's syndrome, a form of hereditary nephritis accompanied by sensorineural hearing loss and ocular abnormalities, is caused by mutations in the genes encoding the α3, α4, or α5(IV) collagen chains which prevents the assembly of the α3α4α5(IV) collagen chains in the basement membrane. Alport's post-transplantation nephritis is mediated by the deposition of alloantibodies to the α3NC1 and α5NC1 domains in response to the "foreign" α345 collagen network that is absent in the kidneys of patients with Alport's syndrome but present in the renal allograft. Thus, the α345NC1 hexamer is targeted by antibodies that arise in both Goodpasture's disease and Alport's post-transplantation nephritis, but these antibodies have different binding properties. Alloantibodies bind epitopes exposed on the native hexamer, whereas in Goodpasture's disease the autoantibodies require hexamer dissociation to unmask hidden epitopes (Pedchenko et al. 2010). There is transient appearance of low titers of these antibodies, but the risk of developing severe nephritis is small and the overall outcome for renal transplantation in Alport's is good. Severe crescentic

GN may occur and is undistinguishable from Goodpasture's syndrome and should be treated the same.

Diagnosis

The detection of anti–GBM antibodies either in the circulation or in kidney tissue is required to make the diagnosis of anti-GBM antibody disease. Anti-GBM antibodies are normally detected in serum using a direct enzyme-linked immunosorbent assay (ELISA) method or by Western Blot to confirm specificity of the antibody if doubts exist. False-positive and false-negative results occasionally may occur using this method. The former generally result from sera containing high levels of polyclonal immunoglobulin and can be excluded by both appropriate negative controls and using the more sensitive and specific Western blotting method, only accessible in reference laboratories. False-negative results are less common but may occur in patients with low antibody titers or because non-IgG immunoglobulins (IgA) cause disease, which may not be detected in standard anti-GBM ELISAs (Salama et al. 2002). Occasionally, false positive results occur from commercial ELISA assays that do not use native or recombinant human alpha-3(IV) antigen substrates which are more sensitive and specific (95% sensitive and 100% specific) (Sinico et al. 2006).

Unless contraindicated, a renal biopsy should be performed right away because prognosis and response to therapy is closely tied to duration of disease, level of renal function prior to diagnosis and treatment, and to ascertain whether another disease is present. Treatment is related to the degree of crescent involvement and the amount of sclerosis and fibrosis found at presentation. On light microscopy, the early changes are of a focal proliferative GN. This proliferative response usually progresses to destruction of the glomerular basement membrane and cellular proliferation leading to necrosis and extensive crescent formation and interstitial inflammation. Crescents are formed by parietal cells and macrophages in combination with GBM destruction. The diffuse inflammation with segmental or total necrosis and extensive crescent formation eventually leads to scarring and the appearance of an end-stage kidney. Linear binding of IgG along the glomerular capillaries and sometimes along the distal tubular basement by direct immunofluorescence microscopy is universally detected and is pathognomonic. However, this pattern of staining has been reported in a number of other circumstances (Table 1).

Aside from testing the serum for anti-GBM antibodies, the serum should also be tested for antineutrophil cytoplasm antibodies (ANCA) because patients with acute glomerulonephritis with or without pulmonary hemorrhage may also have a vasculitic syndrome. They have similar clinical manifestations at presentation but usually also have signs of systemic vasculitis. It is estimated that between 20% and 30% of patients with anti-GBM disease also test positively for ANCA at time of diagnosis, almost always of the MPO-ANCA (anti-myeloperoxidase) and about 8% of ANCA-positive patients will have anti-GBM antibodies. The reason for concurrent ANCA and anti-GBM antibody production in selected patients is not known. It is possible that ANCA-related proteases damage or expose the nephritogenic epitope in alpha-3(IV) collagen in GBM, and this in turn leads to anti-GBM antibody production. There does not appear to be a structural relationship between ANCA and alpha-3(IV) collagen so a cross reactivity is unlikely (Kalluri et al. 1997). Rapid and correct diagnosis of the

Table 1 Cause of linear staining on direct immunofluorescence microscopy of kidney tissues

Anti-GBM disease
Goodpasture's syndrome
Idiopathic RPGN
Membranous nephropathy with secondary anti-GBM disease
ANCA positive vasculitis
Non-anti-GBM disease
Alport's syndrome after renal transplantation
Diabetic nephropathy
Severe nephrotic syndrome
Systemic lupus erythematosus
Transplant biopsies
Post-infectious glomerulonephritis

underlying tissue lesion is essential for the choice of appropriate therapy. Patients with ANCA-associated disease may be more likely to have treatable disease than those with only anti-GBM disease.

Treatment

The pathological diagnosis has major importance in the choice of appropriate therapy, the response to therapy, and long-term prognosis. Without treatment, the prognosis for patients with anti-GBM disease is dismal. Early intervention improves prognosis, therefore time from development of symptoms to diagnosis is critical, as response to therapy are closely tied to duration of disease and level of renal function prior to diagnosis and treatment. The prognosis at presentation is worse if there is oliguria, the plasma creatinine is above 5 mg/dl (442 μmol/L), advanced fibrosis, more than 50% crescents on renal biopsy, or a need for dialysis. The use of steroids or immunosuppressive drugs has shown little benefit, but the introduction of combined treatment with plasmapheresis, cyclophosphamide, and steroids dramatically improved the outcome and survival of patients with this disease. The rationale for this approach is that plasmapheresis removes circulating anti-GBM antibodies and other mediators of inflammation, cyclophosphamide prevents further new antibody formation, and steroids act as a powerful anti-inflammatory agent. The need to be aggressive in removing pathogenic anti-GBM antibodies is necessary in view of the fulminant clinical course with devastating consequences in terms of morbidity and mortality which cannot be achieved with drug therapy alone. Although most of the reported studies have been uncontrolled, renal function improves with this treatment in patients who present with serum creatinine less than 5–6 mg/dl, but in far fewer of those with higher levels, or those who require dialysis. Patient and renal survival vary with severity of disease at presentation. In the absence of pulmonary hemorrhage, the benefits of treatment may outweigh the risk in patients who present with advanced renal failure. The likelihood of a renal response in patients who present with dialysis-dependent renal failure is very low but because it is difficult to assess the dialysis-dependent patient who may recover renal function or patients whom irreversible injury is less predictable, combined plasmapheresis and immunosuppressive therapy is given. Trials are difficult in such rare disease, but the improved outcome with plasma exchange reported in many series makes it generally recommended for the treatment of patients with anti-GBM disease. Recommended protocols include intensive plasmapheresis for 2–3 weeks, initially daily then alternate day until anti-GBM antibodies are reduced to near normal levels or if the patient has improved. Plasmapheresis may be continued longer if anti-GBM antibodies are still detectable or in the presence of clinical evidence of disease activity. Plasmapheresis is usually accompanied with immunosuppressive therapy which includes corticosteroids and cyclophosphamide. Initially, steroids are given as pulse methylprednisone daily for 3 days (15–30 mg/kg to a maximum dose of 1000 mg) followed by oral prednisone at 1 mg/kg per day (maximum of 80 mg), eventually tapered over months once remission is induced. Cyclophosphamide is given orally at 2 mg/kg per day (maximum of 100 mg), adjusted to maintain a white blood cell count of approximately 5000. Intravenous cyclophosphamide at 1 gm/m^2 is used in patients who cannot take oral medications or who have severe renal failure and pulmonary hemorrhage. Bladder toxicity from cyclophosphamide may be increased if oliguria is present. The initial treatment of acute life threatening pulmonary hemorrhage is with pulse methylprednisolone for 3 days. The duration of immunosuppressive therapy is not well established. Anti-GBM antibodies must be monitored at regular intervals because it may take up to 6–9 months before cessation of autoantibody formation occurs. In patients who achieve remission, cyclophosphamide is continued for 2–3 months and prednisone for another 6–9 months. Patients who continue to have clinical or serologic active disease at 3–4 months need longer immunosuppression (6–9 months). Azathioprine may be substituted for cyclophosphamide to reduce adverse effects, especially in

patients needing prolonged immunosuppression. Recurrence of disease with presence of positive anti-GBM antibodies warrants another course of plasmapheresis. Rituximab, a chimeric monoclonal antibody which depletes CD20-positive B cells, has been used as an alternative approach in the treatment of anti-GBM antibody disease with some success. (Syeda et al. 2013)

Data in the literature on pediatric anti-GBM disease are primarily limited to case reports, likely due to the relative infrequency of this disease at any one institution. Although rare, anti-GBM disease is considered in the differential diagnosis of pediatric patients with RPGN.

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IgA Nephropathy: Clinical Features, Pathogenesis, and Treatment

19

Gerald B. Appel

Contents

Abstract

IgA Nephropathy is recogniszed as the most frequent form of glomerulonephritis worldwide. The disease is defined by the presence of IgA immune deposits in the glomereuli. Although the presentation is variable, the course is often one of insidous progression to end stage kidney disease with 15-20% of patients reaching this point by 10 yrs and more with furhter follow. Recent studies have helped define which patients are high risk for progression using clinical and histopathologic features defined by a uniform pathology scoring system. Although much has recently been discovered about the pathogenesis of IgAN treatment studies have given conflicting results.

Keywords

IgA nephropathy · Glomerular disease · Henoch schoelein purpura · Glomerulonephritis

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Introduction

Worldwide, IgA nephropathy (IgAN) is recognized to be the most frequent form of idiopathic glomerulonephritis (Wyatt and Julian 2013; Barratt and Feehally 2005; Li and Liu 2004; Magistroni et al. 2015). At present IgAN is defined by the presence of the IgA deposits in the glomerulus. Its clinical presentation can vary from isolated asymptomatic microscopic hematuria to fulminant crescentic rapidly progressive glomerulonephritis. The course is often one of an insidious progression to end-stage kidney disease (ESKD) with 15–20% of patients reaching ESKD by 10 years, 30–40% in 20 years, and a greater number over longer periods of time. Clinical and histopathologic studies now help define the "high-risk" patients who are likely to progress over these time intervals. Recent studies have also helped clarify the putative pathogenesis of IgAN and its relationship to Henoch-Schönlein purpura (HSP). This pathogenesis includes production of an abnormal IgA, antibody formation against this immunoglobulin, and the deposition of immune complexes in the glomeruli with subsequent inflammation and sclerosis. Newer and more extensive studies are clarifying the role of heredity in IgAN. Finally, controlled treatment trials are now adding to many anecdotal, uncontrolled trials in clarifying the therapy of the disease.

Epidemiology

In virtually all studies, IgAN is more frequently found in Caucasians and in those of Asian background than in those of African descent (Magistroni et al. 2015; Kiryluk et al. 2012; Crowley-Nowick et al. 1991). IgAN is also more prevalent in East Asia than in Europe or the United States (Li and Liu 2004; Magistroni et al. 2015; Tojo et al. 1987). IgAN was the most common form of glomerular disease in China until quite recently, when diabetes overtook it in frequency. An analysis of over 13,000 biopsies from China showed IgAN to be present in 45% of all cases of primary glomerular disease (Li and Liu 2004). Many studies of the disease have been performed in Asian populations where a high percent of biopsies performed show IgAN (Sugiyama et al. 2011; Zhou et al. 2009). Whether data from one genetic population can be applied to others is only now being investigated. Predominant IgA mesangial deposits have been found in a variety of other forms of glomerular disease including minimal change disease, thin basement membrane disease, and diabetic nephropathy. While some of these findings are likely coincidental, the frequency of others, such as minimal change disease, raises the possibility of a predilection for the concurrence of the two diseases.

IgAN is most commonly diagnosed in young adults, although it can affect anyone from the pediatric to the geriatric age group, and in the North America and Europe, it is more common in males than females. The presentations may vary with the age and nature of the population studied. In developed countries children and young adults often present with episodes of gross hematuria following upper respiratory infections or physical exertion even though there has been no evidence of traumatic injury. In adults it is not uncommon to have patients first findings detected when they are asymptomatic or have minor symptoms or only mild hypertension. This may occur on insurance physicals, sports physicals, pregnancy screening for proteinuria, or screening for military induction. Less commonly adults will present with gross hematuria, the nephrotic syndrome, or a nephritic or rapidly progressive glomerulonephritis picture.

IgAN is typically a primary disease affecting only the kidneys. Mesangial IgA deposits have also been found in up to 10% of healthy individuals (Suzuki et al. 2003). IgA deposition in the glomeruli has occurred as a secondary process in a number of systemic diseases including celiac disease, cirrhosis of the liver, and HIV infections. Up to one third of patients with celiac disease will have glomerular deposits of IgA (Pasternack et al. 1990). However, the vast majority have no clinical symptoms. This is also found in alcoholic cirrhosis and at times in cirrhosis due to hepatitis B and hepatitis C infection (Pouria and Feehally 1999). Glomerular IgA immune deposits have also been noted in patients with AIDS and HIV

infection. Most have no clinical renal disease related to the deposits (Beaufils et al. 1995; Weiner et al. 2003). Rarely idiotypic IgA antibodies directed against anti-HIV immunoglobulins have been noted in the glomeruli of these patients. Some patients with granulomatous polyangiitis, inflammatory bowel disease, and dermatitis herpetiformis have all also been noted to have IgA glomerular deposition.

IgA vasculitis, also known as Henoch-Schönlein purpura, is a systemic disease that occurs most commonly in children and is characterized clinically by glomerulonephritis, skin purpura, gastrointestinal disease, and joint involvement. Its pathology whether by dermal or other biopsy is that of a small vessel vasculitis with IgA deposition observed on immunofluorescence microscopy. The renal findings and presentations are similar if not identical to those of IgAN (see clinical features below).

Diagnosis and Histopathology

Currently the diagnosis of IgAN can only be made with a kidney biopsy (Magistroni et al. 2015; Roberts 2014; Working Group of the International IgANN, the Renal Pathology Society and Roberts 2009). IgAN is defined by the presence of dominant or codominant glomerular deposition of IgA. On immunofluorescence microscopy, staining for IgA should be at least of 1+ intensity and show diffuse glomerular involvement. Although the staining is often most prominent in the mesangial region, it can extend to the glomerular capillary wall (Roberts 2014; Working Group of the International IgANN, the Renal Pathology Society and Roberts 2009). Most often there is also variable staining for IgM and IgG. In a composite of published series including over 2,200 cases of IgAN, IgA was positive in all cases by definition, but 43% had IgG deposition and 54% had IgM deposition. C3 is also often found in the deposits (Haas 2015). The IgA deposits in IgAN have been shown to consist of polymeric IgA1 subclass immunoglobulins (Valentijn et al. 1984).

The light microscopic findings in IgA are quite variable and cover the range of those seen in glomerular disease with immune complex deposition (Working Group of the International IgANN, the Renal Pathology Society and Roberts 2009). These findings usually include some degree of mesangial cell proliferation often in association with some degree of endocapillary proliferation and sclerosis. The proliferation may be focal, involving less than 50% of the glomeruli, or diffuse, with more than 50% of the glomeruli involved. There may be areas of necrosis, and a small percentage of glomeruli contain crescents with are usually only segmental. In biopsies performed after longer disease duration, areas of segmental and global glomerular sclerosis are often found along with tubulointerstitial fibrosis. Erythrocyte casts may be found in the tubules, especially in cases with gross hematuria. The findings in patients with IgA vasculitis are identical to those of isolated IgA nephropathy (Haas 2015; Jennette et al. 2013). However, crescent formation and more severe glomerular proliferative involvement are more common in IgA vasculitis than in isolated IgAN (Haas 2015).

Along with the classic immunofluorescence findings, electron microscopy almost always reveals mesangial electron-dense immune complex-like deposits (Magistroni et al. 2015). These are usually found in a paramesangial location, i.e., along the glomerular basement membrane reflection over the mesangial region. Deposits may also be found in the subendothelial location and rarely in a subepithelial location. Foot process effacement is variable and usually concordant with the degree of proteinuria.

The Oxford Classification

Over time a number of classification systems have been developed to correlate the renal biopsy in IgAN with both clinical findings and prognosis (Magistroni et al. 2015; Haas 1997; Lee et al. 1982). More recently the Oxford IgAN classification was developed by a group of clinicians and pathologists under the auspices of the International IgA Nephropathy Network and the Renal Pathology Society (Working Group of the International IgANN, the Renal Pathology Society and

Roberts 2009). It developed a scoring system based on reproducible histologic findings from the review of 265 biopsies from patients from multiple continents and backgrounds. Given certain limitations of the study population (e.g., exclusion of patients with <0.5 g proteinuria, GFR < 30 cc/min, those progressing to ESRD in less than 12 months, and those with rapidly progressive GN), the Oxford classification has become a standard tool for both clinical and treatment studies. In this system three features, mesangial hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis, all correlate independently with renal function loss and renal survival. A fourth finding, endocapillary hypercellularity, correlated with response to immunosuppression. The MEST scoring grades biopsies as M0 or M1 (mesangial hypercellularity in < or > 50% glomeruli) E0 or E1 (endocapillary proliferation in none or at least one glomerulus), S0 or S1 (segmental glomerulosclerosis in none or at least one glomerulus), and T0, T1, or T2 (tubular atrophy/interstitial fibrosis (in <25%, 26–50%, or >50% of glomeruli) (Magistroni et al. 2015). The higher the score, the worse the prognosis for the patient.

The MEST-Oxford classification has been validated by a number of independent studies including children and adults with IgAN in Europe, North America, and Asia at this point (Herzenberg et al. 2011; Almartine et al. 2011; Zeng et al. 2012; Shi et al. 2011; Working Group of the IgANN, the Renal pathology Society and Coppo 2010; Coppo et al. 2014). A meta-analysis of 16 retrospective studies involving almost 4,000 patient confirmed the predictive value of the M, S, and T lesions (Lv et al. 2013). It did not find predictive value in the E lesion. Looking at those studies that evaluated almost 1,500 patients for crescent formation (which was not evaluated in the original Oxford classification), this analysis found that any degree of crescent formation was associated with progression to renal failure. A recent analysis of almost 1,150 patients from 13 countries also provides validation for the Oxford classification. M, S, and T again were predictive of outcome, and the E lesion again was not (Haas et al. 2014). Only one study has used the Oxford scoring system to evaluate biopsies of HSP patients. This single-center study of 61 adult Korean HSP patients concluded that features of this classification were independently predictive for patients with HSP (Kim et al. 2014). Thus, one can currently include the renal biopsy as an independent predictive variable when predicting prognosis and evaluating the need for further therapeutic interventions in patient with IgAN.

Pathogenesis

There is evidence for a genetic predisposition to IgAN (Magistroni et al. 2015). A small percentage of patients will have direct relatives with the disease as well. There are rare families with concordance for the disease in identical twins. While an autosomal dominant inheritance has been suggested in some familial cases, others appear to have more complex genetic patterns. One of the strongest supports for a familial predisposition is the presence of high levels of circulating galactose-deficient IgA1 in both IgAN patients and their first-degree family members. Four genome-wide association studies (GWAS) have been performed in populations of IgAN patients and identified 15 distinct genetic risk for IgAN (Magistroni et al. 2015). It should be emphasized that all 15 genetic loci explain only a small part of the risk for IgAN. The genes that have been implicated in these studies, in general, deal with the major histocompatibility complex, the complement system, mucosal IgA production, and innate immunity against pathogens. The greater the burden of genetic risk alleles, the younger the age of presentation of IgAN. Moreover, there is a greater genetic risk burden in East Asia than in areas where IgAN is less prevalent, e.g., Africa.

These findings have led to a refined multi-hit model of the pathogenesis of IgAN (Magistroni et al. 2015; Suzuki et al. 2011). In this model the first hit is the production of high levels of abnormal IgA1 which is deficient in galactose residues at the hinge region of the IgA molecule. Both patients with IgAN and their close relatives have high circulating levels of galactose-deficient IgA (Gharavi et al. 2008; Kiryluk et al. 2011). This has

been noted in populations from different regions of the world, in children, in adults, and in patients with IgA vasculitis. In certain individuals, these high levels evoke an autoimmune response, leading to the production of anti-glycan antibodies directed against epitopes on the galactose-deficient IgA molecule (Suzuki et al. 2009). Why some patients at a given time develop this autoimmune response is unclear but may relate to infections, oxidative stress, or other factors (Camilla et al. 2011). This second hit leads to the production of immune complexes which deposit in the mesangial region of the glomerulus. This in turn then stimulates mesangial inflammation, release of cytokines, and secretion of matrix proteins which produce glomerular damage, proteinuria, glomerular sclerosis, and interstitial fibrosis.

In support of this hypothesis, IgA1 is the major subtype of IgA in the circulation, immune complexes, and the mesangial deposits of IgAN patients (Pabst 2012; Mestecky et al. 2013). Higher levels of circulating galactose-deficient IgA1 are a risk factor for renal disease and renal disease progression in IgAN (Kiryluk et al. 2011; Mestecky et al. 2013; Novack et al. 2008; Moldoveneaus et al. 2007). Anti-glycan antibodies recognize epitopes of exposed N-acetylgalactosamine at the hinge region of IgA from patients with IgAN. There is a suggestion that antibody production against the IgA molecule is a form of molecular mimicry with antibody production against N-acetylgalactosamine, which is found on the surface of bacteria and viruses. Cultured mesangial cells are activated by IgA1-IgG immune complexes but not by isolated galactose-deficient IgA. Indeed, higher circulating level of antibodies against galactose-deficient IgA have been found to correlate with greater degrees of proteinuria, more histopathologic damage, and a poorer renal outcome in patients with IgAN (Suzuki et al. 2009; Berthoux et al. 2012). Of interest is the role of the complement system in IgAN (Magistroni et al. 2015). More than 90% of renal biopsies from patients with IgAN contain C3 glomerular staining on immunofluorescence, while C1q staining is generally negative or low intensity (Roberts 2014; Haas 2015). This suggests activation of either the lectin or alternative pathway of complement activation. Mannose-binding lectin has been found in one quarter of biopsies from IgAN patients. Likewise, complement-related genes have been found to be highly expressed in GWAS studies of IgAN patients (Magistroni et al. 2015; Kiryluk et al. 2012, 2014; Gharavi et al. 2011).

Clinical Features, Correlates of Progression, and Outcome

There are a number of presentations for patients with IgAN (Wyatt and Julian 2013; Galla 1995; Donadio and Grande 2002). The two most common presentations are that of gross hematuria and incidental discovery of abnormal urinalysis on a routine examination. The former, more common in children and young adults, is typically an episode of visible hematuria in association with an upper respiratory infection or sporting event. When associated with respiratory infections, this has been called "synpharyngitic hematuria" as there is no time lag between the respiratory infection and the onset of the kidney involvement compared to that observed in post-streptococcal glomerulonephritis. Some patients will have flank pain or low-grade fever with these episodes. Episodes may be solitary, but most are recurrent for a period of time and then gradually decline in frequency.

In adults asymptomatic detection of microscopic hematuria and mild proteinuria is the most common presentation (Hall et al. 2004; Topham et al. 1994). Only a small percentage of patients with IgAN will present with either the nephrotic syndrome or a rapidly progressive crescentic glomerulonephritis. Patients with a true rapidly progressive glomerulonephritis can present with oliguria and acute kidney injury as can some patients with major gross hematuria, presumably related to tubular obstruction by red blood cell casts.

Some patients present with the acute onset of severe nephrotic syndrome and only minimal mesangial proliferation in the presence of diffuse effacement of the epithelial foot process that is typically found in podocytopathies such as minimal change disease (Westhoof et al. 2006).

These patients have heavy proteinuria, hypoalbuminemia, and edema and respond to corticosteroids and other immunosuppressives much as minimal change disease patients do.

The outcome of patients with IgAN is quite variable. In part this is due to a selection bias in which patients are biopsied and have a firm diagnosis of IgAN (McQuarrie et al. 2009). Thus, in many countries, such as the United States, only patients with a significant amount of proteinuria (usually over 1 g daily) or a reduced GFR would receive a biopsy. In other countries, patients with isolated microhematuria or mild proteinuria would comprise a much larger proportion of the IgAN population. This difference was noted in a review of over 700 patients from four different countries with survival varying from 62% to 96% at 10 years. The highest survivals were in the groups biopsied with less clinical findings (Geddes et al. 2003). Regardless, it is clear that renal survival declines in the overall IgA population slowly with time. In one large study of over 1,100 Chinese patients with IgAN, renal survival free of ESRD was 83%, 74%, and 64% at 10, 15, and 20 years, respectively (Le et al. 2011). Likewise, in 542 patients with IgAN from the Toronto registry followed for a mean of 78 months, GFR declined at −4.56 ml/min/1.73 m^2/year and 30% reached ESRD (Reich et al. 2007).

Along with key histologic features elucidated from using the Oxford classification for IgAN, certain clinical features have been shown to predict renal progression in patients with IgAN. Data from many studies show that patients who develop more than 500–1,000 mg of proteinuria daily are at risk for progressive renal failure (Reich et al. 2007; Wakai et al. 2006; Rekola et al. 1991; Donadio et al. 2002). Even patients with a relatively preserved GFR have been shown to have progressive disease in the presence of this degree of proteinuria. With increasing levels of proteinuria above 1 g daily, the rate of histologic damage and progressive decline in GFR correlates with increasing degrees of proteinuria. For example, a study of over 330 IgAN patients found a significantly higher rate of death or dialysis in patients with over 1 g proteinuria versus those with less (Berthoux et al. 2011). In another long-term follow-up of almost 550 patients with IgAN follow for over 6 years, renal function declined 24 times faster in patients excreting over 3 g proteinuria daily versus those excreting less than 1 g daily (Reich et al. 2007). Of note, those patients with over 3 g proteinuria daily who had a reduction of proteinuria to less than 1 g daily had a similar prognosis to those patients who presented initially with less than a gram daily. While most studies have used over 1 g proteinuria daily as a marker of poor renal outcome, some have confirmed a better prognosis even for those with less than 0.5 g proteinuria daily over those with a gram daily.

In general, episodes of gross hematuria with preserved GFR are not predictive of a poor renal outcome. Persistent microscopic hematuria in some studies even without concomitant proteinuria has been associated with progressive renal dysfunction (Szeto et al. 2001; Vivante et al. 2011).

A reduced GFR is generally found later in the course of patients with IgAN and, as expected, predicts a worse long-term outcome. In limited studies serologic findings such as higher levels of circulating poorly galactosylated IgA1 have correlated with a worse renal outcome as have higher circulating levels of autoantibodies against this form of IgA1 (Berthoux et al. 2012; Zhao et al. 2012).

IgA vasculitis (HSP) is a systemic small vessel vasculitis with IgA vascular deposits and a glomerular picture identical to that of IgAN. It is the most common form of vasculitis in children (90% pediatric – peak age 3–15 years old). However, although less common in adults, in two recent series, 25–30% of patients with IgA vasculitis were adults (Calvio-Rio. . .417 HSP pts 2014; Kang et al. 2014). Patients may develop any of the tetrad of palpable purpura (without thrombocytopenia or coagulopathy), abdominal pain, arthritis/arthralgias, and glomerulonephritis. Several differences have been noted in the clinical picture and course of IgA vasculitis patients between children and adults. For example, a retrospective 10-year study of 160 patients with HSP at single center in Korea found purpura to be the most common finding, but this was more common

on the upper and lower extremities in adults, while truncal lesions were also common in children. Arthralgias occurred in 55% of children and only 27% of adults. Gastrointestinal symptoms, with diarrhea as most common, were found in 16% children and 20% adults. Most striking was that severe renal involvement was far more common in adults than children (79% vs. 30%) (Kang et al. 2014).

The outcome of IgA vasculitis has been reviewed in a number of studies. One retrospective study of 250 adults with HSP nephritis who underwent biopsy found that within 4 months of presentation, 32% had renal insufficiency almost always associated with hematuria (93%) and proteinuria (99%). At median of 15 years of follow-up, 11% had progressed to ESRD, 13% had a creatinine clearance <30 cc/min, and 14% had a creatinine clearance between 30 and 50 cc/min. A complete remission was found in only 20% (Pillebout Thervet et al. 2002). The following features were found to be prognostic of severe renal failure by multivariate analysis: serum creatinine >120 umoles/L, proteinuria >1 g daily, > 10% glomerular necrosis, > 20% glomerular sclerosis, and >10% interstitial fibrosis. Another study of 136 adults followed for over 5 years found that 13% developed ESRD, 25% doubled their serum creatinine, and 16% had a normal serum creatinine with proteinuria (Coppo et al. 2006). This study found age (adults faring worse), gender (females faring worse), and heavier proteinuria all to predict a bad outcome.

The Treatment of IgA Nephropathy

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis were published (Kidney Disease Improving Global Outcomes (KDIGO) 2012). They provided recommendations from an evidence-based analysis of the literature on treating glomerular diseases including IgAN. However, most of the studies dealing with IgAN are underpowered and uncontrolled and often have conflicting conclusions. Thus, these guidelines at best can be suggestions, and many reviews rely on "expert opinion" in the treatment of IgAN. A number of new studies have been published, and a number of trials on promising medications are already underway.

Renin-Angiotensin System Blockade and Blood Pressure Control

Both KDIGO and others recommend the use of ACE inhibitors or ARBs (RAS blockade) for blood pressure treatment and control of proteinuria in IgAN (Kidney Disease Improving Global Outcomes (KDIGO) 2012). For patients with less than 1 g daily of proteinuria, a blood pressure goal of <130/80 mm Hg is recommended, while for patients more than 1 g proteinuria daily, the recommendation is for a goal of <125/75 mm Hg. The dose of the ACE inhibitor or ARB should be titrated to the goal desired as tolerated by the reduction of blood pressure and symptoms of hypotension. Controlled, randomized trials have shown that the use of blockers of the RAS both reduce proteinuria and delay the progressive loss of glomerular filtration rate seen in the control groups (Coppo et al. 2007; Li et al. 2006; Praga et al. 2003). For example, one randomized controlled trial compared the use of RAS blockade versus other blood pressure medications in IgAN patients with a serum creatinine <1.2 mg/dl and a 24-h urinary protein excretion greater than 500 mg daily (Praga et al. 2003). At 75 months a 50% increase in serum creatinine was seen in 13% of the RAS blockade patients versus 57% of the non-RAS blockade group. Another randomized controlled study of 66 IgAN patients found a significant difference in survival without reaching the endpoints of 30% reduction in creatinine clearance or increase in proteinuria to nephrotic range favoring the RAS blockade group (Coppo et al. 2007). Although combined ACE inhibition and ARB blockade have been shown to reduce proteinuria more than either agent alone, at present there is no clear data showing a combination of these agents prevents less ultimate renal failure or mortality (Russo et al. 1999). Given the potential risks of such combinations admittedly in older and high-risk cardiovascular populations,

the combination is generally not advised (Mann et al. 2008). While blockade of the RAS is recommended in proteinuric IgAN patients, it is not clear whether patients with low levels of proteinuria (<500 mg/day) will also benefit from therapy over the long term. Low-salt diets may potentiate the efficacy of ACE inhibition and ARBs at reduction of proteinuria. Because all CKD patients are at greater risk for cardiovascular events, optimal control of serum cholesterol including therapy with HMG Co-A reductase inhibitors is indicated.

Tonsillectomy

Tonsillectomy has been recommended by some as a method of removing an antigenic stimulus for the initiating IgA disease process. Although some studies have suggested a benefit of tonsillectomy (Xie et al. 2003; Hotta et al. 2001), none has been prospective, large, randomized, and controlled. The conclusions are equivocal. One study evaluated the efficacy of tonsillectomy in the long-term outcome of 118 patients (Xie et al. 2003). At 240 months renal survival by Kaplan-Meier analysis was 90% for the 48 patient tonsillectomy group and 64% for the 70 other patients. However, survival differences did not appear in this retrospective nonrandomized study until 10 years post tonsillectomy. Likewise, a retrospective 10-year follow of 71 patients (Akagi et al. 2004) and a third retrospective trial of 200 Japanese patients found improved survival with tonsillectomy (Maeda et al. 2012).

Again, neither was a randomized trial, and there was variable use of steroids and RAS blockade. A multicenter prospective randomized trial of 72 IgAN patients, all of whom received oral corticosteroids and periodic pulses of methylprednisolone, found no benefit in a tonsillectomy group in terms of clinical remission defined by disappearance of proteinuria and hematuria at 12 months and concluded the benefits of tonsillectomy were marginal (Kawamura et al. 2014). Even here the study was small in numbers and of short duration, had inconsistent RAS blockade, and suffered from a 20% dropout rate. Another retrospective study of 55 IgAN patients also found no benefit of tonsillectomy at 10 years (Rasche et al. 1999). Finally a meta-analysis of seven studies including 858 patients found more remissions and less ESRD in the tonsillectomized patients, but only in those who received corticosteroids as well (Wang et al. 2011). Taken all together the benefits of tonsillectomy do not appear convincing. Many would not suggest the routine use of tonsillectomy, rather only when indicated by episodes of tonsillitis that would warrant this as standard practice.

Fish Oil

In contrast to tonsillectomy, the use of fish oils as therapy for IgAN has been evaluated in a number of prospective controlled trials. Yet, like tonsillectomy, the use of fish oils remains controversial. Fish oils have cardiovascular benefits and anti-inflammatory properties, inhibit cell proliferation, and can ameliorate animal models of glomerular disease (Donadio and Grande 2004). In humans, a trial randomized 106 patients for 2 years to 12 g of omega-3 fish oils or 12 g of olive oil daily. Despite no difference in proteinuria, at 4 years patient and renal survival was significantly better in the fish oil group (90% vs. 60%) (Donadio et al. 1994). This was confirmed at 6-year follow-up (Donadio et al. 1999). While smaller or short duration studies have shown such a benefit, other randomized controlled trials have shown no benefit of similar regimens (Bennett et al. 1989; Petterson et al. 1994). Meta-analyses of the benefit of fish oil therapy and a Cochrane analysis have also given equivocal results (Strippoli et al. 2003). Finally, a prospective trial randomized almost 100 patients to alternate-day corticosteroid therapy, fish oils, or placebo (Hogg et al. 2006). Although the fish oil group had the highest degree of proteinuria at baseline, this was a randomized and well-performed trial. At 3 years while neither treatment group showed benefit over placebo, the fish oil group actually had the highest incidence of renal progression (19% vs. 9% vs. 9%).

Overall, fish oils have not been established to benefit IgAN patients. Fish oils can certainly be

considered for patients with persistent proteinuria despite optimized supportive care. Many feel the decision to use them should be left to the choice of the individual patient and their clinician. Certainly, use of fish oils should not take precedence over use of RAS blockade and other more proven therapies.

Corticosteroids

The study of corticosteroid treatment of IgAN has given conflicting results. Both the 2012 KDIGO guidelines and many clinicians suggest a 6-month trial of corticosteroids in IgAN patients with persistent proteinuria (Kidney Disease Improving Global Outcomes (KDIGO) 2012). Clearly this should be done after optimal supportive care (RAS blockade) has failed to reduce proteinuria to desired levels.

In the past uncontrolled and small randomized controlled trials supported the use of steroids (Lai et al. 1986; Mustonen et al. 1983; Komatsu et al. 2008). Three larger, randomized controlled trials have subsequently found a beneficial effect of a short (up to 6 months) course of corticosteroid treatment. One study of 86 patients with 1.0–3.5 proteinuria daily and a serum creatinine <1.5 mg/dl compared 6 monthly pulses of methylprednisolone and alternate-day steroids to placebo for 6 months (Pozzi et al. 1999). At 10-year follow-up, renal survival was better in the steroid-treated group (97% vs. 53%) regardless of biopsy histologic class (Pozzi et al. 2004). This study has been criticized for low use of RAS blockade and suboptimal blood pressure control.

However, two subsequent randomized controlled trials of a tapering 6-month course of corticosteroids have confirmed these effects (Manno et al. 2009; Lv et al. 2012). One trial of 97 patients (proteinuria >1 g daily and GFR > 50 cc/min, all treated with ramipril) showed that the mean annual loss of GRF was markedly reduced by use of steroids (Manno et al. 2009). The 8-year survival was 98% in the corticosteroid as opposed to 70% in the control group. The second trial using the ACE inhibitor cilazapril in 63 patients with 1–5 g proteinuria daily randomized patients to receive 6 months of tapering oral corticosteroids or placebo (Lv et al. 2012). The endpoint of 50% increase in serum creatinine was reached in more patients receiving RAS blockade alone than RAS blockade in combination with corticosteroids (24% vs. 3%). An American trial of corticosteroids versus fish oils versus placebo in almost 100 patients showed no significant differences in renal progression. However, the steroid group actually had the lowest number of patients reaching the endpoint (Hogg et al. 2006). A recent meta-analysis also concluded that steroids reduce the progression to renal failure (Stripoll ajkd 2009).

A recent large, randomized, placebo-controlled trial, the STOP-IGA trial, evaluated IgAN patients on RAS blockade and statins who had persistent proteinuria over 0.75 g daily after optimal supportive care (Rauen et al. 2015). Patients with a GFR > 60 ml/min were randomized to every other day corticosteroids for a 6-month period with methylprednisolone pulses months 1, 3, and 5 versus placebo, while those with a GFR 30–60 cc/min were randomized to a regimen of cyclophosphamide for 3 months followed by azathioprine versus placebo for 3 years. They found that the use of steroids was associated with more remissions of proteinuria but no difference in outcome of GFR and ESRD over time. Again this study has been criticized for the selective nature of the patients ultimately randomized. A recent double-blind, global, randomized, placebo controlled trial of oral methylprednisolone for 6-8 months in 262 IgAN patients was stopped early due to side effects of the corticosteroid (infection in 8%). (Lv et al. 2017) However, fewer treated than placebo patients reached the primary end point (40% reduction in GFR or development of ESRD), and the rate of GFR loss was slower in the treated group, and proteinuria was reduced more. This gives impetus to study redesign to reduce the side effects of corticosteroids while retaining efficacy.

Thus, although there is conflicting data, many clinicians favor of a trial of 6 months of corticosteroids (some preferring every other day corticosteroid treatment) in patients with preserved renal function (GFR > 30 cc/min) and proteinuria >1 gm daily, as long as there are no

contraindications to its use. A crucial question for both patients and their physicians is at what level of reduced GFR the use of steroids will not provide any benefit but only increase adverse events. This has been called "the point of no return," the point at which progression of the renal disease will occur regardless of therapeutic interventions. It also remains unclear whether patients with over 500 mg proteinuria should be so treated since they have been found to have a poor prognosis than those with less than 500 mg proteinuria in a recent large analysis (Coppo et al. 2014).

Additional Immunosuppression

A number of other immunosuppressive agents have been studied in IgAN including cyclophosphamide, azathioprine, mycophenolate mofetil (MMF), and rituximab. Oral cyclophosphamide (1.5 mg/kg/day) for 3 months followed by azathioprine (1.5 mg/kg/day) for 2 years along with prednisolone was used in a randomized trial of 38 patients with progressive IgAN (Ballardie 2004). The treated group had improved renal survival at 5 years (72% vs. 6%). This study was faulted for unclear use of RAS blockade, suboptimal blood pressure control, and a very poor survival in the control group. Two older trials using cyclophosphamide along with anticoagulation/antiplatelet agents found no benefit (Woo et al. 1991; Walker et al. 1990). The recent STOP IgAN also does not support the use of cyclophosphamide in IgAN (Rauen et al. 2015). Older small trials found a benefit to using azathioprine with corticosteroids (Yoshikawa et al. 1999, 2006). However, a more recent, well-designed, randomized controlled trial in over 200 patients (serum creatinine <2 mg/dl and proteinuria >1 g daily) comparing the use of corticosteroids to corticosteroids plus 6 months of azathioprine found no difference in progression of renal dysfunction between the groups or in 5-year renal survival (Pozzi et al. 2010). Moreover, the azathioprine group had significantly more side effects. Overall, the data supporting the use of these agents is equivocal at best.

Likewise the use of MMF has given conflicting results in a number of randomized controlled trials, all of which suffer from small size or other design problems. In one trial 2 g of MMF was compared to placebo for 3 years in 34 patients with preserved renal function and mean proteinuria of 1.8 g daily (Maes et al. 2004). Neither this study nor a blinded placebo-controlled North American trial randomizing 32 patients showed any benefit for the MMF (Frisch et al. 2005). Both studies were small and the later included many patients with low GFRs at entry. In contrast a Chinese trial of 40 patients with preserved GFR and a mean of 1.8 g proteinuria daily who were given MMF for 6 months had significant reductions in proteinuria at 18 months and better preserved renal function at 6-year follow-up (Tang et al. 2010). Whether racial differences, dosage differences based on body weight, or small numbers confounding the statistics play a role here is unclear. A recent trial of Mycophenolate mofetil combined with corticosteroids versus corticosteroids alone (but at greater doses) revelaed no difference in complete remissions at 6 and 12 months, but less side effects in the mycophenolate group (Hou et al. 2016). At this time the role of MMF in IgAN remains one of unproven benefit. Some clinicians use MMF for patients who have failed conservative therapy and corticosteroids and are at high-risk group for progressive renal failure.

Rituximab has recently been studied in a controlled randomized trial of patients with significant proteinuria (Lafayette et al. 2017). No beneficial effect on proteinuria or GFR was found. Its use should be restricted and considered experimental until more data is available. There are also insufficient beneficial data to recommend using IVIG, calcineurin inhibitors, ACTH, and antiplatelet agents. However, these agents may prove beneficial in certain patients.

Two special forms of glomerular disease in IgA patients are worthy of comment: patients with minimal change disease and mesangial IgA deposits and those with crescentic IgAN. The former are treated similar to other patients with minimal change disease (Westhoof et al. 2006; Mustonen et al. 1983) and usually respond well

to corticosteroid therapies and other second-line agents for minimal change disease. For the rare patients with over 50% crescents on biopsy, although there are sparse data, the course is highly likely to lead to progressive renal failure (Abe et al. 1986; Tang et al. 2002) Pulse methylprednisolone followed by oral corticosteroids and cyclophosphamide has been used successfully in one small trial (Tumlin et al. 2003).

A number of recent clinical trials on the role of immunomodulatory medications have contributed to our knowledge of the treatment of IgAN patients (Tam and Pusey 2018). A recent trial of budesonide, a glucocorticoid locally released in the ileo-cecal region of the gut near the Peyer's patches, has proven successful (Smerud et al. 2011; Fellstrom et al. 2017) in reducing proteinuria and stabilizing the GFR. It is still unclear whether this will prove superior and with than systemic corticosteroids. Other studies examine the role of agents blocking B cell survival and maturation factors such as atacicept. Finally, pilot trials of agents inhibiting complement activation, and in particular the mannose lectin pathway, are underway. Thus, we still do not have the ideal treatment for many IgA patients at this time. More studies will be needed to determine which agents are the safest and most effective in which IgAN populations.

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IgA Nephropathy and Henoch Schönlein Nephritis, Pediatric

20

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Abstract

Immunoglobulin A (IgA) nephropathy is the most common form of glomerulonephritis worldwide and an important cause of chronic kidney disease in both children and adults. It is characterized by mesangial deposition of IgA that is seen on immunofluorescence of a kidney biopsy. The initial step in pathogenesis seems to be the aberrant glycosylation of IgA

molecules. Proximate step/s to this aberrant glycosylation are still under investigation. While the clinical features can be variable, recurrent episodes of macroscopic or gross hematuria are the hallmark of pediatric IgA nephropathy. Currently, there is not one accepted treatment for IgA nephropathy, and most of the proposed regimens are lacking definitive evidence. The mainstay of therapy involves supportive measures that aim at slowing the progression of IgA nephropathy.

Henoch-Schönlein purpura (HSP) or IgA vasculitis has been described as a small vessel, leukocytoclastic vasculitis that affects the skin, gastrointestinal tract, joints, and kidney. While HSP is the most common form of vasculitis in children, nephritis occurs in only about 20–50% of all cases. As compared to IgA nephropathy, renal biopsy findings in HSP nephritis are often severe, showing acute glomerular inflammation. Currently, physicians rely on clinical case series and experience in the management of HSP nephritis. There is a need for large, well-designed clinical studies to determine the best regimens for the treatment of HSP nephritis in children.

Keywords

Glomerulonephritis · IgA nephropathy · Aberrant glycosylation · Hematuria · Henoch Schönlein Nephritis

Introduction

IgA nephropathy was first described by Berger and Hinglais in 1968 (Berger and Hinglais 1968). In many parts of the world, it is recognized as the most common form of glomerulonephritis (Hogg 2010). The difference in the incidence of IgA nephropathy within/among countries may be due to kidney biopsy criteria as well as environmental and genetic factors. Primary IgA nephropathy is an immune complex-mediated glomerulonephritis characterized by glomerular mesangial IgA deposits and several different histopathological lesions that usually cause microscopic hematuria or recurrent episodes of macroscopic hematuria. Primary IgA nephropathy is recognized as is an important cause of chronic kidney disease and end-stage kidney disease (ESKD) throughout the world. It is important to bear in mind the highly variable nature of IgA nephropathy (Table 1), which makes decisions about best management practices difficult. IgA nephropathy has an incidence of 5–50 per million children (Wyatt and Julian 2013) with a peak age of onset between 15 and 30 years (Davin et al. 2001) and higher prevalence in males (Emancipator 1993). The prevalence of IgA nephropathy varies by geographic location (seen in about 40% of native kidney biopsies in Asia, 20% in Europe, 5–10% in the United States (Fabiano et al. 2016; Mestecky et al. 2013). The differences in guidelines for performing a kidney biopsy may explain some of the variabilities in prevalence of IgA worldwide (Levy and Berger 1988).

Table 1 IgA nephropathy is a *variable* disease

Variable incidence
Variable clinical presentation
Variable indications for renal biopsy
Variable renal histopathology
Variable treatment
Variable outcomes

In children, as compared with IgA nephropathy, renal biopsy findings in Henoch-Schönlein purpura (HSP) nephritis (or IgA vasculitis) are more often severe, showing acute glomerular inflammation (Davin 2011). The diagnosis of HSP rests on the presence of a leukocytoclastic vasculitis in the wall of the dermal capillaries and hence presence of palpable purpura (Wyatt and Julian 2013).

Pathogenesis of IgA Nephropathy

IgA nephropathy appears to be a systemic disease as evidenced by the recurrence of the disease in 30–40% of patients after renal transplantation (Odum et al. 1994). Furthermore, studies have observed that the IgA complexes resolve when kidneys of patients with IgA nephropathy are transplanted into patients with other forms of kidney

disease, suggesting that the mesangial complexes are the result of deposition and not in situ production.

IgA exists in both monomeric and polymeric forms. Monomeric IgA is secreted by plasma cells and lymphocytes of the spleen and bone marrow and is found as circulating IgA. On the other hand, polymeric IgA is secreted by plasma cells in the mucosa of the respiratory and gastrointestinal tract, with very little reaching the systemic circulation. There is evidence that IgA nephropathy is an immune complex disease in which the initiating event is the deposition of predominantly dimeric or polymeric IgA of the IgA1 subclass (Rifai and Millard 1985). Initial studies suggested decreased mucosal immunity in patients with IgA nephropathy (Bene and Faure 1988) and, in some patients, an increased production of IgA1 in the bone marrow (Layward et al. 1993). More recent studies suggest that the most likely mechanism for this displacement is abnormal homing of mucosal plasma cells to systemic sites (Barratt et al. 1999).

The current hypothesis suggests that IgA nephropathy best fits a multi-hit model (Fig. 1) (Barratt and Feehally 2011). The initial event seems to be aberrant *O*-glycosylation, with oligosaccharides including *N*-acetylgalactosamine and *N*-acetylneuraminic acid, of the serine and threonine residues in the hinge region of IgA1 molecules. Thereafter, glycan-specific IgG and IgA antibodies form against the "neo-epitope" of the under-galactosylated hinge region of the IgA1 molecule (Suzuki et al. 2009). Some bacteria and viruses in the respiratory or gastrointestinal tract may facilitate synthesis of antibodies that cross-react with the galactose-deficient IgA1 molecules. This results in increased immune complex formation with decreased catabolism of galactose-deficient IgA in the liver (Lai 2012). IgA immune complex deposition occurs by mesangial trapping and increased affinity of poorly glycosylated IgA1 to the extracellular matrix. Recognition of deposited immune complexes is mediated by mesangial IgA receptors including transferrin receptor CD71 (Novak et al. 2002; Boyd et al. 2012). These complexes activate mesangial cells that in turn induce cellular proliferation and overproduction of extracellular matrix due to various cytokines/chemokines such as interleukin-6, angiotensin II, tumor necrosis factor α, platelet-derived growth factor, transforming growth factor β, and reactive oxygen molecules (Fig. 2). It seems that IgA1 must be within an immune complex to activate mesangial cells. Activated mesangial cells are

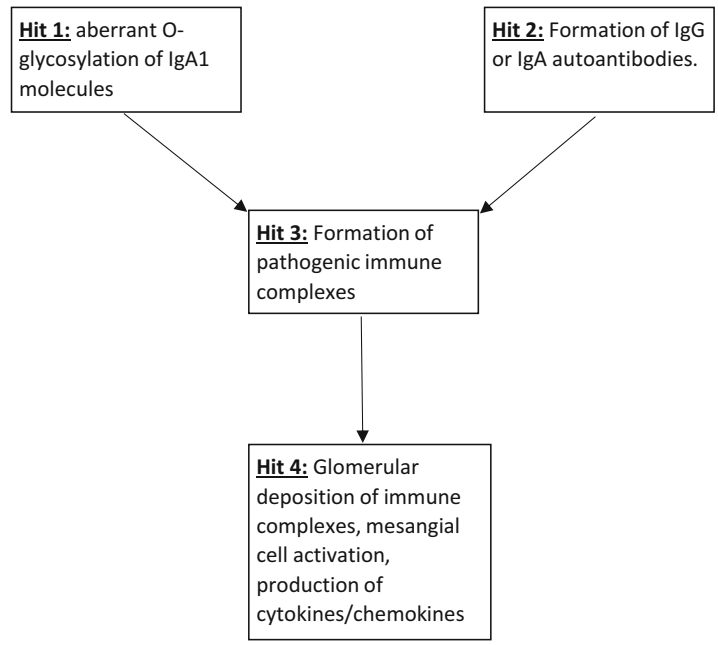

Fig. 1 Multi-hit model in the pathogenesis of IgA nephropathy (Adapted from Novak 2015)

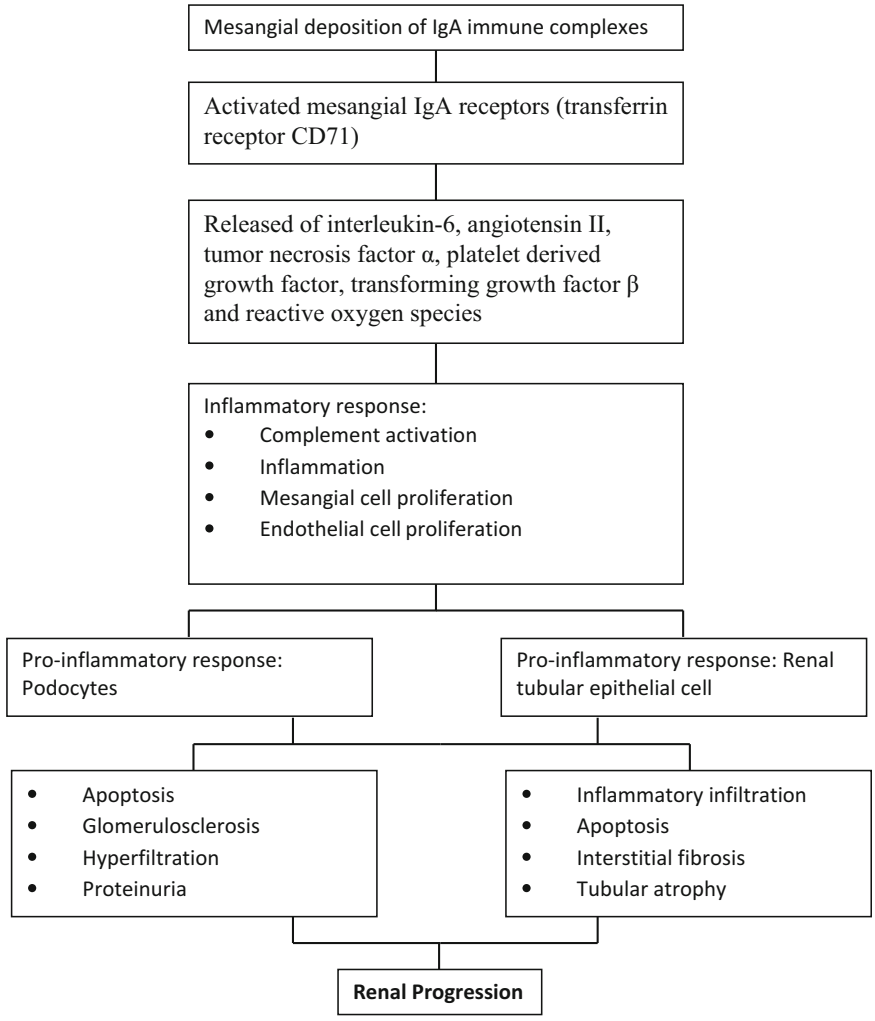

Fig. 2 Pathway to renal injury in IgA nephropathy (Adapted from Fabiano et al. 2016)

able to initiate (i) tubulointerstitial infiltration of monocytes and macrophages and (ii) glomerulus-podocyte-tubule cross talk (Fabiano et al. 2016; Lai 2012).

Another hypothesis outlines a role for the soluble form of Fcα receptor (sCD89) that can generate complexes with galactose-deficient IgA1 (Novak 2015). The alternative complement pathway may also have a pathogenic role suggested by the deposition of C3 and properdin in the absence of C1q and C4. Serum levels of C3 and C4 remain normal indicating local complement activation only. MicroRNAs are important mediators of tissue fibrosis and may also have a role in the pathogenesis and progression of IgA nephropathy (Lorenzen et al. 2011; Szeto and Li 2014).

Genetics of IgA Nephropathy

Although most cases of IgA nephropathy are sporadic, familial forms may account for up to 5% of cases (Julian et al. 1985; Schena et al. 1993). Most studies suggest an autosomal dominant inheritance pattern with incomplete penetrance. In four families in whom IgA nephropathy was extensively studied, the genetic linkage differed in each of them (Gharavi et al. 2000; Bisceglia

Table 2 Genome-wide association studies in IgA nephropathy (Adapted from Feehally and Barratt 2015)

Study	Feehally, 2010	Gharavi, 2011	Yu, 2012	Kiryluk, 2014
Population	European	Chinese	Chinese	Chinese + European
Susceptibility loci	6p21 MHC (multiple)	6p21 MHC (multiple)	6p21 MHC (multiple)	6p21 MHC (multiple)
	–	6p21 TAP1/PSMB8	–	6p21 TAP1/PSMB8
	–	1q32 CFHR1/3	–	1q32 CFHR1/3
	–	22q12 LIF/OSM	–	22q12 LIF/OSM
	–	–	17p13 TNFSF13	17p13 TNFSF13
	–	–	8p23 DEFA	8p23 DEFA
				6p11 ITGAM-ITGAX
				1p13 VAV3
				9q34 CARD9

et al. 2006; Paterson et al. 2007; Karnib et al. 2007). This argues strongly against the generalizability of these findings to sporadic IgA nephropathy (Feehally and Barratt 2015).

Genome-wide association studies have identified various susceptibility loci in patients with IgA nephropathy (Feehally et al. 2010; Gharavi et al. 2011; Yu et al. 2012; Kiryluk et al. 2014). The implicated pathways include antigen processing and presentation (major histocompatibility complex (MHC) region), the complement system (CFHR1/3 and ITGAM/ITGAX loci), regulation of mucosal IgA production (TNFSF13 and LIF/OSM loci), and intake immunity against pathogen (DEFA, CARD9, ITGAM-ITGAX, and VAV3 loci) (Table 2) (Magistroni et al. 2015).

Heritability of poorly *O*-glycosylated IgA1 is reported to be high as 80% (Kiryluk et al. 2011; Yeo et al. 2017). *O*-glycosylation of the hinge region of IgA molecules is mediated by enzyme *N*-acetylgalactosaminyltransferase (GalNAcT2), encoded by gene C1GALT1 (Woof and Russell 2011). Serum levels of poorly *O*-glycosylated IgA1 have been shown to be associated with changes in the noncoding region of C1GALT1 (Gale et al. 2017). Epigenetic factors as well as microRNAs (miR-148b) may be associated with aberrant glycosylation of IgA1 (Serino et al. 2012).

Common genetic variants influence the risk of IgA nephropathy across ethnically diverse populations and implicate adaptive immunity in pathogenesis (Wyatt and Julian 2013). Variations in disease prevalence among populations may also occur because of the disparate influence of environmental (epigenetic) factors.

Table 3 Variable click manifestations of IgA nephropathy

Microscopic hematuria
Macroscopic hematuria
Recurrent episodes of macroscopic hematuria
Macroscopic hematuria with nephrotic syndrome
Nephrotic syndrome
Acute kidney injury
Malignant IgA nephropathy with loin pain
Chronic kidney disease

Clinical Presentation of IgA Nephropathy in Children

Berger described IgA nephropathy as the occurrence of synpharyngitic macroscopic hematuria, i.e., occurring during or within 7 days of a bout of pharyngitis (Berger 1969). However, the initial clinical features of IgA nephropathy in children can be very variable and depend to a large degree on the level of suspicion of the nephrologist and the criteria for doing a renal biopsy (Table 3). Nearly 70% of patients with IgA nephropathy in Japan have microscopic hematuria or asymptomatic proteinuria (Yoshikawa et al. 2001). Some asymptomatic patients are diagnosed at routine school screening programs (Park et al. 2005; Yoshikawa et al. 2006), while others develop

frank symptoms and signs of renal disease. In up to 80% of patients, the presentation is with macroscopic hematuria accompanied by red blood cell casts, concomitant with an upper respiratory tract infection or other mucosal infection such as sinusitis or diarrhea (Lee et al. 2006). Recurrent episodes of hematuria are the hallmark of pediatric IgA nephropathy (SPNSG 1982). Some children may present with classic nephrotic syndrome, which in some has been considered a coincidence of two independent diseases, IgA nephropathy and minimal change disease (Coppo 2008).

Presentations with hypertension or chronic kidney disease are rare occurrences in the pediatric population (Coppo et al. 2000) as compared with adults, where up to 50% patients may have CKD. Progression to end-stage kidney disease (ESKD) can occur within 4 years of onset in children or adults who present with macroscopic hematuria, loin pain, persistent microscopic hematuria, and crescents on renal biopsy (Nicholls et al. 1985). The term "malignant" IgA nephropathy was coined to describe this subset of patients.

Indications for Biopsy in Pediatric IgA Nephropathy

There are no specific guidelines for a kidney biopsy in an asymptomatic patient with IgA nephropathy. However, a biopsy is indicated in children with a combination of unexplained macroscopic hematuria with red cell casts, proteinuria more than 1 gm/1.73m^2/day, clinical features of nephrotic syndrome, and azotemia. Indications for doing a biopsy with microscopic hematuria vary among pediatric nephrologists and from country to country.

Histopathology of IgA Nephropathy

Biopsy findings in IgA nephropathy can be variable (Hogg 2010). On light microscopy, the most common alteration is focal or diffuse mesangial hypercellularity (more than three cells per peripheral mesangial area) and matrix expansion (Fig. 3a) (Fogo et al. 2015). Biopsies in children with IgA nephropathy often show significant mesangial hypercellularity, whereas adults often have increased matrix expansion with more severe tubulointerstitial damage. Proliferative or sclerosing endocapillary lesions may be noted in some children (SPNSG 1982). Cellular and fibrocellular crescents usually affect less than 50% of the glomeruli, although in approximately 10% of patients, more than 50% of glomeruli are involved. Tubulointerstitial changes include interstitial inflammation and fibrosis and tubular atrophy. Vascular changes of arteriolar sclerosis are less common in children than adults (Nicholls et al. 1984).

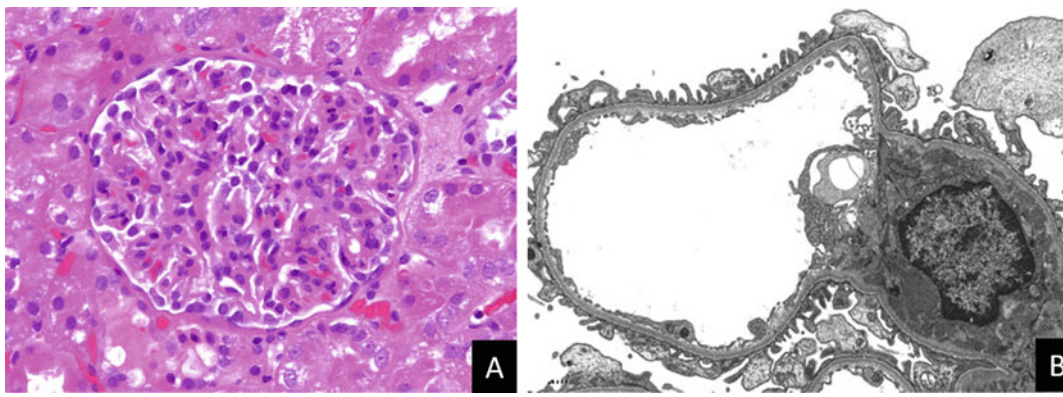

Fig. 3 Biopsy findings in IgA nephropathy. (**a**) Hematoxylin-eosin stain demonstrating expansion of mesangial matrix with mesangial hypercellularity. (**b**) Electron microscopy significant for expansion of mesangial matrix and presence of large mesangial dense deposits

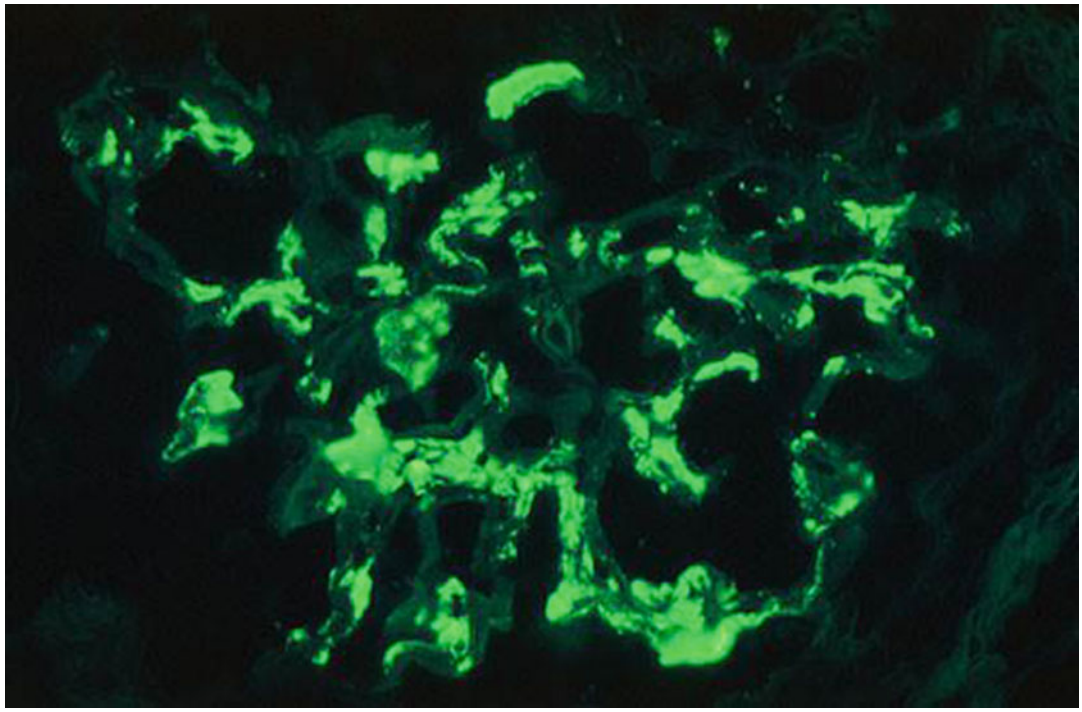

Fig. 4 Immunofluorescent microscopy showing staining for IgA immune complexes within glomerular mesangium

Immunofluorescent studies of the glomeruli are key to making the diagnosis of IgA nephropathy (Fig. 4). There is deposition of IgA in the mesangium of the glomerulus that may extend into capillary loops. The IgA deposition may occur in isolation or be associated with IgG and IgM deposition (Wyatt and Julian 2013). A study by Yoshikawa et al. showed that IgA nephropathy was associated with IgG deposits in 32% of the subjects, IgM in 8%, and both IgG and IgM in 11% (Yoshikawa et al. 1987). Complement C3 is also present in 95% of renal biopsies. It is important to note that mesangial IgA deposition can occur in children with lupus nephritis or hepatic disease. The presence of C1q suggests that one should look for lupus nephritis as a possible cause of renal symptoms.

Electron microscopy usually shows electron-dense deposits in the mesangium (Fig. 3b). Periglomerular and capillary wall deposits are usually associated with high-grade proteinuria and may portend a worse prognosis (SPNSG 1982; Andreoli et al. 1986). Rarely, there may be a membranoproliferative pattern (Hogg 2010).

Classification of IgA Nephropathy

There have been multiple histology classifications proposed for IgA nephropathy. Initial classifications of IgA by Lee et al. (1982) and Haas et al. (1997) were criticized due to lack of definitions, vague terminology, and lack of reproducibility (Lee et al. 1982; Haas 1997; Park et al. 2014). In 2009, a Working Group of the International IgA Nephropathy Network and Renal Pathology Society described the Oxford Classification of IgA Nephropathy (a Working Group of the International IgA Nephropathy Network and Renal Pathology Society described the Oxford Classification of IgA Nephropathy 2009; of the International AW, Network IN 2009). They studied 256 renal biopsies and identified four major pathologic variables (MEST criteria) of prognostic significance – (i) **m**esangial hypercellularity (**M**),

Table 4 Oxford classification (MEST score) for IgA nephropathy

Criteria	Definition	Score
Mesangial hypercellularity score	<50% glomeruli with mesangial hypercellularity	M0
	>50% glomeruli with mesangial hypercellularity	M1
Endocapillary proliferation	Absent	E0
	Present	E1
Segmental sclerosis	Absent	S0
	Present	S1
% interstitial fibrosis/tubular atrophy	0–25%	T0
	26–50%	T1
	<50%	T2

(ii) **e**ndocapillary proliferation (**E**), (iii) **s**egmental sclerosis (**S**), and (iv) percent of **t**ubular atrophy/interstitial fibrosis (**T**) (Table 4). Multiple validation studies have attempted to confirm the conclusion of the Oxford study (Coppo et al. 2010; Le et al. 2012; Alamartine et al. 2011; Herzenberg et al. 2011). In general, most studies support the MEST criteria as prognostic markers in IgA nephropathy (Lv et al. 2013). Glomerular crescents have also been found to be of prognostic value in some studies that include patients with rapidly progressive disease (excluded from the original cohort). Published in 2014, the VALIGA study including 1,147 subjects, of which 15% were children, provided a validation of the Oxford MEST score classification (Coppo et al. 2014). The authors concluded that clinical features including proteinuria, glomerular filtration rate, and treatment given prior to the biopsy need to be considered when predicting prognosis based on the MEST score. Shima et al. assessed the validity of the Oxford classification of IgA nephropathy in 161 children (Shima et al. 2012). The renal outcome was defined as $\geq$ CKD stage III. They concluded that M, T, and crescents were significant while S was not significantly associated with renal outcome. Their findings suggest that the Oxford classification of IgA nephropathy may be influenced by the interval between disease onset and biopsy, since M and E are seen in acute disease while S is a chronic lesion. In 2013, Tanaka et al. developed and then validated a new integrated prediction rule based on degree of proteinuria, estimated glomerular filtration rate, M, S, and T (Tanaka et al. 2013). They found that the incidence of ESKD increased with increases in total risk scores. They found that the prediction rule demonstrated good discrimination and calibration in the validation cohort. Most recently, in 261 young patients with IgA nephropathy enrolled in VALIGA, those with mesangial hypercellularity score of M1 were at risk of developing higher time-averaged proteinuria (Coppo et al. 2016).

Clinical Markers of Outcome

There are many difficulties in interpreting published results of long-term outcomes of patients with IgA nephropathy. These include ascertainment bias of initial cases, indications for kidney biopsy, and loss of cases for follow-up. In the United States, the predicted kidney survival in children from the time of apparent onset was 94% at 5 years, 87% at 15 years, and 70% at 20 years (Wyatt et al. 1995). Unfortunately, in this study, 63 of 103 patients were lost to follow-up by 10 years from diagnosis.

Despite these caveats, poor prognostic features for renal survival are severe hypertension, elevated serum creatinine at the time of diagnosis, and persistent proteinuria greater than 1 g per 24 h (Wyatt et al. 1995; D'Amico et al. 1986). Age at diagnosis, gender, and angiotensin-converting enzyme-1 (ACE-1) polymorphisms are not associated with a poorer outcome. Familial IgA nephropathy has a poorer outcome than sporadic IgA nephropathy (Schena et al. 2002). In VALIGA, a study that included children and young adults, children aged less than 16 years of age with a mesangial hypercellularity score of zero (M0) and well-preserved renal function (glomerular filtration rate > 90 ml/min/1.73 m^2) at presentation had a higher probability of proteinuria remission and a higher remission rate following treatment with corticosteroid and/or immunosuppressive therapy (Coppo et al. 2016). Additionally, initial proteinuria of greater or equal

to 0.4 g/day/1.73 m^2 and glomerular filtration rate less than 90 ml/min/1.73 m^2 were determined to be risk factors for progression. In a recent study from Spain, 112 patients with IgA nephropathy were followed prospectively for a mean period of 14 years (Sevillano et al. 2017). Time-averaged hematuria, time-averaged proteinuria, renal function at baseline, and the presence of tubulointerstitial fibrosis on renal biopsy were found to be independent predictors of ESRD. Patients with time-averaged proteinuria >0.75 g/day and persistent hematuria had significantly worse renal survival.

Biomarkers for IgA Nephropathy

Biomarkers related to the pathogenesis of IgA nephropathy may (i) provide alternative noninvasive approaches to replace renal biopsies, (ii) distinguish children at risk for progression, and (iii) inform development of new targeted therapies (Coppo 2016; Mestecky et al. 2013).

Serum levels of galactose-deficient IgA1 have a low sensitivity and specificity for IgA nephropathy as compared to renal biopsies (Wyatt and Julian 2013). However, the serum level of glycan-specific IgG antibodies has been shown to correlate with the degree of proteinuria and the risk of progression to ESKD (Suzuki et al. 2009; Chau et al. 2012). Urinary cytokines (epidermal growth factor, low molecular weight proteins, and mannose-binding lectin), increased plasma levels of advanced oxidative protein products and fibroblast growth factor 23, and decreased levels of serum CD89-IgA complexes have been evaluated as markers of histopathological changes and as predictors of poor clinical outcome (Wyatt and Julian 2013; Mestecky et al. 2013). In adult Japanese patients, elevated serum IgA/C3 ratio is a robust diagnostic marker and predictor of poor renal outcome (Tomino et al. 2000; Komatsu et al. 2004). Since urinary microRNAs are relatively stable and easily quantified, they have the potential to be used as biomarkers for the diagnosis and monitoring of IgA disease (Szeto and Li 2014).

Most recently, urine proteomic data using capillary electrophoresis coupled with time-of-flight mass spectrometry has been shown to have a high sensitivity and specificity for differentiating IgA nephropathy from other renal diseases (Hastings et al. 2013) and may also predict the response to treatment with ACE inhibitors (Rocchetti et al. 2008). Additional studies are needed to determine the potential clinical and cost-effectiveness of urinary proteomic analysis in children with IgA nephropathy (Wyatt and Julian 2013).

Differential Diagnosis of IgA Nephropathy in Children

The differential diagnoses of IgA nephropathy can be divided into clinical diagnoses and histopathological diagnoses. Clinical conditions that can present with microscopic hematuria and that must be distinguished from IgA nephropathy include thin glomerular basement membrane disease, Alport hereditary nephritis, and membranoproliferative glomerulonephritis. The renal biopsy can differentiate IgA nephropathy from these other conditions because of the presence of IgA in the mesangium. However, mesangial IgA is also seen in Henoch-Schönlein purpura (HSP) and systemic lupus erythematosus (SLE). SLE is distinguished by the finding of low serum C3 and C4 levels and positive immunofluorescence staining of C1q and other immunoglobulins on biopsy. Other secondary causes of IgA deposition in the mesangium are uncommon in children and are summarized in Table 5 (Donadio and Grande 2002).

Treatment of IgA Nephropathy

There is no accepted treatment for IgA nephropathy, and most of the proposed regimens are controversial (Wyatt and Hogg 2001). The mainstay of therapy involves supportive measures that aim at slowing the progression of IgA nephropathy.

Floege and Feehally classified patients as low risk if they presented with isolated microscopic hematuria, proteinuria less than 0.5 g/day, normal GFR, and no hypertension (Floege and Feehally 2013). Since progressive disease may develop in

Table 5 Differential diagnosis of mesangial IgA deposition

Primary IgA nephropathy		
Secondary IgA nephropathy	Multisystem disorder	Henoch-Schölein Purpura (HSP) – most common; systemic lupus erythematosus (SLE); ankylosing spondylitis
	Gastrointestinal/ liver	Chronic liver disease; celiac disease; Crohn's disease
	Skin disorders	Dermatitis herpetiformis
	Pulmonary disorder	Cystic fibrosis; pulmonary hemosiderosis
	Infections	Mycoplasma infections; toxoplasmosis; leprosy
	Neoplasms	Monoclonal IgA gammopathy; mycosis fungoides; non-Hodgkin's lymphoma; carcinoma of lung/ colon
	Others	Mixed cryoglobulinemia; polycythemia

some children with mild IgA nephropathy, these children should have regular assessment of renal function and monitoring of proteinuria (Wyatt and Julian 2013).

Patients at intermediate risk include those with significant proteinuria (greater than greater than 1 g/day/1.73 m^2) which may be associated with a reduced GFR and/or hypertension (Floege and Feehally 2013). The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) (KDIGO G. Work Group 2012) and National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) for reducing proteinuria and controlling hypertension based on age, gender, and height criteria (American Academy of Pediatrics 2004). The KDIGO guidelines recommend long-term ACE-I or ARB treatment titrated upward to achieve optimal control of blood pressure and proteinuria less than 1 g/day/1.73m^2 (KDIGO G. Work Group 2012). Additionally, the study group suggested that corticosteroids provide little additional benefit above optimized supportive care. However, patients with persistent proteinuria despite 3–6 months of optimized supportive care GFR $<$50 ml/min per 1.73 m^2 should receive a 6-month course of corticosteroid therapy.

There are few studies evaluating the use of steroids as a monotherapy in children. Waldo et al. compared the long-term outcomes of 13 children who received alternate day prednisone for 2 years with 15 children who received no therapy (Waldo et al. 1993). They found that ESKD developed in none of the 13 subjects treated with prednisone but occurred in five (one-third) of the untreated subjects. A meta-analysis of nine randomized control studies showed that relatively high-dose and short-term therapy produced significant renal protection, whereas low-dose, long-term steroid use did not (Lv et al. 2012). Steroid therapy was associated with a higher risk for adverse events. The quality of included studies was low, limiting the generalizability of the results. Most recently, the VALIGA study compared the effects of corticosteroids and renin-angiotensin blockade versus renin-angiotensin blockade alone in a cohort of subjects with similar risk profile for progression (Tesar et al. 2015). They found that corticosteroids reduced proteinuria, reduced the rate of renal function decline, and increased renal survival.

Combined immunosuppressive therapy can be considered in high-risk patients with acute, rapid loss of GFR (Floege and Feehally 2013). KDIGO guidelines suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgA nephropathy patients unless there is crescentic IgA nephropathy with rapidly deteriorating kidney function (KDIGO G. Work Group 2012). In 2015, the STOP-IgA nephropathy investigators randomized 162 subjects with IgA nephropathy and persistent proteinuria into two groups – 80 assigned to supportive care and 82

assigned to supportive care and immunosuppression (Rauen et al. 2015). Over 3 years of follow-up, the investigators found no significant difference in the annual decrease in the renal function between the two groups. However, there was an increased risk of adverse effects including infections, impaired glucose tolerance, and weight gain in the immunosuppression group. The results of this study lack generalizability because of the short follow-up time and the lack of any assessment of the histology and its effect on renal survival (Pozzi et al. 2016).

In 1989, Andreoli and Bergstein suggested using prednisone and azathioprine for the treatment of IgA nephropathy (Andreoli and Bergstein 1989). Two subsequent randomized control trials performed by the Japanese Pediatric IgA Nephropathy Treatment Study Group showed that combining prednisone and azathioprine had a significant reduction in proteinuria as compared to no immunosuppression or prednisone alone (Yoshikawa et al. 1999, 2006). Follow-up biopsies showed progression of glomerular sclerosis in the control group but not in patients who received combined therapy. More recently, in a cohort of adult subjects, Pozzi et al. showed that addition of low-dose azathioprine to corticosteroids for 6 months does not provide additional benefit to patients with IgA nephropathy and may increase the risk for adverse events (Pozzi et al. 2010).

In 1994, Murakami et al. assessed the effect of cyclophosphamide on pediatric patients with significant proteinuria and pathologic features of advanced renal disease (Murakami et al. 1994). The results showed that there was only a temporary improvement in the proteinuria, with rebound deterioration over time. In a randomized control trial in adult patients with poor prognosis of their IgA nephropathy, Ballardie et al. assessed the effect of cyclophosphamide and steroids followed by maintenance with low-dose steroids and azathioprine (Ballardie and Roberts 2002). The study showed significant reduction in proteinuria and decreased rate of decline of renal function. However, the study did not compare the effect of cyclophosphamide to steroid monotherapy. Also, the use of supportive care in the cohort of patients was inconsistent, which could have led to biased results.

KDIGO defines crescentic IgA as IgA nephropathy with crescents in more than 50 % of glomeruli on biopsy with rapidly progressive renal deterioration (KDIGO G. Work Group 2012). The group suggests the use of steroids and cyclophosphamide in patients with rapidly progressive crescentic IgA nephropathy as a few observational studies have purported to show a benefit in these patients (McIntyre et al. 2001; Tumlin et al. 2003; Pankhurst et al. 2009). There are no randomized (control or otherwise) studies to guide the treatment of crescentic IgA nephropathy.

Mycophenolate mofetil (MMF) has been evaluated in randomized control studies and has not been associated with significant reduction in proteinuria or creatinine as compared to placebo (Frisch et al. 2005; Maes et al. 2004). Chen reported MMF to be more effective in reducing proteinuria and associated with less side effects than prednisone, a common therapy for IgA nephropathy patients (Chen et al. 2002). As such, due to the lack of strong evidence, KDIGO recommends not using MMF in the treatment of IgA nephropathy (KDIGO G. Work Group 2012).

In 1999, Scholl proposed the concept of "point of no return." The "point of no return" is the level of renal function below which all patients will progress to ESKD, with doubling of creatinine within 3–21 months (Schöll et al. 1999). However, other reports show that good supportive care can slow the decline in renal function even beyond the "point of no return" (Ota et al. 2000). The KDIGO suggests not using immunosuppression in patients with glomerular filtration rate less than 30 ml/min/1.73m^2 because it may not provide additional benefit and may be associated with adverse events (KDIGO G. Work Group 2012).

There is limited and weak evidence supporting the efficacy of fish oil; however, there are minimal side effects (Hogg et al. 2006). Hence, the KDIGO study group recommends the use of fish oil in the treatment of IgA nephropathy with persistent proteinuria greater than 1 g/day/1.73m^2 (KDIGO G. Work Group 2012).

KDIGO does not recommend tonsillectomy for patients with IgA nephropathy (KDIGO G. Work Group 2012). In a meta-analysis including

14 studies, there was a significantly greater odds of clinical remission with tonsillectomy in about 10 studies (including 1431 subjects) and reduced risk for ESKD in 9 studies (including 873 subjects) (Liu et al. 2015). However, the authors stated that a major limitation was that most included studies were retrospective cohort studies and that they were unable to adjust uniformly for potential confounding variables and treatment with ACE inhibitors. The VALIGA study group paired 17 patients who underwent tonsillectomy after the diagnosis of IgA nephropathy with 51 who did not undergo tonsillectomy and with a similar risk of progression at renal biopsy and subsequent treatments (Feehally et al. 2010). No significant difference was found between the two groups with regard to changes in proteinuria, in the renal end point of 50% reduction in renal function and/or ESKD, or in the annual loss of glomerular filtration rate.

Other potential therapies with limited evidence include vitamin E and anticoagulants. Vitamin E, used as an antioxidant, may be beneficial in reducing proteinuria with a trend toward better preservation of renal function (Chan et al. 2003). Antiplatelet agents and warfarin have been used to treat IgA nephropathy in many studies with no consistent benefit (Yoshikawa et al. 1999). The KDIGO study group does not recommend the use of these agents in the treatment of IgA nephropathy (KDIGO G. Work Group 2012).

There are many other treatments for IgA nephropathy that warrant further evaluation (Lai et al. 2015). Enteric budesonide, targeted to the Peyer's patches, has been shown to reduce proteinuria and increase renal function after 6 months of therapy (Smerud et al. 2011). Recently, the NEFIGAN study reported the use of novel targeted-release formulation of budesonide, designed to deliver drug to the distal ileum in patients with IgA nephropathy (Fellstrom et al. 2017). They found that along with optimized renin-angiotensin blockade, patient receiving target-release formulation of budesonide had a significant reduction in proteinuria as compared to those receiving placebo. Statins have been shown to increase renal function in patients with IgA nephropathy, despite no significant decline in proteinuria (Moriyama et al. 2014). One case report also described the effective use of eculizumab in the management of IgA nephropathy (Rosenblad et al. 2014). Mizoribine, an agent that blocks purine synthesis, has been found to be effective in reducing proteinuria (Ikezumi et al. 2008). In vitro studies suggest that peroxisome proliferative receptor-γ agonists downregulate the angiotensin receptors subtype 1 and may have therapeutic benefit in preserving kidney function when combined with an angiotensin receptor blocker (ARB) (Xiao et al. 2009; Lai et al. 2011).

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) has been described as a small vessel, leukocytoclastic vasculitis that affects the skin, gastrointestinal tract, joints, and kidney (Fig. 5) (Santos and Wyatt 2004; Calvino et al. 2001). Heberden initially reported a case of a young child with abdominal pain, bloody stools, joint pain, purpuric rash, and macroscopic hematuria (Heberden 1801). In 1937, Schönlein first described the syndrome of acute purpura and arthritis in children (Schönlein 1837). Subsequently, Henoch described four children with purpura, abdominal pain, bloody diarrhea, and arthralgia followed by nephritis (Henoch 1874, 1895). Currently, HSP is the most frequently detected vasculitis in children (Davin Coppo 2014). The recent consensus suggested replacing the eponym "Henoch-Schönlein purpura" with IgA vasculitis based on findings that abnormal IgA deposits in vessel walls are the defining pathophysiologic feature (Jennette 2013).

Clinical Features

In 1990, the American College of Rheumatology described the criteria for identifying HSP and distinguishing HSP from other forms of vasculitis (Mills et al. 1990). The presence of two of the following criteria had a high sensitivity and

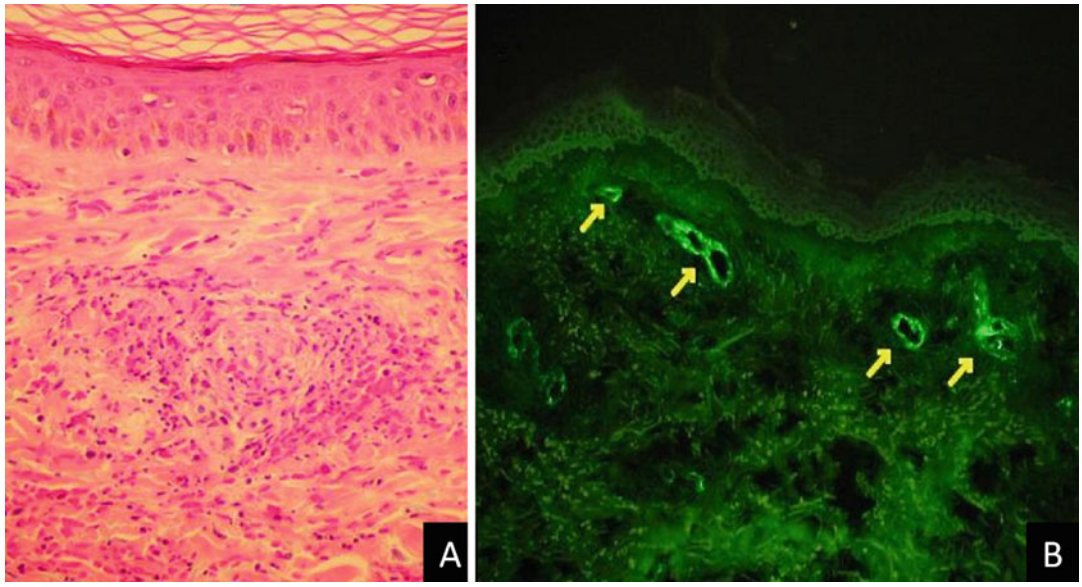

Fig. 5 Skin biopsy findings in children with HSP. (**a**) Leukocytoclastic vasculitis with neutrophil infiltration, leukocytoclastic changes, and fibrinoid necrosis of small vessels in superficial dermis. (**b**) Direct immunofluorescence stain of skin biopsy showing IgA staining of the cutaneous vasculature (*yellow arrows*)

specificity for the diagnosis of HSP: (i) age $\leq$20 years at disease onset, (ii) palpable purpura, (iii) acute abdominal pain, and (iv) biopsy showing granulocytes (neutrophils) in the walls of small vessels. The Chapel Hill Conference on the Nomenclature of Systemic Vasculitis defined HSP as a "vasculitis with IgA-dominant immune deposits affecting small vessels typically involving the skin, gut, glomeruli, and associated with arthralgia and arthritis" (Fig. 5) (Jennette et al. 1994). The modified criteria for HSP was published by the European League Against Rheumatism and the Pediatric Rheumatology European Society – palpable purpura (mandatory) in the presence of at least one of the following: diffuse abdominal pain, any biopsy sample showing predominantly IgA deposition, acute arthralgia/arthritis, or renal involvement (Ozen et al. 2006).

HSP frequently occurs after respiratory tract infections. Some studies have described an association between group A streptococcal infection and HSP (Masuda et al. 2003; Kikuchi et al. 2006). HSP is generally self-limited with relapses occurring in about one-third of the children (Pohl 2015). Not all children with HSP develop nephritis, and the incidence of nephritis in children with HSP ranges between 20% and 50% (Santos and Wyatt 2004). HSP most commonly develops in children over 4 years of age and is heralded by severe abdominal symptoms, gastrointestinal bleeding, and persistent dependent purpura (Kaku et al. 1998; Sano et al. 2002). Renal involvement is the most important factor leading to chronic disease in these children. Low factor XIII levels have been shown to be associated with the development of nephritis (Pohl 2015). Hence, renal function should be closely observed, and if affected, the patient should be referred to a pediatric nephrologist (Santos and Wyatt 2004). Nephritis usually develops within 3 months after initial presentation (60–80%) but can occur as late as 6 months after initial presentation (Saulsbury 1999; Narchi 2005). Of the patients that develop renal involvement, hematuria and/or proteinuria are the most common findings (Narchi 2005). Approximately 7% of all HSP patients (20% of HSP nephritis patients) develop nephrotic or nephritic syndrome. Hypertension may occur in 15–25% of children with HSP nephritis (Santos and Wyatt 2004; Saulsbury 1999).

Table 6 ISKDC histological classification of HSP nephritis

Grade	Biopsy findings
I	Minimal histological changes
II	Pure mesangial proliferation
III	Focal (IIIa) or diffuse (IIIb) mesangial proliferation with < 50% crescents
IV	Focal (IVa) or diffuse (IVb) mesangial proliferation with 50–75% crescents
V	Focal (Va) or diffuse (Vb) mesangial proliferation with > 75% crescents
VI	Membranoproliferative-like lesions

Prognostic Markers for HSP Nephritis

Clinical markers: Renal insufficiency at presentation and nephrotic syndrome at presentation or during follow-up are significant independent predictors of long-term renal impairment (Ronkainen et al. 2002; Schärer et al. 1999). A higher risk of long-term sequelae from renal involvement may increase with age of presentation (Meadow et al. 1972).

Histologic markers: The severity of the histologic changes correlates with the long-term renal outcome (Goldstein et al. 1992). The International Study of Kidney Disease in Childhood (ISKDC) modified the histological classification of HSP nephritis that was initially developed by Meadow et al. (1972) and White 1994) (Table 6). Children having >50% glomeruli on their biopsy have been found to have a poor outcome as compared to those with fewer or no crescents (Halling et al. 2005). However, renal biopsies in HSP suffer from sampling bias and only reflect the pathology at the time of the biopsy. Additional activity and chronicity markers may help increase in utility of biopsies in predicting outcome (Pohl 2015).

Similarities and Differences Between Primary IgA and HSP

Several similarities and difference have been reported between primary IgA nephropathy and HSP nephritis.

Incidence: The incidence of HSP nephritis has been reported to be 15–70 cases per 1 million children as compared to IgA nephropathy which has an incidence of 5–50 per 1 million children (Wyatt and Julian 2013). The peak age of onset ranges between 15 and 30 years for IgA nephropathy, whereas HSP nephritis is mainly seen in early childhood (Davin et al. 2001). Both diseases are more common in males (Emancipator 1993). IgA nephropathy and HSP nephritis have both been reported in families (Julian et al. 1985). While genome-wide studies have identified multiple possible loci for genetic cause of IgA nephropathy, no such studies have been reported in HSP (Gharavi et al. 2011). In a pair of identical twins, one child developed IgA nephropathy, and the other developed HSP nephritis (Meadow and Scott 1985).

Pathogenesis: The pathophysiology of IgA nephropathy and HSP nephritis seems to be identical. However, higher amounts of IgG, larger size of the circulating IgA-containing immune complexes, and a greater incidence of increased plasma IgE levels have been reported in HSP nephritis compared to IgA nephropathy (Levinsky and Barratt 1979; Cederholm et al. 1991). Tissue infiltration by leukocytes is a major feature of HSP vasculitis suggesting that more potent activation of leukocytes in these patients may play a role (Davin et al. 2001). Lastly, eosinophilic cationic protein levels were found to be significantly higher in children with HSP as compared to those with IgA nephropathy (Namgoong et al. 1997). Polymorphisms in genes related to cytokine and cell adhesion molecules may predispose children to HSP (Brogan 2007).

Clinical features: HSP is associated with extrarenal deposition of IgA in dermal capillaries, gastrointestinal vasculitis, and arthralgias all of which are rare in primary IgA nephropathy. HSP presents with more acute signs of nephritis, while IgA nephropathy often has a more insidious onset (Pohl 2015). IgA nephropathy usually presents with macroscopic hematuria coincident with mucosal infection. In HSP nephritis, the incidence of gross hematuria is less common. In HSP, nephritis usually develops within 3 months of initial presentation, even after extrarenal

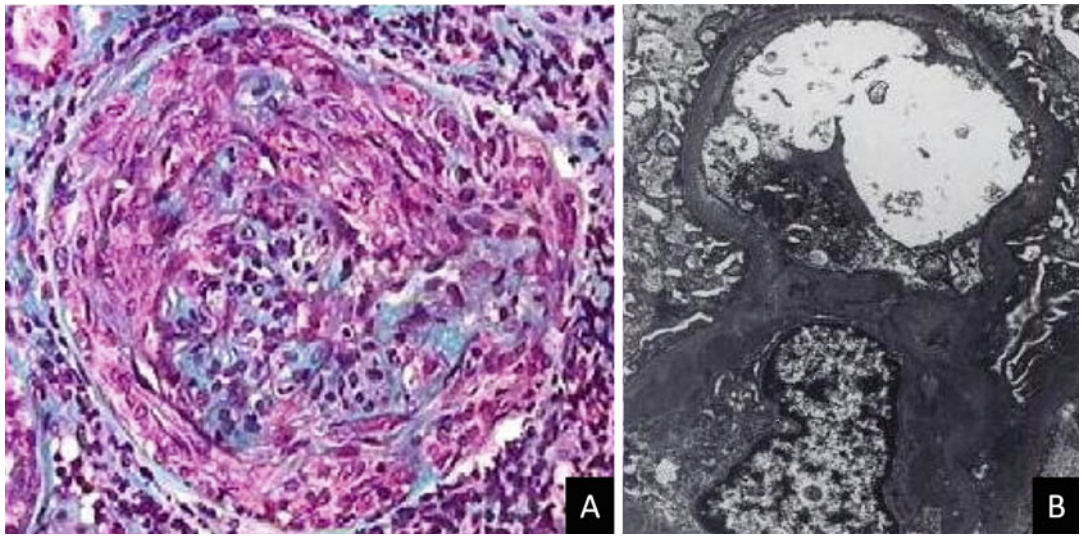

Fig. 6 Biopsy findings in HSP nephritis. (**a**) Circumferential cellular crescents can be seen in biopsies of children with HSP nephritis. In the remaining part of the glomerular tuft, endocapillary proliferation and exudative lesions may be present. (**b**) On electron microscopy, mesangial proliferation and subendothelial electron-dense deposits are commonly detected in HSP nephritis

manifestation have subsided (Saulsbury 1999; Hurley and Drummond 1972). Nephritic and nephrotic syndromes are more frequent in HSP (20%) than in IgA nephropathy (10%) (Narchi 2005).

Histology: In HSP nephritis, the glomerular lesions are more often severe, showing acute glomerular inflammation, increased endocapillary proliferation, frequent tuft necrosis, and epithelial crescent formations (Fig. 6) (Davin and Coppo 2013). These active lesions are rather uncommon in most cases of IgA nephropathy. Biopsies in patients with HSP nephritis show more intense perivascular, subendothelial, and subepithelial IgA deposits as well as a high frequency of endocapillary proliferation (Emancipator 1993; Davin et al. 2001; Davin 2011). In summary, while IgA nephropathy typically presents as slowly progressive mesangial lesions with secondary scarring, HSP nephritis presents with acute episodes of inflammatory glomerular lesions that require treatment to prevent chronic damage (Davin and Coppo 2014).

Outcomes: Clinical remission is more common in HSP nephritis (Wyatt and Julian 2013). ESKD has been reported in 20–40% of patients with IgA nephropathy by 20 years after biopsy compared to only 13% of children with HSP nephritis. Higher risk of chronic kidney disease is noted in HSP when clinical onset is in adulthood. Histological recurrence after transplantation has been reported in both IgA nephropathy (between 19% and 35%) and HSP nephritis (33–42%) (Soler et al. 2005; Poticelli et al. 2001; Moroni et al. 2008).

Treatment of HSP Nephritis

It was previously believed that a short course of corticosteroids might lower the risk of renal involvement in children with HSP (Mollica et al. 1992). However, a study by Saulsbury in 1993 showed that corticosteroids did not prevent nephritis in children with HSP (Saulsbury 1993). More recently, a review of existing literature showed that the current evidence does not support the "prophylactic" use of prednisone in preventing persistent renal disease (Bogdanović 2009). As such, the KDIGO guidelines recommend not using corticosteroids to prevent HSP nephritis (KDIGO G. Work Group 2012).

KDIGO suggests the use of ACE inhibitors and angiotensin receptor blockers in children with HSP nephritis and persistent proteinuria, between 0.5 and 1 g/1.73m^2/day (KDIGO G. Work Group 2012). Ninchoji et al. showed that ACE inhibitors and angiotensin receptor blockers induced remission in 31 children with moderately severe HSP (histological grade I–III) (Ninchoji et al. 2011).

KDIGO recommends the use of corticosteroids only in children with glomerular filtration rate less than 50 ml/min/1.73m^2 and/or persistent proteinuria greater than 1 g/1.73m^2/day, after a trial of ACE inhibitors or angiotensin receptor blockers (KDIGO G. Work Group 2012). Davin and Coppo believe that following the KDIGO guidelines may lead to undertreatment and/or delayed treatment of acute and potentially aggressive glomerular inflammation (Davin Coppo 2013). Late initiation of immunosuppressive therapy in HSP nephritis may be associated with worse outcomes (Andersen et al. 2009). The use of various immunosuppressive therapies has been reported in patients with HSP nephritis. Similar to IgA, corticosteroids are part of most treatment regimens with or without other immunosuppressive drugs (Pozzi et al. 2004; Pohl 2015). In an uncontrolled study, Niaudet and Habib found that methylprednisolone pulse therapy is effective in children at risk of progression of their nephropathy, especially if started early during the course of the disease before fibrous crescents develop (Niaudet and Habib 1998). Flynn et al. retrospectively studied 12 children with HSP nephritis treated with high-dose corticosteroids plus oral cyclophosphamide. They concluded that the therapy was safe and, as in nephrotic syndrome, appeared to significantly reduce proteinuria (Flynn et al. 2001). The KDIGO suggests using steroids and cyclophosphamide in patients with rapidly progressive crescentic HSP nephritis (KDIGO G. Work Group 2012). There are reports showing benefit of other agents including azathioprine, mycophenolate mofetil, cyclosporine, and even rituximab in children with HSP (Pohl 2015; Foster et al. 2000; Jauhola et al. 2011; Pillebout et al. 2011; Ren et al. 2012). Two retrospective studies have reported the favorable effect of plasma exchange in patients with severe clinical and histological features of HSP nephritis (Hattori et al. 1999; Shenoy et al. 2007). To date, there are no large randomized control studies evaluating the benefits of these medications. In children with HSP associated with nephritic syndrome, nephrotic syndrome, and/or cellular crescents, the German Society of Pediatric Nephrology recommends the initial use of 2 months of corticosteroids followed by other immunosuppressive medications in children with insufficient response after 3–6 months (Pohl et al. 2013).

At the present time, physicians rely mainly on clinical case series and personal experience in the management of HSP nephritis. There is a need for a large, well-designed, randomized controlled studies to determine the best regimen for the treatment of HSP nephritis in children.

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Membranoproliferative Glomerulonephritis, Adult

21

Mariam P. Alexander and Sanjeev Sethi

Contents

Abstract

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury seen in varied disease conditions, and in itself does not refer to a specific disease entity. Previously it was classified according to the ultrastructural location of deposits as MPGN type I, II or III. Since then, we have moved onto a classification based on etiology and pathogenesis. The two broad pathogenetic pathways include either glomerular injury secondary to an immune complex/monoclonal immunoglobulin deposition

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or consequent to complement deposition in the setting of dysregulated abnormalities of the complement system. Appropriate classification based on immunofluorescence permits a detailed and tailored evaluation for underlying infections, autoimmune diseases, monoclonal gammopathy and/or abnormalities of the complement system. Recent use of ancillary diagnostic techniques such as pronase immunflourescence and mass spectrometry promote accurate diagnosis in challenging cases.

Keywords

MPGN · Immune complex · Complement · C3 glomerulopathy · Monoclonal immunoglobulin · Infections · Autoimmune diseases

Definition

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury seen in varied disease conditions (Sethi and Fervenza 2012). The name in itself does not refer to a specific disease entity. The characteristic morphology includes a proliferative component represented by mesangial and endocapillary hypercellularity and resolving membrano-component represented by thickened glomerular basement membranes. These changes impart a lobular appearance of the glomerular capillary tufts. Generally speaking, MPGN reflects an active-chronic disease process with both an active component represented by the hypercellularity and the chronic component represented by the double-contour formation. Other names for MPGN include lobular glomerulonephritis and mesangiocapillary glomerulonephritis.

Former Classification

Historically MPGN has been classified into MPGN type I, MPGN type II, and MPGN type III based on electron microscopy. It should be pointed out at the outset that this classification is not based on pathophysiology but rather on ultrastructural characteristics and location of the electron-dense deposits.

MPGN type I, the most common type, is characterized histologically by mesangial proliferation with cellular interposition and double contours resulting in the typical MPGN pattern of injury. Immunofluorescence microscopy reveals immunoglobulins (Ig) and C3 or predominantly C3 deposits. Electron microscopy (EM) shows mesangial and subendothelial deposits. MPGN type II is characterized by an MPGN pattern of injury, bright staining for C3 on IF, and mesangial and intramembranous highly electron-dense deposits on electron microscopy. MPGN II is also called dense deposit disease (DDD). MPGN type III is characterized histologically by an MPGN pattern of injury. Immunofluorescence microscopy reveals Ig and C3 or predominantly C3 deposits. Electron microscopy of MPGN type III is characterized by subendothelial deposits and intramembranous and subepithelial electron-dense deposits. It is further classified into two types: the Burkholder and Anders/Strife type. The Burkholder type (Burkholder et al. 1970) is characterized by many of the features of MPGN type I but with the additional presence of numerous subepithelial electron-dense deposits. The Anders/Strife type of MPGN type III (Anders et al. 1977) has large variably dense intramembranous electron-dense deposits which connect subepithelial and intramembranous deposits.

The disadvantage of this classification is its lack of clinical significance. This classification bears no relation to etiopathogenesis and therefore does not guide therapy. A clearer understanding of etiology has evolved since the original classification, particularly in relation to the role of complement pathways involved in glomerulonephritis. This has led to a more practical approach and reclassification of MPGN termed the "Mayo classification" of MPGN (Sethi and Fervenza 2011, 2012).

Newer Classification Based on Etiology and Pathogenesis

There are largely two broad pathogenetic pathways in the evolution of MPGN based on the new "Mayo Clinic" classification of MPGN (Sethi and Fervenza 2011, 2012):

(a) Immune complex or monoclonal Ig deposition in the glomeruli with or without complement deposition
(b) Complement deposition subsequent to dysregulated abnormalities of the complement system

A third pathogenic pathway which leads to capillary wall remodeling and thickened glomerular basement membranes in the absence of immune complex or complement deposition is seen in the setting of chronic endothelial injury or chronic thrombotic microangiopathy. Other uncommon causes such as cryofibrinogen glomerulopathy, lipoprotein glomerulopathy, etc. that result in endothelial injury and deposition of increased or abnormal proteins along the capillary walls can also result in an MPGN pattern of injury.

Immune Complex/Monoclonal Ig-Mediated MPGN

The MPGN pattern of injury is likely secondary to (1) persistent antigenemia and circulating immune complexes or (2) monoclonal Ig. Typically, in our experience immune complex/monoclonal Ig-mediated MPGN results in the setting of infections and autoimmune disease, while monoclonal Ig-mediated MPGN results in the setting of monoclonal gammopathy (although in some cases MIg is not detected on routing SPEP/IFE studies). The immune complexes and monoclonal Ig deposit in the mesangial and subendothelial areas of the glomerulus. There is subsequent complement activation, which accounts for the hypocomplementemia. A proliferative glomerulonephritis is noted in the acute phase with influx of neutrophils initially, followed by mononuclear inflammatory cells. In the reparative phase, the injured mesangial cells and endothelium lay down new basement membrane, and the mesangial matrix expands. The complex remodeling of the glomerular basement membrane results in the thickened membranes. Taken together, these changes result in an MPGN pattern of injury. The immune complex and monoclonal Ig-mediated MPGN is characterized by the presence of Igs on IF studies; in immune complex-mediated MPGN, the deposits are polyclonal, while in monoclonal Ig-mediated MPGN, the Ig is monotypic. C3 is most often present as well, indicating activation of complement pathway.

Infection-Associated MPGN

There are several infections, mostly chronic, associated with an MPGN pattern of injury. The most common infection associated with an MPGN pattern of injury is hepatitis C infection. Hepatitis C is associated with varied renal diseases including membranous nephropathy, focal segmental glomerulosclerosis (Stehman-Breen et al. 1999), thrombotic microangiopathy (Baid et al. 1999), and fibrillary glomerulonephritis (Markowitz et al. 1998). The exact mechanism of HCV-related glomerular disease is unclear. Toll-like receptors, particularly TLR3, might have a role to play in HCV-related MPGN (Wornle et al. 2006).

Hepatitis B is also implicated in MPGN (Johnson and Couser 1990; Knieser et al. 1974; Myers et al. 1973). The pathology is likely related to the trapping of circulating immune complexes in the mesangium and subendothelial regions. It is also possible that mesangial cells are directly infected by hepatitis B virions (Knieser et al. 1974).

Rarely, MPGN may be seen with acute viral infections such as Puumala hantavirus (Mustonen et al. 2001).

Chronic bacterial infections are well-recognized causes of MPGN. Deep-seated abscesses, such as Pott's abscess from tuberculosis or nocardial abscesses, (Elmaci et al. 2007; Ram et al. 2014) infected indwelling catheters, and shunts, are causes of MPGN due to continuous low-dose antigenemia (Marini et al. 1976; Okada et al. 2016; Takaki et al. 2012; Yared et al. 1999). "Shunt nephritis" as may be seen with ventriculoatrial or ventriculocaval shunts for hydrocephalus is caused most commonly by coagulase-negative staphylococcal infections (Black et al. 1965). Other organisms include coagulase-positive staphylococci or *Propionibacterium acnes*. Catheter infections are often seen in the setting of total parenteral nutrition. Brucellosis may cause an MPGN pattern of renal injury in endemic regions (Ceylan et al. 2009). Filariasis and leprosy

have been recognized as causes of MPGN in the tropical environment (Date et al. 1983). Fungal and parasitic infections are less commonly associated with an MPGN pattern of injury (Altiparmak et al. 2002; Ubesie et al. 2013). Leishmaniasis has been associated with MPGN (Ortiz et al. 2015). Sethi et al. recently described a case of leishmaniasis with MPGN and abundant complement deposition within the glomeruli (Sethi et al. 2016a).

Infections resulting in MPGN are often characterized by the presence of mesangial and capillary wall staining for IgM and C3 in the setting of viral infections; small amounts of IgG may also be present. The presence of IgG (with lesser intensity of IgM) and C3 is more often seen in bacterial infections. In some cases with chronic infections, the Ig staining may be weak compared to the C3 staining. Electron microscopy shows mesangial and subendothelial deposits. The capillary walls are thickened with entrapment of cellular elements, subendothelial electron-dense deposits, matrix like material, and new basement membrane material often resulting in the formation of double contours. A representative figure from MPGN secondary to hepatitis C is shown in Fig. 1. The figure shows an MPGN pattern on light microscopy, IgM and C3 staining in the mesangium and along capillary walls on immunofluorescence studies, and subendothelial electron-dense deposits and double-contour formation along the capillary walls on electron microscopy.

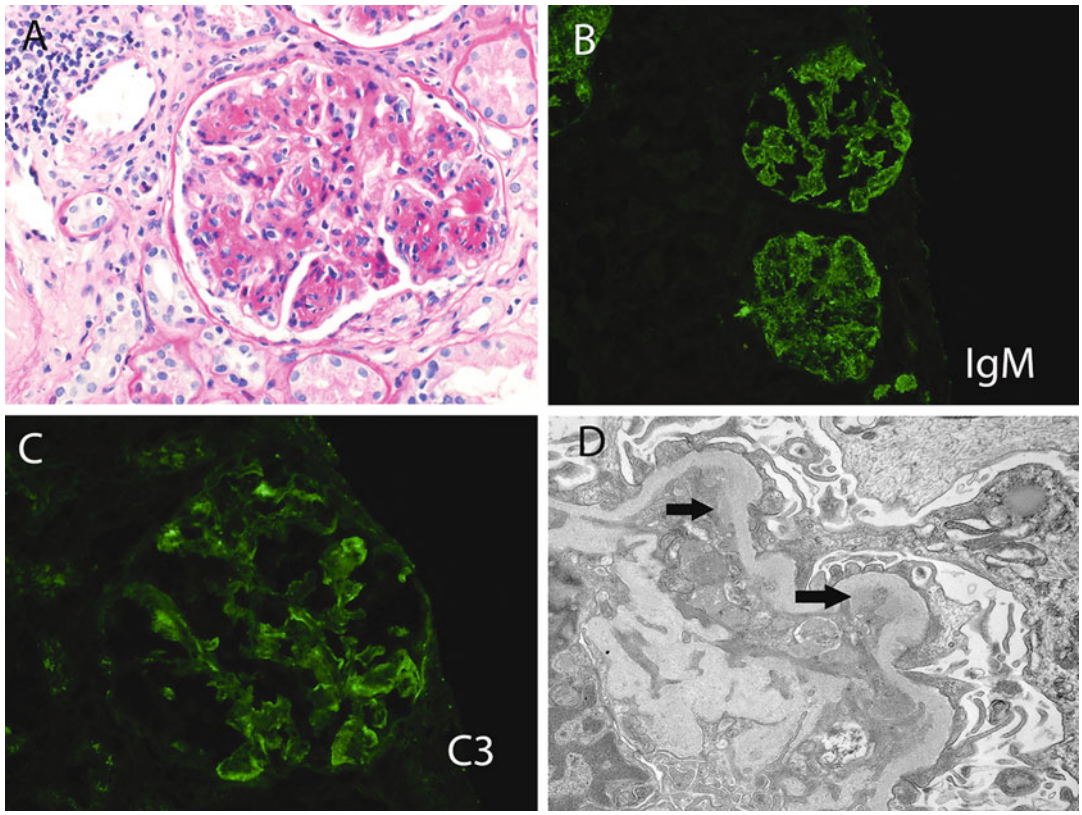

Fig. 1 Immune complex MPGN associated with hepatitis C. (**a**) Light microscopy showing an MPGN pattern of injury (periodic acid–Schiff stain 40×), (**b**) IgM and (**c**) C3 staining in the mesangium and along capillary walls on immunofluorescence studies (IgM 20×, C3 40×), and (**d**) subendothelial electron-dense deposits and double-contour formation along the capillary walls on electron microscopy (13,000×)

Autoimmune Disease-Associated MPGN

Membranoproliferative glomerulonephritis is most commonly seen in systemic lupus erythematosus, as the expression of chronic lupus nephritis (Weening et al. 2004). Other autoimmune diseases known to be associated with MPGN include rheumatoid arthritis, primary Sjögren's syndrome, undifferentiated connective tissue disease, primary sclerosing cholangitis, and Graves' disease (Zand et al. 2014; Cortez et al. 1995; Goules et al. 2000). Ghoules et al. reported renal disease in approximately 4% of patients with primary SS. Interstitial nephritis and glomerulonephritis were the most common causes of renal disease. Glomerulonephritis, which included MPGN and mesangioproliferative GN, occurred later in the course of the disease and was associated with less favorable outcomes. The majority of patients with glomerulonephritis (80%) had mixed monoclonal cryoglobulinemia IgM kappa (type II) and lower complement C4 levels (Goules et al. 2000). Sjögren's syndrome is reportedly the most common cause of non-HCV-related cryoglobulinemia (Khan et al. 1988; Anand et al. 2015).

MPGN associated with autoimmune diseases is often characterized by a full-house pattern of IF staining, i.e., positive staining for IgG, IgA, IgM, C1q, C3, kappa, and lambda light chains, particularly in the setting of systemic lupus erythematosus. On the other hand, IgM may be the dominant Ig in MPGN associated with rheumatoid arthritis and primary Sjögren's syndrome. Electron microscopy shows mesangial and capillary wall electron-dense deposits. With regard to capillary wall deposits, subendothelial deposits are most common. Subepithelial deposits may also be present. In such cases, a membranous component of the disease should be considered. Tubuloreticular inclusions are often present in the endothelial cells. Figure 2 shows an MPGN in the setting of an autoimmune disease (Sjögren's syndrome). Light microscopy shows an MPGN pattern of injury with cryoglobulins in the lumen, immunofluorescence studies show staining for IgG, IgM, and C3 (C1q, kappa, and lambda were also positive but are not shown), and electron microscopy studies show double contours with intraluminal deposits representing cryoglobulins.

Monoclonal Ig-Associated MPGN

Monoclonal gammopathies encompass a heterogenous spectrum of disorders characterized by clonal proliferation of Ig-producing B-lymphocytes or plasma cell clone proteins that results in a monoclonal Ig that can be detected in the blood or urine (M-protein) (Kyle et al. 2002). The physicochemical properties of the monoclonal Ig often result in renal disease, even in the absence of overt malignancies such as lymphoma, multiple myeloma, or Waldenström's macroglobulinemia. The glomerular diseases included in this group include proliferative glomerulonephritis with monoclonal Ig deposits, amyloidosis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and monoclonal immunoglobulin deposition disease (Sethi et al. 2010a, 2016b; Sethi and Rajkumar 2013). The term monoclonal gammopathy of renal significance has been introduced to indicate renal involvement in the setting of a monoclonal gammopathy (Leung et al. 2012). While each of these entities might have a varied morphological appearance, an MPGN pattern of glomerular injury is the common pattern injury. In the next paragraph, we will restrict our discussion to proliferative glomerulonephritis resulting from glomerular deposition of monoclonal Ig.

On kidney biopsy, glomerular deposition of the monoclonal Ig results in a membranoproliferative pattern of injury in most cases. Less commonly, other patterns of proliferative glomerulonephritis can be seen including mesangial proliferative, diffuse proliferative, crescentic and necrotizing, and sclerosing glomerulonephritis (Sethi et al. 2010a; Nasr et al. 2009). Immunofluorescence studies are crucial to the diagnosis and show mesangial and capillary wall monoclonal Ig deposits. The monoclonal Ig most often contains heavy-chain IgG, less commonly IgM or rarely IgA, with kappa or lambda light chain restriction. Less commonly, only heavy or light chains may be present. Electron microscopy shows mesangial and subendothelial electron-dense deposits and

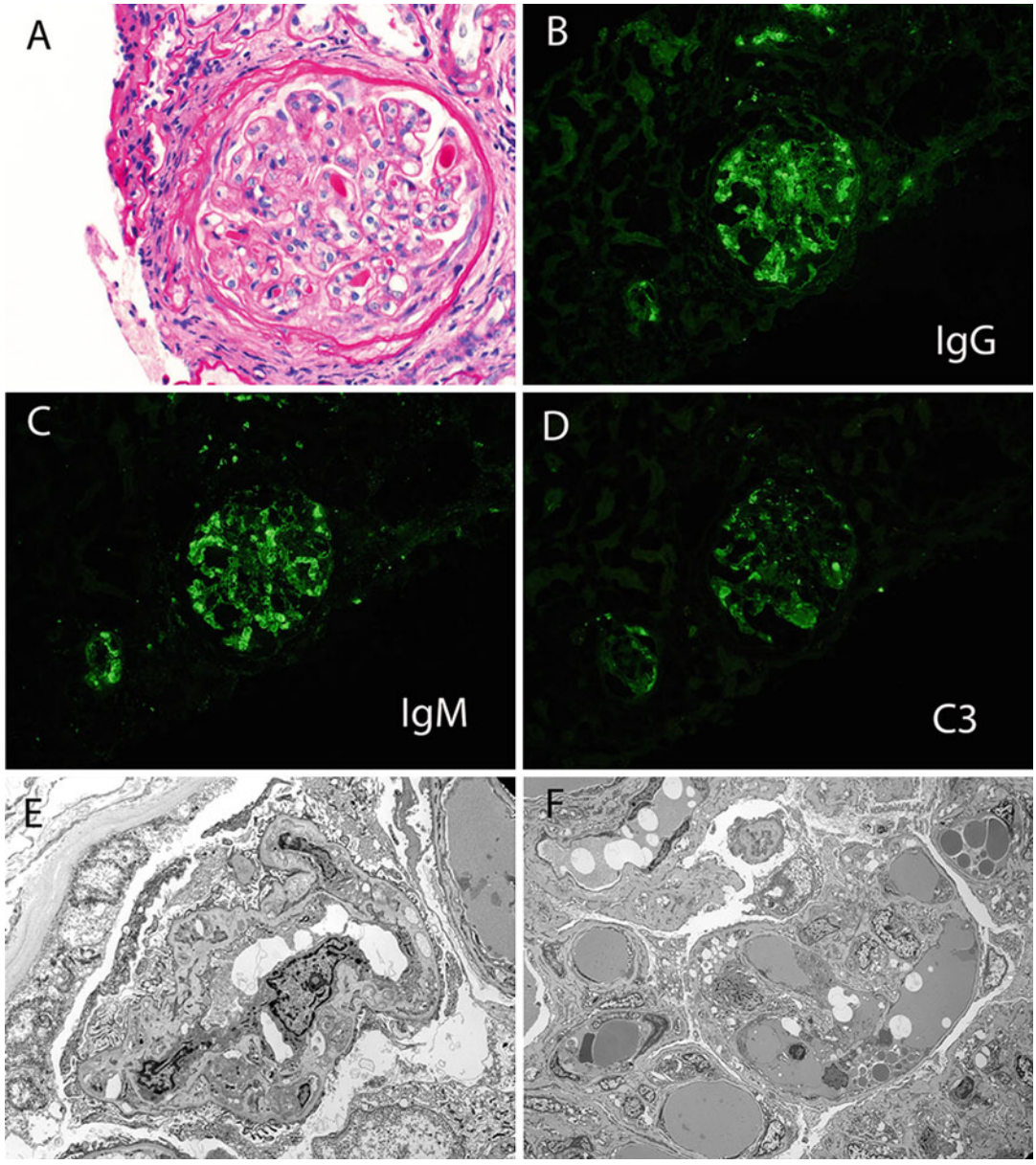

Fig. 2 Immune complex MPGN associated with Sjögren's syndrome. (**a**) Light microscopy shows an MPGN pattern of injury with cryoglobulins in the lumen (periodic acid–Schiff stain 40×), (**b**–**d**) immunofluorescence studies show staining for IgG, IgM, and C3 (C1q, kappa, and lambda were also positive but are not shown) (20× each), and (**e**–**f**) electron microscopy studies show double contours with intraluminal deposits representing cryoglobulins (**e** 2900×, **f** 1400×)

rarely subepithelial and intramembranous deposits. Glomerular capillary wall remodeling with double-contour formation is often present. Features that suggest glomerulonephritis due to monoclonal Ig-associated cryoglobulins (type 1 cryoglobulins) include intraluminal PAS-positive (hyaline-like) deposits on light microscopy, intraluminal MIg on immunofluorescence microscopy, and substructures (microtubules, fibrillary, fingerprints) on electron microscopy.

In cases where the heavy chain consists of IgG, subtyping of the IgG is useful in confirming the diagnosis. The IgG3 subclass is the most common subclass. Interestingly, this class of deposits is most likely to have undetectable circulating MIg by routine serum and urine electrophoresis studies (Bhutani et al. 2015).

In a recent study of monoclonal Ig-associated MPGN, 26 of 28 patients had a positive M-spike on serum electrophoresis, and 27 of the 28 patients had monoclonal or biclonal band on serum immunofixation studies. Furthermore bone marrow studies revealed a MGUS in 16 patients of which two converted to multiple myeloma, two cases showed chronic lymphocytic leukemia, one showed lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, three showed low-grade B-cell lymphoma not further classifiable, and six patients showed multiple myeloma (Sethi et al. 2010a). Thus, it is imperative that all patients with MPGN associated with monoclonal Ig be evaluated for an underlying plasma cell or B-cell proliferative disorder. Figure 3 shows an MPGN in the setting of a monoclonal Ig. Light microscopy shows an MPGN pattern of injury, immunofluorescence studies show staining for IgG kappa with negative staining for lambda light chains, and electron microscopy studies show subendothelial deposits and double-contour formation along the capillary walls. Subtyping of IgG reveals IgG3 subtype.

Cryoglobulins and MPGN

Cryoglobulins can be present in the setting of infections, autoimmune diseases, and monoclonal gammopathy. Thus, all of the three abovementioned causes can present with an MPGN pattern of injury with intraluminal deposits (immune microthrombi) that is then suggestive of cryoglobulins. Cryoglobulins are often divided into three types. Type 1 cryoglobulins show a monoclonal Ig, type II shows a mixture of monoclonal/polyclonal Ig typically monoclonal IgM and polyclonal IgG, and type III shows polyclonal Ig. Type 1 cryoglobulinemia is associated with a single monoclonal immunoglobulin and is associated with renal involvement in up to 40% of cases. Type 1 cryoglobulinemia is related to an underlying B-cell hematological malignancy in 60% of patients. The hematologic diagnoses are typically Waldenström's macroglobulinemia or multiple myeloma. In the remaining cases, in the absence of criteria for malignancy, the diagnosis of monoclonal gammopathy of renal significance should be established (Zaidan et al. 2016). MPGN associated with type II essential mixed cryoglobulins is the most common manifestation of HCV infection and autoimmune diseases, particularly Sjögren's syndrome (Fig. 2) (Zand et al. 2014). In a recent study of 30 patients of Sjögren's syndrome, one third of the patients had type II cryoglobulins (Zintzaras et al. 2005). In another series of MPGN associated with Sjögren's syndrome, all eight cases had evidence of type II cryoglobulins (Tzioufas et al. 1986). Type III cryoglobulins are most often seen in autoimmune diseases, but can be seen in HCV infection as well. Thus, there is significant overlap between the underlying etiology of type II and III cryoglobulins. MPGN with features of cryoglobulins should lead to evaluation of infections in particular HCV, autoimmune diseases in particular Sjögren's syndrome, and finally monoclonal Ig.

Complement-Mediated MPGN (C3 Glomerulopathy)

Dysregulation and abnormalities of the complement system are a less common cause of MPGN. This group of diseases in which there are large deposits of complement products along the capillary walls and in the mesangium is called C3 glomerulopathy. It includes two broad groups: C3 glomerulonephritis and dense deposit disease (DDD). C3 glomerulonephritis is characterized by mesangial and subendothelial, intramembranous, and sometimes subepithelial capillary wall deposits, while in DDD, the deposits are dense, osmiophilic, sausage-shaped intramembranous, and mesangial (Sethi and Fervenza 2014; Smith et al. 2007). The defining feature of C3 glomerulopathy is the abnormality of the alternate

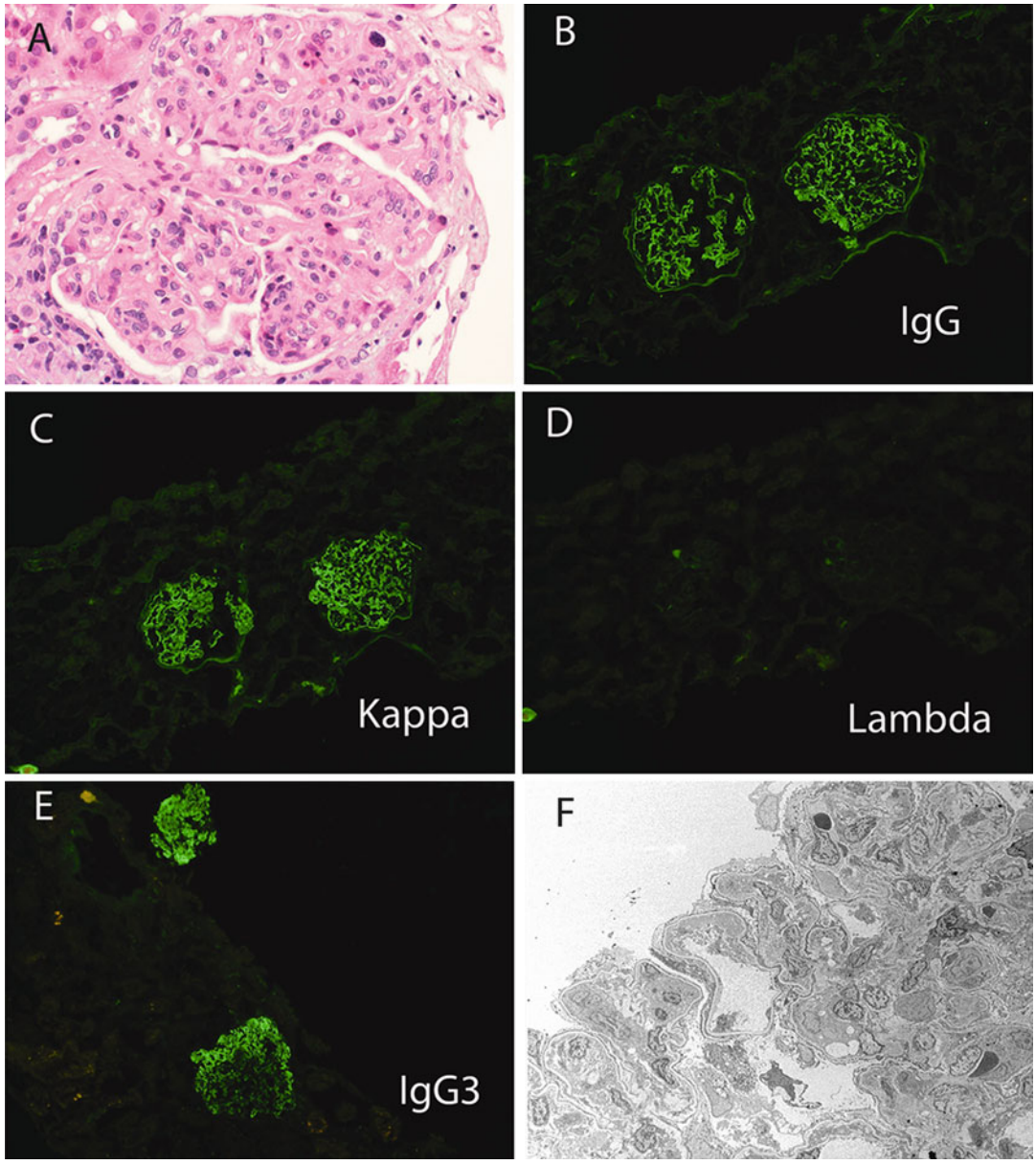

Fig. 3 MPGN associated with monoclonal Ig. (**a**) Light microscopy shows an MPGN pattern of injury (hematoxylin and eosin 40×), immunofluorescence studies show (**b**–**c**) bright capillary wall staining for IgG and kappa, (**d**) lambda light chains are negative, and (**e**) subtyping reveals IgG3, and (**f**) electron microscopy studies show subendothelial deposits and double-contour formation along the capillary walls (1500×)

complement pathway (Fakhouri et al. 2010; Barbour et al. 2013a; Pickering et al. 2013).

On light microscopy the pattern of injury is quite variable and includes mesangial proliferative, membranoproliferative, and endocapillary proliferative, and, in rare circumstance with minimal abnormalities, crescents or sclerosing lesions may also be seen (Fervenza et al. 2012; Nasr et al. 2009; Sethi et al. 2011, 2012a). In DDD thickening of the glomerular basement membranes,

particularly on the periodic acid–Schiff stain, can often be appreciated.

Immunofluorescence microscopy demonstrates a predominance of C3 deposition in the glomeruli which is largely granular staining of the mesangium and peripheral capillary walls. Nasr et al. in their study of 32 patients with DDD demonstrated C3 in the mesangium as granular or ringlike deposits and along glomerular capillary walls in a linear to semi-linear pattern. Sometimes the linear staining appeared as narrow tram tracks outlining the inner and outer aspects of the thickened glomerular capillary walls. Focal linear or semi-linear C3 staining was also seen along tubular basement membranes in 60% of patients and along Bowman's capsule in 30% of patients (Nasr et al. 2009). Similar staining pattern of C3 in the mesangium and along glomerular capillary walls is noted in C3 glomerulonephritis, although the ringlike deposits are not a typical finding. Tubular staining for C3 may be seen in DDD; it is not a feature of C3 glomerulonephritis.

In most laboratories C3 is evaluated by C3c component. However the C3 breakdown products, which include iC3b, C3c, and C3dg, are likely differentially deposited in glomeruli, and their interactions with complement receptors might contribute to the pathophysiology of the disease. The C3GN consensus report suggests it would be ideal if antibodies to the different C3 breakdown products could be employed to enhance our understanding of the disease (Pickering et al. 2013; Sethi et al. 2016c).

Immunoglobulins are often deposited along with C3 in C3 glomerulopathy. It has been observed that if the most restrictive criteria of "C3 only" was utilized, it would capture only half of the cases with DDD (compared with 8% of type I and 10% of type III). Adding the most liberal definition (C3-dominant staining of at least two orders of intensity stronger than any combination of IgG, IgM, IgA, and C1q) identified 88% of those with DDD (compared with 31% of type I and 39% of type III) (Hou et al. 2014). This warrants a more liberal allowance for minimal immunoglobulin deposition to avoid missing cases with alternate complement pathway abnormalities (Fakhouri et al. 2010). The significance of finding immunoglobulins is not elucidated. An initial activation of complement via the classical pathway may trigger or unmask a dysregulation of the alternate complement pathway. On the other hand, the small amounts of Ig may represent nonspecific entrapment of immunoglobulins or podocyte protein reabsorption droplets (Pickering et al. 2013). A useful test to add to the immunofluorescence panel is C4d (Sethi et al. 2015). C4d is a by-product of activation of the classic and lectin pathways. A recent study by Sethi et al. used glomerular staining of C4d to differentiate between immune complex GN and C3 glomerulopathy. C4d represents activation of the classical and/or lectin pathway. The premise of the hypothesis was that patients with immune complex GN likely activate the classical pathway of complement and thus would stain positively for C4d. On the other hand, C4d would be negative in C3 glomerulopathy that were purely a result of activation of alternative pathway. The study showed that specimens of immune complex-mediated GN, except two specimens of IgA nephropathy and one specimen of sclerosing membranoproliferative GN, showed bright (2–3+) C4d staining. C4d staining was completely negative in 80% of C3 glomerulopathy, and trace/1+ C4d staining was detected in 20% specimens (Sethi et al. 2015).

Ultrastructural findings commonly include mesangial expansion and capillary wall thickening. In C3 glomerulonephritis, electron-dense deposits found in the mesangium, in the subendothelium, and often in the subepithelial regions. The deposits vary in appearance. They are often intramembranous but commonly lack the dense osmiophilic characteristics of those seen in DDD. They are often ill-defined with vague borders, and they may rarely resemble immune complex-type discrete deposits. They lack substructure. Subepithelial deposits are often hump shaped, resembling postinfectious glomerulonephritis (Sethi et al. 2011; Servais et al. 2007). In some cases, there is complex multilayering of the deposits with intervening basement membrane material. In all likelihood, most cases of MPGN type III of Strife type represented C3GN (Barbour et al. 2013b; Sethi et al. 2012b, c).

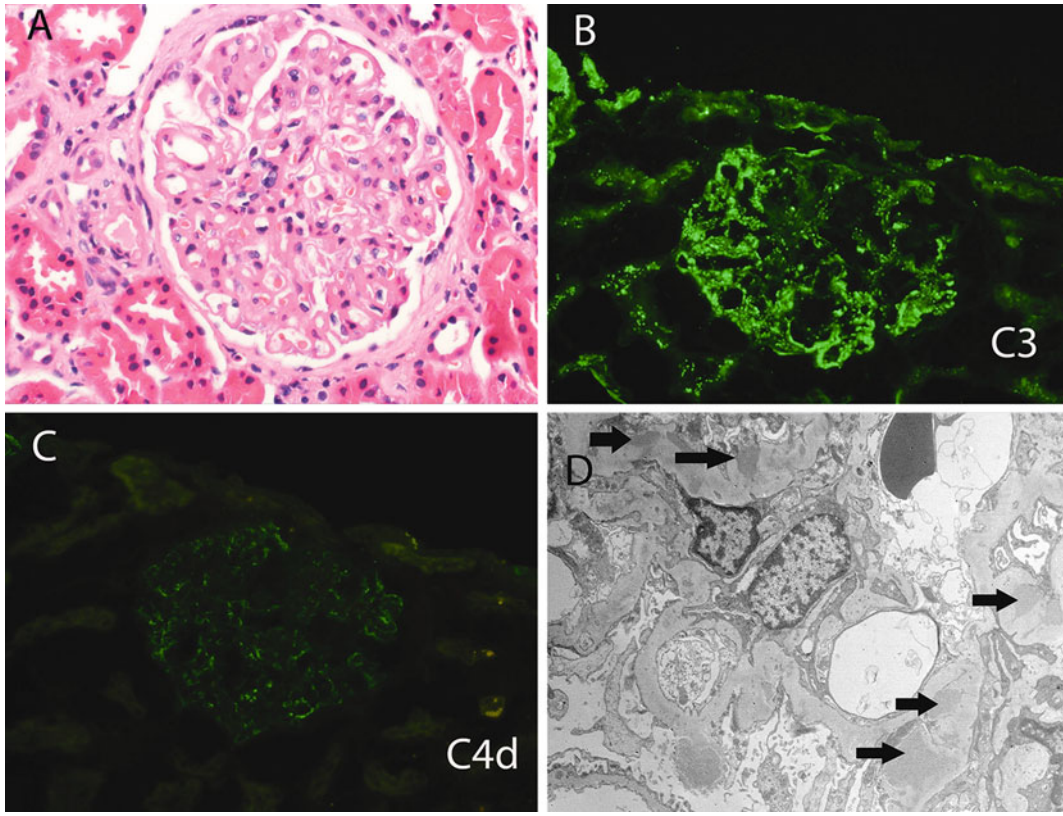

Fig. 4 MPGN associated with C3 glomerulonephritis. (**a**) Light microscopy shows an MPGN pattern of injury (hematoxylin and eosin 40×), (**b**) immunofluorescence studies show staining bright staining for C3 (40×) and (**c**) negative C4d (40×), and (**d**) electron microscopy studies show subendothelial deposits and double-contour formation along the capillary walls (4800×)

In DDD the deposits are typically large and highly electron-dense intramembranous deposits with irregularly thickened lamina densa. The intramembranous deposits might be interrupted giving it a "sausage-string" appearance. Prominent involvement of the glomerular basement membrane reflection over the mesangium with less involvement of the peripheral glomerular capillary walls may be noted in a few cases of DDD. Large hump-shaped, subepithelial electron-dense deposits may be noted. Similar electron-dense deposits may be seen in the Bowman's capsule and tubular basement membranes in DDD. Mesangial deposits forming large rounded nodules ("ring forms") or small and granular deposits may also be noted (Nasr et al. 2009). Despite the apparently distinctive ultrastructural features between C3 glomerulonephritis and DDD, cases often demonstrate an overlap of these ultrastructural features, reflecting the common pathogenic pathway in both these diseases (Sethi et al. 2015). Figure 4 shows an MPGN in a patient with C3 glomerulonephritis. Light microscopy shows an MPGN pattern of injury with thickened glomerular basement membranes, immunofluorescence studies show staining bright staining for C3 (negative staining for all Ig including kappa and lambda light chains) and negative C4d, and electron microscopy studies show subendothelial deposits and double-contour formation along the capillary walls. Figure 5 shows an MPGN in a patient with DDD. Light microscopy shows an MPGN pattern of injury, immunofluorescence studies show staining bright staining for C3, and electron microscopy studies shows intramembranous dense deposits.

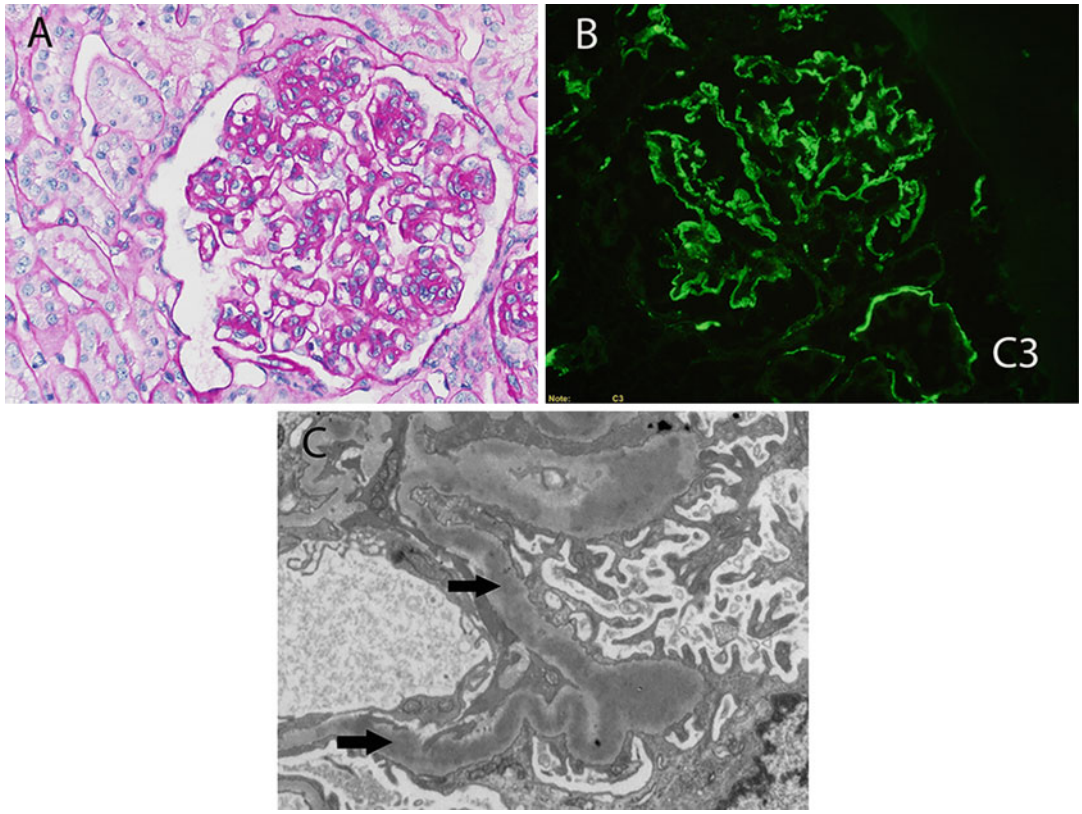

Fig. 5 MPGN associated with DDD. (**a**) Light microscopy shows an MPGN pattern of injury (periodic acid–Schiff stain 40×), (b) immunofluorescence studies show staining bright staining for C3 (40×), and (c) electron microscopy studies shows intramembranous dense deposits (4400×)

The proteomic profile in this subset of diseases has been evaluated by mass spectrometry. In a study by Sethi et al. (2012b), the proteomic profile of patients with C3GN showed accumulation of alternate complement pathway and terminal complement complex proteins. The deposition of C3 and C9 was extensive in all cases. C5, C6, C7, and C8 were also present in all cases. Complement regulating proteins vitronectin, clusterin, and apolipoprotein E were present in abundance. CFHR-1 was present in all cases. Sethi et al. evaluated the proteomic profile of the glomerular deposits in confirmed cases of DDD. They found that all of the glomeruli contained components of the alternative pathway and terminal complement complex. Factor C9 was also uniformly present. Clusterin and vitronectin, two fluid-phase regulators of terminal complement complex, were also identified. Their study demonstrated that in addition to fluid-phase dysregulation of the alternative pathway, soluble components of the terminal complement complex contribute to glomerular lesions found in DDD (Sethi et al. 2009). More recently, on further analysis, the C3 deposits were composed predominantly of C3dg and smaller amounts of iC3b. C3a and C3f were absent indicating that that deposition of C3 in C3 glomerulopathy is an active process with accumulation of mostly the terminal breakdown fragments, i.e., C3dg that remains bound to the glycocalyx over the endothelial cells and glomerular basement membrane via the thioester bond (Sethi et al. 2016c). The proteomic profile of C3 breakdown products was similar in C3 glomerulonephritis and DDD.

Pathogenesis

The alternate complement pathway is constantly activated at a low level by the spontaneous hydrolysis of C3 by a process called the "C3 tick over." The activated C3 often represented as C3 (H_2O) functions like a C3b and binds to factor B. This forms the substrate for factor D (CFD) to act; by cleaving CFB it forms the C3 convertase (C3bBb) which amplifies C3 activation in a feedback loop called the C3b amplification loop. The C3b generated from the lectin and classical complement pathways can also amplify C3 activation (Barbour et al. 2013a; Noris and Remuzzi 2013). Once C3 activation occurs, it progresses to generate the C5 convertase and finally the membrane attack complex.

A closely regulated and controlled system for the AP complement pathway exists in order to prevent tissue damage. One of the main down-regulators of the AP C3 convertase is complement factor I. It inactivates C3b to iC3b. Factor I requires numerous cofactors, which include complement factor H, membrane cofactor protein (MCP/CD46), and decay-accelerating factor (DAF/CD55). Complement factor H-related proteins (CFHR1-5) bear a structural homology to complement factor H and compete with complement factor H to bind to C3b.

Dysregulation may be the sequelae of multiple processes including decreased or suboptimally functioning negative regulators or genetically impaired complete regulatory molecules. The activity of the C3 convertase is particularly regulated. The activity of C3 convertase may be increased by a few mechanisms such as the generation of a C3 convertase stabilizing autoantibody called C3 nephritis factor (C3NeF). This is the most common AP abnormality. This autoantibody is directed against C3 convertase. By stabilizing C3 convertase and preventing its factor H-mediated degradation, C3Nef causes dysregulation of AP control. C3Nef was detected in 50% of C3GN patients in one series (Sethi et al. 2012b). Similarly, loss of functional factor H activity may result from acquired defects of factor H such as antibodies to factor H, leading to the uninhibited activity of C3 convertase. A background of autoimmune disease is thus often seen in C3 glomerulonephritis (Alexander et al. 2016). Dysregulation may also involve mutations in complement genes (such as those encoding factor H, factor B, factor I, or even C3) that prevent normal C3 convertase control. Monoclonal gammopathy is often seen in both C3 glomerulonephritis and DDD (Sethi and Rajkumar 2013; Sethi et al. 2010b; Zand et al. 2013). Monoclonal Ig may stabilize C3 convertase and thus behave as a C3NeF. In cases without C3Nef, the monoclonal Ig may interfere with alternative complement regulation via other mechanisms. For example, monoclonal Ig may act as an autoantibody to complement factor H, resulting in functional abnormality of factor H, resulting in over activity of the alternative pathway of complement (Meri et al. 1992). The existence of limited reports showing clinical improvement in the glomerular disease following chemotherapy for the underlying B-cell neoplasia supports a pathogenic role for the monoclonal Ig.

MPGN with Masked Immune Deposits

This is a recently described entity (Larsen et al. 2015). The pathology is that of a membranoproliferative glomerulonephritis with isolated C3 deposits (by routine IF) in the setting of a monoclonal gammopathy. Paraffin IF unmasks monoclonal immunoglobulin glomerular deposits. The importance of recognizing this entity is to avoid misdiagnosis of these cases as C3GN due to monoclonal gammopathy (Barbour et al. 2013b). Also, as most of these cases are associated with a low-grade lymphoma or plasma cell dyscrasia, an accurate diagnosis will permit treatment of the underlying hematological disorder. A C4d stain is also helpful in detecting masked immune deposits (Sethi et al. 2016d).

MPGN Without Immunoglobulins or Complement

Glomeruli may demonstrate membranoproliferative-like changes in the absence of

immunoglobulin or complement deposits in chronic thrombotic microangiopathy. The differential diagnosis includes hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), antiphospholipid antibody syndrome (Bienaime et al. 2016; Gigante et al. 2009), scleroderma (Mouthon et al. 2014), and malignant hypertension (Nzerue et al. 2014) and certain medications such as gemcitabine (Richmond et al. 2013) radiation treatment, or stem cell transplant (Laskin et al. 2011).

Evaluation of MPGN

The evaluation for MPGN is determined based on the suspected etiology. The diagnostic workup should be guided by clinical presentation and biopsy findings. A standard workup for MPGN should include complement evaluation. Low C3 and low C4 are more typical of classical pathway activation as one might see in immune complex-mediated glomerulonephritis. A low C3 with a normal C4 suggests abnormalities of the alternate complement pathway. These findings along with the biopsy findings; particularly immunofluorescence and electron microscopy can further guide detailed evaluation.

Immune Complex-Mediated MPGN

Infections Workup in the evaluation of infection-related MPGN depends on the suspected pathogen. In the case of hepatitis-related MPGN, tests should include viral serology and quantification of viral load by PCR studies. The workup for parasitic infection-related MPGN should include blood tests for malaria, urine and stool test for schistosomiasis, and serological tests for schistosomiasis and leishmaniasis.

Blood cultures, cultures of indwelling catheter tips, imaging studies for deep-seated abscesses, and transthoracic echocardiograms for valvular vegetations of fungal and bacterial infections must be part of the comprehensive work upto exclude an infectious etiology.

Of note, parasitic and fungal infections are only investigated in the appropriate clinical situation (history of recent travel to endemic regions, prolonged fever of unknown origin, atypical pulmonary infiltrates).

Autoimmune Diseases The evaluation is based on clinical presentation. In cases of suspected systemic lupus erythematosus, the workup should include ANA and ds DNA. In suspected Sjögren's syndrome, a positive anti-Ro/SSA and/or anti-La/SSB and a positive lip biopsy help confirm the diagnosis. The diagnostic tests of the autoimmune diseases should follow the established criteria, e.g., American College of Rheumatology, for Sjögren's syndrome and rheumatoid arthritis (Neogi et al. 2010; Shiboski et al. 2012).

Monoclonal Gammopathy The workup should include serum protein electrophoresis, urine protein electrophoresis, serum and urine immunofixation, and serum-free light chain assays. Bone marrow evaluation should be performed to confirm an underlying plasma cell dyscrasia and/or lymphoproliferative disorder.

Complement-Mediated MPGN (C3 Glomerulopathy)

If the biopsy suggests complement-mediated MPGN, the workup should trigger an evaluation of abnormalities of the complement pathway. The workup for abnormalities of the alternate pathway of complement includes (a) functional assays, (b) quantification of complement components and regulators, (c) measurement of complement activation markers, (d) genetic evaluation, (e) autoantibodies, and (f) testing for monoclonal immunoglobulins (Angioi et al. 2016).

(a) Functional assays: These are based on the ability of complements to lyse sheep erythrocytes. This is an important screening test to determine whether the complement pathway is preserved or disrupted. The two tests available for this purpose include the total

hemolytic component (CH50) assay and the complement factor H functional assay.

(b) Quantification of complement components: C3 and C4 are commonly measured. C3 is lowered in 40–75% of C3GN.

(c) Measurement of complication activation markers: C3 decay products including C3d, C4 decay products including C4d, and terminal complement pathway are often measured.

(d) Autoantibodies: C3 nephritic factor is an autoantibody to C3 convertase; C4 nephritic factor is an antibody to C4 convertase. Antibodies to FH should be studied and ideally antibodies to factor B should also be reviewed.

(e) Genetic analysis: This should be initiated for all the known complement-related genes: C3, CFH, CFI, CFB, and CFHR1–5 (Pickering et al. 2013).

(f) Serum protein electrophoresis, immunofixation electrophoresis, and serum-free light chains – A paraprotein may be responsible for activation of the alternative complement cascade (Zand et al. 2013). If a monoclonal gammopathy is discovered, specialized tests are required to determine whether or not the protein could be responsible for the C3 glomerulopathy (Noris and Remuzzi 2013).

Uncommon Causes of MPGN

1. Cryofibrinogen-related membranoproliferative glomerulonephritis: Cryofibrinogen is a relatively rare resulting in an MPGN pattern of injury. Cryofibrinogen is a cryoprecipitate that develops after refrigeration of plasma but does not occur in cold serum. Cryofibrinogen may be asymptomatic, but can be associated with thromboembolic disease, particularly affecting the skin. We recently published a report of two cases of MPGN with prominent deposits of cryofibrinogen within the glomeruli (Sethi 2017). The deposits did not show immunoreactivity to immunoglobulins. Ultrastructural studies showed the deposits were characterized by haphazardly arranged large fibrils with tubular structures with variable dimensions. The tubules had large central bore, and some had double or triple layering. In addition there were randomly distributed fibers in a matrix. The luminal diameter ranged from 121 to 211 with a mean diameter of 158 nm.
2. C4 glomerulopathy: C4 glomerulopathy is a recently described disease entity characterized by glomerular deposits of predominantly C4 with little or no immunoglobulins or C3 deposition. This glomerulopathy encompasses C4DDD and C4 glomerulonephritis (Sethi et al. 2014, 2016e). Sethi et al. described the first case of C4DDD in a young woman who first manifested with nephrotic-range proteinuria (Sethi et al. 2014). Her biopsy showed a membranoproliferative pattern of injury with extremely thick glomerular capillary walls. Staining with periodic acid–Schiff showed ribbonlike material lining the glomerular basement membrane. This material was negative on methenamine silver staining. Immunofluorescence microscopy showed bright staining for C4d along the capillary walls and no glomerular staining for IgG, IgA, IgM, C1q, C3, C4c, or kappa or lambda light chains. Electron microscopy showed large subendothelial osmiophilic dense deposits lining the glomerular basement membrane. There were no deposits along the Bowman's capsule or tubular basement membranes. The patient workup showed no defects in the classical or alternate pathway of complement, but indicated an overactive lectin pathway of complement.

Summary

MPGN is a pattern of injury and not a diagnostic entity in itself. MPGN can essentially be classified into immune complex/monoclonal Ig-mediated MPGN and complement-mediated MPGN (C3 glomerulopathy). Immune complex MPGN should lead to evaluation for infections and autoimmune diseases. Monoclonal Ig-mediated MPGN should lead to evaluation for an underlying B-cell or plasma cell disorder. Complement-mediated MPGN should lead to evaluation of the

alternative pathway of complement. Identification of the underlying etiology and pathophysiology of MPGN should then lead to appropriate management of the patient.

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Membranoproliferative Glomerulonephritis, Type 1, Pediatric

22

Bernarda Viteri and Jessica Reid-Adam

Contents

Abstract

Membranoproliferative glomerulonephritis (MPGN) Type I is most common among a group of rare glomerular diseases historically classified according to findings on electron microscopy, and is characterized by subendothelial immune deposits. Most of what was traditionally characterized as MPGN type I falls under the category of immune complex-mediated MPGN, while fewer cases of MPGN type I may be attributed to complement dysregulation. In children, MPGN type I is associated with approximately 1.3% of end stage kidney disease (ESKD) patients. Hypocomplementemia, hematuria and proteinuria are common at presentation, with nephrotic syndrome in MPGN associated with a worse prognosis. While there have been various approaches to treatment of MPGN type I in children, the mainstay of therapy is alternate day prednisone.

Keywords

MPGN Type I · ESKD · Immune Complex · Complement

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Introduction

Membranoproliferative glomerulonephritis, or MPGN, refers to a rare group of diseases identified histologically by mesangial and/or endocapillary hypercellularity, with splitting of the glomerular basement membrane by extension of mesangium into the subendothelial space; with clinical presentation of nephritic syndrome which is sometimes also nephrotic, often accompanied by hypocomplementemia. Of the three general subtypes of MPGN, MPGN type I is considered to be the most common, and is largely due to glomerular deposition of circulating immune complexes and subsequent activation of the classical complement cascade. MPGN type I, as with other forms of MPGN, can be idiopathic or be secondary to a myriad of underlying etiologies. In children, MPGN is more commonly idiopathic, while secondary causes are more common in adults who present with MPGN. Hypocomplementemia is present in the majority of patients. Long-term use of alternate-day, high dose prednisone has been shown in some studies to be of some benefit, and remains the mainstay of therapy of MPGN type I.

Classification

It should be noted that the glomerulonephritides as a whole have undergone extensive reclassification, most recently by the 2015 Mayo Clinic/Renal Pathology Society Consensus Conference, which shifted classification focus from histological/morphological and ultrastructural features, to etiology and pathogenesis (Sethi et al. 2016). Historically, MPGN has been classified based on electron microscopy (EM) findings as primary (idiopathic) type I (MPGN I), type II (MPGN II), and type III (MPGN III) or secondary MPGN. In the last decade, due to the increasing understanding of its pathogenesis, there is a push to distinguish the MPGNs based on two principal categories: MPGN which is immune-complex-mediated and MPGN which is complement-dysregulation-mediated (Sethi et al. 2016; Iatropoulos et al. 2016; Lionaki et al. 2016). The immune-complex MPGN category that has been put forth by the consensus includes most of what was previously classified as MPGN I and is often associated with autoimmune disease or with chronic infections (see Fig. 1).

All three types of MPGN are associated with hypocomplementemia and involve complement activation, although the pattern of glomerular injury may vary with MPGN type. MPGN type I is characterized by subendothelial deposits; MPGN II or "dense deposit disease" (DDD) has deposits in the glomerular basement membrane; MPGN III has both subendothelial and subepithelial deposits (Alchi and Jayne 2010). Secondary MPGN is most often due to hepatitis C, although other viral, bacterial, or protozoal infections have also been implicated (Rennke 1995).

On immunofluorescence, immune-complex-mediated MPGN is distinguished by immunoglobulin and complement-positive staining, reflecting activation of the classical pathway (CP). On the other hand, complement-mediated MPGN, or C3 glomerulopathy (C3G), predominantly stains C3 positive and little or no immunoglobulin or C1q staining, resulting from alternative complement pathway dysregulation. The relationship between the historical and current classifications of MPGN is outlined in Fig. 1. MPGN type I and MPGN type III immunohistology can reveal the presence of immunoglobulins and complement, or C3 alone, thus including cases of immune complex-mediated MPGN and cases of C3 glomerulopathy, per modern classifications (Iatropoulos et al. 2016; Noris and Remuzzi 2015).

The pathogenic classification is valuable as it may help to direct the clinical evaluation and/or the treatment plan more effectively. In this chapter, we will focus on immune-complex-mediated MPGN type I. C3G will be discussed separately (see chapter on C3 Glomerulopathies).

Epidemiology

Idiopathic MPGN is one of the least common types of glomerulonephritis in children, accounting for approximately 3–5% of primary renal

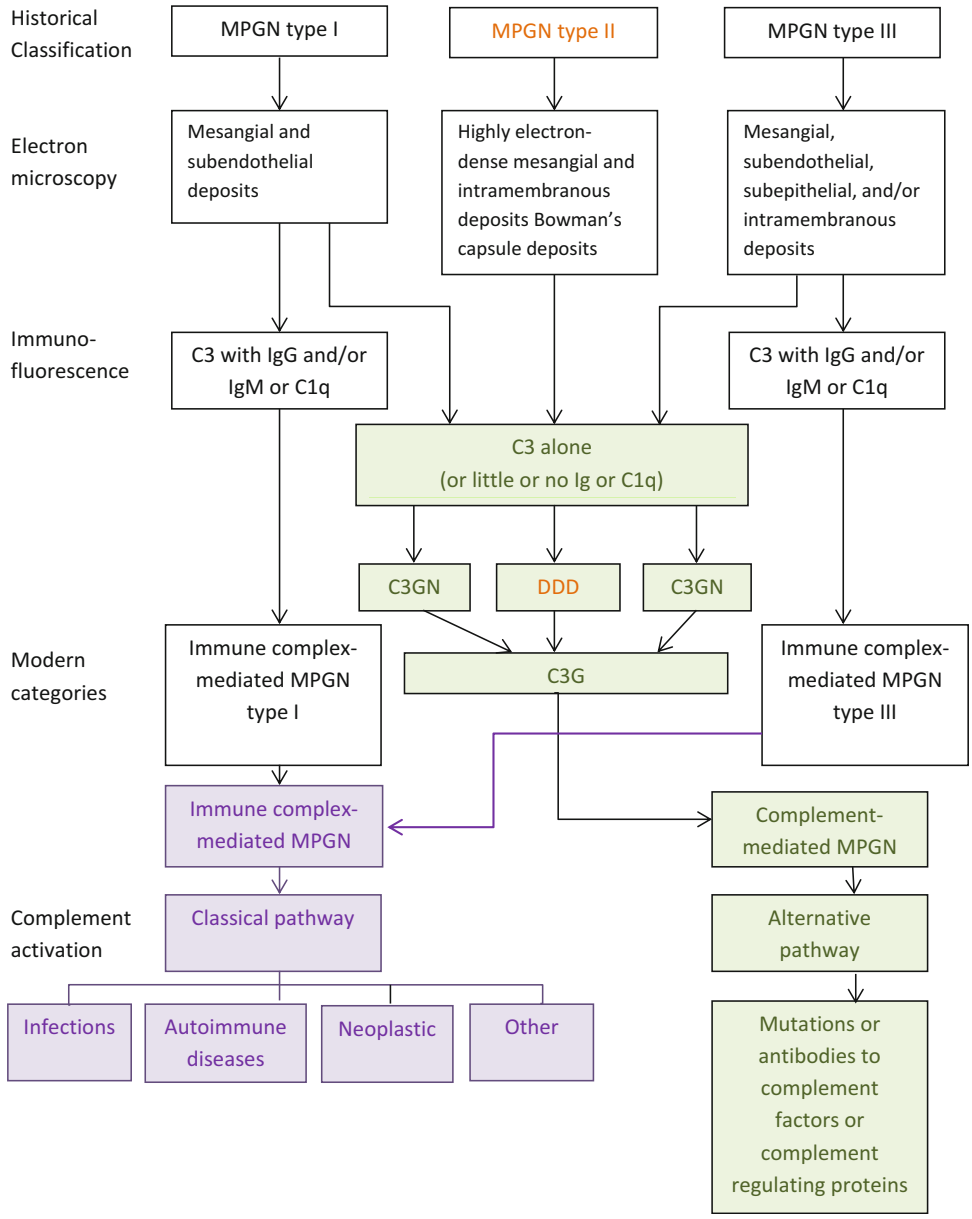

Fig. 1 Historical and current MPGN classification (Adapted from Sethi and Fervenza (2012), Bomback and Appel (2012), Sethi and Fervenza (2011), and Fervenza et al. (2012))

causes of nephrotic syndrome (Bonilla-Felix et al. 1999; Orth and Ritz 1998; Arif et al. 2016; Alchi and Jayne 2010). Interestingly, MPGN incidence varies around the world and has shown a decline in most developed countries (Kawamura et al. 2013). In contrast, because viral, bacterial, and protozoal infections are a common cause of immune-complex MPGN, it is thought that this might be a reason why MPGN is more common in developing countries (Cook and Pickering 2015).

Typically, all types of MPGN show a slow clinical progression over time. Based on U.S. Renal Data System, only 1.2–1.3% of children with end-stage kidney disease (ESKD) have diagnosis of MPGN type I (USRDS 2013). To date, there are not many multicenter large case series

that differentiate between MPGN, DDD, and C3GN since the new classification was proposed in 2012. The current available case series are mostly studies in Northern European populations, and therefore, it is not yet clear if there are ethnic or racial differences in disease prevalence or incidence (Servais et al. 2012; Medjeral-Thomas et al. 2014).

Pathogenesis

The pathogenesis of MPGN type I is not yet completely understood and there are several theories that may apply. Even though it was originally thought that the classic pathway (CP) of the complement cascade plays a primary role in the disease mechanism, recent studies have shown mutations also affecting the alternative pathway (AP) regulatory proteins and C3 nephritic factor (C3NeF) – an autoantibody that stabilizes the AP C3 convertase. These findings suggest that the alternative pathway itself could also play an active role in MPGN type I pathogenesis (Alfandary and Davidovits 2015; Dragon-Durey 2004; Iatropoulos et al. 2016; Leroy et al. 2011; Servais et al. 2012; Radhakrishnan et al. 2012).

In MPGN type I, it is thought that chronic antigenemia and the generation of nephritogenic immune complexes, through activation of innate immunity, result in deposits localized in the subendothelial space associated with local inflammatory responses. The specific nature of most of these antigens and the localization of deposition in the subendothelium versus other glomerular areas are yet to be discovered (Alchi and Jayne 2010). Several antigenic stimuli have been described as triggers of this nephritogenic inflammatory response, some of which are listed in Table 1, with Hepatitis C being one of the most common causes (Reilly and Perazella 2014).

The complement system is a fundamental part of the innate immune system with the purpose of removing immune complexes and assisting antibodies and phagocytic cells in clearing microorganisms. The immunoglobulins or immune complexes activate the complement system via the classical pathway, generating anaphylotoxins (C3a, C5a) which by opsonization mediate the accumulation of platelets and leukocytes and the terminal "membrane attack complex" (C5b-9) to directly induce cell injury and lysis (Alchi and Jayne 2010; Noris and Remuzzi 2015). Leukocytes release oxidants and proteases that promote capillary wall damage, causing proteinuria and a fall in glomerular filtration rate. Cytokines and growth factors released by both exogenous and endogenous glomerular cells lead to mesangial

Table 1 Immunoglobulin – positive MPGN (Adapted from Alchi and Jayne (2010), Sethi and Fervenza (2012), and Riedl et al. (2017))

Antigenic stimulus	Associated systemic disease
Infectious diseases	Viral: Hepatitis B and C, Epstein-Barr virus, human immunodeficiency virus Bacterial: Shunt nephritis, visceral abscesses, infective endocarditis Protozoal: Malaria, schistosomiasis Other: Mycoplasma, mycobacteria, brucellosis
Autoimmune diseases	Systemic lupus erythematosus Cryoglobulinemia Scleroderma Sjögren's syndrome Rheumatoid arthritis Hereditary deficiencies of complement components
Neoplasms/ dysproteinemias	Leukemias and lymphomas (with cryoglobulinemia) Plasma cell dyscrasia Fibrillary and immunotactoid glomerulonephritis Light-chain deposition disease Heavy-chain deposition disease Light- and heavy-chain deposition disease Waldenstrom macroglobulinemia Carcinomas, Wilms' tumor, malignant melanoma
Chronic liver disease	Chronic hepatitis (B, C) Cirrhosis Alpha-1-antitrypsin deficiency
Miscellaneous	Cystic fibrosis Thrombotic microangiopathy Sarcoidosis Sickle cell disease Partial lipodystrophy Hemolytic uremic syndrome Drugs (i.e., heroin, α-interferon) Transplant glomerulopathy Niemann–Pick disease (type C)

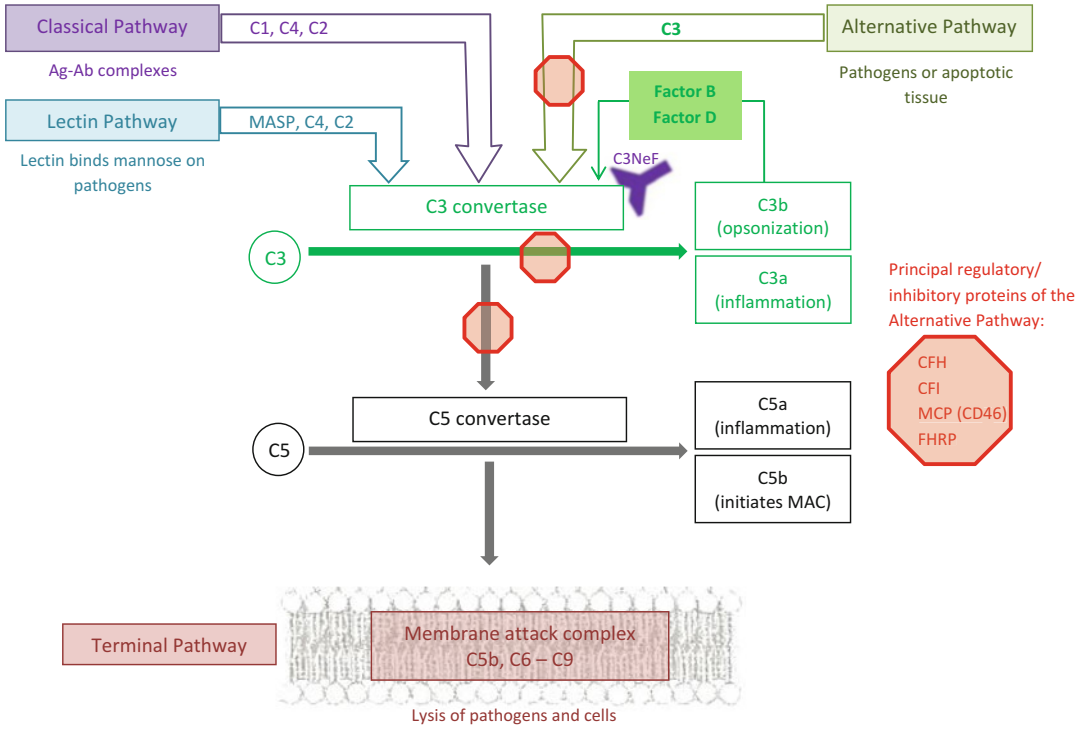

Fig. 2 Complement pathways, activation and inhibitory proteins. *MASP* mannose-binding lectin-associated serine proteases, *CFH* complement factor H, *CFI* complement factor I, *MCP* membrane cofactor protein, *FHRP* factor H related proteins, *C3Nef* C3 nephritic factor (Adapted from Bomback (2014) and Murphy et al. (2008)

proliferation and matrix expansion (Nakopoulou 2001).

The alternative complement pathway is constitutively active at a low level and requires constant regulation to maintain homeostasis between physiological activation and to prevent uncontrolled overactivation (Riedl et al. 2017). Key factors of this pathway are complement factor B (CFB), complement factor H (CFH), complement factor I (CFI), and membrane cofactor protein (MCP). Initiation of the AP takes place spontaneously, and all factors operate in a sequential manner at different levels of the pathway and control the activity of C3 convertase (see Fig. 2) (Janssen Van Doorn et al. 2013; Licht et al. 2016). In some patients, the presence of an autoantibody called C3 nephritic factor (C3NeF) interferes with these normal regulatory mechanisms. Mutations in the genes that encode some of the proteins of the alternative complement pathway have been well documented in cases of MPGN type I.

In some cases of MPGN type I, AP dysregulation is thought to be at least one contributing factor that leads to the immune complex glomerulonephritis observed in this disease. There may be several explanations for this, one being that in the presence of genetic or acquired alternative-pathway dysregulation, antibody activation of the classical complement pathway could uncover a defect of the AP and consequently trigger an uncontrolled amplification of C3 and enhanced complement-mediated renal damage (Fakhouri et al. 2010; Servais et al. 2012; Pickering et al. 2013) (see Fig. 2). Genetic causes of complement abnormalities, such as CFH and CFI mutations, have been described in various case reports. Further, a genetic abnormality in the AP was identified in more than 50% of a French cohort with MPGN type I (Servais et al. 2011; Servais et al. 2012; Radhakrishnan et al. 2012; Alfandary and Davidovits 2015; Dragon-Durey 2004). Further studies are required to determine

the extent to which AP dysregulation contributes to immune-complex-mediated MPGN. While AP dysregulation has been more recently identified in some cases of MPGN, AP dysregulation has long been established as a major cause of atypical hemolytic uremic syndrome (aHUS), which is a phenotypically distinct manifestation of complement dysregulation. In aHUS, the genetic defect of one or more soluble and/or membrane-bound complement regulatory proteins (CFH deficiency or acquired CFH autoantibodies most frequently implicated) is the predisposing factor. The disease is characterized by erythrocyte lysis, endothelial damage, platelet activation, and fibrin microthrombus formation. Two-thirds of aHUS cases are associated with an identifiable complement-activating condition such as autoimmune diseases, infection, malignant hypertension, pregnancy, and organ or tissue transplant (Laurence et al. 2016).

Histopathology

MPGN type I glomerular lesions seen in light microscopy are characterized by two basic changes: mesangial expansion and thickening of the glomerular capillary wall. Active injury to the mesangium, the endothelium and the more inner layers of the capillary wall is followed by a phase of cellular proliferation and repair of the cell injury. As a result, there is mesangial hypercellularity, and the regenerated endothelium forms a second basement membrane, often at a distance from the original lamina densa. Usually in between remain immune-complexes, infiltrating mononuclear cells, cell debris, and products of thrombotic events, and/or deposits of paraproteins (Rennke 2011). Deposits can occasionally be demonstrated subendothelially by trichrome staining. This feature gives the glomerular capillary wall a double-contoured appearance, also known as "tram-track," splitting, duplication of the GBM, or chain-like appearance. The duplication of the GBM is better appreciated with Periodic acid-Schiff and silver stains (Rennke 2011; Alchi and Jayne 2010; Bonsib 2013).

At different stages of the disease process, either the inflammatory component or the repair process may dominate the structural changes seen and as a result some kidney biopsies will show more hypercellularity and active inflammation, while others will show more signs of tissue repair (Rennke 2011).

On immunofluorescence, the most common findings are a fine to course granular pattern along the glomerular capillaries of immunoglobulin (Ig) deposits, mainly IgG and sometimes C1q, IgM, and/or IgA, as well as positive staining for C3 (Rennke 2011; Alchi and Jayne 2010; Bonsib 2013). On electron microscopy, the expanded mesangium and subendothelial space contain cells, matrix, and electron-dense deposits. Effacement of podocyte foot processes and occasional subepithelial small electro-dense deposits can also be seen (Servais et al. 2012).

Presentation/Clinical Manifestations

There is extensive overlap among all classes of MPGN with respect to clinical presentation or features, and therefore, renal pathology must be used in distinguishing MPGN I from other types, rather than rely on clinical features alone. Microscopic hematuria and proteinuria at presentation are common, occurring in about half of those ultimately diagnosed with MPGN. Many of these patients are asymptomatic (Licht et al. 2016). In contrast, about one-third of patients with MPGN I present with edema, which indicates significant urinary loss of protein with hypoalbuminemia. Nephrotic syndrome is associated with a worse prognosis. In addition, ~67% of patients will have low C3 levels, and about 30–60% present with hypertension (Licht et al. 2016). In about 25% of patients with MPGN, gross hematuria is observed with red cell casts, indicative of ongoing inflammation. This nephritic presentation (with accompanying hypertension and azotemia) may or may not be accompanied by

nephrotic-range proteinuria. Presentation with gross hematuria may make one suspicious for poststreptococcal or postinfectious glomerulonephritis, which is often accompanied by low C3 levels. Failure of C3 to return to normal levels by 6–8 weeks raises the suspicion for MPGN. In addition, low C4 is often also observed in patients with MPGN I, which reflects the classical pathway activation observed in this form of MPGN, where immune-complex deposition may play a role (West 1992; Alchi and Jayne 2010).

Workup/Lab Findings

The clinical and laboratory evaluation of patients with suspected MPGN type I should exclude differential diagnoses and attempt to identify the underlying triggering disease in order to begin appropriate disease-specific therapy (Sethi and Fervenza 2012; Alchi and Jayne 2010). Therefore, relevant tests for detection of infections, autoimmune diseases, and monoclonal gammopathies are indicated (see Table 2). In patients where there is activation of the CP, evaluation of the complement system will show normal to low C3, low C4, and low CH50 (Alchi and Jayne 2010; Sethi and Fervenza 2012; Nakopoulou 2001). When there are concurrent AP abnormalities, low C3, normal C4, and low CH50 can also be seen. In these cases, one has to consider that the deposition of immune complexes in the glomeruli drives the disease process, and therefore, one should plan for thorough workup to determine the etiology of the deposited immunoglobulins. Though "idiopathic" MPGN refers to that subgroup where the origin of the deposited Ig could not be determined, newer techniques to identify proteins contained in glomerular deposits may aid in determining etiology. Glomerular isolation of biopsy specimens by laser capture microdissection and mass spectrometry, along with the enhanced proteomic and genetic analysis which is now available, may extend the understanding of glomerular diseases, and increase the likelihood of finding the underlying etiology in cases of MPGN once deemed idiopathic (Caster et al. 2015; Satoskar et al. 2012; Sethi and Fervenza 2011; Sethi and Fervenza 2012). A summary of the clinical and laboratory workup is outlined in Table 2.

Table 2 Diagnostic workup (Adapted from Alchi and Jayne (2010))

History	Prior episodes of upper respiratory tract infection Urinary symptoms: oliguria, hematuria, frothy urine, etc. Symptoms of anemia: fatigue, pallor, palpitations, etc. Uremic symptoms: anorexia, vomiting, mental status changes, etc. Symptoms suggestive of secondary MPGN: jaundice, joint pains, weight loss, etc. Blood transfusion Familial history of C3G and Ig/IC-mediated glomerulonephritis, aHUS, or unclear renal insufficiency
Examination	Blood pressure Presence of nephrotic syndrome Stigmata of chronic liver disease Features of cryoglobulinemia: Muscle pain, acrocyanosis, peripheral neuropathy, etc. Ophthalmic examination for drusen Features of partial lipodystrophy
Laboratory findings	Biochemistry, creatinine clearance, 24-h urinary protein or spot urine protein/creatinine ratio, serum cholesterol, lactate dehydrogenase, angiotensin-converting enzyme, α1-antitrypsin Urine dipstick analysis Hematology: Full blood count, clotting screen Monoclonal gammopathy: Serum and urine immunoglobulin electrophoresis, immunofixation studies, and free light-chain assays, bone marrow studies Immunology: Complements (C3,C4, CH50), C3NF, ANCA, ANA, rheumatoid factor, cryoglobulins Microbiology: HCV, HBV, HIV, blood cultures Radiology: Chest X-ray, renal ultrasound Histopathology: Kidney biopsy

C3NF C3 nephritic factor, *ANCA* antineutrophil cytoplasmic antibodies, *ANA* antinuclear antibodies, *HC(B)V* hepatitis virus C(B), *HIV* human immunodeficiency virus

Treatment

Treatment of MPGN I, as in other varieties of MPGN, has ranged from use of corticosteroids, to use of cyclophosphamide, to use of cell cycle inhibiting agents like mycophenolate mofetil, to calcineurin inhibitors such as cyclosporine or tacrolimus, to antiplatelet inhibitors. The mainstay of therapy, however, remains prednisone. In children with MPGN, the International Study of Kidney Disease in Children (ISKDC) study demonstrated benefit of prednisone in a randomized, double-blind, placebo-controlled trial examining alternate-day prednisone at 40 mg/m^2 (maximum dose 60 mg) (Tarshish et al. 1992); other studies have found benefit using higher doses, up to 80 mg every other day. Common prednisone dosage for initial treatment of MPGN I with significant proteinuria and/or decline in renal function is 40 mg/m^2 or 2 mg/kg to a maximum of 80 mg every other day for 6–12 months, although some groups continue treatment for 2 years. The fact that a patient requiring prednisone will be on therapy for at least 6 months begs a discussion of steroid toxicity. Long-term use of prednisone is associated with a multitude of side effects including weight gain with increased BMI and obesity, glucose intolerance, cataract formation, mood or behavioral disturbance, body disfigurement, and hypertension. In addition to the aforementioned toxicities, growth impairment is another side effect of prednisone with particular importance in the pediatric population.

However, in patients with no decline in renal function or non-nephrotic range proteinuria, our current practice is to withhold steroid or anti-cell proliferation therapy, because clinically milder cases have much slower progression of disease (Alchi and Jayne 2010; Licht et al. 2016; Servais et al. 2012). Rather, more conservative therapy with an ACE inhibitor or angiotensin receptor blocker is recommended to control hypertension and proteinuria (Alchi and Jayne 2010).

In MPGN type I, one should assume a secondary cause for production of antibodies and immune complexes, and identification and treatment of the underlying disease is indicated. In many cases, treating the primary disease will halt the production of antibodies and subsequent deposition of immune complexes in the glomeruli (Alchi and Jayne 2010; Sethi and Fervenza 2012). In cases where there is suspicion for MPGN associated with AP dysregulation, our current knowledge as well as available AP functional assays and genetic testing may enable future use of therapies that directly target the AP. Further studies are needed in both children and adults to more effectively tailor therapy for MPGN type I in these cases.

Prognosis

The natural course of MPGN was described by Cameron et al. (1983), where generally poor outcome was described – 50% of those in the study had progressed to ESKD by 10 years, and 90% had progressed to ESKD by 20 years after diagnosis (Cameron et al. 1983). This study, as many studies of MPGN, do not specifically describe MPGN type I as most are studies which include subjects with type I and type III MPGN. One study attempting to differentiate MPGN type I from type III note a lower GFR at time of diagnosis compared to MPGN type III but an overall better response to steroids when compared with MPGN type III (Braun et al. 1999).

As in most other etiologies of pediatric kidney disease, the decision to proceed with renal transplantation should be based on factors relating to morbidity and mortality of the patient. It is well established that transplantation is the best therapy for end-stage organ failure, and specific to kidney disease is superior to other forms of renal replacement therapy. More children than adults with chronic kidney disease (CKD) are considered for pre-emptive renal transplantation, thus obviating the need for dialysis prior to transplantation. When considering renal transplantation in patients with late-stage CKD secondary to MPGN I, attention should be paid to allograft source. While there is not an absolute contraindication to living related transplantation, there seems to be an increased likelihood of disease recurrence in allografts from living related donors, which may reflect a genetic predisposition that exists

among family members (Alasfar et al. 2016). MPGN type I recurrence post transplant has been reported at variable rates. The incidence of renal graft loss at 10 years secondary to MPGN I recurrence was reported ~14.5% in two separate studies, which is a higher reported rate than for the other traditional MPGN classifications combined (Angelo et al. 2011). One pediatric-specific study noted recurrence in 23.5% of patients, with graft loss in 56% (Moroni et al. 2011). Clinical features that seemed to be predictive of recurrence included younger age at diagnosis of MPGN and low C3 at time of transplantation (Moroni et al. 2011), in addition to donor source as previously mentioned.

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Secondary Membranous Glomerulonephritis

23

Hilary Hotchkiss

Contents

Abstract

Membranous nephropathy, one of the most common causes of NS in adults, is uncommon in children, representing at most 5% of new cases of nephrotic syndrome in the pediatric age group. Similar to the adult population, the etiology of membranous nephropathy (MN) can be primary (idiopathic) or secondary. Both can be seen in all pediatric age groups from the neonate to the young adult. However, among children younger than 10 years, a secondary diagnosis is usually identified. The identification of the target antigen in primary MN, M type phospholipase A_2 receptor (PLA_2R), and the increasing availability of testing for the PLA_2R antibody has shaped significant research in primary MN over the course of the past decade. In contrast, the literature describing secondary MN in children is limited. Data is extrapolated from studies that originate in the adult population or from pediatric case reports or small case series.

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Secondary causes of membranous nephropathy in children include several broad categories including systemic autoimmune diseases, infections, drugs, and malignancy. Case reports have broadened this list to include several other systemic illnesses that have been associated with MN. The following review will focus on secondary membranous nephropathy, including the prevalence and epidemiology, the histopathology, clinical manifestations, and the specific etiologies with their pathogenesis and prognosis.

Keywords
Secondary membranous · NSAIDs membranous · Autoimmune membranous · Medication membranous · Malignancy membranous · Hepatitis membranous · Membranous lupus

Epidemiology

The prevalence of membranous nephropathy in the pediatric population is difficult to know with certainty, as many patients with steroid sensitive nephrotic syndrome no longer undergo renal biopsy. Based upon historical data and an aggregate of biopsy data from studies in Asia, Europe, the Americas, and the Middle East, the prevalence of membranous nephropathy among *younger* children (<10 years old) with nephrotic syndrome is thought to be about 3%. Among children older than age 12 years, membranous nephropathy may represent as much as 18% of all new diagnoses of nephrotic syndrome (Mubarak et al. 2012; Hogg et al. 1993; Ayalon and Beck 2015). Among younger patients, under 10 years, it is reported that up to 75% of cases are secondary. That percentage drops significantly among adolescents, in large part, due to the increasing incidence of idiopathic PLA_2R-related disease in this age group. Idiopathic membranous nephropathy occurs more commonly in males, in a ratio of just under 1.5:1. Secondary membranous nephropathy occurs more frequently in females, likely due to the increased prevalence of SLE among young women.

Histopathology

The classic histopathology on light microscopy of membranous nephropathy is a diffuse thickening of the glomerular basement membrane (GBM) throughout all glomeruli, in the absence of significant hypercellularity. In more advanced cases, spikes of GBM between immune deposits may appear. Chronic sclerosis and scarring in the glomerulus and significant tubulointerstitial changes occur as the disease progresses. Immunofluorescence microscopy reveals a diffuse granular pattern of IgG and C3 staining along the GBM. Electron microscopy reveals subepithelial electron-dense deposits on the outer aspect of the GBM, effacement of the foot processes, and expansion of the GBM by deposition of new extracellular matrix between the deposits. These spikes are best seen with Jones' silver stain.

There are several histopathologic characteristics that can distinguish primary MN from secondary MN. Among patients with primary MN, the dominant IgG subclass seen in the subepithelial deposits is IgG4 (noncomplement activator). In secondary MN, IgG1, IgG2 and/or IgG3 (complement activators) are usually the dominant subclass. The deposits in primary MN are exclusively subepithelial or intramembranous. Subendothelial or mesangial deposits can suggest the presence of circulating immune complexes, characteristic of secondary MN. The presence of tubulo-reticular inclusion bodies or a "full house" pattern on immunofluorescence can be clues to the diagnosis of lupus nephopathy (Jennette et al. 1983).

Clinical Manifestations

Classic nephrotic syndrome, including heavy proteinuria, edema, hypoalbuminemia, and hyperlipidemia is the presenting clinical picture in 70–80% of new diagnoses of MN (Noel et al. 1979). The remaining 20–30% have proteinuria, non-nephrotic range. Among nephrotic patients, the onset of edema is typically more gradual than what is seen in minimal change disease or focal segmental glomerulosclerosis. Microscopic

hematuria is common, reported in 69% of children and adolescents with either idiopathic or secondary MN (Chen et al. 2007). Macroscopic hematuria has also been described in children with MN, up to 30% among children of Asian descent (Tsukahara et al. 1993; Wang et al. 2011). Hypertension is seen in about 10%. Renal function, as measured by serum creatinine and/or cystatin C, is typically normal at initial presentation. This contrasts with adults who are diagnosed with MN, in whom renal function is often diminished at the time of diagnosis.

Complications of clinical nephrotic syndrome are well known and include infection, renal insufficiency, and thromboembolism. It is important to note that thromboembolism is more common among patients with MN than among patients with other underlying histopathologic diagnoses. Among children, the risk of thromboembolism in nephrotic syndrome as a whole has been reported to be just under 3%. Among adolescents with MN, that risk has been reported up to 25% (Kerlin et al. 2012). The risk of thromboembolism among secondary forms of membranous nephropathy has not been well described or differentiated from the risk among patients with primary MN.

Secondary Causes of Membranous Nephropathy in Children

Autoimmune Disease

The most common autoimmune disease associated with MN is systemic lupus erythematosus (SLE) (see Chapter XX). Membranous lupus nephritis, also termed class V, can be the initial presentation of SLE. Among patients with new onset SLE, it is not uncommon for serum complement levels to be initially normal and for dsDNA antibodies to be absent. Thus early on, nephrotic syndrome may be the sole feature of the systemic disease. The clinical presentation of class V lupus nephritis is typically associated with preserved renal function.

Several pathological features suggest lupus as the underlying etiology of MN and can offer a clue to the diagnosis before systemic signs or symptoms of the disease. The presence of intraendothelial tubule-reticular structures seen on electron micrograph (EM) is a clue to the diagnosis of SLE, as is mesangial hypercellularity on light microscopy (LM), or the presence of subendothelial and mesangial immune deposits (Jennette et al. 1983; Hogg et al. 1986). Membranous lupus nephropathy can also be associated with full house immunofluorescence staining, including IgG, IgA, and IgM; C3; and C1q.

MN has been described as a rare complication among patients with chronic inflammatory bowel disease. A recent review of the renal complications of inflammatory bowel disease highlighted ESRD caused by several different glomerular diseases. Two of 25 cases had biopsies with the finding of membranous nephropathy. One of the cases occurred in a patient with Crohn's disease, the other was a patient with ulcerative colitis. Several case reports have described children with Crohn's disease and autoimmune enteropathy in association with membranous nephropathy. The mechanism for these associations is not yet well described (Ridder et al. 2005; Colletti et al. 1991).

Eosinophilic gastroenteritis is an uncommon and heterogeneous disease characterized by eosinophilic infiltration of the gastrointestinal tract. The disease can present at all ages, including among children. In as yet unpublished data, our group has identified a patient with secondary membranous nephropathy associated with eosinophilic gastroenteritis. In this patient, while the enteritis improved with the use of corticosteroids, the nephropathy did not, eventually recurring following transplantation.

Infection

Hepatitis B virus-associated Membranous Nephropathy (HBV-MN) has become rare in developed countries, where hepatitis B virus immunization programs are well established in clinical practice. In the USA, children with chronic hepatitis B infection are likely to have immigrated from endemic areas where they may have been infected perinatally. Among children with chronic hepatitis B infection, renal

manifestations are relatively common. The most common manifestation is MN. When present, the hepatitis B surface antigen is typically positive, as is the anti-core antibody and usually the hepatitis B e antigen. Often the patients are asymptomatic carriers with normal or only mildly elevated serum transaminases. By biopsy, the e antigen and anti-e antibody are primarily deposited in the glomeruli. An interesting 2015 study out of China, where Hepatitis B is endemic, demonstrated that 64% of 39 patients with HBV-MN were renal PLA_2R positive and tested positive for the presence of PLA_2R antibodies (Xie et al. 2015). In children with HBV-MN, spontaneous resolution of proteinuria has been described (Lai et al. 1991).

Hepatitis C virus can also be associated with renal manifestations. Among patients infected with hepatitis C, the most common renal manifestation is a membranoproliferative glomerulonephritis histopathological pattern with mixed cryoglobulinemia representing up to 50% of cases. FSGS has been described infrequently. MN can also be present. One study of renal biopsies among patients with the Hepatitis C virus found that 18% of the patients had the MN lesion.

Syphilis has been associated with MN in children. The data is derived from several studies that were completed in the early to mid-1970s (Gamble 1975; Hunte et al. 1993; Losito et al. 1979). Nephrotic syndrome and the glomerular disease can be seen in patients with congenitally acquired syphilis or can present during the secondary stage of sexually acquired syphilis, about 4–10 weeks after the initial presentation of disease. Glomerular deposits are thought to contain antibodies specific for Treponema pallidum antigen and immunofluorescence staining may be positive for treponemal antigens. The glomerular disease associated with syphilis typically resolves completely with appropriate treatment of the infection.

Drugs

Several medications have been associated with the development of MN. Classically, several medications that have been used to treat rheumatologic diseases have been cited, including penicillamine, parenteral gold salts, and bucillamine. The use of these drugs in children has been largely replaced by newer medications. More commonly used medications have also been associated, although rarely with MN, including NSAIDs and lithium.

Penicillamine, parenteral gold salts, and bucillamine have long been associated with the development of MN. One hypothesized mechanism is that the medications are thought to convert large circulating immune complexes to smaller ones, which circulate longer and can deposit in glomerular basement membranes (Manabe et al. 2015). Another hypothesis is that the medications induce the development of autoantibodies. The incidence among patients treated with penicillamine may be as high as 7%, although it is less among patients treated with parenteral gold salts at 1–3% (Hall et al. 1988; Katz et al. 1984). Proteinuria induced by these medications typically resolves within 6 months of discontinuation of therapy.

Tiopronin, a medication that is structurally similar to penicillamine, is used to treat patients with cystinuria, a condition that leads to an increased risk of forming cystine stones. Approximately, 30 cases of nephrotic syndrome have been reported in association with tiopronin, mostly in children. Of those who were biopsied, most demonstrated MN. Resolution occurred in most patients following discontinuation of the medication (Zheng et al. 2014).

NSAIDs are associated with several mechanisms of acute and chronic kidney injury, primarily related to the inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis which can lead to renal ischemia. Classical interstitial nephritis is also commonly described and can be associated with nephrotic range proteinuria, usually secondary to minimal changes by light microscopy. Less commonly, NSAIDs have been associated with MN, typically characterized by rapid remission upon withdrawal of NSAID therapy. Of importance, biopsy in these patients has demonstrated weak IgG4 staining as is common among patients with secondary MN.

Lithium, a medication commonly used to treat manic depressive disorder in children, has been

associated with several forms of nephrotoxicity. The most commonly described are diabetes insipidus, acute tubular necrosis, and chronic tubulointerstitial nephropathy, which combined can impact up to 40% of patients treated with lithium long term. Glomerular injury associated with lithium use is rare. When seen in children, the histopathology can vary, presenting as minimal changes, focal segmental glomerulosclerosis, or MN (Kala et al. 2009; Grunfeld and Rossier 2009; Markowitz et al. 2000). In most cases of glomerular injury, removal of lithium induces remission.

Anti-TNF agents have also been associated with the onset of membranous nephropathy. A case series describing the treatment of several adults with long-standing rheumatoid arthritis with etanercept, infliximab, or adalimumab has reported the temporal association with the development of MN (Stokes MB, Foster K). The mechanism is unclear but may be secondary to immune dysregulation induced by the medications.

Malignancy

Among older adults with membranous nephropathy, up to 20% have been reported to have a malignancy, either a solid tumor or less commonly a hematologic malignancy. Among children, the association is seen, although it is much rarer. Of children with secondary MN, malignancy accounts for about 2%. Excision of the tumor is typically associated with resolution of the nephrotic syndrome (Kohorst et al. 2014).

MN has been reported in association with graft versus host disease. In these patients, IgG4 is typically dominant which is more commonly seen in primary MN rather than secondary forms. In contrast, PLA_2R antibodies is typically negative.

Systemic Illnesses

Several case reports have described MN as a rare association with systemic sarcoidosis in adults. One case report included the association between MN and childhood sarcoidosis, in a 13-year-old adolescent. MN has also been described in a child with common variable immunodeficiency (Yim and Yoo 2012; Dimitriades et al. 1999).

Treatment of Secondary Membranous Nephropathy

The prognosis among patients with secondary MN is usually related to treatment of the underlying disease or infection. In the case of medication-associated disease, removal of the offending medication is usually sufficient to induce remission of the proteinuria. It would be prudent to monitor patients that are currently undergoing treatment with NSAIDs, Tiopronin, lithium, or the anti-TNF alpha class of medications for proteinuria in order to detect renal disease early in its course. Similarly, among patients with malignancy, removal of the tumor is usually associated with remission from the nephrotic syndrome. In contrast, among patients with systemic autoimmune disease or immune dysregulation, the treatment and prognosis is heterogeneous.

Summary

Membranous nephropathy is relatively rare among pediatric patients. When it is seen in children younger than 10 years, a secondary cause is usually identified. As a result, among children with new onset nephrotic syndrome in whom membranous nephropathy is seen on a renal biopsy, a thorough evaluation for a not yet identified underlying disease or infection may be warranted.

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Infection-Associated Glomerulonephritis

24

Laura Malaga-Dieguez

Contents

Abstract

The association between infection and kidney disease has been known since the mid-1800s ("edematous swelling with scanty, dark, and at times totally suppressed urine" Burserius). Infections can cause a variety of glomerular diseases. Many microorganisms, including microbes, viruses, and parasites, can cause postinfectious glomerulonephritis (Table 1).

Keywords

Infection · Glomerulonephritis · PIGN

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Introduction

The pathogenic links between an infection and renal disease are not always easy to establish. The criteria for proving causality are complex and include recognition of the clinical syndrome, a serological diagnosis, identification of a specific antigenemia, and detection in the glomerular structures of antigens and host antibodies. According to Koch's postulates, the causative agent of a particular disease should be confirmed by complete cure following eradication of the infectious agent, but this is not always possible.

Infection-associated glomerulonephritis is an immunological disease. During an infection, there is the introduction of a specific antigen

Table 1 Infectious agents associated with glomerulonephritis

Bacteria	Viruses	Parasites
Streptococcus	Hepatitis B	*Plasmodium malariae*
Staphylococcus	Hepatitis C	*Schistosoma mansoni*
Pneumococcus	Hepatitis A	*Plasmodium falciparum*
Enterococcus	Parvovirus B 19	*Schistosoma japanocum*
Meningococcus	Hantavirus	*Leishmania donovani*
E. Coli	Echovirus	*Loa loa*
Salmonella Typhi and enteritidis	Adenovirus	*Ochocerca volvulus*
Treponema pallidum	Coxackievirus	Toxoplasma
Brucella	Cytomegalovirus	Trichinosis
Leptospira	Epstein-Barr virus	Histoplasmosis
Yersinia	Enteroviruses	
Rickettsia	Measles	
Legionella	Mumps	
Pseudomonas aeruginosa	Varicella	
Hemophilus influenza	Rubella	
Campylobacter jejuni	Yellow fever	
Klebsiella pneumoniae	HIV	
Serratia marcescens	Influenza	
Enterobacter cloacae		
Proteus mirabilis		
Acinetobacter baumannii		
Capnocytophaga		
Coxiella burnetii		
Bartonella henselae		
Propionibacterium acnes		
Corynebacterium		
Mycobacterium		
Mycoplasma pneumonia		
Chlamydia pneumonia		
Borrelia burgdorferi		

with a subsequent antibody response resulting in circulating or in situ immune complex formation. There is consequent leukocyte recruitment and activation of the complement and coagulation systems to result in an inflammatory response which, if it occurs in the glomerulus, leads to glomerulonephritis. The classic pathologic picture is one of acute exudative glomerulonephritis, capillary wall immune deposits containing C3 with or without immunoglobulins (IgG, IgA, and IgM), and electron-dense deposits consisting of subepithelial humps (with or without intramembranous, mesangial, and subendothelial deposits) (Jennette and Heptinstall 2007). Infections, however, may produce other lesions depending on the nature and the severity of the illness including acute tubular necrosis or interstitial changes. This chapter focuses on the classic infection-associated glomerulonephritis.

Bacterial Infections

Historically, most cases of bacterial infection–associated glomerulonephritis occurred in children following streptococcal upper respiratory tract or skin infections and were called post-infectious glomerulonephritis. Over the past three decades, however, there has been an important shift in epidemiology, bacteriology, and

outcome of infection-associated glomerulonephritis (Nast 2012; Nasr et al. 2013). A significant percentage of cases now target adults, particularly the elderly or immunocompromised. Because adult infections are often ongoing at the time of diagnosis, there is discussion about whether the term infection-related glomerulonephritis should substitute postinfectious glomerulonephritis. (Glassock et al. 2015).

Pathogenesis: The classic postinfectious glomerulonephritis (PIGN) is an immune-mediated glomerulonephritis triggered by nonrenal bacterial infections (e.g., β-hemolytic strotococci).

The putative nephritogenic bacterial antigens cause glomerular injury through multiple potential mechanisms, including the following: (1) passive glomerular entrapment of circulating bacterial antigen–antibody immune complexes (ICs) as subendothelial and/or mesangial deposits that can activate the alternative and classical complement pathways; (2) glomerular in situ IC formation by antibodies directed against planted cationic bacterial antigens or intrinsic glomerular antigens via "molecular mimicry," leading to subepithelial deposits and activation of the alternative complement pathway; and (3) glomerular in situ localization of circulating cationic bacterial antigens without immunoglobulin, potentially promoting plasmin activation in the mesangium and glomerular basement membrane and triggering complement activation through the alternative or lectin pathways. Any combination of these mechanisms may act in concert. The resultant complement activation in glomeruli leads to the generation of chemotactins C3a and C5a, recruitment of neutrophils and monocytes, and leukocyte-mediated injury. In addition, locally activated plasmin degrades the glomerular basement membrane directly or through the activation of metalloproteinases and may promote inflammation. Predisposing host factors such as genetic susceptibility and dysregulation of the alternative complement pathway may contribute to pathogenesis.

Epidemiology: Acute postinfectious glomerulonephritis (PIGN) is a common cause of acute glomerulonephritis in children. While it may occur at any age, it is far more commonly encountered between the ages of 2 and 15 years, and most studies report a slight male preponderance. It has, however, also been found in the adult, often related to other infective agents. Geographical variation in the incidence of postinfectious glomerulonephritis is well known: The classical pediatric form is still present, but severe cases are now found almost exclusively in developing countries while, in the last decades, it has almost disappeared in industrialized countries. In developed countries, PIGN is now often found in elderly patients with complex comorbidities and is related to methicillin-resistant *Staphylococcus aureus* (MRSA) and characterized by an immunoglobulin A (IgA)-dominant deposition (Stratta et al. 2014).

Clinical presentation and natural history: The onset of PIGN typically occurs 7–14 days after an upper respiratory tract infection and as long as 6 weeks after impetigo. In some cases, the primary infection may be subclinical and remain undetected.

The typical clinical presentation of PIGN is an acute nephritic syndrome with macro- or microscopic hematuria, proteinuria, hypertension, edema, and acute kidney injury of variable degree ("azotemia"). Dysmorphic erythrocytes, granulous, and epithelial casts as well as leukocytes in the urine are common. Abdominal or flank pain can be present due to renal capsule distension. Besides the "coca-cola" or brown-colored urine, edema is the most common symptom prompting the patient to seek medical advice. It may be localized, but also diffuse, particularly on the face and lower extremities, with a hard consistency and erythematous aspect due to the diffuse – not only renal – capillaritis. Patients may present with significant malaise. Severe hypertension and hypertensive encephalopathy, manifesting as headache or even seizures, may be the initial presenting symptoms in children. Partial forms with brownish (Coca Cola-or-tea-colored) urine without edema, hypertension, proteinuria, or acute kidney injury (AKI) are very common. Nephrotic syndrome and pure AKI are uncommon, but may occur.

Patients with the disease typically recover within days to weeks and the overall prognosis is

excellent. Isolated microhematuria might, however, continue for some months.

A few PIGN cases present with atypical features, such as persistent proteinuria, low C3 complement level, and, sometimes, a decline in renal function. A defect in the regulation of the complement alternative pathway (CAP) has been detected in these patients. In addition, the kidney biopsies reveal features of C3 glomerulopathy, a glomerulonephritis arising from CAP dysregulation. This striking overlap of clinical and histopathological symptoms may indicate that PIGN and C3 glomerulopathy are situated at the two ends of a spectrum of a glomerular disease involving dysregulation of the CAP (Khalighi et al. 2016; Al-Ghaithi et al. 2016). Close clinical follow-up is needed in these subset of patients to determine whether further testing and designation as a C3 glomerulopathy is warranted.

Diagnosis and Monitoring: In addition to the classic findings of nephritic syndrome, low C3 complement levels are frequently present in post-infectious GN. C3 complement returns to a normal level by 8 weeks. Persistence of low C3 complement levels beyond 8 weeks should indicate a diagnosis other than PIGN. Approximately 15% of patients with PIGN, however, do not demonstrate a low C3 level, perhaps reflecting a transient complement utilization and recovery prior to diagnostic testing.

Kidney biopsy is rarely needed. The most common histological picture in poststreptococcal PIGN is a proliferative glomerulonephritis with diffuse hypercellularity. In the early phases, the cellular infiltration is "exudative" and characterized by the endocapillary presence in every glomerulus of neutrophils, endothelial cells, monocytes, and rare lymphocytes (CD68, CD3, CD20), with an expansion of the tuft and a reduction of capillary lumens and urinary space. Subepithelial "humps" are often seen on ultrastructural examination with the electon microscope. Co-deposition of immunoglobulin (Ig) G and C3 is commonly observed in PIGN. In a later phase of the disease (starting about 2 weeks after onset), the glomerular hypercellularity is progressively reduced and the histology is characterized by a mesangial hypercellularity with a mesangial expansion of variable degree and a complete recovery of glomerular damage in the following weeks.

Treatment: There is no specific therapy for PIGN. The treatment is purely supportive and directed towards management of the volume expansion, hypertension, electrolyte problems, or acute kidney injury related to the disease process. Patients with renal impairment or electrolyte abnormalities generally require hospitalization for monitoring and appropriate fluid and electrolyte management. Hyperkalemia, which may reflect volume expansion and suppression of the renin-angiotensin axis, is most urgent. Since hypertension is the result of sodium retention and volume expansion, due to an impaired glomerulo-tubular feedback, it is frequently managed with modest sodium restriction and diuretic therapy, in addition to antihypertensive medication, if necessary. The combination of loop or thiazide diuretic with a calcium channel blocker is usually effective. Antibiotic treatment of the antecedent pharyngitis does not prevent PIGN nor does it alter the course of the disease after the onset of PIGN. In typical forms, a steroid or immunosuppressive therapy is not indicated.

Viral Infections

Viral infections can cause different glomerular syndromes. Renal involvement associated with viral infections can be related to tropism of the virus to the kidney and direct cytopathogenic effects, or be secondary to an immune response to an extra-renal infection. Cytomegalovirus, herpes simplex virus, adenovirus, hantavirus, BK virus, and human immunodeficiency virus (HIV) all cause direct renal parenchymal disease following infection of the kidney leading to viral toxicity and/or antibody reactions against antigens of these viruses. On the other hand, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and parvovirus B19 can cause renal injury mainly through depositions of immune complexes, which are produced in the extra renal space by antibody reactions against viral antigens.

The diagnostic criteria for virus-related nephropathy include detailed clinical and laboratory data and a renal biopsy to define virus-related glomerular lesions and guide prognosis and therapy.

Hepatitis B Virus (HBV)

Hepatits B virus (HBV) is a hepatotropic, double-stranded DNA virus, member of the *hepadnaviridae* family that is endemic in many areas across the world. An estimated 240 million people worldwide are infected with HBV. HBV is transmitted through blood and body fluids. In endemic areas, pediatric HBV transmission is usually vertical, from an infected mother to the child. Horizontal transmission occurs via direct contact with blood (e.g., during blood transfusions) or mucous membranes (e.g., during sexual contact), or via the percutaneous route upon contact with blood or body fluids (e.g., during intravenous drug use and needle sharing). Familial clustering of the virus occurs in some regions. HBV infection causes transient and/or persistent infection in the liver. HBV may also infect extrahepatic tissue such as the bile duct, the pancreas, the lymphoid system, and the kidneys (Seeger and Mason 2000). HBV itself is not cytopathic; as an example, hepatitis develops as a result of the host's immune reaction to infected hepatocytes.

Chronic Glomerulonephritis Caused by HBV

In 1971, Combes and coworkers first described the association between chronic hepatitis B virus (HBV) infection and glomerular diseases (Combes et al. 1971). Unfortunately, the underlying pathogenesis, including the exact contributions of HBV, remains largely unknown (Lin 1990; Gilbert and Wiggelinkhuizen 1994; Tomonaga et al. 1996; Bhimma and Coovadia 2004; Kusakabe et al. 2007; Elewa et al. 2011; Gupta and Quigg 2015). The prevalence of HBV-GN can only be estimated, but it closely parallels the geographic prevalence of HBV (Levy and Chen 1991).

Pathogenesis

Glomerular HBV antigen-containing immune complexes: Following infection with HBV, the host's humoral immune response is directed towards three main HBV antigens: surface (s), core (c), and extracellular (e) antigens (Ag). While this is a necessary response to clear the virus, it can also lead to the formation of pathogenic immune complexes key to the development of HBV-associated glomerulonephritis (HBV-GN). Glomerular immune complexes can result either from the deposition of circulating immune complexes and/or in situ formation. The coexistence of HBV DNA and the presence of HBV antigens in the kidney tissue implies that HBV antigens, particularly HB core antigen (HBcAg) and its immune complex, arise locally (Lai et al. 1996; Brzosko et al. 1974). Glomerular capillary loop staining for the three main antigens has been observed to a variable degree among patients. The three major HBV antigens are anionic and two of them, HBsAg and HBcAg, are large (>106 Da). Thus, given the size and net charges of HBsAg- or HbcAg-containing immune complexes, they are unlikely to directly deposit within the subepithelial space to lead to characteristic immune deposits in HBV-MN. Instead, their molecular characteristics promote their deposition within the mesangium and subendothelial spaces. To this end, there is evidence that immune complexes containing HBsAg are pathogenic in HBV-MPGN. Circulating immune complexes have been shown to contain anti-HBsAg/HBsAg, and anti-HBsAg has been eluted from the kidney tissue of 1 patient with HBV-MPGN (Ozawa et al. 1976). HBeAg-containing circulating immune complexes are relatively small (~2.5 × 105 Da) compared to the other two antigens (Tedder and Bull 1979), and anti-HBeAg IgG antibodies tend to be cationic, which raises the net charge of HBeAg-containing immune complexes (Neurath and Strick 1977). These properties facilitate the accumulation of these immune complexes in the subepithelial space, both from the circulation and in situ (Johnson and Couser 1990). The potential importance of HBeAg in HBV-MN is further supported by the

observations that circulating HBeAg-containing immune complexes correlate with disease severity, and HBeAg often is the predominant antigen in glomerular immune deposits (Gregorek et al. 1986, 1991).

Direct viral infection of renal tissue: HBV may directly infect glomerular cells and contribute to the pathogenesis of HBV-GN. This is supported by studies documenting expression of HBV DNA in glomeruli (He et al. 1998) and the finding that purified HBV can induce mesangial cell proliferation and expression of extracellular matrix proteins in vitro (Diao et al. 2013). The exact mechanism of the direct viral effects, however, remains unknown.

Host and viral genetic factors: There is limited evidence that HBV-associated glomerular diseases are linked to particular major histocompatibility complex Class II alleles. In HBV-MN, relatively small but significant increases have been noted in the frequency of DQB1*0603 in black children (Bhimma et al. 2002), DQB1*0301 in Polish children (Vaughan et al. 1998), and DRB1*1501 in Korean adults (Park et al. 2003). In this last population, DRB1*1502 was strongly associated with HBV-MPGN, being present in 23% of patients, compared with 9% of HBV-MN and 2% of controls.

There are significant differences in the epidemiology of HBV infection between continents and regions (Gupta and Quigg 2015). There are eight recognized genotypes of HBV (A through H); genotype A is predominant in North America, Europe, and Africa. Relevant to HBV-GN is the relative responsiveness of HBV/A to interferon (IFN)-α therapy. Whether different genotypes influence clinical presentation of HBV-associated glomerular diseases is not entirely clear.

Clinical presentation and natural history: The clinical manifestations of HBV-associated chronic glomerulonephritis (HBV-GN) are difficult to distinguish from other forms of glomerulonephritis, and HBV GN can present as mild to moderate proteinuria, hematuria, or nephritic syndrome (Lai and Lai 1991).

Membranous nephropathy (MN) is the most common pathologic type of hepatitis B virus-induced glomerulopathy comprising up to 15% of all MN cases in endemic areas (Gupta and Quigg 2015). It is the most frequently reported in Asian populations (Lai and Lai 1991) and in children (Lin 1991). Although idiopathic MN is associated with a slight male predominance, as many as 80–100% of children with HBV-MN are males (Levy and Chen 1991). Pediatric HBV carriers often do not have overt liver disease, and transaminase levels are usually normal.

HBV-MN tends to manifest slightly different in pediatric and adult patients. Children with HBV-MN typically present between the ages of 2 and 12 years (mean 6 years) with proteinuria that often is within the nephrotic range (urine protein/urine creatinine ratio >2 mg/mg), and microscopic or, rarely, macroscopic hematuria. Hypertension is present in less than 25% of cases. Kidney function is typically preserved.

The prognosis of HBV-MN in children is favorable, with stable renal function and high rates of spontaneous remission. Prior to the availability of antiviral therapy, the natural history of HBV-MN in children was one of slow resolution over several years, with an average 5-month period of duration of the nephrotic syndrome and 18–20-month average time to resolution of proteinuria. The cumulative probability of remission at 4 years is 64% (Gilbert and Wiggelinkhuizen 1994) and is more likely in younger patients and those with a smaller burden of subepithelial immune deposits (Hsu et al. 1989). Progression to chronic kidney disease is rare. The course of disease is unrelated to persistence of HBsAg, but recovery of renal injury is associated with development of antibodies to HBeAg.

In adults, proteinuria or nephrotic syndrome is the most common renal manifestations of HBV infection. Adult male predominance is less obvious than in pediatric populations. Adults are more likely than children to have hypertension, renal dysfunction, and clinical evidence of liver disease with elevated serum transaminases and hypocomplementemia. Despite the presence of nephrotic syndrome, serum cholesterol and triglyceride levels may not be elevated. The natural history in adults is not as benign as in children,

and adults with HBV-MN typically develop progressive disease. Spontaneous remission is uncommon. The prognosis is even worse for patients with nephrotic-range proteinuria and abnormal liver function tests at presentation. Over 50% of the patients require renal replacement therapy within 3 years (Tang et al. 2005).

HBV has also been linked to other glomerular diseases such as IgA nephropathy (IgAN), membranous proliferative glomerulonephritis (MPGN), and focal segmental glomerulosclerosis (FSGS). (Bhimma and Coovadia 2004; Wang et al. 2005; Lai et al. 1988, 1994). In HBV-IgAN, mesangial proliferative glomerulonephritis coexists with predominant mesangial IgA deposits and persistent HBV antigenemia (Nagy et al. 1979). The histological lesion is typically a mesangial proliferative GN with predominant mesangial IgA deposits with or without coexisting MN with capillary IgG deposits (Lai et al. 1988). There are no clear differences between the clinical course of patients with IgA nephropathy who have evidence of HBV infection from those who do not (Sun et al. 2013). In HBV-MPGN, nephrotic syndrome and microscopic hematuria are the most common presentations. Hypertension is present in 50% of patients and abnormal renal function in 20%. Serum complement levels are often depressed, and circulating immune complexes may be present. The kidney lesion is histologically similar to MPGN type I, with deposition of circulating HBeAg or HBsAg-anti HBs Ab complexes in the mesangial area and subendothelial space (Takekoshi et al. 1991). HBV-FSGS has been reported in younger men who presented with nephrotic syndrome with proteinuria, anasarca, hypercholesterolemia, and severe hypoalbuminemia (Khaira et al. 2009). Occasional concomitance of the pathologic subtypes can lead to "double" glomerulopathies, e.g., MN and IgAN have been reported to coexist in an HBV carrier (Tang et al. 1999). Polyarteritis nodosa, an antineutrophil cytoplasmic antigen-negative necrotizing small- and medium-vessel vasculitis, has a strong association with HBV (Gocke et al. 1970; Trepo and Thivolet 1970).

Diagnosis and Monitoring: Diagnosis of HBV-associated glomerulonephritis is based on persistence of circulating HBV or HBV DNA, absence of other causative agents, and presence of HBV specific antigen(s) or viral genome in the glomerulus. In clinical practice, regression of pathology following viral eradication is not easy to demonstrate because of ethical concerns relating to repeat renal biopsies in humans following clinical remission. Standard laboratory testing includes liver biochemistries (serum alanine aminotransferase, γ-glutamyltransferase, and bilirubin levels), HBV serologies (hepatitis B surface antigen, HBeAg, antihepatitis B core antigen). HBeAg is present in up to 80% of patients, who might also have high titers of antihepatitis B core antigen (Lai et al. 1991). Patients with serologic evidence of hepatitis should be tested for circulating HBV DNA and undergo liver biopsy. An α-fetoprotein assay could be an important adjunct. Serum C3 and C4 levels can be low in 20–50% of patients. Measurement of antiphospholipase A2 receptor antibody titers (anti-PLA2R) can help differentiate idiopathic MN from HBV-MN (Qin et al. 2011). In a study from China, only 1 in 16 with HBV-MN was positive for anti-PLA2R compared with 82% of patients with idiopathic MN (Qin et al. 2011). In idiopathic MN, IgG4 tends to be the dominant or co-dominant IgG subclass. In contrast, IgG1 tends to be the predominant IgG subclass in secondary forms of MN, including HBV-MN (Huang et al. 2013). Thus, in those patients with HBV infection and MN, the presence of IgG1 in glomeruli supports the diagnosis of HBV-MN.

Treatment: Current KDIGO guidelines recommend antiviral therapy for HBV-GN with interferon alpha or nucleoside analogs following standard clinical practice guidelines for HBV infection, with dosing adjusted to the degree of renal function (2012; Elewa et al. 2011). Active immunization remains the most effective means of immunoprophylaxis and prevention of glomerular disease. Active immunization of newborns over the past two decades has shown a dramatic decline in the incidence of neonatal HBV infection and its renal complications (Liao et al. 2011). In 2003, the WHO recommended that all countries establish universal HBV immunization programs for infants and adolescents (Duclos 2003).

Acute Glomerulonephritis Caused by HBV

A recent report suggests that HBV infection may also be associated with acute glomerulonephritis (Zhang et al. 2016). Ten chronic HBV carriers, ages 7- to 20-years-old, developed acute glomerulonephritis, and had positive glomerular staining for HBsAg, and detectable presence of HBV DNA in the glomeruli. These patients presented with proteinuria, hematuria, and hypertension, similarly to patients with non-HBV postinfectious GN (used as controls in this study), but had a higher incidence of AKI and worse prognosis. Indeed, 4 out of the 10 patients with HBV-associated acute glomerulonephritis showed no improvement 6 months after onset. The renal biopsy findings were similar to those in classic PIGN cases, with diffuse glomerular endocapillary proliferation, but HBV-associated PIGN showed fewer subepithelial glomerular "hump-shape" immune complex deposition.

Parvovirus B19 (PVB19)

Parvovirus B19 is a small, nonenveloped, single-stranded DNA virus, member of the *Parvoviridae* family (Cossart et al. 1975). Infection with parvovirus is very common and occurs worldwide. While it is often acquired during childhood, infection continues at lower rates throughout adulthood such that between 70% and 85% of adults show serologic evidence of past infection (Cohen and Buckley 1988). Infection is more common in winter and spring in temperate climates and occurs by inhalation of the virus in aerosol droplets (Anderson et al. 1985). Parvovirus B19 Infection also can be transmitted vertically from mother to fetus and horizontally (less commonly) through transfusion of blood products, bone marrow transplants, and solid-organ transplants (Jordan 1996; Azzi et al. 1999; Heegaard and Laub Petersen 2000; Broliden 2001; Egbuna et al. 2006).

Parvovirus B19 infection causes several clinical syndromes (fifth disease, transient aplastic crisis, pure red cell aplasia, and hydrops fetalis) and may contribute to other illnesses. This virus has been linked to renal disease in three settings: acute glomerulonephritis, anemia in ESKD, and kidney transplantation (Waldman and Kopp 2007). The role for B19 infection is based on the temporal association of renal findings with viral infection, positive serology, and by immunohistochemistry or identification of the viral genome in the glomerulus.

Pathogenesis: Following infection, the virus targets the erythroid progenitors in the bone marrow causing cell death either by lysis or by apoptosis (Umene and Nunoue 2002). In a normal infection, intense viremia lasts several days. Recovery is associated with production of parovirus B19-specific IgM antibodies 10–12 days after infection. This is followed by the production of IgG antibodies. Parvovirus B19 is thought to cause renal disease mainly through depositions of immune complexes in the glomeruli (Nakazawa et al. 2000; Ieiri et al. 2005; Onguru et al. 2006).

Clinical presentation and natural history: Parvovirus B19 has been associated with acute glomerulonephritis in numerous case reports that describe onset of nephritic or nephrotic syndrome after onset of parvovirus infection. Multiple and varied clinical presentations and histologic patterns have been described (Onguru et al. 2006; Ieiri et al. 2005; Ohtomo et al. 2003; Iwafuchi et al. 2002; Moudgil et al. 2001; Komatsuda et al. 2000; Uchida et al. 2014; Nakazawa et al. 2000; Tanawattanacharoen et al. 2000; Diaz and Collazos 2000; Tolaymat et al. 1999; Murer et al. 2000; Marco et al. 2016). However, the most common presentation involves women in the second or third decade of life, who present either with nephritic syndrome or mild proteinuria and microhematuria, as well as low serum C3 complement levels. The renal involvement follows a prodrome of fever, rash, and arthritis.

Renal biopsy findings often show endocapillary and/or mesangioproliferative glomerulonephritis with subendothelial deposits together with granular deposition of C3 and IgG along capillary walls and mesangium, a pattern that is consistent with acute postinfectious glomerulonephritis. In some cases, viral genome has been detected in renal biopsies by PCR, and

immunohistochemical analysis has demonstrated B19 antigen within glomeruli (Ohtomo et al. 2003; Komatsuda et al. 2000; Nakazawa et al. 2000; Marco et al. 2016). The prevalence of parvovirus B19 DNA in renal biopsies (78%) and peripheral blood (87%) is significantly higher in patients with collapsing glomerulopathy than in those with other nephropathies (Nakazawa et al. 2000). Glomerular and tubular infection with parvovirus B19 might trigger collapsing glomerulopathy, but only in patients with immune defects and a racial predisposition (African descent) (Moudgil et al. 2001). In an intriguing study, Parvovirus B19 DNA was detected in 80% of patients with "idiopathic" FSGS, a number greater than in patients with other renal diseases (Tanawattanacharoen et al. 2000). This reflects the presence of latent DNA from past infection and indicates a possible pathogenic role for the virus in certain patients with FSGS. Glomerular involvement is mostly transient and self-limited. However, some cases progress to chronic kidney disease or persistent proteinuria.

Diagnosis and Monitoring: The choice of diagnostic tests for detection and monitoring of parvovirus B19 must consider the immunologic status of the patient (Jordan 2001). In immunocompetent patients, serologic testing for B19 virus-specific antibodies using enzyme immunoassays is most practical. IgM antibodies directed to viral capsid antigens indicate acute infection, while previous infection is usually confirmed by detecting IgG antibodies toward viral capsid proteins in the absence of IgM antibody. In immunosuppressed patients, however, the diagnosis of B19 infection can be missed if only viral serologies are obtained because these patients may not mount an antibody response. Thus, identification of the viral DNA by PCR is preferred for diagnosis in these patients, both in DNA from peripheral blood and/or DNA extracted from renal tissue (Peterlana et al. 2006).

Treatment: There is no specific antiviral therapy to treat B19 infection. The approach to therapy depends on host factors such as immune status, underlying conditions, and manifestations of infection. Supportive management with low-sodium diet, diuretic treatment, and ACE inhibitors is often needed. Most cases of infection in immunocompetent hosts, however, do not need treatment because the symptoms are transient, and spontaneous recovery common.

Hantavirus

Hantaviruses are a diverse group of infectious agents, members of the genus *Hantavirus* (family *Bunyaviridae*), which are zoonotic in nature and transmitted to humans through rodent reservoir (Jonsson et al. 2010). Hantaviruses are globally distributed and each human pathogenic hantavirus is carried by different rodents. The virus is mostly transmitted to humans by inhalation of virus particles present in rodent secreta. It causes hemorrhagic fever with renal syndrome (HFRS) or hantavirus pulmonary syndrome (HPS) depending on the hantavirus species. The observed syndromes are not independent entities, as they are both the result of a common pathogenetic mechanism: the increase of capillary permeability through direct and immune-regulated pathways.

The peculiar distribution of rodent host species has led to specific geographical pattern of hantaviruses and associated diseases. In Eurasia, hantaviruses cause HFRS of various severity. HFRS in Asia is caused by Hantaan, Seoul, and Amur-Soochong viruses, which affect mostly China, South Korea, and the far-eastern region of Russia (Bi et al. 2008; Zhang et al. 2010). In central and northern Europe, in addition to the above-mentioned Seoul virus, Puumala, Dobrava-Belgrade, Saaremaa, and Tula viruses are found, often in co-circulation (Bi et al. 2008; Vaheri et al. 2013; Vapalahti et al. 2003). Endemic area includes northern and central Europe (Denmark, Finland, Norway, Sweden, Belgium, Chech Republic, France, Germany, and Slovakia), Alpe-Adrian region (Austria, Croatia, Hungary, and Slovenia), the Balkans (Albania, Greece), and the European part of Russia. In Scandinavia and northern Europe, a milder form of HFRS associated with the Puumala virus and termed nephropathica epidemica (NE) is prevalent, and it usually presents with a mild clinical course, and less frequent severe complications.

There has been a recent "explosion" in a number of newly discovered hantaviruses, and it is safe to assume that the list of hantaviruses causing HFRS will get longer with time. "Hemorrhagic fever with renal syndrome" is an acute interstitial nephritis that results from direct vascular injury of renal tissues. The first four cases of HFRS were described in Croatia and south-eastern Europe in 1954 (Radosevic and Mohacek 1954). In the following years, the disease occurred mainly sporadically; however, a few outbreaks were also reported (Vesenjak-Hirjan et al. 1971; Ledina et al. 2002; Markotic et al. 2002; Mulic and Ropac 2002; Bergstedt Oscarsson et al. 2016), the largest of which was in 2002, with >400 cases (Cvetko et al. 2005; Medved et al. 2002).

Pathogenesis: Viral antigens are excreted in host-reservoir feces, urine, and saliva; when aerosolized, these can be inhaled by humans that are subsequently infected. Upon infection, pathogenic Hantavirus virions enter endothelial cells by binding to αvβ3-integrins on the cell surface. The virions do not exert a cytopathic effect, although they do multiply within and egress from infected cells. The mechanism of kidney damage is not fully understood but is related to platelet and endothelial cell dysfunction and capillary hyperpermeability, the cardinal feature of all hantavirus infections. In addition, there is indirect damage from an excessive immune response. This is supported by the histologic findings of microvascular inflammation, especially cortical peritubular capillaritis, and tubular necrosis (Gnemmi et al. 2015). In addition, complement and immune-complex deposits have been found in renal biopsies of patients with HFRS (Ferluga and Vizjak 2008).

Clinical presentation and natural history: Overall disease severity is mainly determined by the hantavirus species that causes the disease, but it also varies in individual patients from subclinical presentation to fatality. HFRS is considered to progress through febrile, hypotensive, oliguric, polyuric, and convalescent phases. Hantavirus infections follow a 2–4 week incubation period and are characterized by sudden onset of flu-like symptoms, such as fever, headache, abdominal pain, and nausea. During this febrile period, patients can present with hemorrhagic manifestations such as subconjuctival hemorrhage and mucous membrane injection. Patients may complain of headache and vertigo early on, while less common neurological complications, such as epileptic seizures, hemiparesis, focal encephalitis, structural central nervous system lesions, and isolated cranial nerve palsies, have been reported (Sargianou et al. 2012). This febrile phase is followed by a hypotensive phase often with severe thrombocytopenia (often with petechial rash) and increased vascular permeability, leukocytosis, elevated levels of lactate dehydrogenase, and C-reactive protein (Krautkramer et al. 2013; Sargianou et al. 2012). During the hypotensive phase, up to 30% of patients show clinical signs of shock (Heyman et al. 2009). After this phase, the infection manifests in different organs. In HFRS, kidney function is predominantly affected. Laboratory findings in HFRS demonstrate an elevated serum creatinine and low serum albumin, and urinalysis shows hematuria and proteinuria. Renal replacement therapy is often required during this phase (Tulumovic et al. 2010). Platelet dysfunction is augmented by uremia during the oliguric phase, leading to frequent hemorrhagic complications (26–59% of patients). Disseminated intravascular coagulopathy may also present (Heyman et al. 2009). The oliguric phase with AKI is followed by the diuretic (polyuric) phase in which renal function improves. Daily urinary excretion volume can reach 3–6 L and may require aggressive fluid replacement. Finally, during the convalescent phase, patients recover completely. Patients may experience muscular weakness, tremors, and polyuria even throughout the convalescent phase, which usually disappears within 2 months (Bi et al. 2008). Death due to HFRS may be because of several complications: renal insufficiency, edema and hemorrhages, encephalopathy, or shock. Signs and symptoms of hantavirus infection may present differently and can affect different organs (Hautala et al. 2010; Dzagurova et al. 2012). The long-term prognosis is favorable and most patients recover full renal function. Hypertension is discussed to be a long-term consequence (Miettinen et al. 2006).

Diagnosis: Diagnosis of Hantavirus infection is made according to the classic clinical, serological, and molecular findings. There is often a history of probable exposure in an endemic area. Immunodiagnostic tools are vital due to the limited success with molecular detection and because the viremia is short-lived (Vaheri et al. 2008). Serological tests for the detection of IgM and IgG antibodies based on indirect immunofluorescence assays, strip immunoblot, or enzyme-linked immunosorbent assays (ELISA) are commercially available (Sjolander et al. 1997). IgM response starts with the onset of symptoms, is early detectable, and indicates acute infection. In some patients, reverse transcriptase polymerase chain reaction (RT-PCR) may be used to confirm clinical suspicion during the first 1–5 days of symptoms (RT-PCR tends to be positive during the incubation period and early prodrome). Imaging findings that have been associated with acute HFRS include enlargement of both kidneys on ultrasound (100%), hepatosplenomegaly (50%), pleural effusion (14.3%) and ascites (28.6%), increased thickness of the bladder wall (14.3%), gallbladder enlargement (7%), and edema of the pancreas (7%) (Tulumovic et al. 2010).

Treatment: There is no specific antiviral medication available, and the treatment of infection is limited to supportive therapy often involving cardiovascular, respiratory, and renal function support, with fluid and electrolyte homeostasis being crucial components of care (Sargianou et al. 2012). In regards to antiviral therapies, the nucleoside analog, ribavirin, reduces mortality in HFRS, but the usefulness is still controversial and has not been properly studied (Moreli et al. 2014). New strategies for vaccination and treatment are currently under investigation.

In order to facilitate effective patient management, efforts have been made to stratify patients according to the risk of severe complications. One study of HFRS showed a correlation between serum levels of inflammatory and regulatory cytokines with disease (Saksida et al. 2011). Specifically, patients suffering from a more severe clinical course of Dobrava/Belgrade virus infection had higher serum levels of Interleukin-10 and tumor necrosis factor-α, when compared to those with a milder course. Other studies suggest that interleukin-6 was a better indicator of disease severity than C-reactive protein in the milder HFRS due to Puumala virus (Outinen et al. 2010). Serum fibronectin concentration is increased in patients with HFRS and correlates with disease stage and severity (Han et al. 2010). In addition, increased urinary levels of the biomarker cystatin-c during the oliguric phase have been linked to the severity of AKI due to HFRS (Ma et al. 2010).

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Fibrillary Glomerulonephritis

25

Charles E. Alpers

Contents

Abstract

Fibrillary glomerulonephritis (FGN) is a progressive glomerulopathy characterized by the deposition of abnormal fibrils having an ultrastructural appearance similar to amyloid fibrils. FGN is a morphologically defined entity that is somewhat clinically heterogeneous. Until recently, the composition of the fibrillary deposits was unknown but several recent studies have shown the deposits are composed of DnaJ Heat Shock Protein Family B Member 9 (DNAJB9), immunoglobulins and complement components. While DNAJB9 has recently been identified as a highly sensitive and specific marker of FGN, its mechanistic role in the development of FGN remains unknown. A kidney biopsy and, in particular electron microscopy or DNAJB9 staining, is required for establishing the diagnosis. There is a strong propensity to end-stage renal disease. Randomized controlled clinical trials of therapies for this disease remain to be reported.

Keywords

Fibrillary glomerulonephritis · Fibrils · Mesangium · Basement membranes · Electron microscopy · DNAJB9

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Introduction

Fibrillary glomerulonephritis is a morphologically defined entity characterized by glomerular accumulation of non-branching, randomly arranged fibrils. These fibrils are morphologically indistinguishable from those of amyloid but differ from amyloid by virtue of their larger size and lack of reactivity with Congo red and other histochemical reagents that are typically reactive with amyloid. Numerous studies have revealed an approximate incidence of 0.5–1.0% of cases of fibrillary glomerulonephritis in native kidney biopsies accessioned in large renal biopsy practices in the United States (Alpers and Kowalewska 2008; Nasr et al. 2011).

Pathogenesis

The etiology of fibrillary glomerulonephritis remains unknown. The deposition of immunoglobulin suggests an etiology involving immune dysfunction, and the fibrils may be of immunoglobulin origin, but this has not been definitively established (Alpers and Kowalewska 2008). It remains a possibility that the deposited immunoglobulin represents a response to the fibrils and represents a uniform coating of the fibrils, although this hypothesis is not widely accepted nor has it been adequately tested. A study of fibrillary glomerulonephritis using laser microdissection and proteomic analysis of involved glomeruli revealed the absence of amyloid P protein in fibrillary glomerulonephritis, in contrast to its abundant presence in amyloidosis. This study did not provide further clues as to the identity of the fibrils in fibrillary glomerulonephritis (Sethi et al. 2013). Two more recent studies conducted in independent laboratories using laser microdissection and liquid chromatography-assisted tandem mass spectrometry identified DnaJ heat shock protein family B member 9 (DNAJB9) as being overabundant in FGN, when compared with amyloidosis and a variety of other immune complex mediated glomerular diseases (Andeen et al. 2018; Dasari et al. 2018). Andeen and colleagues propose that DNAJB9 is the most likely candidate autoantigen in FGN and is the target of an IgG-mediated autoantibody response that results in the development of glomerulonephritis, including activation of the classical complement pathway. Both of the groups above also demonstrated that DNAJB9 colocalizes with IgG. A further study by Nasr and colleagues included immunoelectron microscopy on 3 cases of FGN that showed localization of DNAJB9 to the fibrils (Nasr et al. 2018). Several disease entities have been reported in patients with fibrillary glomerulonephritis, such as hepatitis C virus infection, diabetes, and rheumatoid arthritis, but overall these associations involve only a small minority of affected patients and hence have not contributed as yet to an understanding of underlying pathogenesis. A somewhat larger minority of patients has an associated lymphoplasmacytic disorder, but again these cases lack a sufficient unifying pathophysiologic characterization as to provide a clear clue as to underlying pathogenesis. An animal model of this disorder has not been identified to date, which has further hampered our ability to understand underlying pathogenetic mechanisms.

Histopathology

Fibrillary glomerulonephritis is histologically manifest by a variety of morphologic patterns (Alpers and Kowalewska 2008). These include a membranoproliferative pattern of injury, in which there is both expansion of mesangial regions due to accumulations of the fibrillary material within the mesangium in conjunction with abnormalities of the glomerular capillary walls. The capillary wall changes in these cases may include thickening of basement membranes due to infiltration by pathologic fibrils and/or patterns of duplication of basement membrane matrices as occurs in immune complex-mediated membranoproliferative glomerulonephritis as a chronic response to capillary wall injury. Another common histologic manifestation is a mesangial proliferative glomerulonephritis pattern without histologically detectable alterations

in the adjacent capillary walls, in which the dominant abnormality is expansion of the mesangial regions, due to accumulations of fibrils and in part to accumulations of various matrix proteins as a chronic injury response. Sometimes the glomerular involvement by pathologic fibrils is limited to accumulations within the peripheral capillary walls, often in subepithelial locations. Such a pattern of injury is indistinguishable from membranous nephropathy, although ancillary immunofluorescence and electron microscopic studies enable the distinction from classic membranous nephropathy due to immune complex formation. In some cases with prominent capillary wall involvement, the fibrils may appear to erode through the glomerular capillary walls and into the adjacent urinary space. Such deposits may have a spicular configuration which is striking when identified in a silver methenamine-stained histologic tissue section. The fibrillary accumulations often can be accentuated by silver methenamine stains but otherwise lack specific staining characteristics with the hematoxylin and eosin and PAS and trichrome stains routinely used for diagnostic renal biopsy tissue sections. In the majority of cases, there is little inflammatory injury within the involved glomeruli. However, there is a subset of cases in which there is a diffuse endocapillary proliferative glomerulonephritis with influx of inflammatory cells into the glomerular capillary loops, and in a subset of cases, there may be segmental necrosis and or crescent formation (Figs. 1, 2, and 3).

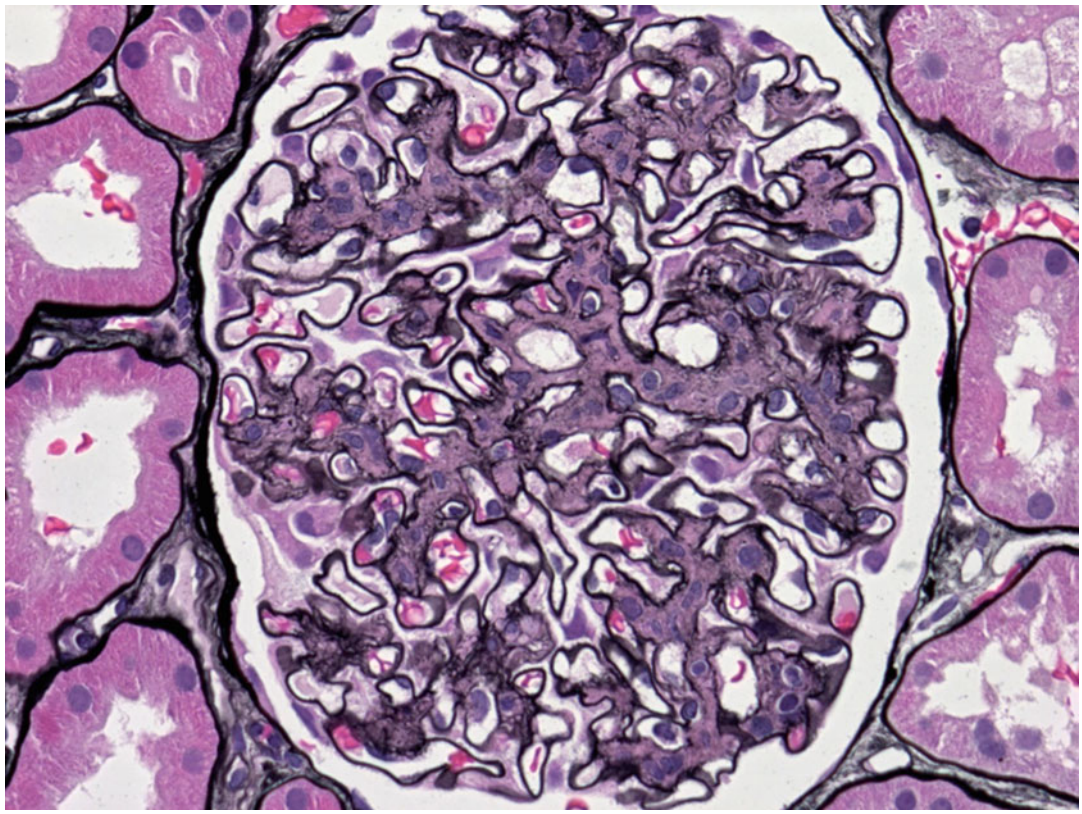

Fig. 1 A glomerulus involved by fibrillary glomerulonephritis shows modest expansion of mesangial regions (*M*) by acellular material. The capillary loops are widely patent, but glomerular basement membranes show mild thickening. The glomerulus is without a prominent inflammatory cell infiltrate. Silver methenamine stain, with hematoxylin and eosin counterstain

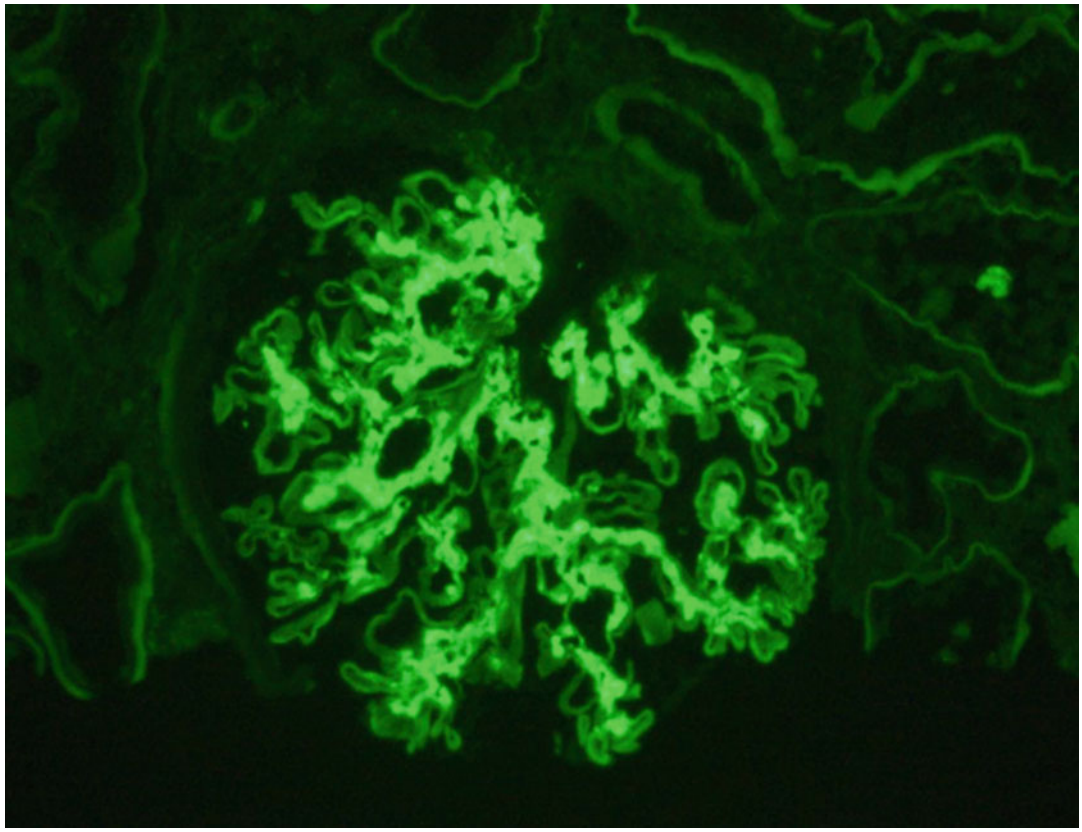

Fig. 2 Immunofluorescence study shows deposition of IgG predominantly in mesangial regions. The adjacent extraglomerular parenchyma is without immunoglobulin deposits

Immunofluorescence Microscopy

The great majority of cases of fibrillary glomerulonephritis show prominent deposition of IgG, corresponding to the locations of the abnormal fibrils. In most cases, there is a somewhat discrete and somewhat granular or clumpy character to the deposits. The deposits are typically polyclonal, evidenced by equivalent and concurrent staining for kappa and lambda light chains in a similar distribution as the IgG. Rare cases of monoclonal immunoglobulin deposits have been reported, as have extremely rare cases in which no detectable deposition of immunoglobulins could be identified. Some reported series suggest the deposited IgG is predominantly of IgG4 subclass, while other studies suggest both IgG1 and IgG4 subclasses are predominately deposited (Javaugue et al. 2013; Hemminger et al. 2016).The deposits of IgG can be present in either mesangial regions and peripheral capillary walls or commonly both, corresponding to the fibrillary accumulations. The immunofluorescence staining for IgG often has a somewhat dull and band-like appearance, in contrast to the bright and sharp staining of deposits of immune complexes. In very rare cases, in which glomerular basement membranes may be diffusely permeated by accumulations of pathologic fibrils, the immunofluorescence picture may reveal a linear pattern of IgG staining that can mimic the pattern of anti-glomerular basement membrane antibody deposition as occurs in anti-glomerular basement membrane antibody-mediated glomerulonephritis.

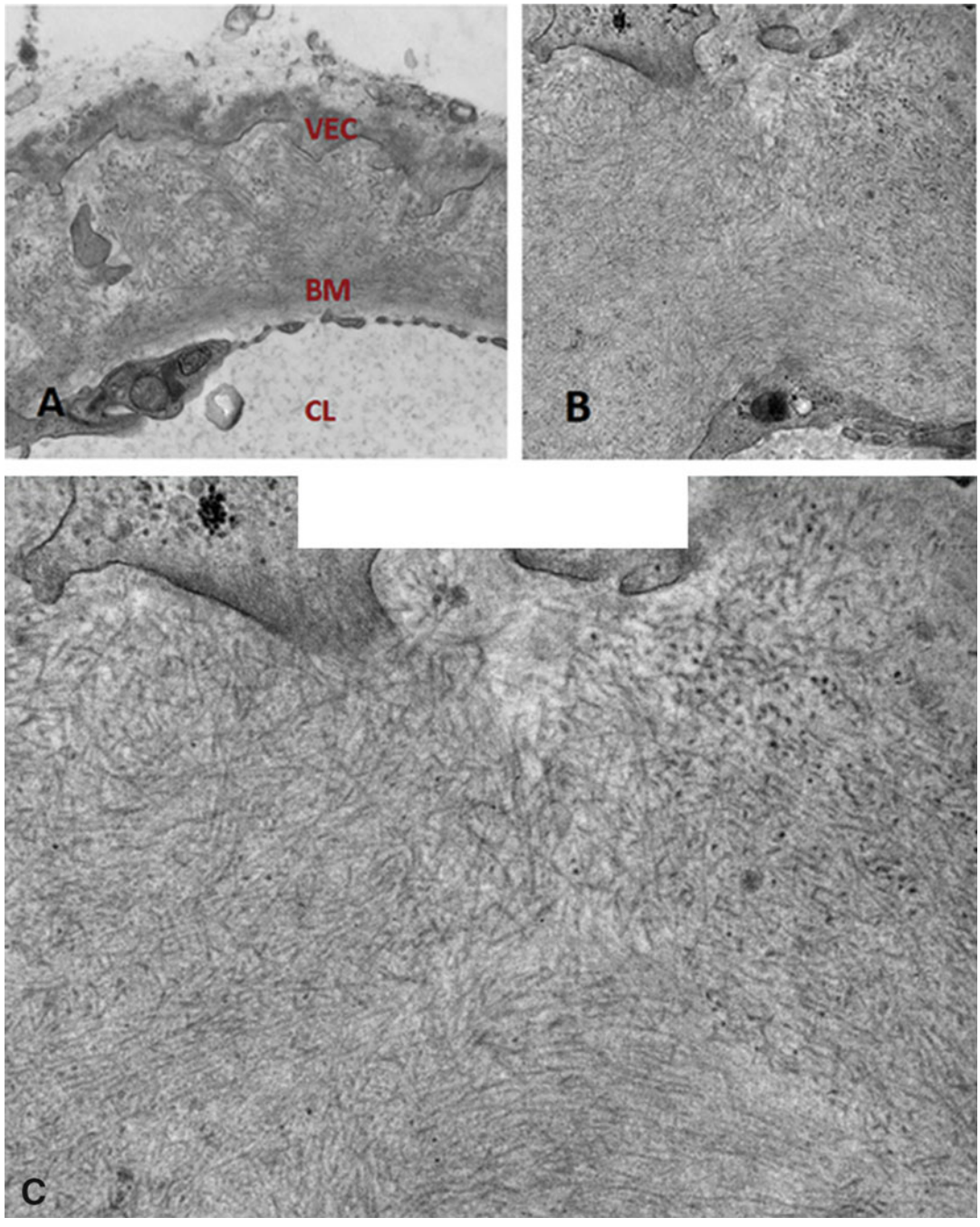

Fig. 3 (**A**) Electron micrograph of a glomerular capillary wall showing diffuse infiltration of the basement membrane (*BM*) by randomly arranged nonbranching fibrils. The glomerular endothelium shows normal fenestrations; the overlying visceral epithelial cell (*VEC*) foot processes are extensively effaced. *CL* capillary lumen. (**B**) Higher-power electron micrograph showing the characteristic appearance of the fibrils in fibrillary glomerulonephritis. Original magnification **A**, 18,500×; **B**, 30,000×. (**C**) Higher-power electron micrograph showing the characteristic appearance of the fibrils of fibrillary glomerulonephritis shown in Fig. 3B

Electron Microscopy

The defining feature of fibrillary glomerulonephritis is the ultrastructural finding of accumulations of randomly arranged-nonbranching fibrils within glomeruli (Alpers and Kowalewska 2008). Typically the process is diffuse; i.e., it involves all of the glomeruli to at least some degree within a biopsy sample. The fibrils usually are present within the mesangial regions and frequently permeate the glomerular basement membranes as well, even in cases where the involvement of the basement membranes was not apparent in histologic tissue sections. As noted in the introduction, the fibrils are indistinguishable in appearance from those of amyloid but differ from their larger size (approximately 16–24 nm in diameter in most cases) when measured carefully in a calibrated electron microscope, which contrasts with the usual accepted diameter of 8–15 nm (most often 8–12 nm) for amyloid fibrils. This distinction is not absolute, and the potential for overlap in size requires that other characteristic features such as histochemical staining qualities must be considered when making a diagnosis of fibrillary glomerulonephritis. In some cases, the deposits may be located exclusively in the subepithelial aspect of glomerular basement membranes. Involved glomeruli typically show effacement of glomerular epithelial cell foot processes where they overlie the fibrillary deposits. Extra-glomerular deposits have been rarely identified. Such deposits have been identified in tubular basement membranes, but not other renal structures. There are extremely rare reports of extrarenal deposits of fibrils, particularly in the lung. Such reports are of uncertain validity due to the difficulty in distinguishing the fibrillary deposits from degenerated elastin and elastic tissues in damaged lung parenchyma.

Differential Diagnosis

The pathologic differential diagnosis includes distinction from immune complex-mediated forms of glomerulonephritis (which can be distinguished from fibrillary glomerulonephritis by the distinct appearance of accumulations of fibrils versus granular deposits of immune complexes as revealed by electron microscopy), amyloidosis (which can be distinguished by smaller measured diameter of the fibrils and the lack of reactivity with histochemical reagents that characteristically react with amyloid), and glomerulopathies due to deposits of microtubular structures, such as cryoglobulinemic glomerulonephritis and immunotactoid glomerulopathy, both of which are distinguished from fibrillary glomerulonephritis by the typically larger diameter of the microtubules and the different ultrastructural appearances of microtubules and fibrils. Microtubules are characterized by a cylindrical structure, often with a hollow core when viewed en face versus the more solidified appearance of fibrils. Furthermore, the microtubular deposits corresponding to cryoglobulinemic glomerulonephritis and/or immunotactoid glomerulopathy often are focally arranged in organized, parallel arrays rather than the randomly arranged haphazard appearance of the fibrils of fibrillary glomerulonephritis. The differences in immunofluorescence findings are also key to establishing the diagnosis of fibrillary glomerulonephritis versus immunotactoid glomerulopathy as noted above. Fibrillary glomerulonephritis typically has polyclonal deposits of immunoglobulin and is only rarely associated with lymphoplasmacytic disorders, while immunotactoid glomerulopathy most often is characterized by deposition of a monoclonal immunoglobulin and is often associated with a lymphoplasmacytic disorder. In cases where the findings described above are inconclusive, or in cases where tissue for immunofluorescence or electron microscopy is unavailable, DNAJB9 staining by immunohistochemistry has been recently shown to be both a sensitive and specific marker for FGN (Fig. 4) (Nasr et al. 2018). The key clinical and pathologic features that distinguish fibrillary glomerulonephritis from amyloidosis and immunotactoid glomerulopathy are summarized in Table 1.

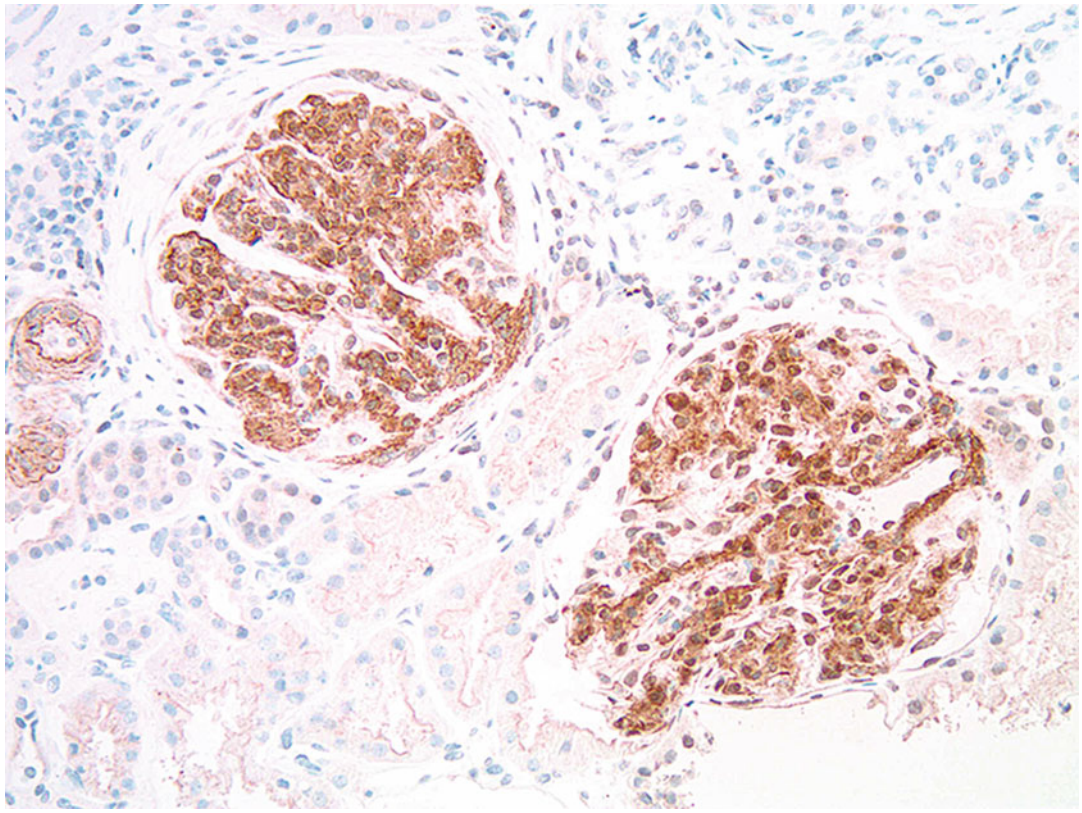

Fig. 4 Immunohistochemical staining for DNAJB9 in a case of fibrillary glomerulonephritis. Strong glomerular staining is seen in mesangial areas and peripheral capillaries, helping to establish the diagnosis. DNAJB9 staining is particularly helpful in cases where the diagnosis of fibrillary glomerulonephritis is unclear because of overlapping features with other entities, or in cases where there is insufficient material for either electron microscopy or immunofluorescence

Table 1 Immunopathologic features of fibrillary/microtubular glomerulopathies

Characteristics	Amyloidosis	Fibrillary glomerulonephritis	Immunotactoid glomerulopathy
Appearance	Fibrils	Fibrils, rarely microtubular	Microtubules
Fibril/microtubule size	8–15 nm (most often 10–12)	12–24 nm (most often 18–20)	> 30 nm (most often 34–49)
Fibril arrangement in tissues	Random	Random	Often organized in parallel arrays
Reactions with histochemical dyes Congo red and thioflavin T	Yes	No	No
Immunoglobulin deposition	Monoclonal light Chains in AL type	Usually polyclonal Occasionally oligo- or monoclonal IgG	Monoclonal or oligoclonal IgG common
Association with lymphoplasmacytic disorders	Yes, if AL type	Uncommon	Common

Clinical Setting

Several large series of patients with fibrillary glomerulonephritis provide a generally consistent characterization of their clinical presentation. Patients most often are of age 50–65 at the time of diagnosis, but the age range is wide and even patients in the pediatric age range have been reported with this disease. Patients present with proteinuria and frequently with nephrotic syndrome. Approximately two thirds of patients have renal insufficiency at the time of diagnosis, and the majority of patients demonstrate hematuria and hypertension at the time of diagnosis. The prognosis for patients is dismal. Approximately 40–60% of patients will progress to end-stage renal disease within a period of 2–3 years. Only a small percentage of patients will respond to therapy, manifest as partial or complete remissions of proteinuria. A variety of clinical interventions have been attempted, but there are no random controlled clinical trials to support the use of any one specific agent for the treatment of this disorder. Rituximab has been reported to be of benefit in some patients, but within the reported series there are patients who do not respond (Javaugue et al. 2013; Hogan et al. 2014). Therapy is frequently supportive and directed toward controlling hypertension, if present, and ameliorating nephrosis. Patients who progressed to end-stage renal disease have undergone transplantation, and recurrence in transplant kidneys has been well documented. In one large series, it was found that patients with fibrillary glomerulonephritis who progressed to end-stage renal disease have comparable dialysis and renal transplant outcomes compared with patients with other causes of end-stage renal disease (Mallett et al. 2015). In those patients in which immunofluorescence microscopy demonstrated a monoclonal immunoglobulin, a workup should be performed to evaluate a possible underlying clonal plasma or B cell population.

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Mixed Cryoglobulinemia

26

Pietro A. Canetta and Jordan G. Nestor

Contents

Abstract

Cryoglobulins are proteins that precipitate from the blood at temperatures below 37 °C and redissolve upon rewarming. They are largely composed of immunoglobulins and characterized according to the types of immunoglobulins involved. Monoclonal cryoglobulins (type I) are usually associated with hematologic disorders, while mixed cryoglobulins (types II and III) are found in many infectious and systemic disorders, and are most commonly associated with hepatitis C virus infection. Mixed cryoglobulinemia can cause a systemic inflammatory syndrome

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characterized by small and medium vessel vasculitis. The ensuing syndrome manifests clinically with fatigue, arthralgias, purpura, neuropathy, and frequently an immune complex glomerulonephritis. Treatment consists of identifying and controlling the underlying cause of the cryoglobulinemia, with supportive care that may include immunosuppression and plasmapheresis in severe cases.

Keywords
Cryoglobulins · Mixed cryoglobulinemia · Immune complex · Glomerulonephritis · Hepatitis C · Rituximab · Apheresis

Introduction

Cryoprecipitation is a term used to describe certain proteins in the blood that become insoluble at temperatures below normal body temperature (less than 37 °C). There are two types of these proteins, cryoglobulins and cryofibrinogen. Cryoglobulins are either immunoglobulins or mixtures of immunoglobulins and components of complement. Cryofibrinogen is composed of fibrinogen, fibrin, fibronectin, and/or fibrin degradation products. Cryoglobulins precipitate from serum and plasma, whereas cryofibrinogen by definition precipitates from plasma only. Both redissolve with rewarming.

Cryoprecipitation was first described in 1933 in a patient with multiple myeloma who showed signs and symptoms of hyperviscosity (Wintrobe and Buell 1933). The term cryoglobulin was introduced in 1947 to describe cold precipitable serum globulins (Lerner and Watson 1947). Cryoglobulinemia strictly refers to the presence of cryoglobulins in the serum and plasma, while the terms cryoglobulinemic disease and cryoglobulinemic vasculitis are more appropriately used to describe patients with symptoms related to the presence of cryoglobulins. Serum cryoglobulins are found in many illnesses but are often transient and their presence is not always associated with a clinical disease. Most patients with cryoglobulinemia are asymptomatic (Dammacco et al. 2016).

In 1966, the clinical syndrome of mixed cryoglobulinemia was formally described (Meltzer and Franklin 1966). It was characterized by a constellation of clinical features that consisted of the triad of palpable purpura, weakness, and arthralgias, as well as glomerular lesions, lymphadenopathy, and hepatosplenomegaly in some patients. The cause was unknown at that time, and it was only until after 1989, with the first-generation ELISA for hepatitis C virus (HCV) antibodies, that its strong association with HCV became apparent. Though HCV is the most common cause of cryoglobulinemic disease, a variety of other systemic conditions may also induce mixed cryoglobulinemia, including other infections, systemic rheumatologic disease, and malignancies.

Mixed cryoglobulinemia is a highly heterogeneous syndrome in terms of clinical manifestations, organ involvement, and immunological abnormalities. The clinical course may vary from a relatively benign disease with minor manifestations to multiorgan involvement with life threatening complications.

Classification

Cryoglobulin composition is heterogeneous. The most commonly used classification was established by Brouet and colleagues in 1974 and describes three distinct subsets of cryoglobulins, based on the clonality and type of immunoglobulins produced (Brouet et al. 1974). An adapted version of this classification is presented in Table 1. Type I cryoglobulins consist of a monoclonal immunoglobulin, usually IgM or IgG. Type I cryoglobulinemia is most often related to B-cell lineage lymphoproliferative disorders, such as Waldenström's macroglobulinemia or myeloma, and is typically associated with hyperviscosity. (Type I cryoglobulinemia is discussed in a separate chapter). The other types of cryoglobulins are

Table 1 Classification and features of cryoglobulins

Cryoglobulinemia type		Components	Predominant clinical features	Commonly associated diseases
Monoclonal	Type I	Monoclonal Ig, most often IgM or IgG	Hyperviscosity Acrocyanosis Raynauds Gangrene Arthralgias rarely	Waldenström's macroglobulinemia Multiple myeloma B-cell lymphoma MGUS
Mixed	Type II	Monoclonal IgM with RF activity against polyclonal IgG	Weakness (>80%) Purpura (>75%) Arthralgias (60–90%) Neuropathy (20–80%) Nephritis (20–50%) Cutaneous ulcers (10–20%) Sicca (5–50%) "Meltzers triad" of purpura, weakness, arthralgias (25–80%)	**Infection** *Hepatitis C* *HIV* *Other viruses* *Endocarditis* *Lyme disease* *Rickettsia* *Syphilis* **Autoimmunity** *Sjögren's syndrome* *SLE* *Rheumatoid arthritis* *Other systemic rheumatologic disease* **Lymphoproliferative disorders** **Idiopathic ("essential")**
	Type III	Polyclonal IgM against polyclonal IgG		
	Type II-III	Both monoclonal and oligoclonal or polyclonal IgM against polyclonal IgG		

MGUS Monoclonal gammopathy of undetermined significance, *RF* Rheumatoid factor, *HIV* Human immunodeficiency virus, *SLE* Systemic lupus erythematosus

all considered "mixed" because they are composed of more than one antibody clone. Type II cryoglobulins are characterized by the presence of both a monoclonal IgM and a polyclonal IgG. The IgM component of type II cryoglobulins has rheumatoid factor (RF) activity (i.e., reactivity of an IgM component to the Fc portion of IgG). Type III cryoglobulins are composed of polyclonal IgM and IgG. Type III is considered by some investigators as a transient state between polyclonal hypergammaglobulinemia and type II cryoglobulinemia (Sene et al. 2004; Ramos-Casals et al. 2012). Some investigators also consider separately an overlap class of "type II–III" cryoglobulins which have a mix of monoclonal and polyclonal or oligoclonal IgM (Tissot et al. 1994).

Despite the biochemical differences, the various mixed cryoglobulins have largely overlapping clinical features and etiologic associations (Table 1). The earlier or transient forms, type III and the II–III overlap, may be more often associated with autoimmune disorders, whereas hepatitis C is more often seen with type II cryoglobulin.

Epidemiology

There is meager data on the prevalence of cryoglobulinemia. An incidence of 1:100,000 persons has been estimated, with a female to male ratio of 3:1 (Ferri 2008). However, detectable levels of cryoglobulins in the sera are found in many patients with chronic infections and/or inflammation (Cicardi et al. 2000; Ramos-Casals et al. 2009; Bonnet et al. 2003; Garcia-Carrasco et al. 2001). Cryoglobulinemia is more common in Southern Europe than in Northern Europe or North America, but the distribution is closely associated with the prevalence of HCV infection.

The prevalence of HCV infection in patients with mixed cryoglobulinemia varies from 30% to almost 100% according to the series, with the highest prevalence in Mediterranean patients (Sansonno and Dammacco 2005). Conversely, the percentage of HCV-infected patients with variable amounts of circulating cryoglobulins has been reported as being between 12% and 56%, again with the highest frequency in Mediterranean patients (Cacoub et al. 2000; Cicardi et al. 2000; Garini et al. 2005; Monti et al. 1995; Ramos-Casals et al. 2012; Dammacco et al. 2016). This condition is typically asymptomatic, and it is estimated that only a minority (5–15%) of HCV-positive patients will have a cryoglobulin-related illness.

Etiology and Pathogenesis

Cryoglobulins can cause various clinical symptoms due to physical obstruction of small vessels by plugs of cryoglobulin (so-called "immune pseudothrombi" or "hyaline thrombi") as well as vascular inflammation from immune complex deposition. The latter scenario is referred to as cryoglobulinemic vasculitis, which affects mostly small vessels.

Type II cryoglobulins are strongly associated with HCV infection and Sjögren's syndrome, along with other chronic viral infections and systemic mixed connective tissue disorders. Immune complex formation, initiated by the binding of polyclonal IgG to the monoclonal IgM with RF activity, very effectively induces activation of the complement system on the vessel walls. An immune activation cascade ensues, leading to vasculitis. Type III cryoglobulinemia is also associated with chronic viral infections and systemic autoimmune disorders, and it shares the pathologic and clinical vasculitic manifestations of type II cryoglobulinemia. In contrast to type II, type III cryoglobulinemia is more likely to be asymptomatic (Damoiseaux 2014). It also appears to be more transient, and patients with type III cryoglobulins often later convert to type II cryoglobulinemia, contributing to the hypothesis that it is an intermediate state in the development of type II cryoglobulinemia (Sene et al. 2004).

By far the most common etiologic association with cryoglobulinemia is systemic infection, and specifically hepatitis C. Among noninfectious cases of mixed cryoglobulinemia experiencing vasculitis and included in a French cohort (CryoVas), 30% were found to have connective tissue disease, 22% had hematologic disease, and 48% were thought to have essential mixed cryoglobulinemia (Terrier et al. 2012).

Infections

Historically, the majority of cases of mixed cryoglobulinemia was of unknown cause and therefore referred to as "essential" mixed cryoglobulinemia. However, with the discovery of hepatitis C virus and widespread availability of antibody and RNA testing, it became clear that most patients with "essential" mixed cryoglobulinemias could be shown to have HCV infection (Roccatello et al. 2007; Trendelenburg and Schifferli 1998). It has been reported that >90% of all cases of mixed cryoglobulinemias have circulating HCV-RNA; however, those studies were in Italian cohorts, and subsequent cryoglobulinemia series have found wide geographical variations in the prevalence of HCV (Agnello et al. 1992; Dammacco and Sansonno 1992; Ferri et al. 1991; Lamprecht et al. 1999; Lauletta et al. 2012; Misiani et al. 1992; Persico et al. 2003).

HCV infection nevertheless remains the most frequent cause of mixed cryoglobulinemia. HCV is predominantly associated with type II cryoglobulinemia. The direct involvement of HCV antigens in immune complex mediated cryoglobulinemic vasculitis has been suggested by the discovery of antibodies to HCV antigens in the serum, anti-HCV antibodies localized by immunohistochemistry to glomerular deposits, and HCV RNA detection in the cryoglobulins of these patients by in situ hybridization (i.e., immune complex deposits also contain viral proteins) (D'Amico and Fornasieri 1995; Sansonno et al. 1997). Liver cells and lymphocytes share the same HCV receptor, CD81, and HCV has the ability to cause infection via this cell

surface protein in liver cells, as well as in lymphocytes and other cells and tissues (Pozzato et al. 2016; Lerat et al. 1996; Zignego et al. 1992). HCV infection likely triggers a collection of immunological pathways responsible for the development of different autoimmune diseases and/or lymphoproliferative disorders. Interactions between HCV and lymphocytes directly modulate B- and T-cell function, resulting in polyclonal activation and expansion of B-cell producing IgM with RF activity. In addition, regulatory T-cells, which have been shown to control autoimmunity, are reduced in patients with HCV-associated mixed cryoglobuliemic vasculitis (Boyer et al. 2004; Saadoun et al. 2011).

The HCV lymphotropism, along with defective immune regulation, possibly account for the expansion of peripheral autoreactive B-cells that leads to some of the extrahepatic manifestations of chronic HCV infection, including cryoglobulinemic vasculitis. In addition, there is evidence suggesting a host genetic susceptibility for mixed cryoglobulinemic vasculitis. A recent genome-wide association study (GWAS) in a large sample of mixed cryoglobulinemic vasculitis patients with HCV identified two significant regions implicating polymorphisms near NOCTH4 and MCH class II genes (Zignego et al. 2014).

Other infections have also been associated with mixed cryoglobulinemia, particularly chronic subacute viral infections including HIV and hepatitis B virus (HBV) infection. In HIV-infected patients, the percentage of patients with cryoglobulinemia is usually <20% but increases to 35–64% in those coinfected with HCV. It is infrequently associated with other infections, such as Epstein-Barr virus, *Mycobacterium tuberculosis*, *Streoptococcus*, *Brucella*, and *Klebsiella* species (Ramos-Casals et al. 2012).

Autoimmune Diseases

Patients with systemic autoimmune diseases can present with complications of mixed cryoglobulinemia. It is most commonly associated with Sjögren's syndrome (Ramos-Casals et al. 2001; Ramos-Casals et al. 2009). The prevalence of cryoglobulinaemia is five times higher in patients with both Sjögren's syndrome and HCV infection compared with those not infected with HCV (Ramos-Casals et al. 2005). Other systemic mixed connective tissue disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are also associated with cryoglobulins. Cryoglobulins are detected in nearly 10% of patients with SLE or RA (Garcia-Carrasco et al. 2001; Perlemuter et al. 2003), although the rate of clinically significant disease appears much lower.

Hematological Disease

While B-cell lymphoproliferative disorders are more commonly associated with type I cryoglobulinemia, a substantial portion of non-infectious mixed cryoglobulinemia can also be associated with hematological disease. In the French CryoVas cohort, 22% of patients with noninfectious mixed cryoglobulinemia had hematological disease: nearly two-thirds had marginal zone lymphoma or low-grade B-cell non-Hodgkin's lymphoma and the remainder various other forms of lymphoma. Some authors consider cryoglobulinemia itself to be a form of smouldering lymphoma, in that it is a condition of proliferating B-cell clones producing pathogenic antibodies. However, it must be noted that HCV is itself a risk factor for the development of low-grade lymphoma, and so viral infection and other systemic diseases must be ruled out even if a primary hematological disease is suspected.

Essential Cryoglobulinemia

The current nomenclature for cryoglobulinemic vasculitis was revised to place focus on the etiologically associated systemic disease. When there is no apparent underlying disease identified, the term "idiopathic" or "essential" is used. Otherwise, the underlying cause can be designated in the diagnosis, e.g., Sjögren's syndrome-associated cryoglobulinemic vasculitis or HCV-

associated cryoglobulinemic vasculitis (Jennette et al. 2013).

Approximately 10% of cases of mixed cryoglobulinemia (with or without cryoglobulinemic vasculitis) are classified as essential, and that percentage rises to up 25% in HCV-negative patients (Trejo et al. 2001; Terrier et al. 2012; Quartuccio et al. 2012). Some investigators have speculated that occult HCV infection and monoclonal gammopathies of unknown significance may account for a substantial percentage of these cases (Ramos-Casals et al. 2012). This is further addressed in the section on diagnosis below.

Clinical Manifestations

Cryoglobulinemic vasculitis, predominantly involving the small vessels, can involve any organ system though it mainly affects the skin, joints, peripheral nerves, and the kidneys. The percentage of patients with circulating cryoglobulins who develop symptoms varies widely, and the classic "Meltzers triad" of purpura, arthralgia, and weakness has been reported to occur with a wide range of prevalence between cohorts, from 27.5% to 80% of cases at disease onset (Monti et al. 1995; Ferri et al. 2004).

Extrarenal Manifestations

Skin is the most frequently involved target organ. The main symptom of this cutaneous vasculitis is palpable purpura, which occurs in >80% of patients in most cohorts, but chronic leg ulcers can also occur. In addition, Raynaud's phenomenon and acrocyanosis may also occur, though these are more common in type I cryoglobulinemia. This may evolve to digital ulcerations. Skin symptoms frequently manifest in extremities exposed to the cold due to cryoglobulin precipitation and obstruction of the small vessels.

Musculoskeletal manifestations, such as arthralgia and myalgia, are also common in patients with mixed cryoglobulinemia. The metacarpophalanges, proximal phalanges, knees, and ankles are more frequently affected. Cold exposure is again noted to exacerbate these lesions.

Neurologic manifestations are variable. They can range from a pure sensory axonopathy to a mononeuritis multiplex. Peripheral neuropathy can often be the presenting symptoms of cryoglobulinemia, with the most frequently described neurologic symptom being paresthesias. This distal sensory or sensory-motor polyneuropathy can lead to very painful asymmetric paresthesias that later can become symmetric. Mononeuritis multiplex occurs less frequently (Ramos-Casals et al. 2012; Cacoub et al. 2000).

Pulmonary symptoms are rare and associated with more severe cases. Respiratory symptoms such as dyspnea, cough, and pleurisy have been observed more frequently in patients with mixed cryoglobulinemia than in patients with type 1 cryoglobulinemia. There have also been reports of associated small airway disease and impaired gas exchange. Pulmonary hemorrhage has also been described in cases with severe vasculitis.

Finally, as described earlier, mixed cryoglobulinemia is a B-cell (lympho)proliferative state with polyclonal activation and autoantibody production, and thus it is considered by some to represent a smouldering lymphoma. The proximal cause of this lymphoproliferation is important to discern, since chronic infections and systemic inflammation itself may cause B-cell hyperactivation and/or hyperproliferation inducing selective expansion of B-cell clones that lead to the production of cryoglobulins. Occasionally, an overtly malignant lymphoma can develop (Saadoun et al. 2006; Pozzato et al. 2016; Ferri et al. 2002). In such cases, it may be difficult to discern whether cryoglobulinemia is a complication of the lymphoma, as opposed to the lymphoma being a complication of cryoglobulinemia.

Renal Manifestations

Among the most morbid manifestation of mixed cryoglobulinemia is renal injury, typically manifested as glomerulonephritis. While this is present in only a minority of patients at

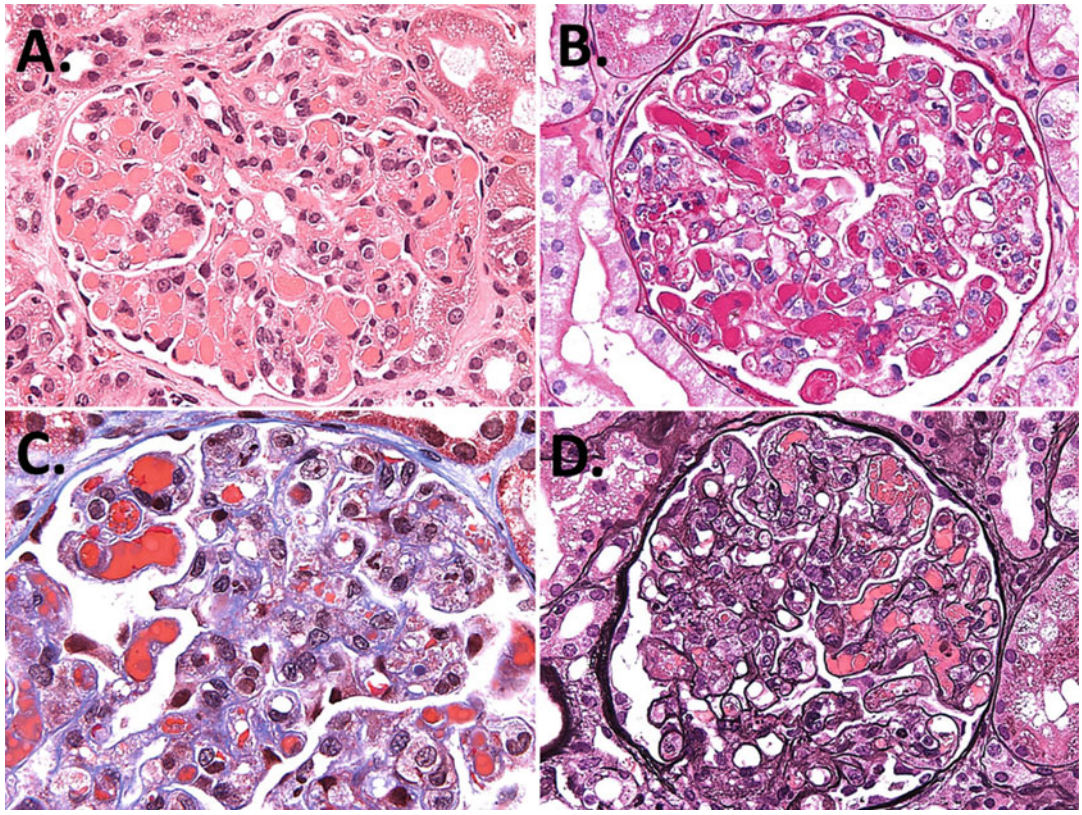

Fig. 1 Light microscopic images of a renal biopsy demonstrating the features of acute cryoglobulinemic nephritis. This glomerulus shows global occlusion of capillary loops by glassy eosinophilic (**a**, hematoxylin & eosin), strongly PAS-positive (**b**, periodic acid–Schiff stain), fuchsinophilic (**c**, trichrome stain) immune material forming "hyaline thrombi" or "immune pseudothrombi." In addition to focal infiltrating monocytes/macrophages, mild mesangial hypercellularity with segmental mesangial cell interposition and duplications of glomerular basement membrane produce a membranoproliferative pattern (best seen in panel (**d**) Jones methenamine silver stain) (magnification ×400) (Images courtesy of Dominick Santoriello, Division of Renal Pathology, Columbia University)

presentation, at least half may develop it over the course of follow-up. In one large series, the most common presenting symptom was subnephrotic proteinuria with microscopic hematuria in 41% of cases, with nephrotic syndrome in 21%. Hypertension was present in around three-quarters of patients at the time of biopsy, and elevated serum creatinine (>1.5 mg%) in one-third. Overall survival was about 80% at 10 years and the rate of renal failure was 11% over an average 5 years of follow-up (Roccatello et al. 2007). Heavy proteinuria and edema can be particularly problematic in this patient population with frequent co-occurring vasculitis of the skin, since patients are at risk of skin breakdown and superinfection.

On renal biopsy, pathology typically shows a membranoproliferative glomerulonephritis (MPGN). This is also a typical finding in hepatitis C-associated kidney disease without detectable cryoglobulins (see ▶ Chap. 28, "Glomerular Diseases Associated with Hepatitis B and C Infection, Adult"). However, cryoglobulins themselves may be visible on biopsy as intraluminal "pseudothrombi" (occasionally called, incorrectly, "hyaline thrombi") that precipitate in the glomerular capillaries (Fig. 1). The deposits may demonstrate a characteristic curvilinear fibrillar substructure by electron microscopy (Fig. 2a). Immunofluorescence typically shows segmental or diffuse capillary loop staining for IgM in particular (Fig. 2b, c), colocalizing with complement deposition.

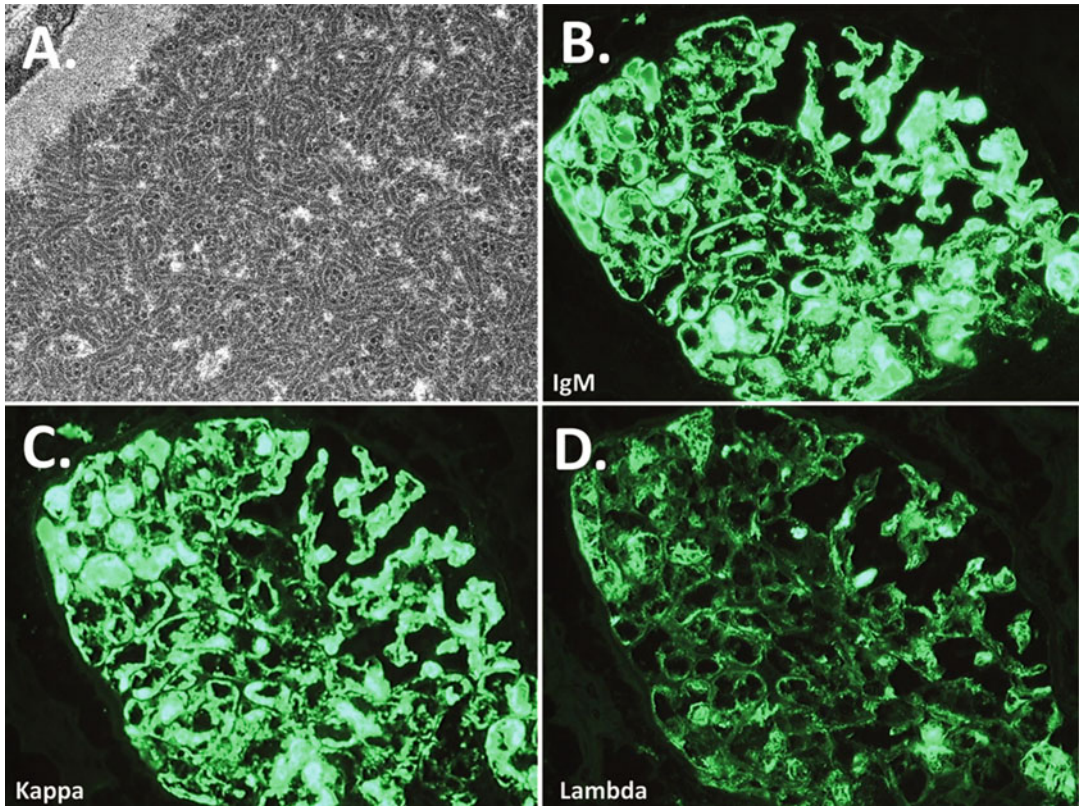

Fig. 2 (**a**) Cryoglobulin deposits show characteristic annular-tubular substructure on ultrastructural examination (transmission electron microscopy; magnification 60,000×). (**b**) Immunofluorescence shows intense staining of capillary walls and intracapillary "hyaline thrombi" for IgM, with (**c**) kappa greater than (**d**) lambda light chain staining in the same distribution (Images courtesy of Dominick Santoriello, Division of Renal Pathology, Columbia University)

Diagnosis

Diagnosing mixed cryoglobulinemic syndromes is based on laboratory evidence of serum cryoglobulins, associated clinical signs and symptoms, and histopathology. Cryoglobulins are quantified either by the cryocrit or with the measured protein concentration. Collecting and handling the sample correctly is crucial. Serum must be drawn in a prewarmed syringe, transported, and prepared (clotted and centrifuged) at 37–40 °C, with serum then stored at 4 °C for up to 7 days. Immunofixation is performed for immunochemical typing of the cryoglobulin. Since low levels of cryoglobulins have been detected in healthy individuals and transient infections can be associated with polyclonal cryoglobulins, expert laboratory interpretation is required. There is a high possibility for false-negative testing of cryoglobulins given the technical difficulties associated with appropriate sample collections, and thus, a negative test does not necessarily exclude cryoglobulinemia. Serial assays are required when suspicion is high. Elevated levels of RF and cryoglobulins, and low levels of complement (particularly C4, and more variably C3 and CH50) are characteristic findings in mixed cryoglobuliaenemia. Decreased levels of serum complement components likely reflect ongoing activation and consumption of complement by cryoglobulin-mediated immune complexes.

Detection of cryoglobulins warrants further evaluation to identify the underlying disease process. HCV testing is crucial. It is important to note that HCV antibodies and HCV RNA may precipitate out of serum within cryoglobulins, leading to false-negative antibody or PCR testing. Thus, precautions must be taken to prevent cryoglobulin precipitation from the sample prior to HCV testing (Van Thiel et al. 1995). With negative HCV testing, further evaluation for other chronic infections (e.g., HIV, HBV) and mixed connective tissue diseases is also recommended, and in the absence of these conditions being diagnosed, evaluation by a hematologist is prudent to evaluate the possibility of an underlying lymphoproliferative disorder.

Prognosis

Prognosis of cryoglobulinemia depends on the underlying associated disease, the degree of organ involvement, and the treatment options available. In a literature review on the mortality of patients with mixed cryoglobulinemia, the 10-year survival rate was <60% (Della Rossa et al. 2008). Renal involvement carries particularly elevated morbidity.

In a retrospective Italian series of 231 mixed cryoglobulinemia patients in which 92% had HCV (seen between 1972 and 2001), at presentation 42% had disease manifestations without vital organ involvement and 20% had renal involvement (Ferri et al. 2004). Over follow-up, an additional 30% developed renal involvement. By the end of follow-up nearly two-thirds had evidence of hepatic disease, and 15% had been diagnosed with malignancy (B-cell lymphoma was most common, less common were hepatocellular carcinoma and thyroid carcinoma). In the same series, cause of death was determined for 79 of 97 deceased participants, with glomerulonephritis with renal failure as the most frequent (33%) complication leading to death.

Poor outcomes in mixed cryoglobulinemic vasculitis are associated with older age, male sex, chronic HCV infection and longer duration of infection, type II mixed cryoglobulinemia, a high cryoglobulin serum level, and clonal B-cell expansions in the blood and liver. The worst prognostic factors are age over 60 years at diagnosis and renal involvement (Bryce et al. 2006; Della Rossa et al. 2008; Ramos-Casals et al. 2006). However, treatment of cryoglobulinemia (and in particular, of the underlying cause) may substantially abrogate the associated morbidity.

Treatment

All patients with symptomatic mixed cryoglobulinemia should have the underlying cause of their cryoglobulinemia identified and treated. In some cases, particularly in the modern era of highly effective hepatitis C therapy, this may be sufficient in producing a remission. In other cases, for example, with chronic rheumatologic disease or smouldering hematologic disease, eliminating the underlying cause may be more challenging. In cases of aggressive disease, particularly causing vital organ damage such as progressive kidney disease, immunosuppression may be required.

Antiviral Therapy

In patients with HCV and mixed cryoglobulinemia causing glomerulonephritis, an attempt at viral eradication is mandatory and considered as first-line therapy according to formally published guidelines including the European League Against Rheumatism (EULAR) and the Kidney Disease Improving Global Outcomes guidelines for the treatment of glomerulonephritis (Pietrogrande et al. 2011; Group 2012).

Historically, antiviral treatment centered on interferon-based regimens was poorly tolerated and only marginally effective, particularly in patients with renal disease. Until recently, pegylated interferon and ribavirin were considered standard treatment, but ribavirin is challenging to use in renal disease because it is renally excreted and accumulation can lead to devastating hemolytic anemia. Sustained virologic response rates in patients with kidney disease were

therefore poor, only 30–40% in hemodialysis patients, and return of viremia was often associated with relapse of cryoglobulinemia (Misiani et al. 1992; Gordon et al. 2008). With the advent of highly effective direct-acting antivirals that do not require coadministration of interferon, prospects for achievement of virologic remission have been dramatically improved. For further discussion on the treatment of HCV in renal disease, see ▶ Chap. 29, "Glomerular Diseases Associated with Hepatitis B and C Infection, Pediatric".

In patients presenting with severe manifestations of cryoglobulinemia, it has traditionally been recommended to delay the attempt at viral eradication for a period of a few months while immediate immunosuppression is given to rapidly reduce the cryoglobulinemia activity. It is unclear whether this rationale will remain applicable in the modern era of direct-acting antivirals against HCV, which can achieve viral remission in a matter of weeks. However, faced with organ-threatening disease, immediate immunosuppression aimed at reducing tissue inflammation and cryoglobulin burden is rational even if antiviral therapy is coadministered.

Immunosuppression

Patients with organ-threatening mixed cryoglobulinemia are typically treated with a combination of corticosteroids to reduce inflammation and another agent to decrease cryoglobulin production. Historically, this was the alkylating agent cyclophosphamide, though recent years have seen a marked increase in the use of rituximab instead. Corticosteroids are broadly effective and provide an acute anti-inflammatory benefit, though relapses are common upon withdrawal. For example, in one large French cohort of non-HCV-associated mixed cryoglobulinemia, corticosteroids as first-line monotherapy were associated with a complete clinical response in 44% of patients and complete renal response in 61% (Terrier et al. 2012).

In order to sustain this response, immunosuppressive agents can be added to the anti-inflammatory effect of corticosteroids. Because of the importance of IgM, which is produced by B-cells, anti-B-cell therapy is a particularly attractive option. Rituximab, a monoclonal antibody against CD20, rapidly depletes B-cells and has been shown to have good efficacy for mixed cryoglobulinemia in small studies including small randomized controlled trials of patients with HCV-associated and non-HCV-associated cryoglobulinemia (De Vita et al. 2012; Sneller et al. 2012). While these studies suffer from small sizes and some methodological limitations, they have generally shown dramatic treatment responses with rituximab. Alkylating agents such as cyclophosphamide have also been used for severe mixed cryoglobulinemia. Importantly, rituximab and cyclophosphamide have not been directly compared in a large prospective study. However, some retrospective data suggest advantages of rituximab. For example, in the same French cohort mentioned above, treatment with rituximab and glucocorticoids was associated with a 3.7-fold greater hazard of achieving complete response compared to corticosteroids alone, whereas cyclophosphamide was comparable to steroids.

Regardless of the therapy chosen, infection rates with immunosuppression for mixed cryoglobulinemia are high. Particular care must be taken with patients who have skin ulcers that can serve as sites for pathogen entry. Additionally, if an underlying infection is present as the cause of cryoglobulinemia, it may be exacerbated by the immunosuppression. While this is usually well-tolerated in the case of hepatitis C, cases of cholestasis and acute fatal hepatic failure have been reported due to accelerated viral replication. In the case of hepatitis B in particular, fulminant hepatic failure is a major risk and rituximab should not be given without suppressive antiviral therapy.

Apheresis

When cryoglobulinemia causes severe vasculitis, rapidly progressive glomerulonephritis, or the hyperviscosity syndrome, immediate removal of cryoglobulins from the circulation is desirable. Because of their relatively large size, apheresis is a very effective modality for acutely reducing the circulating cryoglobulin load. The American

Society for Apheresis in its most recent guidelines considers therapeutic plasma exchange a category II treatment for symptomatic cryoglobulinemia, supported by grade 2A evidence (Schwartz et al. 2016). Category II indicates "Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment." Of interest, in past guidelines it had been considered category I (first-line), but with publications of rapid and effective symptom control with rituximab the indication for apheresis was stepped down. Typical prescriptions will treat 1–1.5 plasma volumes every 2–3 days for 5–7 sessions. This achieves immediate reduction of cryoglobulin burden, allowing time for concomitant therapy such as corticosteroids and immunosuppression to achieve their effect. Technical aspects worth noting are the performance of the procedure in a warm room and using warmed replacement fluids (plasma or albumin), since there have been reports of acute cryoglobulin precipitation in cool extracorporeal circuits. If rituximab is used, timing of apheresis should be adjusted to avoid treatment within the first few days following a rituximab infusion (or alternatively, rituximab should be delayed until after apheresis is completed), lest the drug itself be removed from the circulation.

Summary

The consequences of mixed cryoglobulinemic disease can involve many organ systems, and the kidneys are both particularly suspectible to injury as well as particularly important harbingers of poor outcomes when affected by cryoglobulinemia. The pattern of renal disease is typically the nephritic syndrome with membranoproliferative glomerulonephritis seen on biopsy, but additional acute injury can happen from intravascular cryoglobulin precipitation and vasculitis. Thorough evaluation for the underlying cause of cryoglobulinemia should be undertaken, with particular consideration of HCV, other smoldering viral or bacterial infections, systemic rheumatologic disease with Sjogrens syndrome in particular, and hematologic malignancies. If HCV is present in this situation, it should be treated. It remains to be seen for how many patients the highly active direct-acting antiviral drugs are sufficient in achieving remission of cryoglobulinemia. For now, immunosuppression with steroids and rituximab or alkylating agents should be considered in aggressive or rapidly progressive disease, especially if the underlying cause cannot otherwise be targeted. Apheresis still provides an immediately effective temporizing measure for those most ill.

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Idiopathic Immune Complex Glomerulonephritis

27

Renu Regunathan-Shenk and Pietro A. Canetta

Contents

Abstract

Immune complex glomerulonephritis (GN) is characterized by the presence of immune complexes in the glomerulus, typically detected by immunofluorescence microscopy and containing both immunoglobulin and complement components. These complexes trigger complement activation and inflammatory cell recruitment, leading to glomerular injury. By light microscopy, the histologic pattern is often that of membranoproliferative GN. A variety of diverse conditions have been associated with immune complex GN, including chronic infections, hematologic disease, and autoimmunity. The history of this condition reveals that over the past several decades, an increasing portion of disease originally thought to be "idiopathic" has had its underlying cause identified. Thus true idiopathic

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immune complex GN, in which no identifiable cause is found, is increasingly rare and should be considered a diagnosis of exclusion. The finding of an unexplained immune complex GN should prompt a thorough search for an associated systemic disease, especially hepatitis C infection, hematological malignancy, and collagen vascular diseases such as systemic lupus erythematosus. In the absence of an underlying cause, treatment is based on maintaining glomerular health with blood pressure control and proteinuria reduction, while aggressive cases require immune suppression to decrease immune complex formation and the subsequent inflammatory cascade.

Keywords
Idiopathic · Immune-complex · Glomerulonephritis · MPGN

Introduction

Immune complex-mediated glomerulonephritis (GN) is a relatively rare, but often devastating form of GN. The histologic pattern of disease is typically membranoproliferative (MPGN), consisting of mesangial and endocapillary proliferation. While only 7–10% of renal biopsies for GN in developed countries show an MPGN pattern, it is among the leading causes of end-stage renal disease from primary GN (Sethi and Fervenza 2012). In the developing world, it accounts for a larger proportion of GN biopsies due to a higher rate of bacterial and parasitic infections (McGrogan et al. 2011; Hanko et al. 2009; Woo et al. 2010). It commonly presents in childhood and young adulthood, with a mean age of onset of 8–30 years old (Little et al. 2006).

Pathogenesis

The etiologies of immune complex GN include chronic infections, autoimmune disease, and hematologic disease including the monoclonal gammopathies. These conditions lead to the formation of antigen and antibody complexes which deposit in the glomerular mesangium and endothelium, activating the classical complement pathway. Deposition of complement including the terminal complement membrane attack complex (C5b-9) leads to cell injury and activation of inflammatory pathways, which disrupt the basement membrane and cause endocapillary and mesangial cell proliferation. In chronic cases, this eventually leads to matrix expansion and accumulation of cellular debris that is not ameliorated by repair mechanisms (Fig. 1). It remains

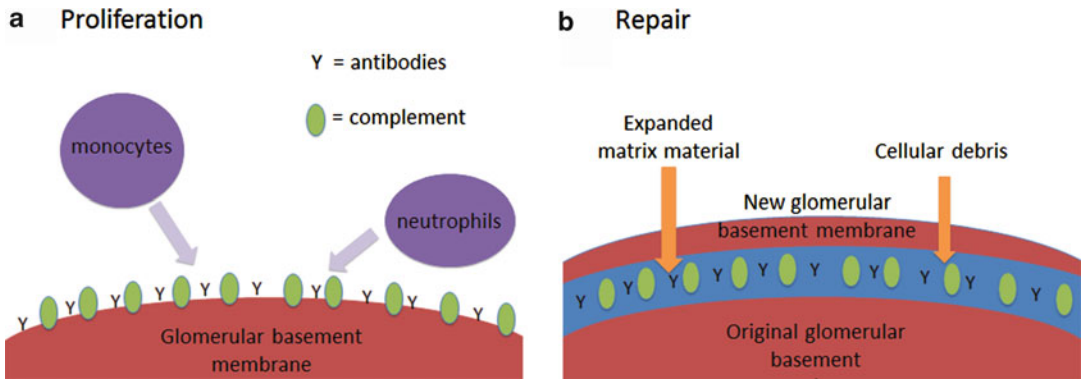

Fig. 1 A simplified model of immune complex glomerulonephritis leading to membranoproliferative pattern of injury. (**a**) In the proliferative phase, antibody/antigen complexes recruit complement, and these immune complexes deposit in the subendothelial or intramembranous portion of the glomerular basement membrane, attracting and activating infiltrating leukocytes. (**b**) During repair driven by activated mesangial cells and leukocytes, the mesangial matrix expands and new glomerular basement membrane is laid down alongside it, leading to the classic double-contour appearance.

unclear whether immune complexes first form in the circulation and then become trapped in glomeruli, or if some part of formation or complement attraction happens in situ, though it is likely both possibilities play a role in different cases. In certain cases of immune complex GN of known cause, specific antigens have been demonstrated within the glomerular deposits (e.g., hepatitis C). In idiopathic immune complex GN, the antigen driving the formation of the immune complexes is unknown by definition.

Intriguingly, some reports have found evidence of alternative complement dysregulation in a significant portion of patients considered to have MPGN type I (i.e., with immunoglobulin deposits on biopsy). This suggests there may be substantial pathogenic overlap of the etiology of truly idiopathic immune complex GN with the C3 glomerulopathies (Servais et al. 2012).

Histopathology

On biopsy, immune complex-mediated GN typically adopts a membranoproliferative (or mesangiocapillary) pattern. Light microscopy reveals endocapillary and mesangial proliferation, leading to a lobular or cauliflower-like appearance. The glomerular basement membrane appears thickened and may show "tram track" double contours due to deposition of immune complexes, cellular debris, and matrix material within the membrane (Fig. 1) (Fogo 2006). In more aggressive cases, a diffuse proliferative pattern may be seen, including extracapillary proliferation and cellular or fibrocellular crescent formation (see ▶ Chaps. 4, "Histopathology of Glomerular Diseases," ▶ 21, "Membranoproliferative Glomerulonephritis, Adult," and ▶ 22, "Membranoproliferative Glomerulonephritis, Type 1, Pediatric").

Idiopathic MPGN was traditionally classified as types I, II, and III based on histologic pattern under electron microscopy as described below:

Type I: mesangial and subendothelial deposits
Type II (aka dense deposit disease, DDD): continuous, linear deposits along the GBM
Type III: subendothelial and subepithelial deposits

It was subsequently recognized that the same electron microscopy patterns could be produced by etiologically and pathophysiologically distinct processes. In particular, it became clear that many cases of both type I and III MPGN, and essentially all of DDD, are caused by dysregulation of the alternative complement pathway and do not involve antibody deposition in the kidney nor immune complex formation. These forms came to be termed "C3 glomerulopathy," because of the prominent C3 deposition in the absence (or near absence) of antibody.

With the recognition that electron microscopy is insufficiently specific in identifying disease etiology, immunofluorescence has become the determining modality for disease classification. Careful attention to the immunofluorescent staining is critical when presented with a purportedly idiopathic immune complex GN, since patterns can point to an identifiable etiology. Staining of both IgG, kappa and lambda light chains, and complement components (C1Q, C3, C4), known as "full house staining," is consistent with autoimmune disease such as lupus nephritis, (see ▶ Chaps. 13, "Lupus Nephritis (Including Antiphospholipid Antibody Syndrome), Adult," and ▶ 14, "Lupus Nephritis (Including Antiphospholipid Antibody Syndrome), Pediatric"). Deposition of C3 alone (or C3-dominant deposition) is consistent with C3 glomerulopathy (see ▶ Chap. 40, "C3 Glomerulopathy"). Deposition of exclusively kappa or lambda light chains, with a single isotype of heavy chain (when isotype staining is available), is diagnostic of proliferative GN with monoclonal immunoglobulin deposition (PGNMID).

Diagnostic Evaluation

Because many serious systemic illnesses can result in immune complex GN, a thorough workup is necessary before settling on the diagnosis of "idiopathic" disease. The diagnostic approach includes an evaluation for infectious etiologies, autoimmune disease, and hematologic disease including paraproteinemia. A careful clinical history is necessary to help guide a focused evaluation, since the initial presentation may be similar regardless of

cause. Two thirds of patients will present with nephrotic syndrome; other common features of presentation include microscopic hematuria (with dysmorphic red blood cells), non-nephrotic range proteinuria, hypocomplementemia, hypertension, and acute kidney injury.

In the developing world, infection is a common cause of immune complex GN. However, even in the developed world, infection should not be underestimated; a previous study showed that 25% of MPGN thought to be idiopathic was HCV related (Johnson et al. 1993). Excluding infection is critical before treating patients with immunosuppression. Common infectious causes of immune complex-mediated GN are listed in Table 1.

Evaluation for autoimmune disease includes a serological evaluation for connective tissue diseases, such as lupus and rheumatoid arthritis, as well as Sjogren's disease (Table 2).

Monoclonal gammopathy, the result of the proliferation of a single lymphocyte or plasma cell clone causing the circulation of a monoclonal paraprotein, is another potential cause of immune complex-mediated GN. A single-center study demonstrated that 41% of patients with MPGN pattern on biopsy without evidence of autoimmune disease or chronic infection had a positive serum and/or urine protein electrophoresis (Sethi et al. 2010). Serum protein electrophoresis with immunofixation, 24-h urine protein electrophoresis with immunofixation, and kappa to lambda free light chain ratio are recommended tests to screen for paraproteinemia.

Finally, C3 glomerulopathy must be carefully excluded prior to the diagnosis of idiopathic immune complex GN. While this should be evident from the absence of immunoglobulin, immunofluorescence staining may be ambiguous, particularly in labs with less experience diagnosing C3 glomerulopathy or if limited sample is available. Testing for C3 nephritic factor or anti-factor H antibodies may be useful both diagnostically and to establish biomarkers to follow the disease course. The role of genetic testing is less clear, in the absence of a suggestive family history. This is particularly true given the studies mentioned earlier finding substantial incidence of alternative complement dysregulation in patients with apparently antibody-mediated immune complex GN.

Table 1 Infections associated with immune complex glomerulonephritis

Viral	Hepatitis C, hepatitis B, parvovirus B19, HIV
Bacterial	Endocarditis, bacterial abscesses, ventriculoatrial shunt infection, meningococcus, *Nocardia*, *Streptococci*, *Brucella*, *Coxiella*, *Mycoplasma*, *Mycobacteria* (including tuberculosis), Lyme disease, syphilis
Parasitic	Malaria, schistosomiasis, *Echinococcus*

Table 2 Serologic workup of idiopathic immune complex glomerulonephritis to evaluate for systemic rheumatologic disease

Disease	Test
Systemic lupus erythematosus	Antinuclear antibody (ANA), anti-double stranded DNA, anti-Smith antibody
Rheumatoid arthritis	Rheumatoid factor (RF), Anti-cyclic citrullinated peptide antibody
Sjogren's disease	Anti-SSA, anti-SSB, ANA, RF
Mixed connective tissue disease	Anti-ribonucleoprotein antibody

Prognosis

The true prognosis of idiopathic immune complex GN can be challenging to discern from the literature because older studies included patients who today would be found to have an identifiable cause and thus no longer considered idiopathic (e.g., hepatitis C). MPGN patients have progressive renal disease with an estimated renal survival of 50% at 10 years from diagnosis. In a single-center study of patients with MPGN followed over an average of 13.8 years, predictors of progression to end-stage renal disease (ESRD) included severity of interstitial fibrosis, crescent formation, and mesangial proliferation on biopsy (Little et al. 2006). In the same study, younger age and presence of crescents on initial biopsy were also associated with higher rate of recurrence after transplant. Recurrent disease will be further discussed later in this chapter.

Treatment

Treatment of immune complex-mediated GN is based on etiology. For nephritis secondary to infection or monoclonal gammopathy, treatment of the underlying disease should be the foundation of management. Because these conditions are discussed in detail in separate chapters, this section will focus on the treatment of idiopathic disease. It is worth emphasizing that older literature almost certainly included many patients considered "idiopathic" at the time, but that today would have an recognized cause for their nephritis, making it difficult to draw firm conclusions on the extent of the benefits of therapy. Additionally, while most studies have focused on immunosuppression, clinicians should base their approach with the usual conservative measures appropriate for all glomerulopathies, including blood pressure control, use of inhibitors of the renin-angiotensin system, and, particularly in adults, management of cardiovascular risk factors such as tobacco use and dyslipidemia. Degree of proteinuria is the most commonly used and best validated biomarker to assess for disease activity and adjust intensity of treatment, when considered along with the trend of glomerular filtration rate (GFR).

Glucocorticoids

Studies in pediatric populations have suggested a benefit to using an alternate-day glucocorticoid regimen for idiopathic immune complex GN. In a randomized, double-blind, placebo-controlled trial of 80 children with idiopathic MPGN with heavy proteinuria and preserved GFR (>70 mL/min/1.73m^2), every other day prednisone use over a mean duration of 41 months helped preserve renal function. The study included 42 patients with MPGN type I, 14 with MPGN type II, 17 with MPGN type III, and 7 with non-typeable disease. Using life table analysis, the estimated renal survival, or preservation of renal function, was 61% among subjects receiving steroids versus 12% in the placebo group (Tarshish et al. 1992). Other uncontrolled trials have demonstrated similar benefits in children; however, in adults these results have not been replicated (Bergstein and Andreoli 1995; Chapman et al. 1980; Emre et al. 1995). There are no randomized trials of corticosteroid therapy for idiopathic MPGN in adult patients and retrospective studies have not shown an unequivocally clear benefit.

Mycophenolate

Mycophenolate-based pharmacologics such as mycophenolate mofetil (MMF) are another option for the treatment of immune complex-mediated GN. MMF is a prodrug of mycophenolic acid, an inhibitor of guanosine nucleotide synthesis, an important step in B and T cell proliferation. Small cases series have demonstrated its efficacy in treating MPGN pattern lesions. For example, a series comparing five patients treated with MMF (uptitrated to a maximum dose of 2 g daily) and prednisone (tapered off over 1 year) with six patients not treated with immunosuppression showed promising results (Jones et al. 2004). At 6 months, proteinuria had significantly declined in the treatment group (from a mean of 5.09 to 1.97 g) and serum creatinine concentration had stabilized. These effects were sustained over 18 months of follow-up. It is difficult to differentiate the relative contribution of prednisone and MMF to the improved outcomes.

MMF has also been effective in patients thought to be resistant to steroids and other immunosuppression. In a case series of 13 patients with MPGN who remained nephrotic after at least 8 weeks of steroid treatment, addition of MMF (at 1.5 g per day) improved proteinuria and improved renal function over 1 year of follow-up (Yuan et al. 2010). In a study of 98 patients with various forms of primary GN resistant to other forms of immunosuppression (including 15 patients with MPGN), 54% of patients treated with MMF (average dose 2 g daily) over 1 year achieved a complete or partial remission of proteinuria. Notably, serum albumin, blood pressure, and low-density lipoprotein (LDL) improved, and GFR remained stable over the follow-up period (Segarra et al. 2007).

Alkylating Agents

Alkylating agents, such as cyclophosphamide, have also been investigated in idiopathic immune complex GN but have shown an ambiguous benefit. An observational study of 19 patients with MPGN treated with pulse IV steroids and then oral steroids and oral cyclophosphamide (withdrawn slowly over an average of 10 months) demonstrated remission in 15 patients, improvement in 3 patients, and progression of disease in 1 patient. Of those with positive results, six patients relapsed off therapy; three out of four patients who underwent repeat cycles of steroids and cyclophosphamide went back into remission (Faedda et al. 1994). In a prospective, randomized control trial of 59 patients with MPGN (type I or II) with a creatinine clearance of less than 80 mL/min/1.73 m^2 and/or proteinuria greater than 2 g/day, 27 patients were randomized to cyclophosphamide (1.5–2 mg/kg), warfarin (titrated to goal prothrombin time 2–2.5 times control), and dipyridamole (100 mg four times daily) for 18 months. The 32 control patients received no specific therapy. At 2 years, actuarial survival was not statistically significantly different between the treatment and control groups for either disease (Cattran et al. 1985). The benefit of cyclophosphamide may have been underestimated because of the short follow-up period and small sample size. Many clinical experts recommend intravenous cyclophosphamide therapy for MPGN with rapidly progressive GN or crescent formation based on literature from other crescentic diseases, such as ANCA vasculitis.

Other Treatment Options

Several studies have evaluated the efficacy of other immunosuppressants and antiplatelet agents for idiopathic immune complex GN. Many of them were performed before routine screening for hepatitis C as well as enhanced understanding of the role of complement in disease pathogenesis; thus results should be interpreted with caution.

In the 1980s and 1990s, a few studies investigated the role of antiplatelet and anticoagulant therapy for idiopathic MPGN type I. It was thought that platelets played a role in the disease pathogenesis as platelet consumption is increased and platelet activation contributes to complement-mediated glomerular damage. One randomized, double-blind placebo-controlled study examined 40 patients with type I MPGN treated for 12 months with daily high-dose aspirin (975 mg) and dipyridamole (225 mg) versus placebo. Patients were followed for up to 7 years; the rate of GFR decline appeared dramatically reduced in the treatment group (1.3 versus 19 mL/min per $1.73m^2$), and fewer patients progressed to ESRD over the first 5 years of follow-up (Donadio et al. 1984). The investigators later reexamined the data and determined that there was no difference between the treatment and placebo group after 10 years (Donadio and Offord 1989). Another prospective controlled study evaluating 18 patients with idiopathic MPGN types I and II and nephrotic syndrome treated with aspirin (500 mg) and dipyridamole (75 mg) daily demonstrated an improvement in proteinuria but no difference in serum creatinine after 3 years of treatment (Zauner et al. 1994). An uncontrolled Turkish study of 14 patients with MPGN type I treated with daily aspirin (1000 mg) and dipyridamole (300 mg) also showed an improvement in proteinuria and serum albumin but no significant improvement in eGFR or creatinine over 24 months (Harmankaya et al. 2001). While initial small perspective trials showed possible benefit from the use of anticoagulants, larger trials have not proven that the use of anticoagulants added to immunosuppressive or antiplatelet therapy improves outcomes in MPGN (Zimmerman et al. 1983; Cattran et al. 1985). Treatment for immune complex GN with antiplatelet or anticoagulant therapy is no longer recommended.

Rituximab is a monoclonal antibody to the CD20 receptor present on B cells. It has shown promise in treating several glomerular diseases including monoclonal gammopathies of renal significance, cryoglobulinemic vasculitis, and fibrillary GN. Several case reports have reported success in treating proliferative GN related to monoclonal gammopathy and leukemia with

rituximab (Vilayur et al. 2009; Guiard et al. 2011; Bhat et al. 2007). The use of rituximab for idiopathic immune complex-mediated GN is less established. A small, prospective, open-label trial of six patients with type I MPGN (four with idiopathic disease, two with cryoglobulinemia) showed promising results. Patients received two 1 g doses of rituximab (given 2 weeks apart) and were followed over 12 months. At 1 year, proteinuria had improved; however, creatinine clearance did not change significantly (Dillon et al. 2012). Eculizumab, a monoclonal antibody that acts as a terminal complement inhibitor, is increasingly being used to treat complement-mediated glomerulopathy as well as atypical hemolytic uremic syndrome. Any potential role in idiopathic immune complex GN remains undefined.

Calcineurin inhibitors (CNI), such as tacrolimus and cyclosporine, inhibit the transcription factors involved in the activation of cytokine genes such as interleukin (IL)-2, IL-3, IL-4, tumor necrosis factor alpha (TNF-alpha), interferon gamma, and granulocyte colony-stimulating factor. They also cause vasoconstriction of the glomerulus and have been shown to reduce proteinuria in glomerular diseases such as focal segmental glomerulosclerosis (FSGS). In a small study of 18 patients with MPGN and nephrotic range proteinuria who previously failed steroid and antiplatelet therapy, 94% of patients achieved partial remission (50% reduction of proteinuria) or complete remission (less than 200 mg/day with stable renal function) using a combination of cyclosporine and low-dose corticosteroids; 12/17 responders achieved partial (not complete) remission (Bagheri et al. 2008). The patients were treated at a starting dose of cyclosporine 4–5 mg/kg/day (in divided doses), prednisone 0.15 mg/kg/day (maximum 15 mg), and an ACE inhibitor. They were monitored over 12 months, and cyclosporine was gradually titrated off if patients achieved complete remission of proteinuria. One patient relapsed once off the cyclosporine. In a case report of two pediatric patients with MPGN previously treated with steroids (with suboptimal results), tacrolimus treatment also induced complete remission of proteinuria (<0.2 G/day) (Haddad et al. 2007).

Recurrence after Transplant

Patients with idiopathic immune complex GN may progress to ESRD and transplant. Unfortunately, several observational studies have shown a high rate of disease recurrence post-transplant (27–65%) with variable rates of allograft loss (Ponticelli and Glassock 2010). For example, in data from a large Australian registry, rates of allograft loss due to recurrent GN were highest for MPGN type I, with 14.4% 10-year allograft loss due to recurrent disease (Briganti et al. 2002). This may overestimate recurrent disease as the MPGN type I lesion closely resembles the microscopic appearance of transplant-related glomerulopathy.

Single-center studies from large transplant centers have described the timeline to recurrence, factors that may influence it, and attempted treatments. For example, a study from Johns Hopkins Medical Center showed that in a cohort of 34 patients with MPGN (89% with immune complex GN, 11% with complement-mediated disease) who underwent renal transplant, 18 patients (45%) had evidence of recurrent MPGN on allograft biopsy (mostly non-protocol biopsies) over 5.3 years of follow-up (Alasfar et al. 2016). Median time to recurrence was 8 months (range 1–108 months). 16 of these patients had immune complex-mediated GN and 7 of them lost their allograft due to recurrent disease. Factors associated with graft loss included having a preemptive transplant, having a living-related donor transplant, having low serum complement prior to transplantation, and having evidence of monoclonal gammopathy (either before or after transplantation). The high rate of graft loss happened in the face of aggressive treatment; 14 patients with recurrent disease were treated with augmentation of immunosuppressive therapy including steroids, rituximab, plasma exchange, a combination of rituximab and plasma exchange, eculizumab (in a patient with complement-mediated GN), and bortezomib (in a patient with multiple myeloma). In this study, historical subtype (type I, II, III MPGN), gender, age, number of transplants, degree of mismatch, race, delayed

graft function, development of rejection, and duration of dialysis pre-transplant did not affect the risk of recurrence.

A study from the Mayo Clinic of 29 patients with MPGN (excluding dense deposit disease, cryoglobulinemia, and fibrillary GN) who underwent renal transplant from 1996–2006 demonstrated recurrence in 12 patients; 22 of the 29 patients had idiopathic disease and 21/29 received dialysis prior to transplant (Lorenz et al. 2010). Of note, 4/29 patients had hepatitis B or C, none of whom had recurrence after transplant. Factors associated with recurrence were living donor source of allograft, low serum complement, and presence of a monoclonal protein (although these factors did not achieve statistical significance). In total, 5 of 29 total grafts were lost (17% death censored), and the proportion of grafts lost due to recurrence was not significantly different from the grafts lost due to other reasons.

Evaluation of patients for transplantation should include careful counseling regarding the risk of disease recurrence, evaluation for paraproteinemia and hypocomplementemia, and cautious planning of post-transplant immunosuppression.

Summary

Idiopathic immune complex GN is an uncommon form of GN which typically adopts a membranoproliferative pattern on renal biopsy. It is a diagnosis of exclusion, made after ruling out chronic infection, autoimmune disease, dysproteinemia, and alternative complement-mediated glomerulopathy. Idiopathic membranoproliferative GN causes progressive renal failure in approximately 50% of patients leading to dialysis and transplant. Several immunosuppression regimens have been investigated for this disease; weak evidence supports the use of steroids and MMF or cyclophosphamide, and consideration of a CNI for nephrotic syndrome related to the disease, although studies of modern populations and novel agents are urgently needed. Patients who undergo renal transplantation are at high risk of recurrent disease and graft loss.

Cross-References

- ▶ C3 Glomerulopathy
- ▶ Glomerular Diseases Associated with Hepatitis B and C Infection, Adult
- ▶ Glomerular Diseases Associated with Hepatitis B and C Infection, Pediatric
- ▶ Glomerulonephritis Secondary to Non-streptococcal Infections
- ▶ Hemolytic Uremic Syndrome, Genetic
- ▶ Histopathology of Glomerular Diseases
- ▶ Infection-Associated Glomerulonephritis
- ▶ Lupus Nephritis (Including Anti phospholipid Antibody Syndrome), Adult
- ▶ Lupus Nephritis (Including Anti phospholipid Antibody Syndrome), Pediatric
- ▶ Membranoproliferative Glomerulonephritis, Adult
- ▶ Membranoproliferative Glomerulonephritis, Type 1, Pediatric
- ▶ Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

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Glomerular Diseases Associated with Hepatitis B and C Infection, Adult

28

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Abstract

Glomerular disease remains an uncommon complication of hepatitis B and C virus infections. A large spectrum of glomerular diseases associated with HBV and HCV has been noted in both native and transplanted kidneys and among adult or pediatric subjects. The most frequent HCV-associated glomerulopathy is type I membranoproliferative glomerulonephritis that is usually, but not invariably, in the context of type II mixed cryoglobulinemia. HCV infection is also the major cause of mixed cryoglobulinemia, a systemic vasculitis characterized by involvement of small- and, less frequently, medium-sized vessels. HCV-associated membranoproliferative glomerulonephritis may present with proteinuria, microscopic hematuria, and nephritic and/or nephrotic syndrome. Membranous nephropathy is the most common glomerular disease associated with HBV infection and usually gives proteinuria and microscopic hematuria. The treatment of the glomerular diseases associated with HBV and HCV infection includes now conventional (corticosteroids, cyclophosphamide, plasma exchange) or modern (mycophenolate mofetil and rituximab) immunosuppressive agents and antiviral (tenofovir or entecavir and direct-acting antivirals) regimens.

Keywords

Hepatitis B · Hepatitis C · Glomerular diseases · Cryoglobulinemic vasculitis

Introduction

It has been calculated that around 170 million individuals are infected worldwide with hepatitis C virus infection. In addition, approximately one third of the world's population shows serological evidence of past or current infection with hepatitis B virus, and 350 million people are chronic carriers of HBsAg all over the world (Babanejad et al. 2016). Thus, HBV and HCV are two of the most common human pathogens worldwide. The clinical manifestations of HBV and HCV range from acute or fulminant hepatitis to various forms of chronic infection, including chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma.

Infection with HBV and HCV can result in a variety of extrahepatic manifestations including dermatitis, arthralgias and arthritis, vasculitis, glomerulonephritis, neuropathy, and pulmonary disease. Renal involvement is an important extrahepatic complication of infection with HBV or HCV. The mechanisms of these extrahepatic manifestations are thought to be linked to immune complex disease, but their pathogenesis is poorly understood.

HCV-Associated Glomerular Disease: Epidemiology and Clinical Manifestations

Although HCV has been identified as an important cause of tubulointerstitial injury in a large case-control study (Kasuno et al. 2003), HCV-associated glomerular disease remains the most frequent kidney disease associated with HCV.

The incidence of HCV-associated glomerular disease is probably low even if the available information on this topic is limited. The largest survey (El Serag et al. 2002) was conducted at a hospital-based case-control study among US male veterans hospitalized during 1992–1999 which identified 34,204 patients infected with HCV (cases) and 136,816 randomly selected patients without HCV (controls). A greater fraction of HCV-infected patients had porphyria cutanea tarda (0.77% vs. 0.06%, $P < 0.0001$), vitiligo (0.17% vs. 0.10%, $P = 0.0002$), lichen planus (0.30% vs. 0.13%, $P < 0.0001$), and cryoglobulinemia (0.57% vs. 0.05%, $P < 0.0001$). A higher rate of membranoproliferative glomerulonephritis (0.36 vs. 0.05%, $P < 0.0001$) but not membranous nephropathy (0.33 vs. 0.19%, $P = 0.86$) was found among patients with HCV. According to a prospective Norwegian study ($n = 864$ patients with community-acquired HCV infection, followed for a median of 7 years), the rate of chronic kidney disease stage V due to membranoproliferative glomerulonephritis was 0.2% (2/864) (Kristiansen et al. 2010). Based on these data, current Kidney Disease Improving Global Outcomes (KDIGO) HCV guidelines recommend serologic testing for anti-HCV antibody in all patients with evidence of glomerulonephritis (Kidney Disease: Improving Global Outcomes 2008). The principal clinical manifestations of glomerular disease in HCV-infected patients are proteinuria and microscopic hematuria with or without reduction in glomerular filtration rate. Why only a minority of patients with HCV infection develop kidney lesions has not been understood. Screening for urinary abnormalities and alterations of kidney function in all HCV-positive patients is strongly recommended, particularly in those with cryoglobulinemia (Kidney Disease: Improving Global Outcomes 2008).

The development of kidney disease among patients with mixed cryoglobulinemia has particular importance as glomerulonephritis is associated with a poor prognosis (Tarantino et al. 1995). Clinically, HCV-associated mixed cryoglobulinemia is characterized by the triad of purpura, arthralgia, and weakness. Kidney involvement in mixed cryoglobulinemia occurs in 8–58% of patients, and in a minority of cases, kidney disease can be the first manifestation of MC. Patients with HCV-related cryoglobulinemic glomerulonephritis can present with nephritic syndrome, asymptomatic non-nephrotic proteinuria, or hematuria and/or reduced GFR. Acute nephritic and nephrotic syndrome can be presenting feature in 25% and 20% of the patients, respectively (Tarantino et al. 1995). Arterial hypertension is common and is frequently resistant to antihypertensive drugs; the severity of hypertension mirrors the severity of kidney disease. The clinical course of HCV-related cryoglobulinemic glomerulonephritis is variable: some patients have an indolent course, whereas others develop progressive renal failure. In around 10% of patients, acute oliguric kidney failure is the first indicator of kidney disease (Tarantino et al. 1995).

Laboratory parameters often reveal the presence of circulating cryoglobulins – these are most commonly type II cryoglobulins composed of monoclonal IgM*k* (the rheumatoid factor) and polyclonal IgG. Serum anti-HCV antibodies and HCV RNA are detected in both the serum and the cryoprecipitate. Positive rheumatoid factor is usually present in serum, whereas C_3 and C_4 levels are commonly depressed. Some patients exhibit normal aspartate aminotransferase/alanine transaminase values or only a mild elevation of liver enzymes.

In addition to non-Hodgkin's lymphoma, mixed cryoglobulinemia is a B-cell lymphoproliferative disorder instigated by HCV infection. Mixed cryoglobulinemia is characterized by chronic stimulation of B lymphocytes by HCV and clonal expansion of rheumatoid factor-expressing B cells in the liver, lymph nodes, and peripheral blood, resulting in the presence of cryoglobulins in the blood. Cryoglobulins, cold-insoluble immune complexes containing rheumatoid factor, polyclonal IgG, and HCV RNA, bind to receptors on endothelial cells, allowing for subsequent deposition and inflammation. Few organs are left unaffected by immune complex

deposition, with vasculitis occurring in the skin, joints, kidneys, lungs, heart, digestive tract, and peripheral nerves (Charles and Dustin 2009).

HCV-Associated Glomerular Disease: Histology

The KDIGO HCV Study Group recommends a kidney biopsy to determine the histological pattern of glomerular damage among HCV-infected individuals with evidence of glomerulonephritis (hematuria, proteinuria, and reduced glomerular filtration rate) (Kidney Disease: Improving Global Outcomes 2008). The most frequent type of HCV-associated glomerular disease is type I (immune complex-mediated) membranoproliferative glomerulonephritis, usually in individuals with type II mixed cryoglobulinemia (D'Amico 1998). Distinctive features of cryoglobulinemic glomerulonephritis, particularly in individuals with rapidly progressive deterioration of renal function, include intra-glomerular deposits, commonly observed in a subendothelial location, which might fill the capillary lumen (intraluminal thrombi). The glomerular basement membrane shows double contours, which are caused by the interposition of monocytes between the basement membrane and the endothelium. Immunofluorescence microscopy reveals granular deposition of the pathogenic immune complexes, in particular IgMk and polyclonal IgG, in addition to complement deposition. On electronic microscopy, large subendothelial deposits occur. Vasculitis of small renal arteries is present in 30% of cases. Histological findings of exudative or lobular membranoproliferative glomerulonephritis are associated with the presence of nephrotic and/or nephritic syndromes, whereas mesangial proliferation is prevalent in patients with intact kidney function and proteinuria and/or microscopic hematuria.

Some investigators have reported cases of membranoproliferative glomerulonephritis without cryoglobulinemia. In these patients, the clinical picture, histological features, and laboratory data are indistinguishable from idiopathic type I membranoproliferative GN. Membranous nephropathy is also observed among patients with HCV infection. The clinical presentation, outcome, and histopathology are similar to those observed in idiopathic MGN. Other glomerular diseases that have been occasionally reported in patients with HCV infection include IgA nephropathy, thrombotic microangiopathy, focal segmental glomerulosclerosis, fibrillary GN, and immunotactoid glomerulopathy (Fabrizi et al. 2013).

Treatment of HCV-Associated Glomerular Disease

The discovery of HCV and a better understanding of the mechanisms of disease has provided the possibility to control HCV-associated GN by the use of targeted approaches: (1) antiviral therapy, motivated by the hypothesis that the underlying infection induces the formation of immune complexes and the ensuing vasculitis, (2) B-cell depletion therapy by targeting B cells that produce cryoglobulins; and (3) nonspecific immunosuppressive therapy targeting inflammation at glomerular level.

Antiviral Treatment of HCV-Associated Glomerular Disease: Historical Perspective

Johnson et al. (1994) were the first investigators to use antiviral therapy for HCV-associated glomerular disease: monotherapy with interferon alpha (3 million units three times weekly for 6–12 months) in 14 patients, mainly with cryoglobulinemic glomerulonephritis, who achieved consistent reduction in proteinuria but no improvement in renal function. The clinical response was linked with disappearance of circulating HCV RNA during treatment. However, relapse of HCV viremia and renal disease was common after cessation of treatment. Unfortunately, no information was available on sustained virologic response (HCV RNA clearance from serum during antiviral therapy which persists at least 6 months after completing treatment) which is now the goal of antiviral therapy of HCV.

Misiani et al. (1994) in a prospective, randomized controlled trial enrolled 53 patients with HCV-associated type II cryoglobulinemia. About three-quarters of the patients had renal involvement, manifested by microscopic hematuria, proteinuria, hypertension, or mild-to-moderate renal failure with serum creatinine levels up to 3.5 mg/dL. A total of 27 patients received recombinant interferon alpha 2a (3 million units three times weekly for almost 24 weeks). In the 15 patients with undetectable serum HCV RNA after the treatment period, a greater improvement in serum creatinine was observed in comparison with the control group ($P < 0.006$).

Antiviral Treatment of HCV-Associated Glomerular Disease: IFN-Based Regimens

After these initial reports, good evidence has been shown for the benefit of antiviral therapy for patients with HCV-associated mixed cryoglobulinemia (only a minority with kidney disease) (Saadoun et al. 2006). Another piece of evidence supporting using antiviral therapy of HCV-associated glomerular disease has been provided by a meta-analysis of controlled clinical trials comparing antiviral versus immunosuppressive regimens for HCV-induced glomerular disease. Six studies ($n = 145$ patients) were retrieved, with most having cryoglobulinemic glomerulonephritis. Pooling of study results demonstrated that proteinuria decreased more commonly after interferon than corticosteroid therapy but no significant difference was noted (odds ratio [OR] = 1.92; 95% CI, 0.39; 9.57, NS). For studies that used the standard IFN dose, IFN was associated with a statistically significant increase in the proportion of patients with a decrease in proteinuria posttreatment compared with immunosuppressive therapy (OR 3.86, 95% CI: 1.44, 10.33, $P = 0.007$). Of note, in all patients with proteinuria reduction, an HCV RNA clearance was recorded at the end of antiviral therapy (Fabrizi et al. 2007a).

The evidence on antiviral treatment of HCV-related glomerular disease consists mostly on IFN-based regimens with several anecdotal reports (Fabrizi et al. 2015b) and small-sized observational studies (Mazzaro et al. 2000; Bruchfeld et al. 2003) rather than large randomized studies undertaken. The low frequency of HCV-induced glomerular disease clearly precludes the implementation of large clinical trials.

Initial reports adopted monotherapy with conventional IFN, but the combined regimens (pegylated IFN plus ribavirin) subsequently superseded monotherapy. The available information shows positive results in terms of proteinuria, hematuria, and improvements of serum creatinine. These changes are usually associated with the disappearance of HCV RNA from serum and a decrease in circulating cryoglobulins. According to an extensive search on the antiviral treatment of HCV-associated glomerular disease in adults with native kidneys (reports in English language), a total of 36 anecdotal reports ($n = 47$ patients) were retrieved (Fabrizi et al. 2015b). A large variety of histological lesions was noted. The majority of these patients had improvement of renal parameters after clearance of HCV RNA, and this confirms the role of the virus in the pathogenesis of the kidney disease. One report emphasized the spontaneous remission of glomerular lesions, which cannot be excluded in a few cases (Dussol et al. 2001). Additional, albeit limited, information on antiviral treatment of HCV-related glomerular disease in renal (Cruzado et al. 1996), liver (Davis et al. 1995; Donato et al. 2013a, 2013b), and liver/renal transplanted population (Montalbano et al. 2007) and among pediatric individuals exists.

Interferon-based therapy of HCV-related glomerular disease has numerous limitations. The HCV eradication is not universal; second, response to antiviral therapy may take weeks or months, but rapidly progressing kidney disease may occur, and kidney failure can develop before viral clearance can be attained. Third, the impact of antiviral therapy on long-term outcomes of kidney disease remains uncertain. Fourth, the clinical benefit in patients who obtained SVR may be transient and/or a dissociation between the antiviral and renal responses can occur. IFN alpha may exacerbate proteinuria in some patients

with underlying glomerulopathies (Fabrizi et al. 2014), and ribavirin use is fraught with the risk of worsening anemia in chronic kidney disease patients. Low-dose ribavirin is recommended in patients with a creatinine clearance of <50 mL/min/1.73 m^2. Among patients with CKD stage 5, 200 mg/daily or 200–400 mg x3/week is recommended (Kidney Disease: Improving Global Outcomes 2008).

Antiviral Treatment of HCV-Associated Glomerular Disease: DAAs

Limited data exist on the benefits and risks of direct-acting antivirals (DAAs) for the treatment of HCV-related glomerular disease. The first DAAs were first-wave protease inhibitors (telaprevir or boceprevir); triple antiviral therapy (pegylated interferon, ribavirin, and telaprevir or boceprevir) has been licensed since 2001. Triple antiviral therapy is fraught with several side effects as various adverse events were found in addition to those associated with pegylated interferon and ribavirin. Thus, first-wave protease inhibitors are currently no longer recommended (Table 1). Nine patients with symptomatic mixed cryoglobulinemic disease (seven with membranoproliferative glomerulonephritis) and HCV genotype 1 underwent triple antiviral therapy [pegylated interferon, ribavirin, and boceprevir ($n = 2$) or telaprevir ($n = 5$) or sofosbuvir ($n = 2$)] (Humphries et al. 2014; Cornella et al. 2015). All patients reached sustained viral response (HCV RNA clearance from serum during antiviral therapy which persists at least 3 months after completing treatment), but serum cryoglobulinemia persisted in two patients; also, the benefits on renal parameters were partial. Membranoproliferative glomerulonephritis remitted in two patients after treatment with corticosteroids or corticosteroids plus rituximab.

In addition, scarce information on the use of interferon-free DAA regimens is available – seven patients with symptomatic mixed cryoglobulinemia and renal involvement underwent sofosbuvir-based regimens (sofosbuvir plus simeprevir or sofosbuvir plus ribavirin) (Sise et al. 2016). SVR12 was reached in most patients (6/7); all patients had an improvement in eGFR and a reduction in proteinuria, particularly in those whose onset of proteinuria was recent. Also, all patients had undetectable HCV RNA by week 4 and remained undetectable while on treatment.

In another series ($n = 10$) of patients with HCV-associated symptomatic mixed cryoglobulinemia, HCV RNA clearance was obtained at week 8 with the 3D regimen ($n = 5$), with or without ribavirin, or with sofosbuvir plus ribavirin ($n = 4$) or sofosbuvir plus daclatasvir ($n = 1$). Renal involvement was 40% at baseline and at week 8 despite viral clearance in all patients. Unfortunately, no further details on kidney involvement were recorded (Gragnani et al. 2016).

Treatment of HCV-Associated Glomerular Disease: Rituximab

Recent information has been accumulated on the use of rituximab for HCV-associated glomerular disease instead of standard immunosuppressive

Table 1 The four classes of direct-acting antiviral agents for the treatment of hepatitis C virus

Classes of direct-acting antiviral agents	Agents	Mechanism of action
NS3/NS4A protease inhibitors (PIs)	Asunaprevir, grazoprevir, paritaprevir, simeprevir	Inhibits protease which enables HCV to survive and replicate in host cells
Nucleoside and nucleotide NS5B polymerase inhibitors	Sofosbuvir	Bind to HCV RNA and inhibit viral replication
NS5A inhibitors	Elbasvir, daclatasvir, ledipasvir, ombitasvir, velpatasvir	NS5A is necessary for replication and for various infection stages of HCV
Non-nucleoside NS5B polymerase inhibitors	Beclabuvir, dasabuvir	Inhibit HCV replication

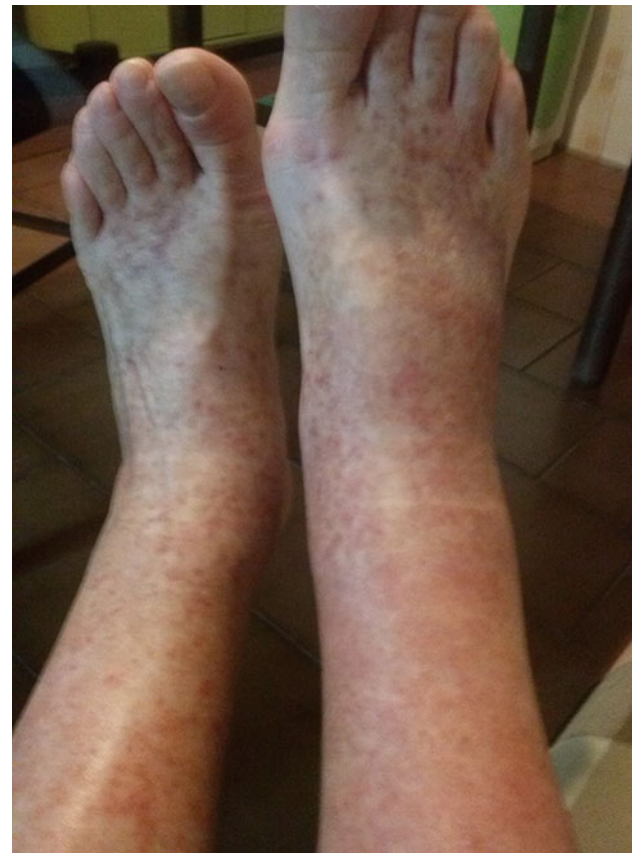

Fig. 1 Palpable purpura in a patient with HCV-induced mixed cryoglobulinemia and glomerulonephritis

therapy. Rituximab is a human-mouse chimeric monoclonal antibody that binds to the B-cell surface antigen CD20, a transmembrane protein expressed only in the B lymphocyte lineage. CD20 appears in the late pre-B stage of development and is lost during terminal differentiation in plasma cells. Rituximab rapidly depletes circulating and tissue B cells. It interferes with synthesis of cryoglobulins, monoclonal IgM, and renal deposition of immune complexes. HCV-driven B-cell lymphoproliferative disorders likely comprise a spectrum of disease, varying from asymptomatic clonal B-cell expansions to pathogenic cryoglobulinemia and lymphoma. Mixed cryoglobulinemia is characterized by the clonal expansion of rheumatoid factor-expressing B cells although it remains unclear how B cells become dysregulated during the course of chronic HCV infection. In a prospective, single-center open study, Roccatello et al. (2016) evaluated the long-term effects of rituximab to 31 patients with severe mixed cryoglobulinemia. The patients presented clinical manifestations which are typical of symptomatic mixed cryoglobulinemia (Fig. 1). They showed membranoproliferative glomerulonephritis ($n = 16$), peripheral neuropathy ($n = 26$), and large skin ulcers ($n = 7$). Rituximab was administered at a dose of 375 mg/m^2, according to a "4 + 2" protocol (days 1, 8, 15, and 22 plus 1 dose 1 and 2 months later). No other immunosuppressive drugs were added. Response was evaluated over a very long-term follow-up (mean 72.47 months, range 30–148). Cryoglobulinemic nephropathy significantly improved during follow-up, starting from the second month after rituximab (serum creatinine from 2.1 ± 1.7 to 1.5 ± 1.6 mg/dL, $P < 0.05$; 24-h proteinuria from 2.3 ± 2.1 to 0.9 ± 1.9 g/24 h, $P < 0.05$). Improvement of cryoglobulinemic serological hallmarks, such as

cryocrit and low complement C_4, was observed. No clinically relevant side effects were recorded. Complete remission of pretreatment active manifestations was observed in all cases of purpuric lesions and non-healing vasculitic ulcers and in 80% of the peripheral neuropathies.

A point of caution is important, as rituximab use has been associated with severe infectious complications including reactivation of HCV. We reported on a renal transplant recipient with hepatitis C who received one single dose of rituximab 375 mg/m^2 for gastric lymphoma (Fabrizi et al. 2007b). Rituximab use was complicated by cholestatic hepatitis C with extremely high serum HCV RNA levels (>7,692,310 IU/L); liver insufficiency occurred, and the patient died of pneumonia. Although other mechanisms could not be excluded, we implicated rituximab in the pathogenesis of cholestatic hepatitis C.

Another patient received one single dose of rituximab (375 mg/m^2) for the treatment of HCV-negative mixed cryoglobulinemia (and biopsy-proven membranoproliferative glomerulonephritis) resistant to conventional immunosuppressive agents. He showed significant benefit on kidney function (serum creatinine going back to 1.6 mg/dL) even if urinary abnormalities were still present. He developed sepsis over the follow-up and died 2 months after rituximab therapy (Fabrizi et al. 2015a).

Treatment of HCV-Associated Mixed Cryoglobulinemic Vasculitis: Rituximab and DAAs

Rituximab was originally approved by the FDA in 1997 for the treatment of relapsed or refractory non-Hodgkin's lymphoma and later for patients with rheumatoid arthritis. More recently, it has been used in MC vasculitis to target the B-cell arm of autoimmunity. Two prospective, randomized controlled trials have examined the safety and efficacy of rituximab for the treatment of patients with HCV-associated cryoglobulinemic vasculitis in whom prior antiviral therapy failed to induce disease remission – only a minority of patients had renal involvement (Sneller et al. 2012; De Vita et al. 2012). These trials have shown the superiority of rituximab monotherapy compared to conventional immunosuppressive therapy (i.e., corticosteroids, azathioprine, cyclophosphamide, and plasma exchange). Rituximab was tolerated well and was an effective treatment in 71.4–83% of patients with HCV-associated cryoglobulinemic vasculitis.

The role of oral interferon-free regimens in HCV-induced cryoglobulinemic vasculitis has been evaluated by Saadoun et al. (2016) who gave sofosbuvir (400 mg/day) and ribavirin (200–1,400 mg/day) (24 weeks) to 24 consecutive patients with HCV-induced cryoglobulinemic vasculitis. Main features of HCV cryoglobulinemia vasculitis included purpura and peripheral neuropathy (67%), arthralgia (58%), glomerulonephritis (21%), and skin ulcers (12%). Seventy-four percent of patients had a sustained virologic response at week 12 posttreatment. Twenty-one patients (87.5%) had complete clinical response at week 24. The cryoglobulin level decreased from 0.35 (0.16–0.83) at baseline to 0.15 (0.05–0.45) g/L at week 24. The C_4 serum level increased from 0.10 (0.07–0.19) to 0.17 (0.09–0.23) g/L at week 24. The most common side effects were fatigue, insomnia, and anemia. Two serious adverse events were observed.

Treatment of HCV-Induced Glomerulonephritis: Nonspecific Immunosuppression

Immunosuppressive agents have been administered to patients with HCV-associated mixed cryoglobulinemic vasculitis with serious life-threatening disease complications such as membranoproliferative glomerulonephritis and severe neuropathy. Cyclophosphamide has been used to improve renal disease by lowering stimulation of B lymphocytes and cryoglobulin synthesis, steroid pulses have been administered to control glomerular inflammation, and plasma exchange to make clearance of circulating cryoglobulins from plasma and consequently to reduce the deposition of immune complexes at renal level.

Combined therapy with corticosteroids and immunosuppressive agents, for example, treatment using both cyclophosphamide and azathioprine, has been tried while awaiting the generally low response to antiviral therapy. In one retrospective study, the clinical outcome of 105 patients with essential MC vasculitis and renal involvement was assessed throughout a median follow-up of 72 months since renal biopsy and 131 months since the clinical onset of MC vasculitis. Anti-HCV antibodies were retrospectively tested in 34 patients and were present in 85% of them. About 80% of patients underwent treatment of corticosteroids (pulse intravenous or oral corticosteroids) and/or cytotoxic agents, whereas 67% underwent plasma exchange. Despite this aggressive treatment, patient survival was 49% at 10 years after renal biopsy, and only 15 (14%) patients had remission of kidney disease over long term. Forty-two patients died primarily from cardiovascular and liver disease or infection, whereas 15 patients developed chronic renal failure. Two patients had complete remission of the disease, while 15 had a remission only of renal signs. Thirty-one patients are alive with persistent renal and extrarenal manifestations. At multivariate analysis, age >50 years, purpura, splenomegaly, cryocrit levels $>10\%$, C_3 plasma levels <54 mg/dL, and serum creatinine >1.5 mg/dL were independent risk factors for death or dialysis (Tarantino et al. 1995).

HBV-Associated Glomerular Disease: Epidemiology and Clinical Manifestations

The association between glomerulonephritis and chronic hepatitis B virus infection was first described by Combes et al. (1971). Around 5% of chronic HBsAg carriers probably show HBV-related glomerular disease. Hepatitis B virus-associated glomerulonephritis (HBV-GN) has been reported from all over the world, but China is known to be the most endemic area (up to 112 million chronic HBV carriers) with a high incidence of progressive HBV-GN and poor prognosis in adults (Zheng et al. 2012).

The advent of universal HBV vaccination in many countries of the developed world has lowered the incidence of HBV-related glomerular disease, possibly through a significant decline in horizontal transmission (negative HBsAg maternal status) of HBV (Liao et al. 2011). Most patients with HBV-associated glomerular disease present with the nephrotic syndrome, and some show mild-to-moderate proteinuria with hematuria. HBV-related glomerular disease is more common in children than adults and in men than women. The natural history of HBV-related membranous nephropathy appears different between children and adults. In contrast to pediatric subjects, in whom spontaneous remission of proteinuria is common and the renal function is often well preserved, adult patients are more likely to have progressive disease, and up to one third of patients might eventually develop renal failure. As many as 10% of these will require maintenance dialysis.

HBV-Associated Glomerular Disease: Histology

The most common histological type of HBV-GN is membranous nephropathy (Lai et al. 1991), followed by membranoproliferative glomerulonephritis. Other morphological patterns of HBV-related glomerular disease include mesangial proliferative glomerulonephritis, IgA nephropathy, and focal segmental glomerulosclerosis. HBV-related membranous nephropathy is characterized by thickened capillary wall and glomerular basement membrane on light microscopy. Although this feature could be subtle in the early stage, the capillary wall can assume a rigid appearance in advanced disease. Immunofluorescent staining and electron microscopy demonstrate granular IgG, C_3, and some IgM staining in the subepithelial region along the glomerular basement membrane accompanied by extensive effacement of the podocyte foot processes and in some cases viral particles in various locations within the glomerulus. Mesangial abnormalities are more common in "secondary" membranous nephropathy compared with the "primary" ("idiopathic") form. Mesangial expansion and capillary wall

thickening resulting in a lobular appearance of the glomerular tuft characterize the light microscopic findings in membranoproliferative glomerulonephritis. The capillary wall also demonstrates a double-contour appearance and hypercellularity with interpositioning of cells. The latter may include infiltrating monocytes and neutrophils. Immune deposits containing IgG, complement components, and IgM appear granular on immunofluorescence microscopy and are located in the subendothelial, mesangial, and para-mesangial areas. In addition to these electron-dense deposits, which could also be present in the subepithelial region, albeit in smaller amounts, electron microscopy also shows subendothelial expansion and the formation of new basement membrane material, which accounts for the double-contour appearance on light microscopy. The subendothelial and mesangial immune deposits trigger complement activation and increased local expression of inflammatory and chemotactic mediators, leading to the infiltration of inflammatory cells. It is noteworthy that the recent discovery of podocyte antigen phospholipase A2 receptor (PLA2R1) supports the reevaluation of the traditional distinction between "primary" ("idiopathic") and "secondary" membranous nephropathy, ultimately determined on clinical grounds (Larsen et al. 2013).

Hepatitis B Virus-Associated Glomerular Disease: Cryoglobulinemic Vasculitis

The relationship between HBV and cryoglobulinemia has been controversial. Levo et al. (1977) were the first authors to suggest an association between HBV and cryoglobulinemia even if later studies offered conflicting findings (Fiorini et al. 1986; Galli 1991). It is now established that HBV is able to induce cryoglobulinemia although infrequently. After the identification of hepatitis C virus, HCV has been recognized as the cause of 80–90% of mixed cryoglobulinemia (Fabrizi et al. 2013); according to a large series of patients with mixed cryoglobulinemia, anti-HCV positive serologic status has been observed in 92% (155/168) of cases, whereas hepatitis B surface antigen was detected in 9% (15/168) (Ferri et al. 2004). The pathogenic role of HBV in mixed cryoglobulinemia was confirmed by the positive finding for the HBV DNA in the cryoprecipitate. Cryoglobulinemia is a pathologic condition in which the blood contains immunoglobulins having the property of reversible precipitation from human serum cooled to 4 °C. Cryoglobulinemia vasculitis is a systemic vasculitis that involves mostly small- and, less frequently, medium-sized arteries and veins. HBV may produce cryoglobulins in a similar way to HCV. The antigenic stimulus maintained by HBV supports the polyclonal and later oligo-monoclonal expansion of B cells with the synthesis of cryoglobulins and rheumatoid factor (Lake-Bakaar et al. 2012). Immune complexes formed by HBV, polyclonal IgG, and monoclonal IgM (provided with rheumatoid factor) are deposited on endothelial surfaces, producing vascular inflammation. The monoclonal IgM component with rheumatoid factor activity is considered to be key in the deposits at kidney level. MC characteristically represents a form of immune complex vasculitis, intravascular cryoglobulin precipitation being instigated by cold temperature, and may involve primarily the skin, peripheral nerves, and kidney.

Antiviral Treatment of HBV-Associated Glomerular Disease: Historical and Current Perspective

The antiviral treatment of HBV-related glomerular disease has been mostly conducted in observational studies provided with small size. It is clear that the low frequency of HBV-related glomerular disease in the western world hampers the implementation of good quality prospective controlled studies to address the efficacy and safety of antiviral therapy in patients with HBV-associated glomerular diseases.

Lai and coworkers were the first investigators to give antiviral therapy for the treatment of HBV glomerular disease (1991). The clinical response to therapy with interferon alpha was disappointing, only one of five adults treated had a complete

remission with seroconversion to antibody to HBeAg. The most important study on this topic was conducted in China where an open randomized trial on the efficacy and safety of recombinant interferon alpha (1 year) in 40 children with HBV-associated membranous nephropathy was made (Lin 1995). At the end of the 12th month, all patients in group 1 were free of proteinuria with no relapse from the end of third month. However, 6 cases (30%) had persisted heavy proteinuria, 12 cases (60%) had mild proteinuria with frequent relapses, and only 2 cases (10%) were free of proteinuria in group 2. In the first group, eight patients with clinical remission after IFN had HBeAg and HBsAg clearance; in the second group, all cases still had HBeAg and HBsAg in sera.

In a retrospective, observational study at the National Institutes of Health, 15 adults were treated with recombinant interferon alpha for HBV-associated glomerulonephritis; eight had viral response (clearance of HBV DNA and hepatitis B e antigen from serum). Seven of them also showed as gradual but marked improvement in proteinuria. In contrast, the seven non-responders continued to have evidence of active renal disease, and one required long-term dialysis therapy (Conjeevaram et al. 1995).

Data on lamivudine use for HBV-related glomerular disease are more limited. Tang et al. (2005) treated ten patients with membranous nephropathy associated to HBV with lamivudine for 12 months and compared their clinical course with a historical group of 12 patients with HBV-related MN followed in the pre-lamivudine era. Six (60%) patients went into complete remission of proteinuria at 12 months; in the control group, significant proteinuria persisted during the first year.

A meta-analysis reported in 2006 showed the efficacy and safety of antiviral therapy (interferon or lamivudine) in HBV-associated glomerular disease with an overall estimate for remission of nephrotic syndrome of more than 60% (Fabrizi et al. 2006). The mean age of the patients ranged from 6.2 to 48.3 years. The majority of the patients had nephrotic syndrome related to membranous nephropathy. All patients showed serological evidence of active HBV replication at the beginning of the study. Studies of patients with functioning renal grafts or studies of previously treated patients were excluded. Six clinical trials (84 unique patients) were included; three had controlled design. Follow-up after antiviral treatment ranged from 6 to 43.2 months.

Table 2 summarizes antiviral treatment of HBV-associated glomerular disease in adults with native kidneys; we have made a search only for reports from western countries (English language). A large variety of histological lesions was found. A total of 19 anecdotal reports ($n = 19$ patients) were retrieved (Garcia et al. 1985; Lidman et al. 1993; Shapiro et al. 1995; Abbas et al. 1999; Izzedine et al. 2006; Wen and Chen 2006; Dede and Ayli 2006; Kanaan et al. 2006; Okuse et al. 2006; Di Marco et al. 2006; Chuang et al. 2007; Mesquita et al. 2008; Ikee et al. 2010; Nakahara et al. 2010; Enriquez et al. 2010; Das et al. 2011; Sakai et al. 2011; Shah et al. 2013; Ochi et al. 2014). All these patients obtained some improvement of renal disease after HBV DNA clearance, confirming the role of the virus in the pathogenesis of the kidney disease. A spontaneous improvement of glomerular lesions has been found in a few reports (Knecht and Chisari 1978; Gonzalo et al. 1999), and it cannot be excluded in some patients. Additional information exists on antiviral treatment of HBV-induced glomerular disease among adults in less-developed countries and among pediatric subjects (De Man et al. 1989; Gonzalo et al. 1999).

HBV-Associated Glomerular Disease: Immunosuppressive Therapy

Immunosuppressive therapies, by virtue of their mechanisms of action, have the potential to have a permissive effect on HBV and HCV replication resulting in an accelerated liver injury and worsening of extrahepatic complications including vasculitis. The available evidence does not support use of corticosteroids in HBV-associated glomerular disease; in fact, corticosteroids alone may enhance viral replication and precipitate hepatic flares (McHutchison et al. 2001; Calabrese et al. 2006). Recently, Zheng et al. (2012) in their

Table 2 Published literature describing the use of antiviral agents for HBV-induced glomerular disease (adults only)

Author (year)	Country	Kidney histology	Viral response	Therapy	Clinical response
Garcia et al. (1985)	USA	MGN ($n = 1$)	HBsAg clearance	Leukocyte interferon	Proteinuria remission
Lidman et al. (1993)	Sweden	MGN ($n = 1$)	Temporary HBV DNA clearance	IFN alpha 2b	Proteinuria remission
Shapiro et al. (1995)	Canada	MGN ($n = 1$)	HBsAg clearance	Lymphoblastoid IFN alpha	Proteinuria remission
Abbas et al. (1999)	UK	MPGN ($n = 1$)	HBV DNA clearance	IFN alpha 2a	Proteinuria remission
Izzedine et al. (2006)	France	MGN ($n = 1$)	HBV DNA clearance	Lamivudine	Proteinuria remission
Wen and Chen (2006)	Taiwan	MPGN ($n = 1$)	HBV DNA clearance	Lamivudine	Proteinuria remission
Dede and Ayli (2006)	Turkey	IgA nephropathy ($n = 1$)	HBV DNA clearance	IFN alpha/ lamivudine	Proteinuria and creatinine improvement
Kanaan et al. (2006)	Belgium	MGN ($n = 1$)	HBsAg clearance	Lamivudine	Proteinuria remission
Okuse et al. (2006)	Japan	MGN ($n = 1$)	HBV DNA clearance	Lamivudine	Proteinuria remission
Di Marco et al. (2006)	Italy	MPGN ($n = 1$)	HBsAg clearance	Lamivudine	Proteinuria and creatinine normalization
Chuang et al. (2007)	Taiwan	MGN ($n = 1$)	HBV DNA clearance	Lamivudine	Proteinuria remission
Mesquita et al. (2008)	Belgium	MGN ($n = 1$)	HBV DNA clearance	Lamivudine	Proteinuria remission
Ikee et al. (2010)	Japan	MGN ($n = 1$)	HBV DNA clearance	Entecavir	Proteinuria remission
Nakahara et al. (2010)	Japan	MGN ($n = 1$)	Intact HBV DNA	IFN alpha	Temporary proteinuria remission
Enriquez et al. (2010)	Spain	MPGN ($n = 1$)	HBV DNA clearance	Lamivudine	Proteinuria and creatinine remission
Das et al. (2011)	Australia	MGN ($n = 1$)	HBV DNA reduction	Tenofovir/ lamivudine	Proteinuria and creatinine improvement
Sakai et al. (2011)	Japan	FSGS ($n = 1$)	HBV DNA reduction	Lamivudine/ entecavir	Proteinuria remission
Shah et al. (2013)	USA	IgA nephropathy ($n = 1$)	HBV DNA clearance	PegIFN alpha 2b	Proteinuria remission
Ochi et al. (2014)	Japan	GNM ($n = 1$)	HBsAg clearance	Entecavir	Proteinuria remission

systematic review with meta-analysis have shown that combined therapy (antiviral and immunosuppressant agents) is an effective and safe regimen for HBV-associated glomerular disease. Twelve clinical trials with 317 adult patients were included. Combined antiviral and immunosuppressant (corticosteroids and mycophenolate mofetil) therapy gave an overall estimated rate for proteinuria remission of 83% There was no significant difference in terms of proteinuria remission between different pathological types of HBV glomerular disease [membranous nephropathy vs. mesangial proliferative glomerulonephritis ($P = 0.68$) and MN vs. MPGN ($P = 0.27$)].

Clinical practice guidelines for the treatment of HBV-induced cryoglobulinemic vasculitis

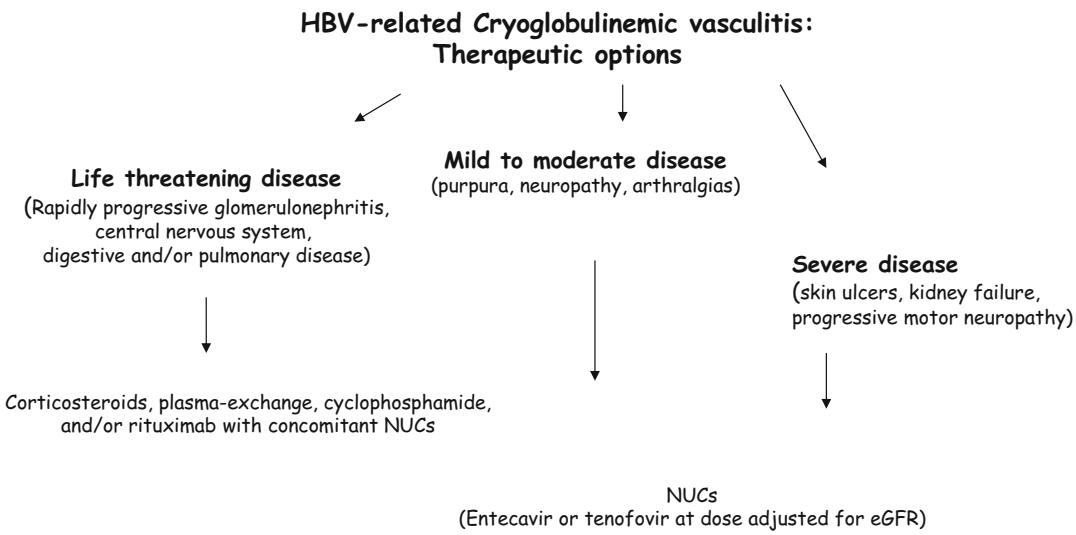

Fig. 2 Treatment algorithm of HBV-related cryoglobulinemic vasculitis according to clinical manifestations

have not been issued to date. We suggest to start antiviral therapy with nucleoside and nucleotide analogues for patients with HBV-induced cryoglobulinemic vasculitis whose disease severity and activity is mild to moderate. For patients having severe disease (defined as progressive motor neuropathy, or rapid kidney insufficiency, or skin ulcers), a treatment with rituximab and/or plasma exchange and/or conventional immunosuppressants is suggested (Fig. 2). No published data exist on the use of rituximab for HBV-associated glomerular disease. Rituximab use has resulted in reactivation of HBV infection resulting in an ominous course in some patients (Koo et al. 2009; Matsue et al. 2010). Preemptive use of antiviral drugs such as entecavir may improve the management of reactivation of HBV, but more data is needed on this point.

Treatment of HBV-Associated Mixed Cryoglobulinemic Vasculitis: Antiviral and Immunosuppressive Agents

Reported cases of HBV-related cryoglobulinemic vasculitis are rare, and a recent multicenter study from Italy (four centers) enrolled 17 patients with HBV-associated cryoglobulinemic vasculitis (Mazzaro et al. 2016). The extrahepatic manifestations were purpura (100%), arthralgias (71%), peripheral neuropathy (29%), chronic hepatitis (47%), liver cirrhosis (29%), and glomerulonephritis (18%). Type II and III mixed cryoglobulinemia occurred in 88% and 12% of patients. The median cryocrit was 3%, rheumatoid factor was 200 IU/L, and C_4 was 12 mg/dL. All patients were HBsAg positive and 80% HBeAg positive. At enrolment, they were treated with steroids (eight), entecavir (five), IFN alpha (two), and adefovir and lamivudine (one each). After treatment with nucleotide and nucleoside analogues, no disease progression was noted, and, in all patients, HBV DNA clearance from serum occurred. Moreover, regression of purpura and reduction of cryocrit were seen. Four patients died during therapy, two of kidney failure and two of liver cirrhosis.

We have previously reported the case of a 40-year-old female Chinese patient with chronic hepatitis B developing cryoglobulinemic vasculitis with multiple organ involvement (liver, kidney, and skin) coupled with weakness, arthralgias, hemolytic anemia, and autoimmune thyroiditis. After a few months of entecavir treatment, hepatitis B viremia decreased below the limit of detection with normal serum aminotransferase levels, HBeAg clearance occurred, and vasculitis regressed with disappearance of purpura and

ascites; in addition, renal function normalized and nephritic syndrome remitted. After a 5-year follow-up, the patient is asymptomatic with intact kidney function, proteinuria in the normal range, and normal liver biochemistry, despite the antiviral treatment was withdrawn and the patient remained HBsAg positive (Viganò et al. 2014). Extremely limited information exists on cases of hepatitis B virus-related cryoglobulinemic vasculitis successfully treated with entecavir suggesting that effective antiviral therapy may counteract both the hepatic and extrahepatic manifestations of infection by hepatitis B virus.

Another patient (55-year-old Caucasian male) with aggressive hepatitis B and extrahepatic manifestations (myopathy at lower limbs and renal failure) was treated with nucleoside analogues (mostly entecavir monotherapy) for 24 months. HBV DNA (at the beginning, $>1 \times 10^8$ IU/mL) was no longer detectable in serum after a few months of antiviral therapy, while HBeAg and HBsAg seroconversion occurred with ALT normalization. He also received a course of intravenous pulse steroids. Clinical signs of vasculitis remitted; 5 months after discontinuation of entecavir therapy, he remained HBsAg negative with detectable anti-HBs antibody in serum. Renal disease partially improved, and stable renal insufficiency (serum creatinine and proteinuria around 2 mg/dL and 500 mg/day, respectively) is still present over a 6-year follow-up (Fabrizi et al. 2011).

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Glomerular Diseases Associated with Hepatitis B and C Infection, Pediatric

29

Elizabeth Brown

Contents

Abstract

The hepatitis B (HBV) and C (HCV) viruses infect billions of people worldwide causing chronic infection in hundreds of millions with high morbidity and mortality. Chronic infection with these viruses is a major cause of hepatitis, cirrhosis, and liver failure in adults throughout the world. HBV and HCV are blood-borne virus transmitted by exposure to infected blood and body fluids. Most children acquire these infections in utero or the perinatal period although the increasing use of IV drugs appears to be leading to a surge in adolescent rates of infection. In addition to liver involvement, HBV and HCV can cause extra-hepatic disease including various forms of glomerulonephritis and vasculitis resulting in proteinuria, hypertension, nephrotic syndrome, and end-stage renal disease. Children with HBV most commonly develop membranous nephropathy with clinical manifestations of proteinuria, hypoalbuminemia, and edema. HBV-associated renal disease has been reported to resolve spontaneously in some pediatric patients, but others may benefit from antiviral therapy. HCV-associated renal disease, most commonly seen as cryoglobulinemia and membranoproliferative glomerulonephritis, is rare in the pediatric population but should be considered and evaluated in high-risk patients. The prognosis,

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long-term sequelae, and treatment recommendations of both HBV and HCV infection are changing rapidly given recent advances in antiviral therapy. Children with chronic HBV and HCV are often not treated unless they manifest overt hepatitis or glomerulonephritis because they are unlikely to have clinically apparent disease until adulthood. Routine vaccination against HBV has decreased the rate of infection and associated disease manifestations substantially. Antiviral therapy in HBV in children is still dependent on interferon-alpha which has significant side effects and is poorly tolerated; however, new medications have been approved for use in adults and will likely change pediatric treatment recommendations in the future as well. Treatment and prognosis of HCV has changed dramatically with the approval of direct acting antiviral (DAAs) in adolescents and adults that can eradicate the virus in some patients with 3 months of treatment. DAAs are often used in combination and recommendations about optimal therapy continue to change frequently. There are ongoing trials to evaluate DAAs in children. Recommendations for when to treat children with HBV and HCV are likely to continue to evolve with the results of current and future clinical trials testing the newer more effective and tolerable antiviral medications.

Keywords
Hepatitis B · Hepatitis C · Membranoproliferative glomerulonephritis · Membranous nephritis · Viral-associated glomerulonephritis

Hepatitis B

Introduction

The hepatitis B virus (HBV) is a small, circular DNA virus that has infected an estimated 2 billion people; more than 350 million persons are affected by chronic hepatitis B, according to 2015 numbers by the Centers for Disease Control and Prevention (CDC). The natural history of HBV infection is diverse and variable. The risk of developing chronic HBV is highest for the youngest children (90% if acquired before 6 months of age) and most individuals with chronic HBV were infected perinatally. Approximately 25% of children who acquire HBV will develop cirrhosis or hepatocellular carcinoma in adulthood. HBV prevalence varies geographically with the highest rate of chronically HBV-infected persons found in Asian-Pacific countries. HBV-related complications and deaths are more common in low- and middle-income countries (Nannini and Sokal 2017; Karnsakul and Schwarz 2017).

Epidemiology and Screening

The CDC estimates that in the United States, approximately 850,000–2.2 million people have chronic hepatitis B infection causing approximately 1800 deaths a year (Centers for Disease Control and Prevention 2015). Cirrhosis, hepatocellular carcinoma, and liver failure are predicted to occur in 15–40% of people with chronic hepatitis B (Abara et al. 2017). High risk populations in the United States include individuals born in high prevalence regions (Africa, Asia, and the Pacific Islands) and their children, as well as injection drug users, people who have been incarcerated, men who have sex with men, and sexual and household contacts of infected persons (Abara et al. 2017). Best practice advisories from the American College of Physicians and Centers for Disease Control and Prevention recommend screening for HBV infection in high risk individuals as defined above, as well as people with end-stage renal disease, those requiring immunosuppressive therapy, blood and tissue donors, HIV and hepatitis C positive persons, pregnant women, and infants born to HBV-infected mothers (Abara et al. 2017). Screening for HBV in children and adolescents is recommended for any patient with elevated transaminases, internationally adopted children, children from endemic areas, children born to

parents from endemic areas, pregnant adolescents, and adolescents engaging high risk drug or sexual behaviors (Karnsakul and Schwarz 2017). Screening tests should include hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to total hepatitis B core antigen (anti-HBc). Other follow-up tests that may be indicated include hepatitis B e antigen (HbeAg), hepatitis B e antibody (HBeAb or anti-HBe), IgM antibody against hepatitis B core antigen (IgM anti-HBc), and HBV viral DNA (Centers for Disease Control and Prevention 2015).

Pathology

Extrahepatic manifestations of hepatitis B are often observed in association with circulating immune complexes and can present as glomerulonephritis, vasculitis, and reactive arthritis. The prevalence of kidney disease associated with HBV parallels the prevalence of HBV infection and is highest in the endemic regions. The link between hepatitis B virus and kidney disease was initially described in 1971 in a patient who had transfusion-related hepatitis B (known at that time as Australian antiginemia) and developed nephrotic syndrome. His renal biopsy showed membranous glomerulonephritis (MGN) with immune complex deposits that stained positive for hepatitis B surface antigen (HBsAg). His liver also stained positive for HBsAg (Combes et al. 1971).

Membranous nephropathy remains the most commonly cited form of HBV-associated kidney disease; however, multiple other pathologic lesions have been described including membranoproliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis, IgA nephropathy, focal segmental glomerulonephritis (FSGS), and minimal change disease (Xu et al. 2003; Lai et al. 1987; Venkataseshan et al. 1990; Asinobi et al. 2018). It is still debatable, however, whether some of the rarely described renal diseases, such as IgA, are truly related to the HBV infection or simply coincidental given the prevalence of HBV in some geographical areas (Elewa et al. 2011). One case series even describes a postinfectious acute glomerulonephritis in ten children with chronic HBV in which hepatitis B surface antigen and HBV DNA were detected in glomeruli (Zhang et al. 2016).

Small case series from multiple areas around the world have demonstrated similar findings in children with HBV membranous nephropathy. These children typically present with nephrotic syndrome; however, hematuria, hypertension, and asymptomatic proteinuria have also been described as clinical features. Serum complement measurements often show low C3, whereas C4 levels are more variable. Compared to children with non-HBV associated membranous glomerulonephritis, there appears to be a higher proportion of male patients and younger age among those with HBV (Southwest Pediatric Nephrology Study Group 1985; Ozdamar et al. 2003; Asinobi et al. 2018). On biopsy, direct immunofluorescence often shows granular deposition of immunoreactants such as IgG, C3, C1q, IgM, IgA, C4, and C5. HBV particles and HBV antigen staining can be seen in some patients along the glomerular capillary wall and in the mesangium. Irregularly thickened glomerular capillary basement membranes with granular subepithelial deposits have been seen on electron microscopy; in addition, some biopsy specimens show mesangial deposits and subendothelial deposits (Venkataseshan et al. 1990). Immune complexes are thought to deposit in the glomeruli from the circulation but likely form in situ as well depending on the specific antigen-antibody complex. HBsAg and HBcAg are large and negatively charged, therefore, unlikely to be filtered and deposit directly in the subepithelial space, and it has been speculated that these complexes are more likely seen in biopsies with an MPGN picture. On the other hand, anti-HBeAg-containing immune complexes are smaller and more likely to accumulate in the subepithelial space (Gupta and Quigg 2015). MPGN is more likely to present with hematuria and hypertension.

Clinical

Progression to renal failure is rare in children with membranous nephropathy secondary to HBV, and it has been reported that there is often spontaneous remission of the renal disease. The spontaneous remission has been associated specifically with seroconversion of HBeAg to anti-HBeAg (Gilbert and Wiggelinkhuizen 1994). Several studies, however, have shown a higher percentage than previously reported of children with HBV and end-stage renal disease (Asinobi et al. 2018; Elidrissy et al. 1988). Contrary to findings in adults, children with HBV renal disease do not often have frank hepatitis although their liver enzymes are frequently mildly elevated (Southwest Pediatric Nephrology Study Group 1985).

In addition to glomerulonephritis, renal manifestations of HBV can present as part of polyarteritis nodosa (PAN), a necrotizing vasculitis with multiorgan involvement. Circulating immune complexes deposit on the walls of small and medium sized blood vessels triggering inflammation and fibrinoid necrosis. HBV+ PAN is considered an early postinfectious disease and typically occurs within a few months to a year of the onset of HBV infection (Guillevin et al. 2005). The vasculitis is not limited to the kidney and clinical features can include arthralgias, fever, fatigue, rash, gastrointestinal manifestations, hypertension, and peripheral neuropathy (Pagnoux et al. 2010). Cryoglobulinemia, usually thought to be a feature of hepatitis C infection, has been described occasionally associated with HBV+ PAN. Renal microaneurysms have been described in association with PAN. The most useful diagnostic tool to evaluate for PAN is often angiography, which can show aneurysms, segmental narrowing, and variations in arterial lumen (Eleftheriou et al. 2013). The vascular nephropathy can result in malignant hypertension (Guillevin et al. 1995). HBV+ PAN is very rare in childhood and typically affects middle-aged adults. A recent European single center study of 69 pediatric patients with PAN showed no incidence of HBV although it has been reported that up to 30% of adults with PAN are HBV positive (Eleftheriou et al. 2013; Guillevin et al. 2005).

Treatment

Treatment of hepatitis B in children varies depending on age and disease manifestation; treatment options and practices are changing with the increase in available medications. It is recommended that high-risk neonates receive both vaccination with HBV vaccine series and immunoprophylaxis with hepatitis B immunoglobulin. The combination can significantly reduce the perinatal transmission of hepatitis B (Karnsakul and Schwarz 2017). Vaccination against HBV is the best method to prevent HBV infection and its complications. More than 90% of people under the age of 40 who receive the full series develop immunity that lasts for at least 30 years; however, vaccination rates are still lower than desired in the United States and elsewhere. Immunocompromised persons and those with end-stage renal disease may require higher doses or extra doses of the vaccine (Abara et al. 2017). Since the advent of the HBV vaccine, the rate of acute infection as well as the frequency of HBV-associated glomerulonephritis and polyarteritis nodosa has decreased in many countries (Guillevin et al. 2005; Abara et al. 2017; Xu et al. 2003).

Treatment of HBV renal disease depends in part on the severity of disease and the type of renal involvement. Rapidly progressive glomerulonephritis and polyarteritis nodosa are often treated with removal of immune complexes with plasmapheresis and concomitant antiviral therapy. Corticosteroids have been used to try to control the inflammation, but there have been concerning reports of increase in viral replication with corticosteroids and they are generally no longer recommended (Shah and Amarapurkar 2018; Elewa et al. 2011). Unlike children who have been reported to have frequent spontaneous remission of their renal manifestations of HBV, adults with HBV renal disease have a significant risk of progression to end-stage renal disease and benefit from antiviral treatment. Medications used to treat HBV include interferon-alpha, pegylated interferon, and nucleoside/nucleotide analogues. Several studies in children with membranous nephropathy showed much higher rates of

remission of proteinuria in patients treated with interferon-alpha compared to control patients. Interferon alpha, despite significant side effects, is still considered the medication of choice for pediatric patients who fit criteria for treatment of their HBV infection. Disadvantages of interferon-alpha treatment include need for frequent subcutaneous injections and poor tolerability due to high side effect profile. Pegylated interferon is FDA-approved for hepatitis C treatment in children but not yet for hepatitis B in children. Nucleoside and nucleotide analogs are better tolerated and often the medication of choice over interferon in adults, but HBV can develop resistance to the medications. In addition, nucleoside/nucleotide analogs suppress HBV replication but cannot eradicate the virus; therefore, long-term treatment is often necessary and HBV DNA levels can rise again if the medication is discontinued prematurely. Nucleoside/nucleotide analogs also need to be dose adjusted in patients with kidney insufficiency. The recommendations for treatment of children appear to be changing with recent and current trials of nucleoside/nucleotide antagonists in pediatric patients (Sokal et al. 2013; Jonas et al. 2016).

Hepatitis C

Introduction

The hepatitis C virus (HCV) was first identified in 1989 as a positive-stranded RNA virus causing non-A, non-B hepatitis (Choo et al. 1989). At the same time, an assay was developed that measured circulating antibodies to HCV. Within a few years, multiple studies were published showing the prevalence of HCV-associated hepatitis and hepatocellular carcinoma (Houghton et al. 1991).

Epidemiology

HCV has six distinct genotypes and multiple subtypes; the genotypes vary in their geographic distribution and in their response to treatment (Pham and Rosenthal 2016; Gower et al. 2014). According to a 2016 study in the Lancet, viral hepatitis accounted for approximately 1.45 million deaths worldwide making it the seventh leading cause of death with HBV and HCV contributing to 96% of the virus hepatitis-related mortality (Stanaway et al. 2016). Various reports suggest a worldwide prevalence of HCV in 80–210 million people (or about 1.6–3%) (Gower et al. 2014; Pham and Rosenthal 2016; Gupta and Quigg 2015; El-Shabrawi and Kamal 2013). Infection rates vary significantly by geographic region with the highest prevalence found in sub-Saharan Africa, Eastern Mediterranean, and Asia (El-Shabrawi and Kamal 2013). Data for the United States suggest that chronic HCV infection can be found in approximately 2–3 million people. Of these, an estimated 23,000–50,000 of these are children (0.1–2% of children in the USA) (Jhaveri and Swamy 2014; Pham and Rosenthal 2016; Barritt et al. 2018; Mack et al. 2012).

The transmission of HCV is through blood and body fluids. Prior to effective screening of transfused blood, HCV was the most common cause of posttransfusion hepatitis; however, with the advent of antibody and nucleic acid testing of donated blood, the risk of acquiring HCV through transfusion in developed countries is negligible. Transmission through blood products and unsafe use and reuse of hospital equipment is still reported, however, in some developing countries (Houghton et al. 1991; Pham and Rosenthal 2016; El-Shabrawi and Kamal 2013). The most common route of infection for children in developed countries is vertical, acquired during pregnancy, delivery, or the perinatal period (El-Shabrawi and Kamal 2013; Pham and Rosenthal 2016; Squires and Balistreri 2017). IV drug use is a significant source of infection in adolescents and young adults, and multiple studies have shown an increase in HCV infection in the 12–29 year age group thought to be associated with the rise in IV drug use. One study examining the Kids Inpatient Database showed a 37% increase in hospitalizations of children with HCV between 2006 and 2012. The mean age of these children was 17.6 years. This finding mirrors an increase in adult HCV incidence associated with use of intravenous opioids (Squires and Balistreri 2017;

Barritt et al. 2018). The rate of perinatal transmission of HCV is estimated by various studies to be between 5% and 15%; however, the rise in HCV in adolescents and young adults raises concerns about a potential increase in the number of infants with HCV (Jhaveri and Swamy 2014; Squires and Balistreri 2017; Tovo et al. 2016).

In adults, chronic hepatitis C is a leading cause of liver transplantation and a significant risk factor for development of hepatocellular carcinoma. HCV infection in childhood is often silent or subclinical. In infants affected by vertical transmission, spontaneous clearance of the virus can occur in approximately 20–40% of cases. Resolution in older children has been described in 6–12% of patients (Lee and Jonas 2015; Tovo et al. 2016; Mack et al. 2012). Clinically apparent acute HCV is thought to be quite rare in childhood; however, chronic infection can lead to slowly progressive liver disease over time. Cirrhosis has been reported in pediatric chronic HCV infection, and over 100 children received a liver transplant for chronic HCV between 1988 and 2009 in the United States. Risk of recurrence of HCV after liver transplantation is high, often resulting in need for re-transplantation (Tovo et al. 2016; Lee and Jonas 2015; Squires and Balistreri 2017; Mack et al. 2012; El-Shabrawi and Kamal 2013; Pham and Rosenthal 2016). Interestingly, in a study of 348 children in Japan with HCV (90% cases due to vertical transmission) between 1986 and 2015, no children developed cirrhosis or hepatocellular carcinoma (Mizuochi et al. 2017).

Pathology

Extra-hepatic manifestations of chronic hepatitis C are common in adults but much less prevalent in children. Some of the extra-hepatic diseases described include mixed cryoglobulinemia with associated vasculitis and glomerulonephritis, non-Hodgkins lymphoma, fatigue, cognitive impairment, and increased rates of diabetes and atherosclerosis. Type 1 membranoproliferative disease (MPGN) is the most frequent renal disease associated with HCV, followed by noncryoglobulinemic MPGN and membranous glomerulonephritis. The most common form of MPGN is associated with type II cryoglobulinemia. Renal manifestations of HCV are reported to be extremely rare in pediatric patients (Indolfi et al. 2012; Morales et al. 2012).

Kidney injury associated with hepatitis C is most commonly seen in the glomerulus and thought to be due to immune-mediated tissue damage, such as from cryoglobulinemia, as well as direct viral effects (Ferri et al. 2017). Multiple pathologic patterns of disease have been reported; the most common is membranoproliferative glomerulonephritis with immune complex deposition with or without the presence of cryoglobulinemia. Other glomerular diseases reported in association with HCV are mesangial proliferative glomerulonephritis, membranous glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis, fibrillary and immunotactoid GN, and cryoglobulinemic thrombotic microangiopathy. Interstitial fibrosis is commonly seen with MPGN but rarely as an isolated nephritis. Cryoglobulinemia is defined by the presence of immunoglobulins that reversibly precipitate in cold temperatures (4 °C) that can cause disease associated with immune-complex deposition and vasculitis. HCV is most often associated with type II mixed cryoglobulinemia in which two types of immunoglobulin are bound together, usually polyclonal IgG and monoclonal IgM with rheumatoid activity. Clinically, mixed cryoglobulinemia often presents as purpura, weakness, arthralgias, and organ involvement. In kidney biopsy specimens, cryoglobulins can be seen deposited on the endothelial surface of the glomeruli and/or in the mesangium, sometimes accompanied by complement factors and HCV RNA. Other biopsy features can include monocyte infiltrate, endotheliitis, and eosinophilic thrombi in the glomerular capillaries. Small artery vasculitis and extracapillary crescents can rarely be seen. Electron microscopy shows double contour basement membranes with subendothelial deposits. HCV-associated glomerulonephritis is often accompanied by hypertension and proteinuria (Fabrizi et al. 2013; Gupta and Quigg 2015; Ferri et al. 2017).

Clinical

One study of 45 children with vertically acquired HCV in Italy showed cryoglobulinemia in 33% with mild proteinuria and low C4 in 2 adolescent patients; none of the children appeared to develop significant renal disease (Garazzino et al. 2014). Two case reports from Japan describe HCV-positive children with renal disease. These children had moderate proteinuria (0.65–1 g/day), normal C3 and C4 complement levels, normal creatinine clearance, and negative cryoglobulins. Renal biopsies were performed which showed a mesangial proliferative glomerulonephritis with partial double contours of the basement membrane. Immunofluorescence for IgM, IgG, C3, and fibrinogen was positive in one biopsy (Sugiura et al. 2009; Matsumoto et al. 2000). The other patient had two biopsies 2 years apart. The initial biopsy showed mild mesangial hypercellularity and positive IgA, C3, fibrinogen in the mesangium and glomerular capillary wall. Immunofluorescent microscopy with HCV core and capsid antibody was negative. The patient was treated with interferon but was unable to clear her viremia completely. Her proteinuria and hematuria resolved; however, a second kidney biopsy 2 years later revealed advanced mesangial proliferation, partial double contours of the basement membrane with positive IgG, IgA, and C3. Electron dense deposits were seen in the mesangial matrix and subendothelial layer of basement membrane. Immunofluorescence staining against HCV core and capsid antigens was positive in the second biopsy with staining seen in the capillary walls. Despite the abnormal pathology, her creatinine clearance remained normal at the time of the case report (Matsumoto et al. 2000).

Multiple studies in different countries have shown a higher prevalence of chronic kidney disease (CKD) in HCV seropositive patients. In addition, dialysis and renal transplant patients with HCV have increased morbidity and mortality compared to comparable uninfected patients (Soderholm et al. 2018; Park et al. 2017; Mendizabal and Reddy 2017; Cacoub et al. 2016). Contrary to findings described in multiple reports, a recent study in a large database of HCV patients in the United States showed no increase in prevalence in CKD (Asrani et al. 2010). In the pediatric population, it has been reported that hepatitis C was a significant risk factor for the development of end-stage kidney disease after liver transplantation (Ruebner et al. 2012).

Treatment

Treatment of hepatitis C has been revolutionized by the development of combinations of direct acting antiviral agents (DAAs) which have been able to induce sustained viral remissions in large populations of HCV patients in a relatively short treatment duration of 12–24 weeks. This ability to potentially cure hepatitis C infection in a majority of patients (95%) is rapidly changing the discussion of whom to treat and when to initiate treatment. Prior to the development of the DAA protocols, standard treatment regimens involved interferon or pegylated interferon and ribavirin which had poor tolerability and limited efficacy. Due to lack of finished clinical trials using DAAs in children, interferon and ribavirin remain the standard of care for children under the age of 12 years. For adolescents, two DAAs have been FDA approved and showed a 98% sustained virologic response after 12 weeks of treatment. Interferon-free clinical trials are being planned for younger children. Because of the success rate and lower side effect profile of the DAA regimens, many hepatologists are waiting to treat asymptomatic pediatric patients until they are old enough for DAA therapy (Squires and Balistreri 2017; Wirth et al. 2017; Balistreri et al. 2017). Treatment for patients with HCV-induced glomerulonephritis often requires treatment of the virus as well as immunosuppression to reduce the viral-induced or cryoglobulinemic inflammation and vasculitis. Various treatment regimens have been described using corticosteroids, plasmapheresis, and rituximab in conjunction with pegylated interferon alpha and ribavirin. The new DAA regimens are also likely to change how HCV positive patients with CKD and/or kidney transplants are treated. The frequency of side effects and poor

efficacy of the prior interferon-based treatment options meant that patients with kidney disease, especially those on dialysis or with a renal transplant, were not treated for HCV until they were significantly effected by the virus. There are several DAA options for patients with glomerular filtration rates <30 ml/min/1.73 m^2 and more are likely to be approved in the future. This will likely make it safer and easier to treat HCV positive renal patients earlier in the course of their illness (Cacoub et al. 2016).

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HIVAN, Adult

30

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Contents

Abstract

HIV infection is associated with an increased incidence of acute and chronic kidney disease. HIV-positive individuals are at risk for HIV-associated glomerular diseases, including HIV-associated nephropathy (HIVAN) and HIV immune complex kidney disease, but are also susceptible to antiretroviral nephrotoxicity and comorbid kidney disease. Kidney biopsy is required for definitive diagnosis in the majority of cases. HIVAN is a collapsing form of focal segmental glomerulosclerosis with associated tubulointerstitial lesions, occurring primarily in individuals of African descent who have advanced HIV disease. The first-line treatment of HIVAN is antiretroviral therapy, with the

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addition of ACE inhibitors or angiotensin receptor blockers as adjunctive therapy. The role of antiretroviral therapy is less clear in HIV immune complex kidney disease and comorbid kidney disease. Even with effective therapy, HIV-positive individuals are at increased risk of progression to end-stage renal disease. The management of end-stage renal disease is largely based on guidelines developed for the general population, with special consideration of drug–drug interactions in patients with well-controlled HIV infection who may be candidates for kidney transplantation.

Keywords
Antiretroviral therapy · HIV · HIV-associated nephropathy · HIV immune complex kidney disease

Introduction

According to UNAIDS estimates, roughly 37 million persons were living with HIV/AIDS worldwide in 2014 (UNAIDS). The advent of combination antiretroviral therapy (ART) in 1996 significantly decreased AIDS-related mortality, and life expectancy among HIV-positive adults now approximates that of the general population (Smith et al. 2014). While early studies estimated the life expectancy of HIV-positive adults to be about two thirds that of the general population (Reichl and Beetham 1988), more recent studies have found no significant difference in life expectancy based on HIV serostatus (Rodger et al. 2013; Mills et al. 2011). Nevertheless, HIV-positive individuals continue to suffer from comorbidities such as cardiovascular disease, non-AIDS defining malignancies, chronic HCV infection, and end stage renal disease (ESRD) at higher rates than the general population (Althoff et al. 2015; Park et al. 2016). The contribution of HIV infection itself, HIV-related medications, and the higher prevalence of traditional risk factors is still a matter of debate. Of particular interest to our discussion is the impact of the above factors on the incidence of kidney disease in HIV-positive individuals. Before focusing on HIV-associated nephropathy (HIVAN) as the classic cause of glomerular disease in HIV-positive individuals, we will examine other HIV-related factors that contribute to the burden of kidney disease in this population.

Acute Kidney Injury in HIV-Positive Patients

Analysis of large administrative databases has demonstrated a higher incidence of acute kidney injury (AKI) in HIV-positive adults than in the general hospital population (Nadkarni et al. 2015; Wyatt et al. 2006), despite the lower average age of HIV-positive patients (Nadkarni et al. 2015). One study reported that the peak incidence of AKI in HIV-positive individuals occurred in 1995 and declined after the introduction of ART in 1996 to a low point in 2006 (Li et al. 2012). Similarly, the incidence of more severe, dialysis-requiring AKI declined in the 1990s in this population, but began to increase again between 2000 and 2006 (Li et al. 2012). A large, nationwide study done in 2015 found that the proportion of HIV-related hospitalizations complicated by dialysis-requiring AKI doubled between 2002 and 2010 (0.71% vs. 1.36%); the association between AKI and in-hospital mortality also increased over time, suggesting that the increase in dialysis-requiring AKI did not merely reflect changes in the use of dialysis. The increased incidence of AKI likely reflects aging and increased comorbidity of the HIV-positive patient population in the United States, although nephrotoxic antiretroviral agents may also contribute, as discussed in the next section (Nadkarni et al. 2015). AKI increases the risk of morbidity and mortality in HIV-positive individuals. In a large study evaluating long-term consequences of AKI in HIV-positive military veterans, the rates of heart failure, cardiovascular events, ESRD, and mortality increased with increasing severity of AKI (Choi et al. 2010b).

Prior to the use of ART, AKI in HIV-positive patients was associated with renal ischemia from septicemia, volume depletion, and medication toxicity, in addition to advanced immunosuppression and opportunistic infections (Roe et al.

2008). In the ART era, the major risk factors in HIV-positive adult patients are now similar to those in the general population (Rao and Friedman 1995). Traditional risk factors for AKI include older age, lower body mass index (BMI), diabetes mellitus, hypertension, dyslipidemia, acute or chronic liver disease, and, perhaps most importantly, chronic kidney disease (CKD). A 2012 study demonstrated that the risk of AKI in HIV-positive individuals with CKD was over five times the risk of AKI in HIV-positive individuals without CKD. Proteinuria was also associated with a graded risk of AKI (Li et al. 2012), while black race was found to be a strong risk factor for dialysis-dependent AKI. HIV-specific risk factors for AKI include high viral load, low CD4+ cell count, AIDS-defining illness, hepatitis C virus (HCV) coinfection, and nephrotoxic antiretroviral therapy (Li et al. 2012).

Because the majority of studies have relied on administrative databases, data on the causes of AKI in HIV-positive individuals are limited. In a prospective cohort study focused on AKI, prerenal causes including volume depletion, septicemia, heart failure, and cirrhosis were among the most common causes for AKI, followed closely by ATN from ischemia and nephrotoxicity. Intrarenal causes such as interstitial nephritis and postrenal causes including intrarenal obstruction (i.e., medication-induced crystalluria) and extrarenal obstruction were rare (Franceschini et al. 2005). This study excluded patients with evidence of glomerular disease including HIVAN, which can also present with AKI.

ART Nephrotoxicity

Current guidelines recommend the initiation of antiretroviral therapy in all patients with HIV infection, with significant benefits for morbidity and mortality. Nonetheless, medication-induced nephrotoxicity is an important contributor to both AKI and CKD in the HIV infected population (Izzedine et al. 2009; Table 1). Several antiretroviral medications have been shown to cause kidney injury by varied mechanisms. Within the class of reverse transcriptase inhibitors (RTIs), tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor (NtRTI), is best documented for its nephrotoxicity. TDF is the preferred drug in its class of NRTIs; it is widely used in the treatment of HIV as part of ART, with the added benefit of efficacy against hepatitis B virus in coinfected patients. The prodrug TDF is metabolized rapidly to tenofovir, which is then renally excreted through both glomerular filtration and tubular secretion (Rodriguez-Novoa et al. 2010). TDF is associated with rare cases of acute kidney injury and proximal tubular dysfunction. Incidence of TDF-induced nephrotoxicity ranges from 2% to 10% (Nelson et al. 2007; Wikman et al. 2013). Clinical manifestations include mild elevations in serum creatinine (Nelson et al. 2007) and proteinuria, aminoaciduria, glycosuria, and phosphaturia, which are hallmarks of proximal tubular dysfunction (Peyriere et al. 2004; Hall et al. 2011). Further, TDF has been associated with a significant but minor decrease in creatinine

Table 1 Nephrotoxicity of antiretroviral and other antimicrobial medications in HIV-positive individuals

Drug	Reported toxicity
Tenofovir disoproxil fumarate	Proximal tubular dysfunction Acute kidney injury Decreased creatinine clearance Chronic kidney disease
Indinavir	Nephrolithiasis and crystalluria Interstitial nephritis Chronic kidney disease
Atazanavir	Nephrolithiasis Chronic kidney disease
Trimethoprim/sulfamethoxazole	Hyperkalemia Acute tubular necrosis Acute interstitial nephritis
Pentamidine	Hyperkalemia
Amphotericin B	Distal renal tubular acidosis Hypokalemia/hypomagnesemia Acute kidney injury
Acyclovir (intravenous)	Obstructive crystal nephropathy
Cidofovir	Proximal tubular injury Acute kidney injury
Foscarnet	Acute kidney injury

clearance compared to the use of alternative antiretroviral agents (Cooper et al. 2010). It is important to note that certain risk factors increase the risk of nephrotoxicity associated with TDF use, namely increased age, preexisting chronic kidney disease, low CD4+ cell count, and coadministration of other nephrotoxic medications (Hall et al. 2011). Observational studies have shown an increased risk of chronic kidney disease with each year of TDF use, which may be partially mitigated by drug discontinuation (Scherzer et al. 2012; Mocroft et al. 2010, 2016).

Protease inhibitors also have well-established nephrotoxic effects. One of the earliest protease inhibitors, indinavir, is associated with nephrolithiasis and interstitial nephritis (Izzedine et al. 2009; Dieleman et al. 2002). Indinavir precipitates into crystals due to its low solubility in urine, leading to crystalluria, nephrolithiasis, and interstitial inflammation in some individuals (Gentle et al. 1997). The newer protease inhibitor atazanavir has also been associated with nephrolithiasis and with increased risk of chronic kidney disease as defined by decreased creatinine clearance or rapid decline in estimated glomerular filtration rate (eGFR) (Scherzer et al. 2012; Mocroft et al. 2010, 2016). The relationship between these potential complications of atazanavir use is not known. Of note, protease inhibitors have also been associated with insulin resistance and diabetes mellitus, independent risk factors for chronic kidney disease (Eastone and Decker 1997).

Nephrotoxicity of Non-ART Agents Commonly Used in HIV-Positive Patients

Besides antiretroviral therapy, HIV-positive individuals are often exposed to other nephrotoxic medications used to treat comorbid conditions, particularly opportunistic infections. Trimethoprim/sulfamethoxazole (TMP-SMX), commonly used in the treatment and prevention of *Pneumocystis jiroveci* pneumonia, can cause kidney injury in several ways. Trimethoprim is associated with hyperkalemia and elevations in serum creatinine, which often resolve after drug discontinuation (Greenberg et al. 1993; Fraser et al. 2012). Sulfamethoxazole can cause acute tubular necrosis and acute interstitial nephritis due to sulfonamide sensitivity (Hayman et al. 2003; Chandra et al. 1985). Pentamidine, used in those who cannot tolerate or experience resistance to TMP-SMX, almost universally causes hyperkalemia when administered in patients with AIDS for more than 6 days (Lachaal and Venuto 1989). Amphotericin B, an antifungal indicated for the treatment of cryptococcal meningitis, is nephrotoxic by several mechanisms, including direct tubular damage and increased permeability of macula densa cells. Clinical manifestations include hypokalemia, decreased eGFR, and metabolic acidosis (Heidemann et al. 1983; Zager et al. 1992). Antivirals used to treat opportunistic viral infections are also nephrotoxic. Acyclovir, used to treat herpes simplex virus (HSV) infections, can cause an obstructive AKI due to direct precipitation of acyclovir crystals in the tubules. This can be prevented with proper volume repletion prior to administration, adequate hydration, slow intravenous infusion of the drug, and dose adjustment in patients with decreased GFR (Berns et al. 1991). Additionally, cidofovir and foscarnet, used to treat cytomegalovirus retinitis and acyclovir-resistant HSV, are also known to cause AKI (Trifillis et al. 1993; Vittecoq et al. 1997).

HIV-Associated Nephropathy

Epidemiology

HIVAN was first described in 1984 as a complication of AIDS, but it has also been reported in acute seroconversion and early stages of infection (Winston et al. 2001b). The earliest cases of HIVAN were identified in African-Americans and Caribbean immigrants, and HIVAN is more closely associated with black race than other causes of ESRD except for sickle cell disease (Abbott et al. 2001). The introduction of effective antiretroviral therapy has led to a significant

reduction in the risk of ESRD and a reduced incidence of HIVAN (System 2012). A recent study utilizing US Renal Data System (USRDS) data from 1989 to 2011 revealed a reduced incidence of ESRD attributed to HIVAN, as well as a decline in mortality among those patients. Compared to the initial cohort of patients initiating dialysis in 1989, the adjusted excess mortality of HIVAN-related ESRD versus ESRD from other causes was reduced from a fivefold increase to about threefold in the later cohort (Razzak Chaudhary et al. 2015).

A French study of 88 HIV-positive patients with biopsy-proven glomerular disease between 1995 and 2007 found a changing pattern of kidney disease over time, with a decreasing incidence of HIVAN and an increasing incidence of noncollapsing forms of focal segmental glomerulosclerosis (FSGS). HIVAN occurred more frequently in black patients with severe immunodeficiency, while the noncollapsing variant of FSGS occurred in older patients who were more likely to have received antiretroviral therapy (Lescure et al. 2012). Similar findings have also been reported in an urban US cohort, with a decline in the proportion of kidney biopsies demonstrating HIVAN over time (Berliner et al. 2008).

Clinical Manifestations

Patients with HIVAN commonly present in the setting of untreated HIV infection with advanced immunosuppression. Classically, patients present with heavy proteinuria and rapid decline in kidney function. In contrast to other kidney diseases that are associated with rapid progression and significant proteinuria, HIVAN does not commonly present with severe hypertension, edema, or hematuria. Proteinuria is typically nephrotic range, although in earlier disease the proteinuria may not be as severe and a HIVAN diagnosis should still be considered (Han et al. 2006). Kidney biopsy is required to make a definitive diagnosis, as it is common to find an alternative histologic diagnosis in patients with suspected HIVAN (D'Agati 1998).

Histology

The classic features of HIVAN first described in 1984 include a pathognomonic constellation of FSGS with collapse of the glomerular capillaries, proliferation of epithelial cells in Bowman's space, podocyte hypertrophy, and mesangial prominence and hypercellularity (Fig. 1). Electron microscopy often reveals endothelial tubuloreticular inclusions in addition to diffuse podocyte foot process effacement (Fig. 2). (Laurinavicius et al. 1999; Rao et al. 1984). Tubuloreticular inclusions were previously considered pathognomonic for HIVAN but have also been observed in lupus nephritis and in the setting of interferon therapy. The glomerular epithelial cells, which are normally terminally differentiated cells, are dedifferentiated and proliferate, forming a pseudocrescent in HIVAN (Barisoni et al. 1999). In addition to the glomerular changes, microcystic tubular dilatation is common (Fig. 3). Microcystic dilatation is an important feature of HIVAN, and when combined together with proteinuria portends poorer outcomes (Wearne et al. 2012).

Pathogenesis

HIV directly infects glomerular and tubular epithelial cells and expresses viral genes within those cells. Viral RNA and DNA can be detected in renal epithelial cells from patients with undetectable viral loads in the peripheral blood, suggesting that the kidney may serve as a reservoir for HIV (Bruggeman et al. 2000). Microcyst formation occurs in HIVAN along multiple nephron segments, suggesting that HIV can infect epithelial cells from all nephron segments. HIV gene expression is associated with increased epithelial cell proliferation, potentially inducing microcyst formation (Ross et al. 2001).

The strong racial predilection emphasizes the importance of genetic factors in the pathogenesis of HIVAN. Single-nucleotide polymorphisms in the *APOL1* gene on chromosome 22 are linked to an increased risk of HIVAN and FSGS, and carrying two APOL1 risk alleles is associated with an earlier age of onset and faster progression to

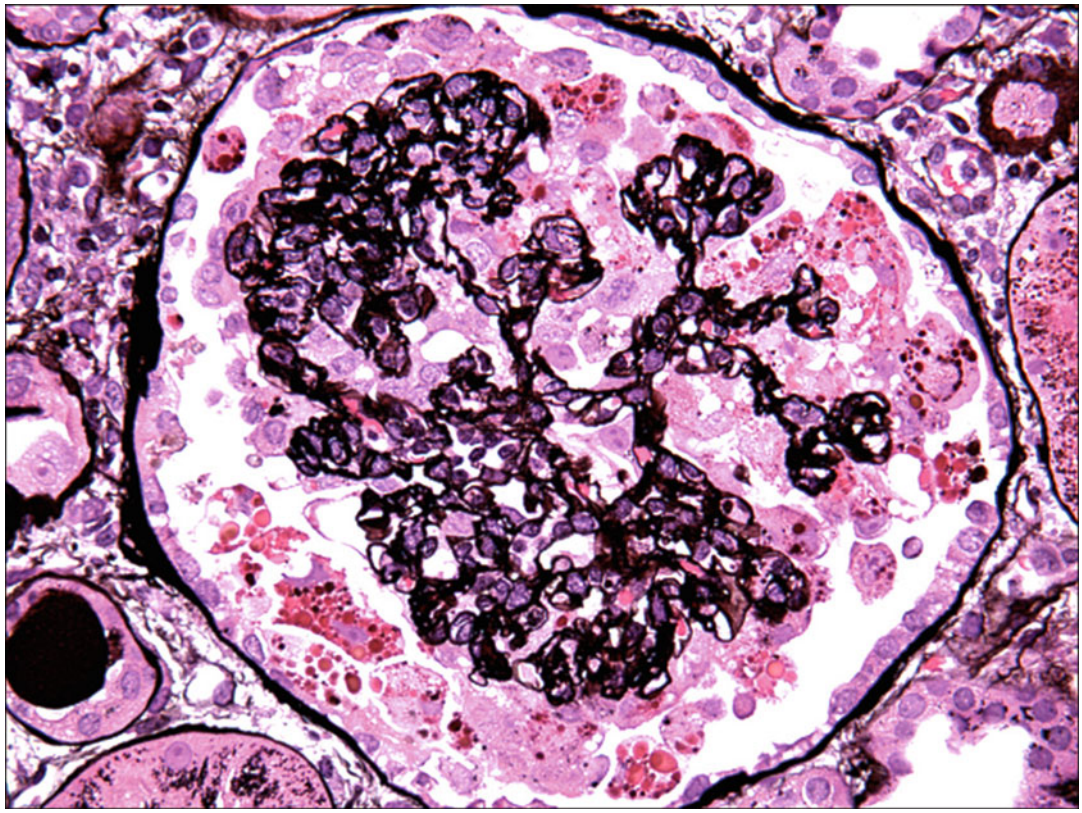

Fig. 1 Light microscopic glomerular changes in HIVAN. Jones methenamine silver staining (400× magnification) highlights the collapse of the glomerular tuft. Glomerular capillaries are no longer readily visible and the glomerular tuft is wrinkled and appears to float inside Bowman's capsule. Bowman's space is largely filled with epithelial cells that are derived from both podocytes and the parietal epithelial cell population. Note the large protein resorption droplets within many of the swollen and hypertrophied epithelial cells. Reproduced from Wyatt et al. (2008)

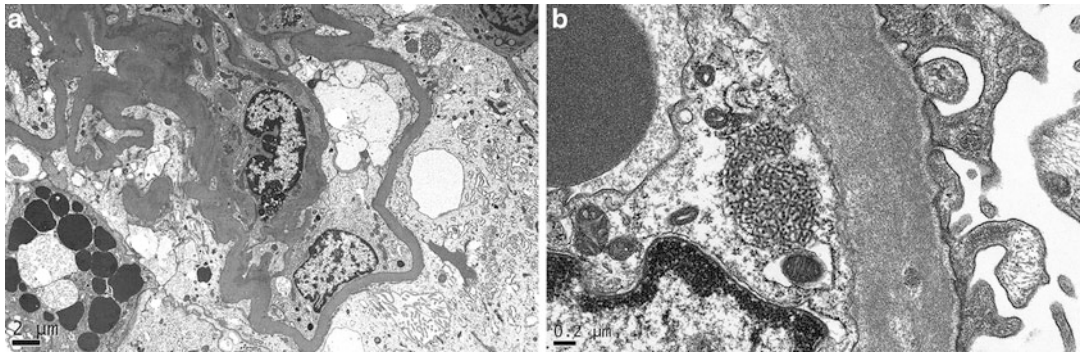

Fig. 2 Ultrastructural findings in HIVAN. Podocyte foot process effacement is typically diffuse both in capillaries that show collapse and in open capillaries. No intact foot processes can be seen in panel (**a**), with the collapsed and wrinkled glomerular basement membrane covered with what appears to be one large sheet of cytoplasm. A podocyte containing large electron dense protein resorption droplets is present in the *lower left corner* of the image (5000× magnification). Endothelial tubuloreticular inclusions, likely reflecting the elevated levels of circulating interferon, are commonly seen in HIVAN. Panel (**b**) centers on a large tubuloreticular inclusion within a glomerular endothelial cell (40,000× magnification). Reproduced from Wyatt et al. (2008)

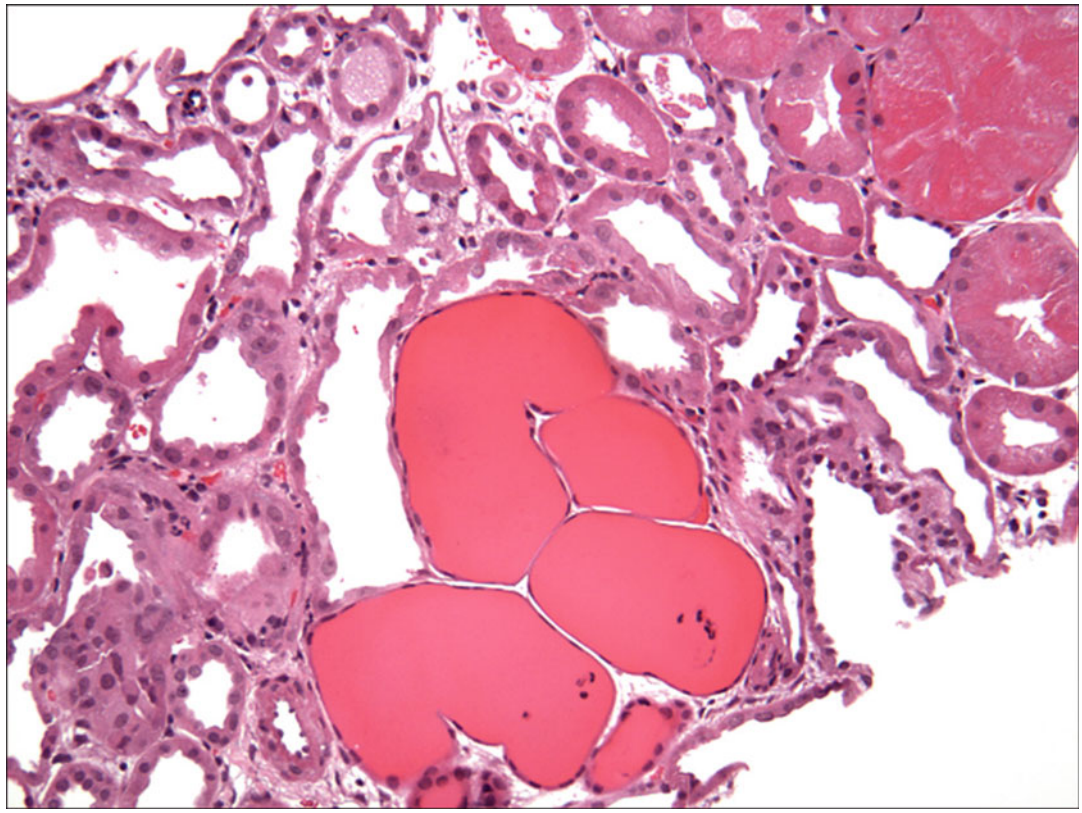

Fig. 3 Tubulointerstitial changes of HIVAN. Proximal tubules often contain prominent intracytoplasmic protein resorption droplets, as seen in the *upper right corner* of the picture (H&E, 200×). Several markedly distended tubules forming microcysts are seen containing eosinophilic proteinaceous casts. Nearby proximal tubules show acute degenerative changes, including loss of apical brush border. Reproduced from Wyatt et al. (2008)

ESRD (Kopp et al. 2011). Adding *APOL1* genotype to traditional HIV-related risk factors in a predictive model improves prediction of non-HIVAN FSGS but does not preclude the need for biopsy (Atta et al. 2016).

Treatment

Although there are no randomized trials to guide the treatment of HIVAN, there is strong observational evidence that effective antiretroviral therapy may prevent the development or induce regression of HIVAN. In addition to the change in the epidemiology of HIVAN with the introduction of antiretroviral therapy, observational studies have demonstrated longer median renal survival of patients with HIVAN who are on antiretroviral therapy (Atta et al. 2006). In hypertensive and proteinuric patients, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may also be protective (Burns et al. 1997). Some experts would also consider the addition of corticosteroids in patients with aggressive disease, although the risk of infection is high.

HIV Immune Complex Kidney Disease

HIV immune complex kidney disease (HIVICK) is a term used to describe a group of immune-mediated glomerulonephritides that have been associated with HIV infection. These diseases include immune complex glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephropathy, "lupus-like" glomerulonephritis,

postinfectious glomerulonephritis, and IgA nephropathy. In some cases, immune complexes composed of antibodies bound to HIV antigens have been demonstrated (Kimmel et al. 1993). Renal cell proliferation in HIVICK primarily affects the mesangial cells leading to mesangial expansion, in contrast to the tubulointerstitial changes in HIVAN. However, tubulointerstitial inflammation is also common in HIVICK, with a mixture of infiltrating macrophages, eosinophils, and B cells. When complement is activated by these immune complexes, a lupus-like pathology without other systemic features or serologic evidence of lupus may occur (Lucas et al. 2014).

When comparing risk factors and outcomes between HIVICK and HIVAN, one single-center study found that patients with HIVICK were older than those with HIVAN, more likely to have hypertension, more likely to use antiretroviral therapy, and less likely to have advanced HIV disease. Patients with HIVICK also had higher eGFR, milder proteinuria, and lower risk of ESRD as compared to those with HIVAN. In contrast to the established benefit in HIVAN, the impact of antiretroviral therapy on HIVICK is less clear. In one study, ART did not appear to influence the progression to ESRD in patients with HIVICK (Foy et al. 2013). However, a recent multicenter study has shown a significant improvement in kidney function and proteinuria in patients with HIVICK who initiated antiretroviral therapy with suppression of HIV viral load; these patients also had lower rates of progression to ESRD compared to patients with HIVAN or IgA nephropathy (Booth et al. 2016). The pathogenesis of HIVICK is poorly understood, with no good animal model available to date. No studies have demonstrated the presence of HIV in renal parenchymal cells in HIVICK (Ross et al. 2001), and *APOL1* genetic variants have not been shown to be a risk factor for HIVICK.

Chronic Kidney Disease in HIV-Positive Individuals

In addition to HIVAN and HIVICK, comorbid kidney diseases also contribute to the burden of CKD in HIV-positive individuals. The reported prevalence of CKD and ESRD in the HIV population is highly variable depending on demographics. In North America and Europe, prevalence of CKD in HIV-positive adults has been reported to range from 4.7 to 9.7%, although it may be higher when taking proteinuria into account. In contrast, in a study of 400 HIV-positive patients in Nigeria, CKD (defined as raised serum creatinine or proteinuria) was found in 38% (Emem et al. 2008). Polymorphisms of the *APOL1* gene that confer genetic susceptibility to HIVAN likely explain much of the variability in CKD risk (Kopp et al. 2011). Unlike studies in West African populations, studies from East Africa, where the prevalence of high-risk *APOL1* alleles is low, have documented a much lower prevalence of CKD in HIV-positive individuals (Cailhol et al. 2011; Wools-Kaloustian et al. 2007).

Both traditional CKD risk factors and HIV-related risk factors contribute to the risk of CKD and CKD progression in HIV-positive adults. Studies have demonstrated that low CD4+ cell count, high HIV viral load, and HCV coinfection are associated with risk for CKD (Lucas et al. 2013). The relationship between antiretroviral therapy and CKD is complex and is discussed elsewhere in this chapter. Risk factors associated with progression to ESRD include a diagnosis of HIVAN, black race, family history of ESRD, heavy proteinuria, and advanced immunosuppression (Lucas et al. 2014). African descent is a notable risk factor for progression to ESRD, regardless of the underlying cause of kidney disease. In a cohort study of HIV-positive adults in Baltimore, the risk of progression from CKD to ESRD was more than 17-fold higher in blacks compared to nonblacks (Lucas et al. 2008). In studies of US military veterans, black individuals with HIV infection were as likely as black individuals with diabetes to develop ESRD (Jotwani et al. 2012). Several studies have suggested that HIV infection accelerates the course of diabetic nephropathy, the leading cause of ESRD (Jotwani et al. 2012; Medapalli et al. 2012). Although the mechanism is not fully known, experimental murine models suggest an upregulation of shared inflammatory pathways (Mallipattu et al. 2013).

As in the general population, CKD in the HIV-infected population is associated with increased risk of ESRD, cardiovascular disease, and all-cause mortality (Choi et al. 2010a). The increased mortality risk observed in HIV-positive individuals with CKD may be in part due to underexposure or inadequate dosing of ART in patients with CKD (Choi et al. 2007).

End-Stage Renal Disease in HIV-Positive Individuals

While HIV-positive patients have enjoyed improvements in life expectancy in the ART era, the risk of ESRD continues to exceed that of the general population. Data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) shows that though the incidence of ESRD has been on the decline since 2000, HIV-positive patients have a threefold higher risk of ESRD compared to the general population. Further, African-American with HIV infection has an even higher risk (Abraham et al. 2015). Racial disparities in ESRD incidence have been attributed to decreased antiretroviral therapy use, increased prevalence of comorbidities like hypertension and diabetes mellitus, and genetic predisposition based on high risk *APOL-1* alleles among African-Americans.

As described above, the incidence of new HIVAN-associated ESRD has declined since the introduction of combination antiretroviral therapy in 2006 (Razzak Chaudhary et al. 2015). A study using the USRDS Dialysis Morbidity and Mortality (DMMS) Wave 2 database estimated the prevalence of HIVAN-associated ESRD at 1% of the US dialysis population (Abbott et al. 2003), but the true prevalence of HIVAN is unknown as definitive diagnosis requires kidney biopsy. Of note, 90% of the nearly 15,000 patients with ESRD attributed to HIVAN between 1989 and 2011 were African-American (Razzak Chaudhary et al. 2015), and HIVAN remains an important cause of ESRD among African-Americans (US Renal Data System, 2009 Annual Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 2009. 2009).

Both hemodialysis and peritoneal dialysis are acceptable modalities for dialysis in HIV-positive patients with ESRD, and typical patient-specific factors should dictate which modality is used. The prevalence of HIV in the dialysis population is difficult to estimate, as the USRDS no longer collects data on HIV status. In a 2002 survey of all chronic hemodialysis centers in the United States, the prevalence of HIV infection among dialysis patients was 1.5% (Finelli et al. 2005). This prevalence is likely dependent on the patient population served; dialysis centers in urban areas, where the prevalence of HIV infection is higher, may have a prevalence of HIV infection as high as 20% (Perez et al. 1989).

Kidney transplant is also an alternative in patients with well-controlled HIV infection. Transplant in the HIV-positive patient requires careful consideration of significant drug interactions between ART and immunosuppressive medications. Observational studies of kidney transplant in HIV-positive patients in the United States and the United Kingdom showed that patient and graft survival are favorable; however, acute rejection rates are higher than in the general transplant population (Gathogo et al. 2014; Stock et al. 2010). Kidney transplant for patients with HIVAN has also been studied. A 2015 study of 11 HIVAN patients undergoing kidney transplant reported graft survival of 81% at three years, with higher rates of acute rejection as observed in other studies (Waheed et al. 2015).

The prognosis of ESRD in HIV-positive patients has significantly improved with the advent and use of antiretroviral (Ahuja et al. 2002). In dialysis-dependent HIV-positive patients with ESRD secondary to HIVAN, antiretroviral therapy can even reverse dialysis dependence (Winston et al. 2001a; Wali et al. 1998). However, while mortality has improved since the widespread use of antiretroviral therapy, mortality of patients with ESRD secondary to HIVAN is still two to three times higher than that of other dialysis patients after adjustment for race, sex, and geographic location (Razzak Chaudhary et al. 2015). Nephrologists and infectious disease

physicians must continue to work together to prevent the development and progression of kidney disease and to optimize the management of ESRD in HIV-positive individuals.

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HIVAN, Pediatric

31

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Abstract

HIV-associated nephropathy (HIVAN) is a renal disease that affects HIV+ people of African ancestry with a high viral load and a genetic predisposition to develop this disease. From the clinical point of view, HIVAN is characterized by heavy proteinuria, nephrotic syndrome, and rapid progression to end-stage kidney disease (ESKD). Renal histological studies show focal segmental glomerulosclerosis (FSGS), collapsing glomerulopathy, which is less common in children, and microcystic tubular dilatation. HIVAN has a significant clinical impact in the quality of life and survival of HIV+ children. This chapter will discuss relevant issues related to the diagnosis, pathogenesis, clinical outcome, and treatment of children with HIVAN, focusing on the most relevant renal pathological, genetic, and virological factors that precipitate this renal disease. HIV-1 infection of renal epithelial cells appears to play a key role in this process, at least partially by inducing chronic renal epithelial injury, and triggering a persistent renal inflammatory and regenerative response that leads to renal enlargement and rapid progression of the renal disease. New antiretroviral therapies (ART) have been efficient in preventing and improving the outcome of children with HIVAN, and significant progress has been made in the field of renal transplantation in HIV+ people. However, physicians have had less success providing chronic ART to HIV+ children and adolescents, and HIVAN remains a problem in children of African ancestry all over the world. In addition, some antiretroviral drugs can induce renal injury per se. Overall, better prevention and treatment programs are needed to eradicate this renal disease in children.

Keywords

HIV-nephropathy · Children · Antiretroviral therapy · APOL-1 risk variants · Heparan sulfate proteoglycans · HIV-1 infection

Introduction

According to the World Health Organization, an estimated 3.2 million children were living infected with HIV-1 at the end of 2013, mostly in sub-Saharan Africa. The majority of these children acquired HIV from their mothers during pregnancy, birth, or breastfeeding. Today, with appropriate antiretroviral therapy (ART), the risk of mother-to-child HIV transmission has been reduced to ~2%. However, such interventions are still not widely accessible in most resource-limited countries, where the burden of HIV-infection is very high. In contrast, in countries where antiretroviral therapy (ART) has been successfully introduced, it has changed the face of HIV infection in a dramatic manner. HIV-infected infants now survive to adolescence and adulthood, but they need to receive daily effective (ART) treatment to remain in good health. Therefore, providing chronic ART and good medical care to HIV+ children remains a big challenge all over the world.

Prior to the widespread use of antiretroviral therapy (ART), more than 40% of all HIV+ children experienced a large number of renal complications associated with the progression of HIV-infection, and leading to poor growth and survival rates. These renal complications included a higher prevalence of acute kidney injury (AKI) (Strauss et al. 1989a; Pardo et al. 1987; Ray et al. 1998b; Mcculloch and Ray 2008), glomerulopathies associated with immunological disorders (Trachtman et al. 1991; Katz et al. 1992;

Connor et al. 1988), lupus nephritis (Mialou et al. 2001), thrombotic microangiopathies (Turner et al. 1997), and HIV-1 associated nephropathy (HIVAN) (Strauss et al. 1989a; Pardo et al. 1987; Ray et al. 1998b; Ingulli et al. 1991). Among these renal diseases, HIVAN received considerable attention because it was considered a novel renal disease induced directly by a new human retrovirus. HIVAN was characterized by a unique combination of clinical and renal histological features leading to end-stage kidney disease (ESKD). Another intriguing feature of HIVAN was its predilection for African-American patients (Kopp and Winkler 2003; Freedman et al. 1999; Pardo et al. 1987). African Americans represent approximately 65% of all children with HIV-1 infection or AIDS in the United States (Fauci 2003; Gallo 2002). Thus, in a short period of time, proteinuria and HIVAN became a common clinical finding in HIV+ children of African ancestry in the United States (Rajpoot et al. 1996; Ray et al. 1998b; Chaparro et al. 2008; Purswani et al. 2012) and all over the world (Steel-Duncan et al. 2008; Mcculloch and Ray 2008; Nourse et al. 2010; Bhimma et al. 2013; Ramsuran et al. 2012; Dondo et al. 2013; Shah et al. 2012; Iduoriyekemwen et al. 2013; Ekulu et al. 2012; Esezobor et al. 2010; Eke et al. 2010). Unfortunately, the true prevalence of childhood HIVAN is unknown, since in many pediatric centers, renal biopsies have not been performed regularly in HIV-infected children with proteinuria. Studies done in early years of the AIDS epidemic reported a prevalence of childhood HIVAN of approximately 10–15% in populations with a majority of HIV+ African-American children (Strauss et al. 1989a; Ray et al. 1998b; Connor et al. 1988). Subsequently with the development of highly effective ART, the prevalence decreased significantly; however, there continues to be children who develop HIVAN because they do not receive timely and appropriate ART. Nonetheless, persistent proteinuria, the first clinical symptom of HIVAN, is also common in HIV+ children receiving ART, with a prevalence all over the world ranging from 5% to 10% or higher in some countries (Dondo et al. 2013; Chaparro et al. 2008; Mcculloch and Ray 2008; Nourse et al. 2010; Shah et al. 2012; Iduoriyekemwen et al. 2013; Ramsuran et al. 2012). In the present chapter, relevant issues related to the history, epidemiology, pathogenesis, diagnosis, and treatment of childhood HIVAN will be discussed.

History of HIV-Associated Nephropathy

In 1981, Michael Gottlieb and colleagues working at the University of California in Los Angeles described for the first time the clinical symptoms of what is known today as the acquired immunodeficiency syndrome (AIDS) (Gottlieb et al. 1981). In January of 1983, Montagnier and colleagues at the Pasteur Institute isolated the virus that causes AIDS (Barre-Sinoussi et al. 1983). In the same year, AIDS was identified in children, and the transmission of this virus from mothers to infants was confirmed (Oleske et al. 1983; Rubinstein et al. 1983; Cowan et al. 1984). At that time, pediatric AIDS in the United States was diagnosed in two distinct groups of children: (1) infants who become infected through perinatal (vertical) transmission, and (2) school-age children, the majority of whom acquired HIV-1 through blood transfusion, mostly patients with hemophilia or those undergoing heart surgery. In 10 years since its first description, HIV-1 infection became the fourth leading cause of death among children 1–4 years of age (Lindegren et al. 2000), and AIDS became a major public health challenge all over the world.

In 1984, HIVAN was identified in adult HIV+ patients from New York and Miami (Rao et al. 1984; Pardo et al. 1984). This renal disease was first named AIDS-associated nephropathy, but the name was changed to HIVAN when HIV+ individuals without AIDS develop a similar renal disease (Bourgoignie and Pardo 1991). Nonetheless, during the first years of the AIDS epidemic, the contribution of HIV-1 to the pathogenesis of HIVAN was questioned on the basis that the renal lesions were indistinguishable from heroin-associated nephropathy (HAN) or idiopathic FSGS. Thus, the identification of HIVAN in African-American children who acquired AIDS through vertical transmission (Strauss et al.

1989a; Connor et al. 1988; Pardo et al. 1987) provided compelling evidence for the existence of a specific HIV-induced glomerulopathy that could evolve independently of intravenous drug use (Strauss et al. 1989a; Pardo et al. 1987).

The HIV-1 Virus

Previous review articles have discussed in great detail the structure of the HIV-1 virus (Fauci 2003; Gallo 2002). Here we will review only key concepts that are essential to understand the pathogenesis of HIVAN. Briefly, the HIV-1 virus is a lentivirus, a subgroup of retroviruses that carries a single-stranded RNA and uses its own reverse transcriptase enzyme to generate DNA inside the host's cells. It is called a retrovirus because it has to "reverse the usual flow of genetic information" in order to generate DNA. This DNA is integrated into the genome of the host cells, where it becomes a provirus, and can undergo the usual transcription and translation processes to generate viral transcripts and HIV-proteins. The HIV-1 provirus is ~9.8 kilobases in length and is flanked by a repeated sequence known as long terminal repeats (LTR) (Fig. 1). The HIV-1 genome contains 9 genes that are located in the central region of the proviral DNA and produce at least 15 individual proteins that are divided in structural, regulatory, and accessory proteins (Fauci 2003; Gallo 2002). Three HIV-1 genes, *gag*, *pol*, and *env*, make the structural proteins, which include Gag (an acronym for group-specific antigen), Gag-Pol precursor, HIV-protease (Pro), reverse transcriptase (RT), integrase (In), and envelope (Env) (Fig. 1). These proteins provide the basic physical infrastructure of the viral nucleocapside. The *gag* gene gives rise to the 55 kD Gag precursor protein p55, which is cleaved by the virally encoded protease (Pro), a product of the *pol* gene. In this manner, Gag generates four smaller proteins designated matrix (MA or p17), capside (CA or p24), nucleocapside (NC or p9), and p6, which comprise the nucleoprotein retroviral core and have different functions. The p24 levels are

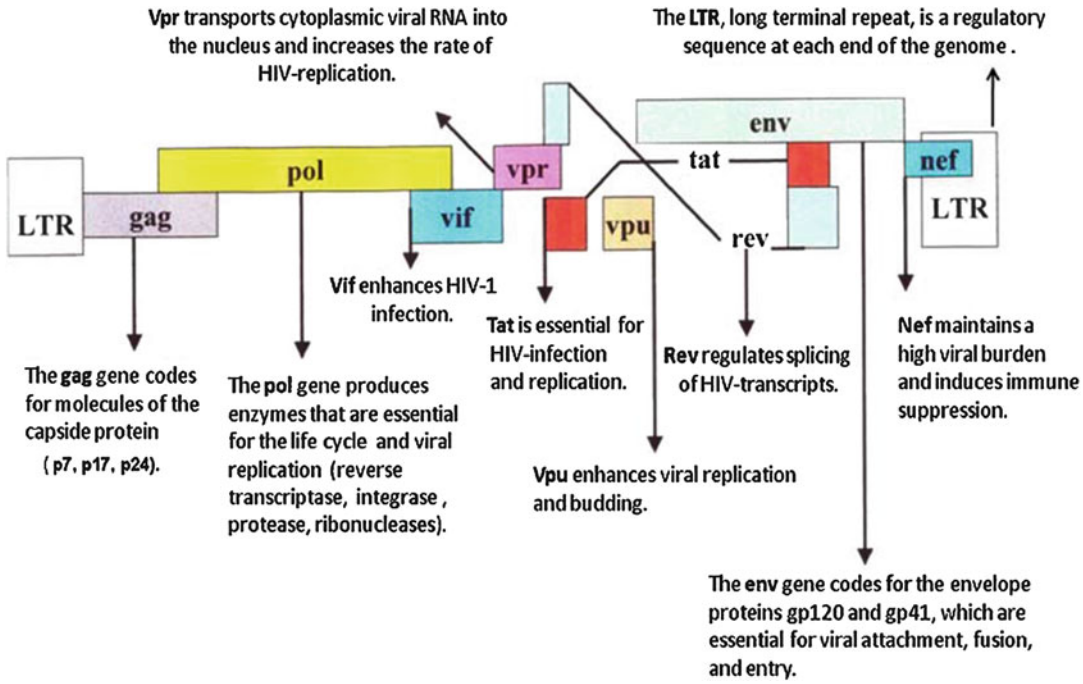

Fig. 1 Function of HIV-1 viral proteins (Figure 1 is reproduced with permission of Springer from Ray PE. "Taking a hard look at the pathogenesis of childhood HIVAN-associated nephropathy" Pediatric Nephrology 24:2109–2119, 2009 (page 2112; License number 3984440284188)

measured in tissue culture supernatants to identify cells that are productively infected. The *pol* gene (DNA polymerase) also generates the enzymes RT and In. These enzymes play a critical role in the processes of reverse transcription and DNA integration, two critical steps in the viral cycle of retroviruses (Bowerman et al. 1989). The *env* gene encodes for the HIV-1 proteins gp120 and gp41, which constitute the viral envelope surface protein of HIV-1 as it "buds" out from the cells, and determines viral tropism and infectivity (Fauci 2003; Gallo 2002). In addition, HIV encodes two important regulatory proteins named Tat (regulator transactivator protein) and Rev (differential regulator of expression of virus protein), which are essential for HIV infection, replication, and for the regulation of splicing of HIV RNA transcripts (Fauci 2003; Gallo 2002) (Fig. 1). Finally, HIV-1 generates four accessory proteins named Nef (auxiliary protein), Vif (virus infectivity factor), Vpu (virus protein U), and Vpr (virus protein R), which play key roles in viral replication and infection (Fauci 2003; Gallo 2002) (Fig. 1). At least four HIV-viral proteins, Env, Tat, Nef, and Vpr, have been linked directly to the pathogenesis of HIVAN (Shirai and Klinman 1993; Singhal et al. 1995; Xie et al. 2014; Hanna et al. 1998; He et al. 2004; Dickie et al. 2004; Zhong et al. 2005), and their specific role in the pathogenesis of HIVAN is currently under investigation. The function of these HIV-proteins has been well studied in lymphocytes. Tat plays an essential role in HIV-replication by recruiting a cellular human protein called cyclin T1, which efficiently increases viral transcription, and also induces the activation of NFκB and the HIV-LTR. In the absence of Tat, the basal activity of the HIV-LTR varies significantly depending on the integration sites; however, in the presence of Tat, viral expression is efficient regardless of the integration site. Tat released by HIV-1 infected cells can be taken up by neighboring cells acting as a secreted cytokine (Gallo 2002). Vpr modulates the cell cycle of host cells and plays a key role promoting the infection of macrophages and nondividing cells, therefore increasing the number and type of cells that can be infected by HIV-1. In addition, Vpr can enter the nucleus of HIV-infected cells and cause changes that facilitate the entry of viral DNA and HIV-proteins into the nucleus. Nef functions at an early phase in the viral replication cycle, therefore enhancing viral replication and infectivity. In addition, Nef downregulates cell surface proteins such as CD4 and major histocompatibility complex (MHC) class I and II, protecting HIV-infected cells, and modulates several signal transduction and endosome trafficking pathways (Gallo 2002).

Classic Mechanism of HIV-Infection

HIV-1 induces a productive infection of T cells predominately by a process that involves the fusion of the envelope protein (gp120-gp41) to the plasma membrane (Stevenson 2003). The fusion of HIV-1 to the cell membranes of T cells is triggered by the interaction of gp120 with the CD4 molecule (major HIV-1 receptor), and one of the HIV-1 coreceptors CXCR4 or CCR5, belonging to the chemokine receptor family (Fig. 2). Once inside the cells, the HIV-1 RNA is copied by the reverse transcriptase into a complementary single strand of DNA. In the cytoplasm, the single-stranded retroviral DNA is copied into double-stranded retroviral DNA (Stevenson 2003) (Fig. 2). Subsequently, the retroviral DNA migrates into the nucleus of the host cells and become integrated as a DNA provirus. At this stage, HIV-1 could remain in a latent form without producing viral proteins or start producing new copies of HIV RNA. HIV-1 preferentially integrates into active genes and has developed mechanisms that permit its replication in nondividing cells (Gallo 2002). Within the host cell, the HIV-proviral DNA, when activated, produces new strands of HIV RNA. Some of the RNA strands behave like mRNA producing proteins essential for the production of HIV-1 while others become encased within the viral core proteins to become the new viruses (Stevenson 2003) (Fig. 2). All the steps involved in the infection of T cells, including the binding of envelope to CD4, CXCR4, or CCR5, HIV-fusion, reverse transcriptase, integration, production of proteases, and budding have been exploited to generate very powerful

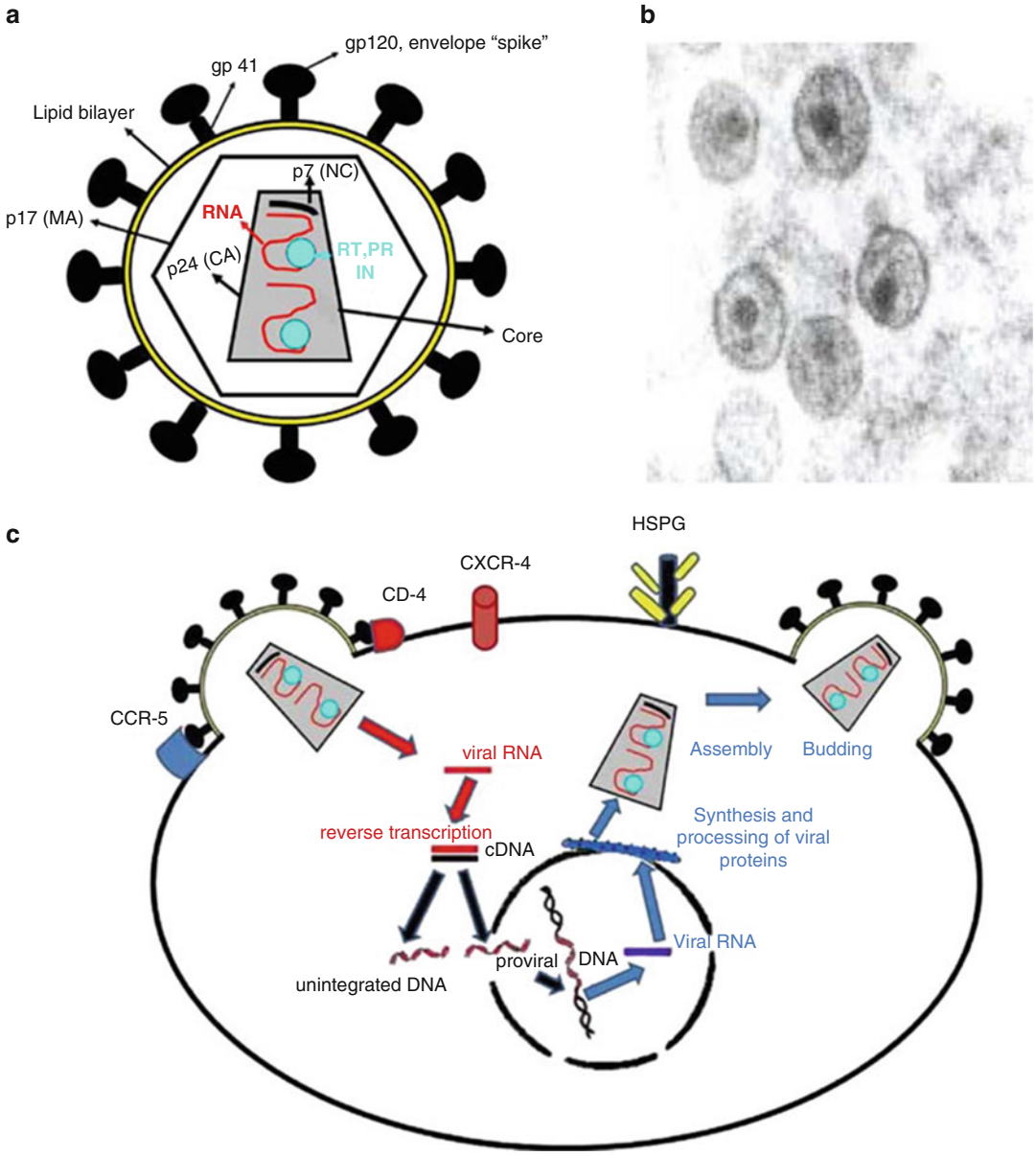

Fig. 2 Structure and viral cycle of HIV-1 in productively infected cells. (**a**) Diagram of the HIV-1 virus. The viral proteins (*p*) are designated with a number corresponding to the protein size (Å ~ 1000). (**b**) Electron micrograph picture of mature viral particles (Å ~ 100,000). (**c**). Representative diagram of the viral cycle in productively infected cells. *MA* matrix protein, *CA* capside, *NC* nucleocapside, *RT* reverse transcriptase, *PR* protease, *IN* integrase, *CD4* HIV-1 receptor, *CXCR-4, CCR-5* HIV-1 coreceptors, *HSPG* heparan sulfate proteoglycans (Figure 2 is reproduced with permission of Springer from Ray PE. "Taking a hard look at the pathogenesis of childhood HIVAN-associated nephropathy" Pediatric Nephrology 24:2109–2119, 2009; page 2111; License number 3984440284188)

antiretroviral therapies (ART) that have changed the clinical outcome of HIV-infection.

Epidemiology

Every day there are approximately 1500 new infections in children under 15 years of age, most of them (90%) occurring in the developing world due to the vertical transmission of HIV-1. If left untreated, HIV-infected infants will develop clinical symptoms in the first year of life, and by 1 year of age approximately one-third of infected infants will have died. According to the World Health Organization, the number of children (younger than 15 years) receiving ART in low- and middle-income countries more than doubled from 2009 to 2013, from 355,000 to 740,000. At the end of 2013, less than one-quarter (23%, range 21–25%) of children living with HIV were receiving ART in low- and middle-income countries compared with more than one-third (37%, range 35–39%) of adults living with HIV. It is expected that more children will receive ART in future years.

Pathogenesis of Childhood HIVAN

Our understanding of the pathogenesis of HIVAN has evolved throughout the last 30 years. The current pathological paradigm of HIVAN is that renal epithelial cells (REc) become productively infected and produce viral transcripts that precipitate the development or epithelial injury and proliferative lesions in people who carry a genetic predisposition to develop this disease. The pathogenic mechanisms responsible for the development of HIVAN in adults appear similar in children and involve a direct role of viral infection of the kidney (Mcculloch and Ray 2008); however, children may respond to HIV-1 in a different manner because their tissues and immune system are undergoing growth and development changes (Ray and Hu 2011). It has been noted that young children can develop the typical tubular-interstitial changes in the absence of FSGS or glomerular collapse, suggesting that HIV-1 is capable of inducing direct tubular-interstitial damage (Mcculloch and Ray 2008). In addition, HIV-infected children are usually not exposed to many of the several comorbidities, drugs, or risks factors that affect adult patients. Here, we will discuss the experimental model systems that have been used to explore the pathogenesis of childhood HIVAN.

HIV-Transgenic Mice

One important clue to understand the pathogenesis of HIVAN was revealed in the early 1990s with the generation of HIV-transgenic (Tg) mice that develop a HIVAN-like renal disease. These mice were developed bypassing the infection process by inserting the HIV-proviral DNA d1443 construct into the mice's genome. This replication defective HIV-construct lacks a 3 kb sequence overlapping the *gag* and *pol* genes and is driven by the HIV-LTR (Dickie et al. 1991; Kopp et al. 1992). HIV-Tg mice show expression of HIV-1 mRNA in a wide range of cells, including glomerular and tubular epithelial cells (Kopp et al. 1992), as reported in patients with HIVAN (Cohen et al. 1989). Heterozygous mice are born with normal kidneys and develop progressive renal disease during their first months of life (Kopp et al. 1992). Severe edema and nephrotic syndrome occur approximately between 60 and 250 days of age (Kopp et al. 1992). At this time, HIV-Tg_{26} mice usually showed BUN levels exceeding 200 mg/dl and elevated serum creatinine ($>$ 1 mg/dl) and die of uremia (Kopp et al. 1992). However, not all mice develop renal disease, and their susceptibility to develop kidney disease, as it was described in humans, is also influenced by mouse host genetic variants (Gharavi et al. 2004; Chan et al. 2009). HIV-Tg rats carrying a similar HIV-proviral construct developed a similar renal disease (Ray et al. 2003; Reid et al. 2001), providing further support to the notion that HIV-genes play a direct role in the pathogenesis of HIVAN. In addition, other HIV-transgenic mouse lines generated years later with different HIV-DNA constructs (Kajiyama et al. 2000; Dickie et al. 1993, 2004; Zhong et al. 2005; Husain et al. 2005;

Hanna et al. 1998), highlighted the role of HIV-genes, including *nef* and *vpr*, in the pathogenesis of HIVAN. In summary, all these models provide key evidence to support the notion that the expression of HIV-genes in renal epithelial cells plays a key role in the pathogenesis of HIVAN.

Infection of Renal Epithelial Cells

A key issue to validate the clinical relevance of the HIV-Tg models described above is to define whether HIV-1 could induce a productive infection of renal epithelial cells. After the initial identification of HIV-1 transcripts in renal epithelial cells reported in the late 1980s (Cohen et al. 1989), several studies failed to detect similar findings in renal sections derived from patients with HIVAN (Barbiano Di Belgiojoso et al. 1990; Alpers et al. 1992; Eitner et al. 2000). In addition, previous studies were unable to detect significant protein levels of HIV-receptors/coreceptors in the epithelial cells of patients with and without HIVAN (Eitner et al. 1998, 2000). Therefore, the question of whether renal epithelial cells could become productively infected or not became a matter of intensive research and controversy, in particular considering that these cells do not express CD4, the major HIV-receptor. Nonetheless, in 1998, renal epithelial cells cultured from the urine of children with HIVAN were used for the first time to demonstrate that HIV-1 isolates derived from children with HIVAN could induce a low-level productive infection of these cells (Ray et al. 1998a). Although these tubular epithelial cells produced significant lower levels of p24 antigen, when compared to HIV-infected macrophages, they transferred viruses and infected cocultured HIV-negative mononuclear cells for at least 20 days in culture (Ray et al. 1998a). In addition, this study showed that the transfer of HIV-particles through cell-to-cell contact between primary HIV+ mononuclear cells and renal tubular epithelial cells was the most efficient manner of infecting these cells (Ray et al. 1998a) (Figs. 3 and 4). However, since renal epithelial cells did not express detectable protein levels of CD4, or the HIV-1 coreceptors CCR-5 or CXCR-4, the infection mechanism remained poorly understood. Follow up studies confirmed the presence of viral transcripts in podocytes and renal tubular epithelial in adult patients with HIVAN (Bruggeman et al. 2000; Marras et al. 2002; Winston et al. 2001; Canaud et al. 2014). However, studies done in podocytes or tubular epithelial cells cultured from HIV-negative people showed that these cells could not become productively infected when exposed to cell-free HIV-1 (Miyauchi et al. 2009; Mikulak et al. 2010; Hatsukari et al. 2007). Alternatively, one study showed that interactions between infected T cells and renal tubular epithelial cells create virological synapses that allow viral uptake and gene expression in renal epithelial cells (Chen et al. 2011). Nonetheless, despite the different results, all these studies support the notion that HIV-1 can enter renal epithelial cells via endocytosis in a CD4-independent manner.

Alternative Mechanisms of HIV-1 Infection

It is well established that HIV-1 can also enter lymphocytes and other cell types via endocytosis and become trapped in endosomal compartments, where it may avoid degradation by escaping into the cytoplasm or undergoing fusion within endosomes (Fackler and Peterlin 2000; Miyauchi et al. 2009). Although the endocytic uptake of HIV particles usually leads to a non-productive infection when the viruses are degraded in the lysosomes, it is possible that some viruses could escape into the cytosol via receptor-mediated fusion. There is evidence that the gradual pH decrease in the lumen of endocytic vesicle may permit the escape into the cytosol of some HIV-1 particles (Daecke et al. 2005). In this manner, HIV-1 could be internalized via endocytosis prior to membrane fusion and complete its fusion process within endosomes inside the cells (Miyauchi et al. 2009). This process is sensitive to dynasore, a small molecule inhibitor of the dynamin GPT-ase activity. Dynamin is a 100 kD GTPase that

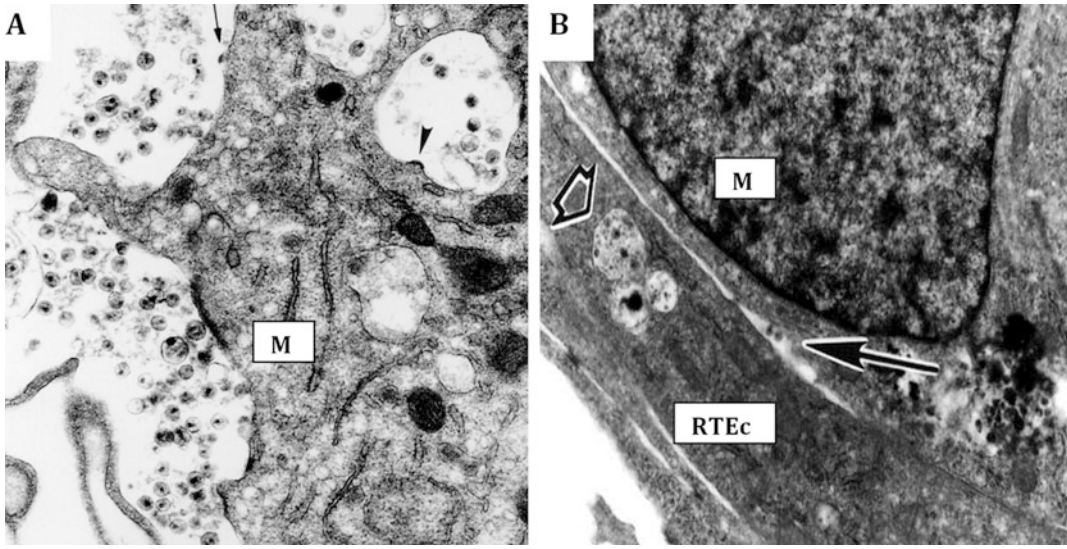

Fig. 3 **Panel A** shows HIV-viruses "budding" from an HIV-infected mononuclear cell (*M*) harvested from an HIV-infected child with renal disease. **Panel B** shows a mononuclear cell (*M*) on top of a renal tubular epithelial cell (RTEc) harvested from an HIV-infected child with renal disease. Viruses released from the mononuclear cell (*M*) (*black arrow*) can be transferred to the RTEc (*open arrow*)

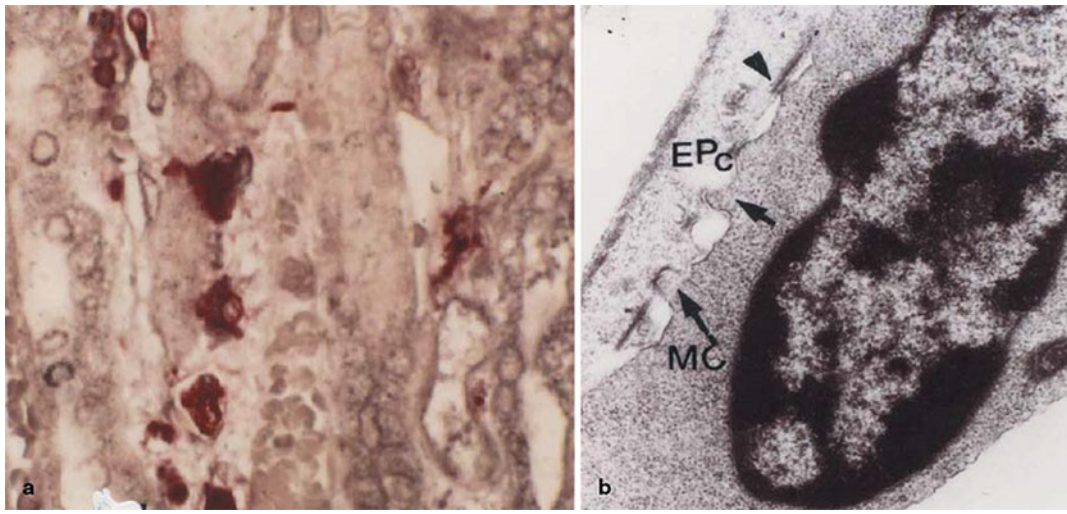

Fig. 4 Immunohistochemistry for the CD68 antigen. The light microscopy picture on the *left* panel (**a**) shows a CD-68 staining of macrophages (*red color*) infiltrating the kidney of a child with HIVAN, original magnification ×400. The electron micrograph on the *right* panel (**b**) shows close contact interactions between cultured primary mononuclear cells (*MC*) and renal tubular epithelial cells (*EPc*). Cells were harvested from a child with HIVAN. Original magnification ×38,000. (Figure 4 is reproduced with permission of Springer from Ray PE, Liu Xu, Rakusan T, Liu Xue-Hui. "A 20-year history of childhood HIV-associated nephropathy" Pediatric Nephrology 19:1075–1092. Figure 2, page 1081; License Number 3984431229899).

mediates the release of endocytic vesicles from the plasma membrane and facilitates the escape of HIV-1 from endosomes (Miyauchi et al. 2009; Daecke et al. 2005). In contrast, dynasore prevents the scission of endocytic vesicles from the inner leaflet of the plasma membrane and inhibits clathrin-mediated endocytosis, as well as the fusion of HIV-1 to endosomes (Miyauchi et al. 2009). Taken together, these findings imply that some cells could become infected via endocytosis and envelope glycoprotein-dynamin-dependent fusion within intracellular compartments (Miyauchi et al. 2009). In support of this notion, HIV-1 infection via endosomes has been reported in macrophages, lymphocytic cells, and HeLa cells (Connell and Lortat-Jacob 2013). In agreement with these findings, two studies showed that HIV-1 can enter into cultured primary human podocytes via dynasore-mediated endocytosis (Khatua et al. 2010; Li et al. 2016). It is well established that HIV-1 particles are efficiently taken up by clathrin-coated vesicles (Marechal et al. 1998; Goto et al. 1988), and that dynamins can facilitate the release of these vesicles from the plasma membrane and endosomes.

Role of Transmembrane TNF-α Facilitating the Low-Level Productive Infection of Cultured Renal Epithelial Cells

A recent study reported that transmembrane TNF-α, (tm-TNF-α) which is abundantly expressed in podocytes cultured from children with HIVAN, plays a critical role in this process, further facilitating the establishment of a low-level productive infection in podocytes and tubular epithelial cells (Li et al. 2017). More specifically, tm-TNF-α increases the viral entry process via a dynamin-mediated mechanism that is blocked by dynasore and enhances the replication of HIV-1 in these cells via the stimulation of NFkB and activation of the HIV-LTR (Li et al. 2017). Heparan sulfate proteoglycans also appear to play a critical role in these cells facilitating the attachment and entry of the HIV-1 envelope protein (Li et al. 2017). Although it could be argued that the role of HSPG may be limited to virus strains cultured in the laboratory, there are studies showing that primary viruses can also use HSGP as attachment and entry receptors (Bobardt et al. 2003; Zhang et al. 2002). The precise mechanisms through which tm-TNF-α may also facilitate the release of HIV-1 into the cytoplasm and integration in the nuclei of podocytes and renal epithelial cells remains undefined, and more studies are needed to understand this process. In this regard, it is worth mentioning that tm-TNF-α is the precursor of soluble TNF-α and can act both as a ligand or as a receptor (Grell et al. 1995). Therefore, in children with HIVAN, tm-TNF-α could induce cell-to-cell contact-dependent signaling and raise the concentration of soluble TNF-α, in the proximity of TNF receptors (TNFR) (Grell et al. 1995). These events could enhance the expression of cell adhesion and signaling molecules involved in viral entry and replication. Furthermore, tm-TNF-α can activate the noncanonical NFkB pathway acting through TNFR2, which has higher affinity for tm-TNF-α, than soluble TNF-α (Al-Lamki et al. 2005; Grell et al. 1995). Finally, through all these mechanisms, tm-TNF-α may facilitate the formation of viral synapses between renal epithelial cells and HIV-infected mononuclear cells, facilitating the infection of tubular epithelial cells (Ray et al. 1998a; Chen et al. 2011) (Figs. 3 and 4). Taken together, all these findings suggest that renal epithelial cells cultured from children with HIVAN may be "primed" by tm-TNF-α to become latently or productively infected, albeit at low levels, when they are either exposed to a high viral load or interact with HIV-infected mononuclear cells.

The role of the APOL1 risk variants that predispose to HIVAN, during the infection of renal epithelial cells is the subject of intense ongoing research. So far, one study reported that endogenous expression of APOL1 in differentiated monocytes contributes to HIV-1 suppression (Taylor et al. 2014), while another study showed that APOL1 G1 podocytes cultured from children with HIVAN can be infected (Li et al. 2017). More research is needed to define how the APOL1 risk variants modulate this process.

Renal Enlargement and Epithelial Proliferative Changes in Children with HIVAN

One distinctive feature of HIVAN is the presence of tubular microcysts and proliferating epithelial cells (Pardo et al. 1984; Rao et al. 1984; Strauss et al. 1989a; Ray et al. 1998b). The pathogenic mechanisms responsible for the renal epithelial proliferative lesions, however, are not completely understood and have been the subject of many studies and controversy during the last 30 years. The initial demonstration that HIV-1 genes/cytokine milieu per se could induce direct proliferative changes in renal epithelial cells was made in the HIV-Tg_{26} mouse model (Ray et al. 1994). Two stages of the renal disease were described in these mice. The early stages are characterized by an upregulated expression of HIV-1 genes in association with the induction of proteinuria and renal epithelial injury (Ray et al. 1994). These findings suggested that activation of HIV-1 genes in vivo induced renal epithelial injury. In support of this notion, activation of HIV-1 genes expression by ultraviolet light irradiation induced apoptosis in cultured tubular epithelial cells (Bruggeman et al. 1997). These findings are also in agreement with the studies done in primary renal tubular epithelial cells cultured from children, which grow at a slower rate when exposed to HIV-1 (Ray et al. 1998a). In contrast, the late stages of the renal disease in HIV-Tg_{26} mice are characterized by a remarkable proliferation of renal tubular epithelial cells, associated with low levels of HIV-1 gene expression, and the accumulation of heparin-binding growth factors bound to renal heparan sulfate proteoglycans (HSPGs) (Ray et al. 1994) (Fig. 5).

HSPGs serve as low-affinity receptors for many heparin-biding growth factors, including FGF-2, VEGF-A, and TNF-α, and therefore facilitate the renal accumulation of these factors, protecting them from proteolytic degradation (Ray et al. 1994). In addition, these heparin-binding growth factors can enhance the renal recruitment of mononuclear cells, as well as the attachment of HIV-1 infected cells to renal epithelial cells (Tang et al. 2005) (Fig. 4). In a similar manner to HIV-Tg_{26} mice, children with HIV-renal diseases also show an upregulated expression of renal HSPG (Fig. 5) and FGF-binding proteins (Ray et al. 1999, 2006; Liu et al. 2001). The renal accumulation of heparin-binding growth factors can induce proliferative changes in podocytes and tubular epithelial cells (Ray et al. 1994, 1999, 2006; Korgaonkar et al. 2008). Podocytes are terminal differentiated cells, and when they are forced to proliferate, they could detach, die, or undergo apoptosis (Sasaki et al. 1999; Kriz et al. 1995). These cells, however, are then replaced by less differentiated parietal epithelial cells or renal progenitor cells (Dijkman et al. 2006; Ronconi et al. 2009), which are also sensitive to FGF-2 and other cytokines (Lam et al. 2014; Barasch et al. 1997; Kanemoto et al. 2003; Ohse et al. 2009; Drummond et al. 1998). Furthermore, FGF-2 and VEGF-A potentiate the ability of HIV-Tat to induce cytoskeletal changes and increase the permeability of cultured renal endothelial cells and podocytes (Das et al. 2016). Alternatively, HIV-Tat can precipitate the development of renal disease in young HIV-Tg_{26} mice by increasing the expression of HIV-1 genes, and these changes are exacerbated by FGF-2 (Xie et al. 2014). Finally, the urinary levels of FGF-2 and VEGF-A are elevated in children with HIVAN, and both factors appear to be candidate biomarkers to follow the course of HIV-renal diseases in children (Perazzo et al. 2015; Soler-Garcia et al. 2009a, b; Das et al. 2016).

An alternative view to explain the pathogenesis of the renal proliferative lesions seen in HIVAN is that HIV-1 genes per se, and *nef* in particular, induce direct proliferative changes by stimulating specific signaling proliferative pathways (Husain et al. 2002; He et al. 2004). In this view, HIV-1 infected podocytes undergo simultaneous dedifferentiation and proliferative changes driven directly by *nef,* through the stimulation of Src family kinases and mitogen-activated protein kinase (MAPK) (Ratnam et al. 2008). This view is based on in vitro studies done in conditionally immortalized cultured murine podocytes (Husain et al. 2002; He et al. 2004) and has not been validated in cultured human podocytes or tubular epithelial cells. Furthermore, transgenic mice expressing *nef* selectively in podocytes failed to

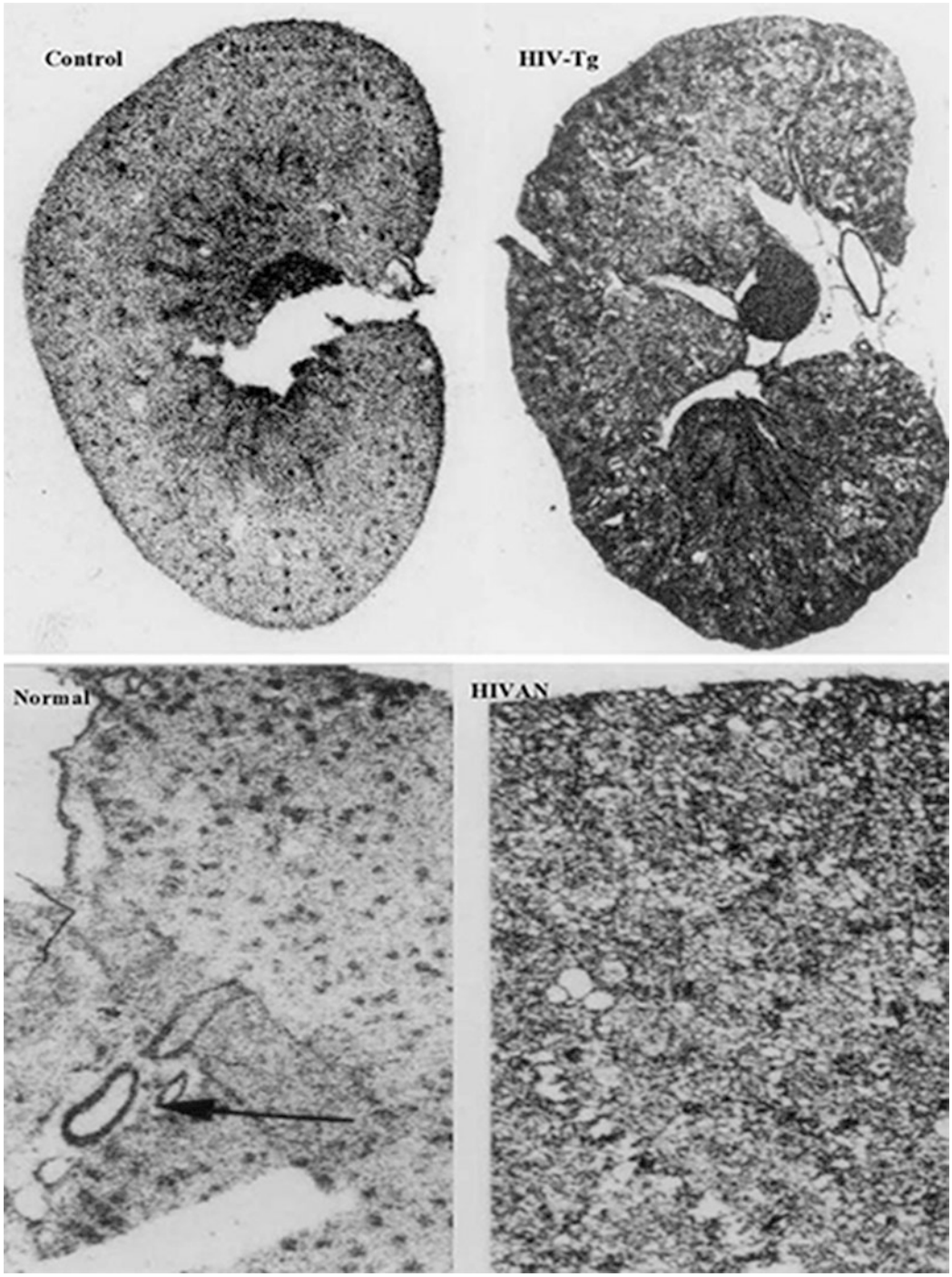

Fig. 5 Total binding of ^{125}I-Fibroblast Growth Factor-2 by ex-vivo autoradiography. The *upper panels* show the kidneys of wild type (control) and HIV-Tg_{26} mice, respectively. Original magnification ×20. The *lower panels* show the renal cortex from a control child (normal) and from a child with HIVAN. The *black arrow* points to FGF-2 binding in renal vessels. Original magnification ×60 (Figure 5 is reproduced with permission of Springer from Ray PE, Liu Xu, Rakusan T, Liu Xue-Hui. "A 20-year history of childhood HIV-associated nephropathy" Pediatric Nephrology 19:1075–1092. Figure 2, page 1083; License Number 3984431229899)

develop significant podocyte proliferative changes or proteinuria and had normal histology by light microscopy (Husain et al. 2005). Other studies have suggested that HIV-1 may induce the proliferation of glomerular parietal epithelial or renal progenitor cells in patients with HIV-collapsing glomerulopathy (Dijkman et al. 2006). Finally, many other pathogenic pathways have been described in the literature to explain the renal proliferative changes in patients with HIVAN. These studies are not discussed in this chapter because they have not been explored in depth in children with HIVAN.

Host Genetic Susceptibility to Develop HIVAN

People of African descent are at markedly increased risk (>18-fold) for developing HIVAN when compared to people of European descent (Kopp et al. 2008). The discovery in 2010 that two common genetic variants of the APOL-1 gene, named G1 and G2, located in a region of chromosome 22q12 were strongly associated with the risk of developing HIVAN, idiopathic FSGS, and hypertension-attributed ESKD constituted a major breakthrough in understanding why mainly people of African descent develop HIVAN (Genovese et al. 2010a). Initially, it was thought that risk variants for the gene MYH9 located in chromosome 22q12 were responsible for the genetic susceptibility of African Americans to develop HIVAN (Kopp et al. 2008; Kao et al. 2008). However, in 2010, using mapping by admixture linkage disequilibrium and database mining in 1000 Genomes Project, three independent studies demonstrated that the APOL1 risk variants were more relevant to identify the association with FSGS and ESKD (Genovese et al. 2010a, b; Tzur et al. 2010). In sum, two haplotypes, harboring three coding sequence mutations of APOL1 were identified as risk variants. The first one, termed G1, is a two-nonsynonymous-SNP haplotype (rs73885319 (A → G; S342G) and rs60910145 (G → T; I384M). The second one, termed G2, is a two-codon-deletion haplotype (rs71785313 (6-bp in frame deletion; DN388Y389). In addition, it was demonstrated that the distribution of the APOL1 G1 haplotype in African populations is consistent with the pattern of African ancestry risk of developing ESKD previously attributed to MYH9 (Tzur et al. 2010). Finally, subsequent studies suggested that the lifetime risk of kidney disease in adult patients with two APOL1 risk alleles increased from <10 to >50% in patients not treated appropriately with ART (Kopp et al. 2011). It should be noted, however, that HIV-infected patients with and without the APOL1 gene risk variants can develop HIVAN, and that they have similar clinical and pathological characteristics (Atta et al. 2012). Moreover, in young children, the relative contribution of two APOL1 risk alleles to the pathogenesis of HIVAN has not been clearly defined, although it is assumed that they should play a similar role than in adults.

Role of APOL-1

The APOL1 gene was first cloned and characterized in 1997 (Duchateau et al. 1997). Only humans, gorillas, and baboons retained a functional expressed APOL1 gene, and the function of this protein is not well understood (Limou et al. 2015). Extracellular ApoL1 interacts with apolipoprotein A1 (ApoA1), as a component of circulating high-density lipoprotein complexes in human plasma (Duchateau et al. 1997). Apolipoprotein L1 (ApoL1) is considered a BH3-only, phospholipid-binding pro-death protein that, when overexpressed intracellularly, induces autophagy and autophagic cell death in all cell types examined thus far, including those originating from normal kidney and cancerous tissues (Wan et al. 2008; Zhaorigetu et al. 2008; Smith and Malik 2009). APOL1 is also the trypanolytic toxin that provides innate resistance of humans against the infection with the African Trypanosoma *brucei (T. b.),* which induces African sleeping sickness (Vanhamme et al. 2003). The parasite internalizes the trypanolytic complex carrying APOL-1 through receptor-mediated endocytosis. APOL1 is then transported to the lysosome, where it is released within the

lysosomal membrane at low pH and forms an ionic channel that provokes osmotic swelling and the parasite's death (Perez-Morga et al. 2005). Resistance of the T. *b. rhodesiense* to APOL1-induced trypanolytic activity is conferred by a trypanosomal protein known as serum resistance-associated protein (SRA), which is a lysosomal protein that interacts strongly with a carboxy-terminal α-helix of APOL1 (Vanhamme et al. 2003; Perez-Morga et al. 2005). Alternatively, *T* b. gambiense becomes resistant to APOL1's tyrpanolytic activity, by producing a glycoprotein (TgsCP) that stiffens the lysosomal membrane preventing APOL1's toxicity. Interestingly, the two risk alleles of APOL1 in ESKD in African–Americans, S342G/ I384M (G1) and Δ N388Y389 (G2), are in the C-terminal domain which interacts with trypanosomal SRA. Consequently, these two mutant alleles lose binding affinity with SRA and are trypanolytic.

The possible pathological consequences of APOL1 risk alleles in kidney cells are discussed in more depth in other chapters of this book. Briefly, since APOL-1 is the only secreted member of the apolipoprotein family, researchers have attempted to determine the role of circulating APOL1 in renal diseases. However, these studies did not show an association between the circulating levels of APOL1 with the APOL1 genotypes, HDL levels, or renal disease (Bruggeman et al. 2014). In addition, the outcome in patients with kidney transplants suggest that the risk factor for a poor kidney allograft outcome is associated with the presence of two risk alleles in the donor kidneys (Reeves-Daniel et al. 2011; Lee et al. 2012). Unfortunately, despite extensive research efforts, we still do not have a good understanding of how the APOL1 risk variants predispose to the development of CKD or HIVAN. However, there are many promising studies done in cultured renal cells (Nichols et al. 2015; O. A. Olabisi et al. 2016a; Zhaorigetu et al. 2008; Mikulak et al. 2016; Lan et al. 2014; Lan et al. 2015), transgenic mice (Bruggeman et al. 2016; Beckerman et al. 2017), zebra fish (O. Olabisi et al. 2017b), and transgenic flies (Fu et al. 2017; Kruzel-Davila et al. 2017) addressing this issue. In general, all these studies agree that the ectopic expression of the APOL1 G1 or G2 risk variants causes more toxic effects than the wild type APOL1. In humans, the expression of APOL1 has been detected in several tissues, including podocytes, tubular epithelial cells, endothelial, and vascular smooth muscle cells (Wan et al. 2008; Zhaorigetu et al. 2008; Monajemi et al. 2002; Madhavan et al. 2011). In addition, the endogenous expression of APOL1 is induced by TNF-α and IFN-γ (Zhaorigetu et al. 2008; Nichols et al. 2015). Taken together, these findings suggest that cytokines released by HIV-infected may upregulate the expression of APOL1 in renal epithelial cells, acting as a second stress to enhance the cytotoxic effects of the risk variants.

Clinical Diagnosis of HIVAN

HIVAN is a clinical and renal histological syndrome that usually occurs in later stages of HIV-infection, although some cases of early onset have been reported. From the clinical point of view, HIVAN is characterized by heavy proteinuria and rapid progression to ESKD (Rao et al. 1984; Pardo et al. 1984). In the early stages of the AIDS, epidemic patients with HIVAN usually presented with severe nephrotic syndrome and renal insufficiency (Rao et al. 1984; Pardo et al. 1984). Both adults and children frequently showed profound hypoalbuminemia, with minimal or absent peripheral edema or hypertension, normal or enlarged kidneys, and rapid progression to ESKD (Strauss et al. 1989a, b; Connor et al. 1988; Ray et al. 1998b; Rao et al. 1984; Pardo et al. 1984). Edema and hypertension, however, are seen during the late stages of HIVAN. Renal sonograms reveal normal to enlarged echogenic kidneys. Isolated proteinuria may be the only clinical sign of HIVAN in children with poor adherence to ART (Dondo et al. 2013; Chaparro et al. 2008; Mcculloch and Ray 2008; Nourse et al. 2010; Shah et al. 2012; Iduoriyekemwen et al. 2013; Ramsuran et al. 2012), and microalbuminuria may predict the development of proteinuria among HIV-infected persons (Szczech et al. 2010). In all cases, however, the only manner to

establish a definitive diagnosis of childhood HIVAN is by doing a renal biopsy. The biopsies of young children with HIVAN may have some unique features that are not typically seen in adults, (Strauss et al. 1989a; Connor et al. 1988; Ray et al. 1998b; Ingulli et al. 1991). Nonetheless, whenever renal biopsies cannot be obtained, several clinical criteria have been used to diagnose HIVAN in young children (<12 years of age). Young children do not frequently develop proteinuria secondary to the range of renal diseases seen in adults, and therefore the diagnosis options are more limited. We have used the following criteria to make a clinical diagnosis of childhood HIVAN (Ray et al. 1998b): (1) Persistent proteinuria defined as Albustix reading above 1+, a urinary protein creatinine ratio > 0.1 +, or a urinary protein creatinine ratio (UPr/UCr) >0.1 for more than 1 month in the absence of infection episodes; (2) abnormal microscopic examination of the urinary sediment under similar conditions; (3) presence of enlarged echogenic kidneys detected by renal ultrasonography in at least two different studies performed 2 months apart; and (4) Black race and clinical history consistent with the typical symptoms of HIVAN (nephrotic range proteinuria without significant edema and/or severe hypertension). The following clinical findings which are not typical of HIVAN were used to increase the suspicion for other renal diseases: (1) macroscopic hematuria; (2) microscopic hematuria without proteinuria; (3) high BUN or SCr levels without significant proteinuria; (4) hematuria and/or proteinuria in Caucasian, Asian, or Hispanic HIV-infected children.

The urinalysis also provides a clinical clue to assess the clinical status of HIV+ children and rule out urinary tract infections. We found all types of epithelial cells in the urine of HIV-infected children, including squamous, transitional, podocytes, and tubular epithelial cells (Ray et al. 1998b). In some cases, renal epithelial cells are seen forming microcysts in fresh urine specimens (Ray et al. 1998b). Urine samples collected from children with HIVAN failed to infect cocultured peripheral blood mononuclear cells (PBMCs) and very few renal epithelial cells cultured from the urine test positive for HIV-DNA by the polymerase chain reaction (PCR) (Ray et al. 1998b). However, recent studies suggest that doing HIV-PCR DNA studies in urine pellets containing several cell types could help identify patients at risk of HIVAN after renal transplantation (Canaud et al. 2014).

Renal Pathology

HIVAN in adults was first characterized by the presence of global or focal segmental glomerulosclerosis (FSGS), often in different stages of evolution, in association with prominent degenerative or hypertrophic changes in visceral epithelial cells, and tubuloreticular inclusions (TRI) in glomerular and peritubular endothelial cells (Rao et al. 1984; Pardo et al. 1984). In addition, mesangial cells showed deposits of complement (C3), IgM, and sometimes IgG, but not IgA. Furthermore, the microcystic tubular dilatation containing large plasma proteins, interstitial edema, (Rao et al. 1984; Pardo et al. 1984) were highlighted as an essential feature of HIVAN. The mesangial deposits were considered nonspecific because they were detected in patients with AIDS who had normal glomeruli and in HIV-negative patients with hypertension and diabetes (Pardo et al. 1987). The initial studies concluded that the renal histological lesions of HIVAN were indistinguishable from heroin-associated nephropathy (HAN) or idiopathic FSGS (Rao et al. 1984; Pardo et al. 1984). Interestingly, it is worth noting that the renal histological features recognized years later as "collapsing glomerulopathy" were not described in the initial reports of HIVAN (Rao et al. 1984; Pardo et al. 1984). In 1986, 2 years after HIVAN was first recognized, the first cases of collapsing glomerulopathy were described in six patients who developed nephrotic syndrome and rapid ESRD (Weiss et al. 1986). One of these patients subsequently developed AIDS, but the other five patients remained HIV-negative (Weiss et al. 1986). Subsequently, a review of several renal biopsies done in 1989 at Columbia University in New York recognized that a significant number of adult patients diagnosed with HIVAN showed

collapsing glomerulopathy (D'agati et al. 1989). The collapsing global pattern of glomerulosclerosis seen in the absence of endocapillary foam cells or glomerular hyalinosis in these patients was considered an early morphological feature of HIVAN. In subsequent years, the diffuse collapsing global pattern described above became a distinctive feature of HIVAN in adults (D'agati and Appel 1997; Bourgoignie and Pardo 1991; Barisoni et al. 1999). Nonetheless, many adults with HIVAN do not show the collapsing glomerulopathy phenotype (Wearne et al. 2012).

The renal histological lesions reported in children with HIVAN were similar to those described in adults and included glomeruli with focal and segmental sclerosis, hypertrophy, and hyperplasia of visceral epithelial cells, in combination with microcystic tubules filled with proteinaceous material and infiltrating mononuclear cells (Pardo et al. 1987; Strauss et al. 1989a) (Fig. 6). Most children do not develop the collapsing glomerulopathy phenotype. The inmmunofluorescence microscopic findings were negative or considered nonspecific. The microcystic tubular changes lead to renal enlargement, a finding that contrasts with the small fibrotic kidneys typically seen in children with CKD of other etiology. At the onset of nephrotic proteinuria, children may only exhibit mesangial hyperplasia in combination with microcystic tubular dilatation, and these patients progress at slower rates when compared to children with FSGS (Strauss et al. 1989a; Ray et al. 1998b). Interestingly, a review of 159 HIV+ renal sections during the late 1980s, revealed a spectrum of glomerular lesions ranging from focal and diffuse mesangial hyperplasia with minor FSGS changes to global glomerulosclerosis (Pardo et al. 1987). Because in the 1980s mesangial expansion was considered to be a precursor of FSGS, these findings were interpreted as the early stages of HIVAN (Strauss et al. 1989a; Pardo et al. 1987). In subsequent years, when it became clear that podocytes and renal tubular epithelial cells were the main targets of HIV-1, our interpretation of the pathogenesis of HIVAN changed, and the relative contribution of mesangial hyperplasia in this process continues to be less clearly understood. It remains to be determined whether these changes are the first step toward development of FSGS, or an independent pathogenic process related to the viral infection per se.

In recent years, a wide spectrum of renal histological variants of HIVAN were described in adults and older children (Wearne et al. 2012), including a new fetal variant of HIVAN that is associated with the worst clinical outcome (Wearne et al. 2012). In the fetal HIVAN variant,

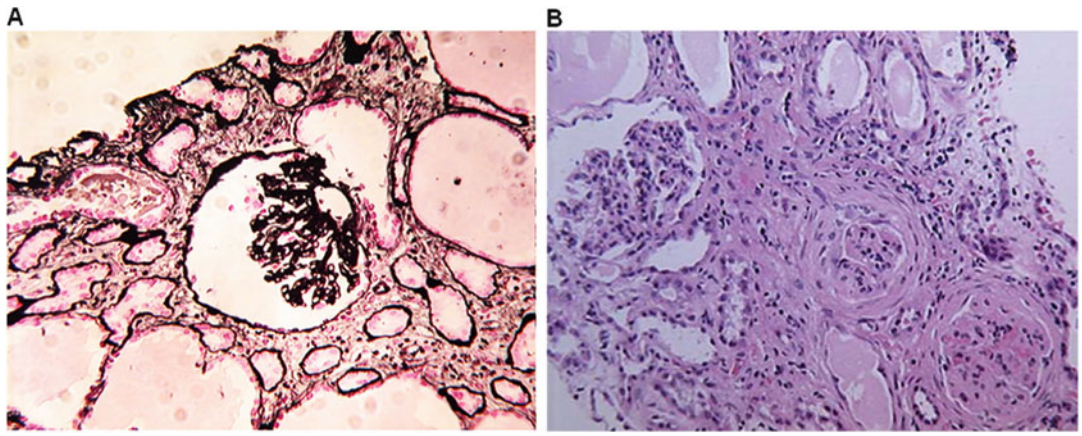

Fig. 6 Representative PAS (**a**) and hematoxylin and eosin (**b**) staining of renal biopsies from two children with HIVAN. Panel A shows a collapsing glomerulopathy. Original magnification ×200 (Panel B is reproduced with permission of Springer from Ray PE, Liu Xu, Rakusan T, Liu Xue-Hui. "A 20-year history of childhood HIV-associated nephropathy" Pediatric Nephrology 19:1075–1092. Figure 2, page 1078; License Number 3984431229899)

glomeruli show a strikingly dense mesangial sclerotic core, with no peripheral loops or collapse, and the surface of the inner core is covered by hypertrophic and hyperplastic visceral epithelial cells (Wearne et al. 2012). Overall, the most persistent and distinctive pathological features of all cases of childhood HIVAN are the microcystic tubular dilatation and interstitial changes associated with the glomerular lesions.

Treatment of HIVAN

In the prehighly active ART era, children with HIVAN progressed very rapidly to ESKD and/or died in less than 2 years (Strauss et al. 1989a; Ray et al. 1998b). ART has substantially changed the face of HIV-infected children and prevented the development of HIVAN and CKD (Chaparro et al. 2008; Nourse et al. 2010; Mcculloch and Ray 2008; Bhimma et al. 2013). In a large multicenter trial evaluating long-term outcomes in HIV+ children, the death rate attributable to CKD was ~2% (Brady et al. 2010). HIV-infected infants now survive to adolescence and adulthood, and their quality of life has improved in a remarkable manner. However, HIV-positive children need to be enrolled in effective chronic treatment programs to stay healthy, and providing continuous acute and chronic care to these patients is a major challenge today. Obstacles to treat all pediatric patients include the lack of screening or simple diagnostic tests, insufficient understanding of the beneficial effects of ART by the parents, and the cost of pediatric ART formulations. In resource-limited countries, even children on ART show poor clinical outcomes (Vermund et al. 2014). Nonetheless, significant treatment progress has been made in the HIV field since 2013. Most countries have moved or are moving to provide lifelong ART regardless of CD4 cell count to all pregnant and breastfeeding women, and many are moving to implement viral load testing as the preferred means of monitoring people who are taking ART. New point-of-care viral load testing technologies offer further potential to expand this approach. Further, safer and more efficacious antiretroviral drugs are becoming available and a newer class of drugs – integrase inhibitors – is becoming more affordable for low- and middle-income countries.

More than 25 antiretroviral (ARV) drugs in six mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). In addition, two drugs, ritonavir (RTV) and cobicistat (COBI) are used solely as pharmacokinetic (PK) enhancers (i.e., boosters) to improve the PK profiles of some ARV drugs. The initial ARV regimen for a treatment-naive adult or adolescent patient generally consists of two NRTIs, plus a drug from one of three drug classes: an INSTI, an NNRTI, or a PK-enhanced PI. A discussion of the potential effects of these drugs in the kidney is beyond the scope of the present chapter; however, nephrologists treating HIV-infected patients with renal diseases should work in close collaboration with infectious disease doctors familiar with these medications. Briefly, all NRTIs except for abacavir (ABC) are excreted by the kidney and their dosage should be adjusted according to the estimated glomerular filtration rate (eGFR). Other classes of ARV drugs (NNRTI, PI, fusion inhibitor, integrase, chemokine receptor antagonists) do not undergo significant renal excretion and do not require adjustments in patients with renal insufficiency.

The 2016 consolidated guidelines on the use of antiretroviral drugs represent an important step towards achieving the goal that the world set itself a decade ago, universal access to ART drugs for treating and preventing HIV, and the ultimate goal of ending the HIV epidemic as a major public health threat (https://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf). To prevent HIV acquisition in a wide variety of settings and populations, clinical trial results have strongly confirmed the efficacy of the antiretroviral (ARV) drug tenofovir disoproxil fumarate alone or in combination with emtricitabine for use as pre-exposure prophylaxis. As discussed in the clinical

practice guidelines for the management of CKD in patients infected with HIV-1 (Lucas et al. 2014), infants with perinatal HIV-1 infection should be treated with ART as soon as the diagnosis is established. Children with microalbuminuria or proteinuria should be followed more closely to prevent the progression of renal diseases. Overall, ART has improved the renal function (Brady et al. 2010; Chaparro et al. 2008) and survival in almost all pediatric patients (Brady et al. 2010; Luzuriaga et al. 2004; Evans-Gilbert et al. 2008).

Adverse Effects of ART

As with most pharmaceutical drugs used in pediatric patients, information on dosing in children with renal disease is limited, and using data on adults as a guide for ART dosing and regimen modification to accommodate renal function is sometimes the only option (Lucas et al. 2014). ART can induce renal injury (Roling et al. 2006) and endothelial dysfunction and may cause renal and cardiovascular complications (Kline and Sutliff 2008). For example, the protease inhibitor Indinavir has been associated with the development of nephrolithiasis, crystalluria, dysuria, papillar necrosis, and AKI (Daugas et al. 2005; Kopp et al. 1997). Ritonavir was associated with reversible forms of AKI (Chugh et al. 1997), although many of the patients reported received other nephrotoxic drugs or had underlying renal pathology (Roling et al. 2006). The NRTIs, tenofovir, adefovir, and cidofovir can cause renal tubular damage (Roling et al. 2006). Tenofovir disoproxil fumarate (TDF) can cause Fanconi Syndrome (Zimmermann et al. 2006), although some patients only develop hypophosphatemia and glycosuria. Risk factors for the development of TDF-induced renal toxicity are: advance HIV disease, its prolonged use, low body weight, impaired renal function, and simultaneous use of other nephrotoxic drugs (Roling et al. 2006). Concomitant use of a pharmacokinetic (PK)-enhanced regimen with a protease inhibitor (PI) or elvitegravir (EVG) can increase the concentration of TDF and place patients at higher risk of renal dysfunction. More recently, Tenofovir Alafenamide (TAF), an oral prodrug of tenofovir (TFV), has been used. TAF is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which is converted to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. Randomized controlled trials suggest that the potential adverse kidney and bone effects are less likely with TAF than with TDF. Unlike TDF, which should be avoided or dose reduced in patients with estimated CrCl <50 to 60 mL/min, TAF-containing regimens appear to be safe and are FDA approved for use in patients with estimated CrCl as low as 30 mL/min (https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/37/whats-new-in-the-guidelines-). The last revision of the Adult and Adolescent Guidelines for treating HIV+ patients (January 28, 2016) reported that clinical trials and cohort studies, as well as experience in clinical practice, show that TAF-containing regimens are as effective in achieving or maintaining virologic suppression as TDF-containing regimens and with more favorable effects on biomarkers of bone and renal structure.

Interestingly, the initial safety and efficacy testing of TDF as salvage therapy in children did not reveal significant renal complications (Hazra et al. 2005; Vigano et al. 2010; Gafni et al. 2006). However, subsequent pediatric studies associated TDF use with a 4–5% renal complication rate involving proximal tubule dysfunction, which was reversible on cessation (Judd et al. 2010; Papaleo et al. 2007; Riordan et al. 2009). Recent clinical guidelines (Lucas et al. 2014), recommended to measure the serum creatinine and urine dipstick for protein and glucose before starting a TDF-containing regimen and to monitor creatinine and dipstick for protein and glucose at intervals during continued therapy, as well as the serum phosphate levels, if there is a clinical suspicion of hypophosphatemia (Lucas et al. 2014). In 2012, TDF received FDA approval to be used in children ≥ 2 years of age but should not be used in younger children due to its adverse bone

effects. In summary, the renal complications associated with ARTs, to some extent, can be prevented by close monitoring of the renal function of children before the initiation and during ART. In particular, careful attention must be given to assessing the potential nephrotoxic effects of other medications that are usually given in a simultaneous manner (acyclovir, Amphotericine B, aminoglycosides, diuretics, foscarnet, pentamidine, TMP-SMZ, etc.). Any changes in serum creatinine levels, proteinuria, crystalluria, extracellular fluid volume contraction, and/or electrolyte-acid base changes should lead to the prompt identification of children at higher risk of developing renal injury.

Steroids, Angiotensin Converting Enzyme Inhibitors (ACEi), and Angiotensin Receptor Blockers (ARBs)

In ART-treated children with continued significant proteinuria, adjunctive therapies frequently used in adults (steroids and ACE-inhibitors) have not been adequately evaluated. Studies in the pre-ART era did not find benefit to steroid use in HIV+ children with nephrotic syndrome (Ray et al. 1998b; Ingulli et al. 1991; Strauss et al. 1989a), and there is no published evidence in the post-ART era to support the notion that steroid use improves outcomes in children with HIVAN. Although the experience is limited in children, the recent clinical guidelines recommend against using corticosteroids in children with HIVAN (Lucas et al. 2014). In contrast, ACE inhibitors appear to provide additional therapeutic benefits in adults (Wei et al. 2003) and could be used to treat proteinuric nephropathy in children with HIV-infection. ACE inhibitors and ARBs can also be used as first-line therapy for hypertension in these patients (Lucas et al. 2014). The use of ACE-inhibitors or ARBs in young children needs to be monitored closely due to the potential induction of AKI associated with episodes dehydration secondary to vomiting and diarrhea (Patzer 2008; Ray et al. 1998b). In teenagers at high risk of becoming pregnant, ACEi may also cause fetal malformations.

Dialysis

In the early years of the AIDS epidemic, dialysis was not indicated in HIV-1-infected children due to poor survival, risk of infections, and presence of other lethal AIDS-related illnesses (Mcculloch and Ray 2008; Strauss et al. 1989a; Ray et al. 1998b). With the more widespread use of ART, the survival rates on renal replacement therapy improved, and the age of CKD diagnosis increased (Gordillo et al. 2009). Children with HIVAN who started dialysis after 1996 showed better outcomes and survival when compared to those who started dialysis in or before 1996 (Ahuja et al. 2004). Both dialysis modalities are used in children. Peritoneal dialysis may be associated with more infection episodes but is more readily available than hemodialysis in resource-limited countries. The peritoneal fluid contains infectious HIV+ mononuclear cells and should be handled with caution (Ray et al. 1998b). Unfortunately, there are no reports comparing the clinical outcome of HIV-positive and negative on peritoneal dialysis. In the United States, hemodialysis is the preferred modality in perinatally infected children because of the availability of resources and expertise for this treatment, as well as the added burden of peritoneal dialysis for the family members. Physicians in New York followed a limited number of HIV+ children treated with ART for 5 years and showed that a low body mass index or the presence of cardiovascular disease were associated with increased mortality in hemodialysis, when compared to HIV-negative children treated in a similar manner (Gordillo et al. 2009, 2011). The authors recommended that these patients should be followed with routine echocardiography (Gordillo et al. 2011). A low CD4 count and a high viral load were also associated with a poor outcome (Strauss et al. 1989a; Gordillo et al. 2009; Chaparro et al. 2008). It is necessary to reduce the HIV-viral load of children undergoing dialysis as much as possible, to make them eligible candidates for kidney transplant. Studies in adults suggest that with appropriate ART, the survival of HIV- positive and negative patients on hemodyalisis is similar (Tourret et al. 2006).

However, there is little data published regarding the outcome of HIV+ children in hemodialysis.

Renal Transplantation

Renal transplantation in HIV-infected children is an accepted treatment modality, although significant outcome data in children are still lacking (Roland et al. 2008). In the early years of the AIDS epidemic, HIV-infection was considered an absolute contraindication to kidney transplantation because the combination of transplantation plus immune-suppression appeared to shortened the AIDS-free time in HIV-infected patients, compared with hemophilic control groups (Tzakis et al. 1990). Subsequently, improvements in HIV-related morbidity and mortality, in combination with the discovery that cyclosporine and mycophenolate mofetil (MMF) can inhibit HIV replication (Streblow et al. 1998; Margolis et al. 1999), and facilitate the immune reconstitution in patients treated with ART (Schwarz et al. 1993), prompted a reevaluation of renal transplantation in this population. Very promising results reported in pilot safety studies performed in highly selected groups of HIV+ kidney transplant recipients also contributed to the acceptance of this treatment modality (Kumar et al. 2005; Bhagani et al. 2006; Stock et al. 2003; Stock and Roland 2007). These highly selected HIV+ kidney recipients showed excellent adherence to ART therapy, lack of severe immunosuppression (CD4 $>$ 200 cells/l), undetectable viremia ($<$50 HIV-1 RNA copies/ml) for 3 months prior to the kidney transplant, absence of AIDS-defining illness, successfully immune reconstitution after ART, no history of opportunistic infections or neoplasms, and no active viral infections for at least 6 months previous to the renal transplant. Standard immunosuppression included prednisone, MMF, and CsA. MMF and CsA were chosen based on their known antiretroviral therapy (Margolis et al. 1999; Streblow et al. 1998).

More extensive studies done in the United States and Europe confirmed that renal transplantation is a safe and effective treatment for ESKD in HIV+ patients (Stock et al. 2010; Touzot et al. 2010), with equivalent patient and allograft survival than uninfected patients (Sawinski 2017; Locke et al. 2016). Unique challenges for HIV+ patients however include the high rates of acute rejection, delayed graft function, and significant drug-drug interactions (Sawinski 2017). In one study done at John Hopkins Hospital in Baltimore, the medical records of all HIV-infected patients older than 18 years who where transplanted between September 2006 and January 2014 were reviewed (Waheed et al. 2015). During this period, 16 patients, predominately from African American background, underwent renal transplantation. Sixty-four percent developed delayed graft function, and 54% required postoperative dialysis within 1 week of transplant (Waheed et al. 2015). Graft survival rates at 1 and 3 years were 100% and 81%, respectively. Acute rejection rates at 1 and 3 years were 18% and 27%, respectively, and during a mean follow up of 3.4 years, one patient died (Waheed et al. 2015). Moreover, another study done in Paris, France, reported HIV-infection of the kidney allograft in a cohort of patients with suppressed viral load (Canaud et al. 2014). The authors observed two different forms of allograft infection. In the first case, podocytes were infected, and these changes were associated with nephrotic range proteinuria, development of FSGS, and poor transplant outcome. In the second case, HIV-1 tubular epithelial cells in the kidney allograft were infected, but these patients showed fewer clinical manifestations (Canaud et al. 2014). In contrast, in the prospective US trial, which included 150 kidney transplants recipients with undetectable plasma HIV-1 RNA, there was no histological evidence of recurrent de novo FSGS on light microscopy nor was there any evidence of nephrotic range proteinuria (Stock et al. 2010). Moreover, recurrent HIV nephropathy was not a factor in early graft loss (within 3 years of transplant in the US trial). Thus, it is unclear why 38% of the HIV+ patients transplanted in Paris developed gross proteinuria and FSGS de novo, despite the suppressed viral load, and why 68% of the recipients underwent significant infection of tubular

epithelial cells without causing a long-term decline in renal function (Canaud et al. 2014).

Unfortunately, very few pediatric nephrology transplant programs worldwide have transplanted a significant number of HIV+ children, and it is advisable to follow the adult guidelines. The transplant study for patients with HIV-1 has proposed very strict selection criteria. These criteria are constantly evolving (Blumberg et al. 2009). The patients selected for the adult kidney transplant studies are not a representative sample of the population of HIV-infected children undergoing dialysis, and it is difficult to find children with HIVAN who meet these renal transplant criteria. The selection of children for transplantation, and the assessment of their immune status, should take into consideration several parameters, including the ages and weight of the child, (>1 years or 10 Kg), and the absolute CD4 count (>25% in children 1–6 years of age; and >200 cells/μl in those older than 6 years). There is concern regarding the susceptibility of children to nosocomial infections with bacteria, viruses, atypical organisms, and tuberculosis, which remains a significant concern for African children. Finally, the limited availability of kidney transplants for children raises ethical concerns. To address this issue, surgeons in South Africa are pursuing kidney transplants using HIV+ kidney donors with good results (Muller et al. 2010). Based on these data, in October 2016, surgeons at Johns Hopkins performed the first liver and kidney transplant in the United States between an HIV+ donor and HIV+ positive recipient.

Conclusion

Since the early years of the AIDS epidemic, great progress has been made in our understanding and treatment of children with HIVAN. However, more work needs to be done to prevent the vertical transmission of HIV-1, provide appropriate ART regimens to all children, maintain their viral suppression throughout childhood and adolescence, and prevent the infection of older children and adults through other routes. Hopeful, better prophylactic treatments and vaccines will be developed in the near future to eradicate this disease.

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Glomerulonephritis Secondary to Non-streptococcal Infections

32

Meidad Greenberg and Frederick J. Kaskel

Contents

Abstract

Postinfectious glomerulonephritis (PIGN) is part of a larger group of infection-related glomerulonephritis (IRGN) that harbor the common PIGN and post-streptococcal glomerulonephritis (PSGN) and the less common infectious glomerulonephritis.

IRGN is considered to be a cluster of glomerular diseases resulted from immunologic insult secondary to systemic nonrenal infection. Two smaller groups of IRGN have been identified. The first is postinfectious glomerulonephritis (PIGN), which shares a clinical resemblance to PSGN and differs in the causing pathogen (see Table 1). The second is more scarce, with a somewhat different glomerular pathology and is secondary to active bacterial or (more common) viral infection (e.g., hepatitis C virus and HIV). This chapter reviews non-strep PIGN.

Keywords

End stage renal disease (ESRD) · Post-infectious Glomerulonephritis (PIGN) · Post-streptococcal Glomerulonephritis (PSGN) · Rapidly progressive Glomerulonephritis (RPGN)

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Introduction

The association between acute renal disease and infection is well known and was first described in the modern era by Sir Richard Bright in 1827, as part of the cluster of a glomerulonephritis (GN) that was called "Bright's disease" (Stratta et al. 2014). The disease, known today as post-infectious glomerulonephritis (PIGN), was first described secondary to streptococcal infection (pharyngitis or scarlet fever) and is an immune-complex-mediated disease. The condition is triggered by foreign pathogens, usually a bacterial infection, that cause secondary complement-mediated renal injury.

Until recently, most of the PIGN in the pediatric population was secondary to streptococcal throat or skin infections, and named

Table 1 Infective agents that might cause an acute post-infectious glomerulonephritis (PIGN) (Stratta et al. 2014; Jain et al. 2011; Garty et al. 2009; Asano et al. 2016; Kanodia et al. 2016; Kanjanabuch et al. 2009; Watanabe et al. 2003)

	Pathogen	Infectious syndrome
Bacteria	*Streptococcus*	
	Group A beta hemolytic type 12	Skin and throat infection
	Streptococcus pyogenes	Skin and throat infection
	Streptococcus equi	Skin and throat infection
	Streptococcus constellatus	Skin and throat infection
	Streptococcus viridance	Bacterial endocarditis
	Streptococcus pneumonia	Pneumonia
	Type M 1–4, 18, 25,31,49,52,55–57, 59–61	
	Group C	
	Group G	
	Staphylococcus epidermidis	*Shunt nephritis*
	Staphylococcus haemolyticus	
	Staphylococcus aureus	Bacterial endocarditis
	Escherichia coli	
	Pseudomonas	
	Acinetobacter	
	Serratia	
	Proteus	
	Klebsiella	
	Enterobacter	
	Salmonalla	
	Campylobacter	
	Legionella	
	Brucella	
	Neisseria meningococcus	
	Neisseria gonorrhea	
	Hemophilus	
	Serratia	
	Yersinia	
	Bartonella	
	Mycoplasma	*Pneumonia*
	Propionobacterium	*Shunt nephritis*
Parasyte	*Plasmodium vivax*	
	Plasmodium falciparum	
	Plasmodium malaria	

(*continued*)

Table 1 (continued)

	Pathogen	Infectious syndrome
	Schistosoma hematobium	
	Schistosoma mansoni	
	Toxoplasma gonadi	*Toxoplasmosis*
	Wuchereria bancrofti	*Filariasis*
	Trichinella spiralis	
	Echinococcus granolosus	*Hydatid disease*
	Entamobea histolytica	*Amoebiasis*
Spirochetes	*Borrelia*	
	Treponema	
Mycobacteria	*Tuberculosis*	
	Avium	
	Lapre	
Virus	*H1N1*	
	Parvovirus B-19	
	Adenovirus	
	Hepatits B virus	
	Varicella zoster virus	
	Epstein–Barr virus	
	Cytomegalovirus	
	HIV	
	Coxsackievirus	
	Echovirus	
	Hepatitis A virus	
	Hepatitis C virus	
	Dengue virus	
	Mumps virus	
	Measles virus	
	Hantavirus	
	Rotavirus	
Fungal infection	*Candida albicans*	
	Histoplasma capsulatum	
	Coccidioides immitis	

post-streptococcal glomerulonephritis (PSGN) (Chadban and Atkins 2005). However, during the last few years, more bacterial and viral pathogens cause IRGN, of which *Staphylococcus aureus* infection (Usui et al. 2016) is the most common PIGN in the elderly population.

Epidemiology

PIGN-like PSGN is more common during the winter season, and primarily affects children at the age of 3–12 years. Although uncommon, it can occur in infants younger than 2 years (Dagan et al. 2016).

The incidence of Streptococcal-related PIGN in the pediatric population in developing and developed countries is 24.3 and 6 per 100,000 person years, respectively, and in adults and children the incidence is 2 and 0.3, respectively (Nasr et al. 2013; Carapetis et al. 2005; Kanjanabuch et al. 2009). Acute PIGN, once a common pediatric disease, has almost completely disappeared from the developed (industrialized) countries, mainly because of antibiotic treatment and improvement in the socioeconomic status (Stratta et al. 2014). The accurate incidence of PIGN is

unknown while that of PSGN occurs with an estimated 472,000 cases per year, worldwide, of which 97% is in developing countries (Steer et al. 2007). In developed countries, PSGN is less common than *Staphylococcus aureus* PIGN, which is considered a disease of the elderly population, and associated with alcoholism and diabetes mellitus (Montseny et al. 1995).

Adult data on acute PIGN suggests male predominance, with male-to-female ratio 1.4–3:1, and the disease is more common in Caucasian and Asians populations (Nasr et al. 2013).

Pathogenesis

The glomerular damage in PIGN is the result of circulating immune complexes deposition and/or in situ formation of immune complexes containing bacterial antigens. In typical PIGN, the pathogenic endotoxin which circulates and binds to the glomeruli initiates activation of the complement alternative pathway through the mannose-binding lectin which induce an antibody response (Couser and Johnson 2014). The atypical PIGN is caused by deregulation of the complement alternative pathway (De Vriese et al. 2015).

The pathogenesis of most acute PIGN resembles that of acute PSGN, and both have an immune complex pathogenesis. While in acute PSGN nephritogenic toxins have been identified, in acute non-streptococcal PIGN, little is known on the specific immune-mediated pathogenesis of the renal injury (Rodríguez-Iturbe and Batsford 2007).

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-associated GN are not considered a PIGN but rather an IRGN because the genesis of HCV- and HIV-associated glomerular disease share a total dependence on the presence of active viral replication to sustain renal injury (Kupin 2017).

Clinical Characteristics

Acute nephritic syndrome, or glomerulonephritis (GN), is characterized by hematuria, proteinuria (nephrotic range or non-nephrotic range), edema, and often by hypertension and a mild degree of acute kidney injury (Kanjanabuch et al. 2009). The classic PIGN clinical presentation is a young child usually 3–7 years old, who abruptly develops eyelid edema followed by smoky and scant dark cloudy urine and increasing blood pressure a few days after a nonrenal infection. Anuria and nephrotic range proteinuria are occasionally observed, and a urine volume usually increases 4–7 days after hospital admission, indicating resolution of the glomerulonephritis.

PSGN usually presents 7–15 days after a throat infection and 3–5 weeks after a skin infection (Rodríguez-Iturbe and Batsford 2007). Most of the reports of PIGN show a latent period that resembles the latent period of the PSGN throat infection. PIGN develops 13 days after the presentation of *P. vivax* malaria (Kanodia et al. 2016), 12 days after Parvo B-19 (Marco et al. 2016) but only 2 days after the presentation of Influenza (H1N1) (Jain et al. 2011). The urinary volume increase is rapidly followed by resolution of the edema and normalization of blood pressure. Microscopic hematuria takes several months to resolve and can persist for 1 year after the acute attack (Kanjanabuch et al. 2009).

A quarter of all PIGN cases will have a subclinical GN (Yoshizawa et al. 1996). The patients usually present with acute, trivial, and self-limited infections develop subclinical glomerular disease, as indicated by low-grade proteinuria (<1 gram per day), pyuria, and microscopic hematuria (Kanjanabuch et al. 2009).

Laboratory

The classic serologic finding of PIGN is a reduction of C3 serum complement levels that occurs in 90% of the cases (Rodríguez-Iturbe and Batsford 2007). In regard to PIGN secondary to staphylococcal infection, the majority of cases will have IgA deposits in the renal biopsy and serum levels of IgA and IgG are elevated; other serological tests including complement, ANCA, cryoglobulins, and rheumatoid factor are usually in the normal range while small elevation in ANA can be seen (Zeledon et al. 2008).

Pathology

Most of the cases of PIGN are diagnosed by the clear clinical and laboratory signs obviating the need for a renal biopsy (Rodríguez-Iturbe and Mezzano 2016). In cases where renal biopsy is performed, the histology is characterized by extracapillary proliferation (Stratta et al. 2014), or in the case of a *Streptococcus aureus* infection, IgA-dominant deposition (Koyama et al. 2017). In most cases, enlarged hypercellular glomeruli with prominent endocapillary proliferation and infiltration with neutrophils and mononuclear cells, with variable degrees of immunoglobulin and complement deposits. The histologic picture consists of diffuse or focal, mesangial or mesangiocapillary proliferation with, in few instances, fibrocellular crescents.

Deposits of IgA, IgG, and C3 have been observed in both the mesangium and the peripheral capillary walls with subendothelial deposits have been reported, while sub-epithelial "humps" characteristic of PIGN are unusual (Zeledon et al. 2008; Fogo 2016). The granular deposition of complement C3 is often coupled with IgG and occasionally with IgM. IgA deposition is rare, except in patients with diabetes and secondary staphylococcal infection. "Full house" immunostaining (IgG, IgM, IgA, C3, C4, C1q) that resembles the pathologic finding of lupus nephritis is frequently reported (Kanjanabuch et al. 2009). The dominant IgA staining in staphylococcal PIGN can be distinguished from IgA nephropathy by electron microscopy (EM) appearance of the deposits (Usui et al. 2016; Fogo 2016; Nasr et al. 2007).

The histologic picture changes over the course of the disease with glomerular endocapillary proliferative GN in the active stage, mesangial proliferative GN in the healing stage, or both types during the subclinical stage, with C3-dominant deposits. In severe disease, crescents are present and rapidly progressive glomerulonephritis is expected. Under EM, small immune deposits are commonly present in the mesangial and subendothelial areas of the kidney with acute PIGN. However, the characteristic finding is large "humps" (dome-shaped deposits) under the effaced epithelium, particularly in the mesangial notch or waist region. The proliferative and exudative changes associated with non-streptococcal acute PIGN are not prominent as those observed in the classic PSGN (Kanjanabuch et al. 2009; Rodríguez-Iturbe and Mezzano 2016).

Treatment

A patient with PIGN suffers from two main problems: a postinfection (bacterial or viral) state and an acute nephritis syndrome (hypertension, acute kidney injury, edema). While managing the patient, these two problems need to be taken into consideration.

Pathogen Treatment

The first question to be considered related to the diagnosis of non-streptococcal PIGN is what is the causative pathogen and what is the best antibiotic (or anti-viral) treatment needed. While in PSGN the treatment of choice will be penicillin (or in cases of penicillin allergy – erythromycin), in the case of non-streptococcal PIGN, the cornerstone of the antibiotic treatment is to identify the correct pathogen. In cases of IgA-dominant GN secondary to staphylococcal infection, the antibiotic treatment depends on the bacterial sensitivity (MRSA vs. MSSA). In cases of other pathogens, the antibiotic or anti-viral treatment needs to be tailored to the specific pathogen (Rodríguez-Iturbe and Mezzano 2016).

Corticosteroid treatment is contraindicated while there is active infection, and can be use in selected cases of RPGN when active infection is no longer present (Rodríguez-Iturbe and Mezzano 2016).

Acute Nephritis Treatment

When treating a patient with glomerulonephritis secondary to a recent infection, the first thing to be considered is whether the patient needs to be

admitted to an inpatient facility or is able to receive sufficient treatment as an outpatient. A patient with subclinical nephritic syndrome with good urine output and without hypertension might benefit from outpatient treatment. In contrast, any patient with acute nephritic syndrome needs to be hospitalized (Rodríguez-Iturbe and Mezzano 2016), mainly for the follow up of any possible exacerbation of hypertension.

The cornerstone for managing of acute nephritis is bed rest, fluid restriction, and low salt diet (Rodríguez-Iturbe and Mezzano 2016). In cases of apparent fluid overload, that manifested as severe edema, elevated blood pressure, and circulatory congestion, the administration of loop diuretics orally or parenterally (Furosemide, 40 mg every 12 hours) is warranted. Antihypertensive medications are required in cases of severe hypertension that is not well controlled with diuretics in order to prevent hypertension-induced seizures. It is recommended to start with nifedipine (5 mg every 4–6 h) or parenteral hydralazine (Rodríguez-Iturbe and Mezzano 2016).

Prognosis and Complications

The overall prognosis of acute PIGN resembles that of acute PSGN, and in the short term, both share an excellent prognosis. Furthermore, the complications that was described during the acute phase are rare (Rodríguez-Iturbe and Mezzano 2016).There are, however, a few rare medical complications that affect the patients during the acute attack: acute kidney injury (Ayoob and Schwaderer 2016); severe hypertension with clinical sequela such as hypertensive encephalopathy, hyperkalemia, and pulmonary edema that might require acute dialysis; cerebral venous thrombosis (Morkhandikar et al. 2016); and posterior reversible leukoencephalopathy (Fux et al. 2006) that resembles hypertensive encephalopathy and manifests as mental disturbances, headaches, visual hallucinations, and convulsions. The last two are extremely rare, severe complications with grave prognoses.

Rapidly progressive glomerulonephritis (RPGN) that presents as dramatic loss of renal function over a few weeks to months is a rare but severe complication of PIGN. Approximately, half of the RPGN cases are associated with PIGN (Piyaphanee et al. 2016), and about one-third of the patients that develop RPGN will deteriorate to end-stage renal disease (ESRD) (Piyaphanee et al. 2016) over the course of time.

The long-term prognosis of acute PIGN in the pediatric population is much better than in the adult population, and deterioration to ESKD in children was reported in less than 1% of the cases (Rodríguez-Iturbe and Mezzano 2016). Non-nephrotic proteinuria was found in 7.2%, hypertension and microhematuria were found in 3% and 5.4%, respectively (Rodriguez-Iturbe and Musser 2008), and the history of PIGN has strong association with reduced glomerular filtration rate (<60 mL/min/1.73 m^2) in later life (Hoy et al. 2012).

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Light Chain (AL) Amyloidosis and the Kidney

33

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Contents

Abstract

Light chain (AL) amyloidosis is a disorder in which clonal plasma cells in the bone marrow produce light chains that deposit extracellularly in tissue as insoluble amyloid fibrils. The kidney is one of the most frequently affected organs in AL amyloidosis, but the disease often affects multiple organs including the heart, autonomic and/or peripheral nervous system, and the liver. Kidney involvement typically results in nephrotic syndrome and progressive loss of kidney function. The management of the manifestations of kidney disease can be complicated by extra-renal involvement. The prognosis for AL amyloidosis has improved substantially over the past

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two decades with the development of effective treatments that target the clonal plasma cells producing the amyloidogenic protein. Treatments that target the amyloid fibrils themselves are currently being studied.

Keywords
AL amyloidosis · Light chain amyloidosis · Autologous stem cell transplantation · Melphalan · Bortezomib · Lenalidomide · Treatment · Renal response

Introduction

The term amyloid, adapted from the Greek word, *amylon,* meaning starch, was introduced in 1854 by the pathologist, Rudolf Virchow, to describe starch-like, waxy, eosinophilic extracellular tissue deposits (Glenner 1980a, b). The deposits were subsequently found to be composed of misfolded, β-sheet fibrils that are characterized by their ability to intercalate Congo red dye and thereby generate "apple green" birefringence under polarized light. Disorders defined by extracellular deposition of these proteins are collectively called amyloidosis, and more than 30 unique amyloid-forming proteins have been identified to date (Sipe et al. 2016). Amyloidosis can be systemic (when amyloid deposition occurs in tissues that are remote from the site of production) or localized (when amyloid deposition only occurs at the site of production). The kidney is a site of involvement for many of the types of systemic amyloidosis (Table 1).

Light chain (AL) amyloidosis, the most common type of systemic amyloidosis, occurs when clonal plasma cells in the bone marrow produce an immunoglobulin light chain that forms amyloid in extracellular tissue. AL amyloidosis and multiple myeloma are both disorders of plasma cells, but they differ in important ways. In multiple myeloma, rapidly proliferating plasma cells comprise the majority of the cellular components of the bone marrow and are responsible for many of the disease manifestations such as anemia, lytic bone lesions, and hypercalcemia. In contrast, in AL amyloidosis, the plasma cell burden is typically in the range of <5–15% of the bone marrow cells, and the disease manifestations result from tissue deposition of the monoclonal light chain as amyloid fibrils. The severity of the clinical manifestations of AL amyloidosis, despite a low burden of clonal plasma cells, reflects the pathogenicity of the amyloidogenic light chain. Approximately 10% of individuals with AL amyloidosis have concurrent multiple myeloma.

For a small proportion of patients with AL amyloidosis, clonal B lymphocytes or lymphoplasmacytic cells rather than plasma cells are the source of the amyloidogenic light chain. Heavy chain (AH) amyloidosis and heavy and light chain (AHL) amyloidosis are rare disorders in which an immunoglobulin heavy chain or combination of heavy and light chain forms amyloid (Kyle and Gertz 1995; Sanchorawala 2006; Said et al. 2013).

During the past two decades, the outcomes for AL amyloidosis have improved substantially because of the development of effective treatments targeting the clonal cells producing the amyloidogenic protein. Additionally, treatments directed at the amyloid itself are currently being evaluated in clinical trials. In this chapter, we provide a review of AL amyloidosis with a particular focus on kidney manifestations and treatment. Renal disease from other types of amyloidosis is covered in ▶ Chap. 49, "Lipoprotein Glomerulopathy, Non-AL Amyloidosis, LCAT, ING" in this handbook.

Renal Pathology and Diagnosis

The diagnosis of amyloidosis requires demonstration of amyloid in tissue. In the kidney, light microscopy of paraffin-embedded tissue shows amorphous material that exhibits weakly positive staining with periodic acid-Schiff in any or all nephron segments (glomeruli, tubules, interstitium, and vessels). Amyloid does not stimulate an inflammatory response; thus, proliferative lesions are absent. Congo red-stained amyloid appears pink under light microscopy and generates a characteristic "apple green" birefringence under polarized light (Fig. 1). This birefringence is required in order to consider the Congo red staining to be "positive." The amyloid

Table 1 Types of systemic amyloidosis with kidney involvement

Type	Precursor protein	Comment
AL	Immunoglobulin light chain	Amyloidogenic protein produced by clonal plasma cells in the bone marrow Broad range of organ/tissue involvement
AH	Immunoglobulin heavy chain	Amyloidogenic protein produced by clonal plasma cells in the bone marrow Much less common than AL
ALH	Immunoglobulin light + heavy chain	Amyloidogenic protein produced by clonal plasma cells in the bone marrow Much less common than AL
AA	Serum amyloid A (SAA)	Amyloidogenic protein is an acute phase reactant produced by the liver Kidney is the most common affected organ but AA amyloidosis can also affect other organs
ATTRm	Mutant transthyretin (TTRm)	Amyloidogenic protein is produced by the liver and choroid plexus Most common type of hereditary amyloidosis Renal involvement is rare; Heart and/or peripheral nervous system involvement is typical Wild-type TTR can cause amyloidosis in elderly individuals (ATTRwt)
AFib	Fibrinogen A alpha chain	Hereditary Amyloidogenic protein is produced by the liver Kidney involvement is common Liver, spleen, and heart can be affected
AApoAI	Apolipoprotein AI	Hereditary Amyloidogenic protein is produced by the liver and other tissues Kidney, liver, and heart involvement is common Kidney deposits are mainly tubulointerstitial and medullary
AApoAII	Apolipoprotein AII	Hereditary Amyloidogenic protein is produced by the liver and small intestine Kidney involvement predominates
AApoAaIV	Apolipoprotein A IV	Non-hereditary Kidney involvement is common
ALys	Lysozyme	Hereditary Amyloidogenic protein produced by multiple tissues Multiple organs and tissues including kidney can be affected
ALECT2	Leukocyte chemotaxin factor-2	Non-hereditary Amyloidogenic protein produced by multiple tissues Kidney involvement predominates

fibrils are visible by electron microscopy. The fibrils are non-branching, 8–12 nanometers in diameter, and oriented in what appears to be a random array (Fig. 1). Podocyte foot process effacement of varying severity is evident. Because different types of amyloid are indistinguishable by light or electron microscopy, immunostaining or proteomic analysis with mass spectrometry is needed to identify the amyloidogenic protein (Said et al. 2013). For AL amyloidosis, immunofluorescence microscopy usually reveals restriction for either a kappa or lambda light chain. For several types of amyloidosis, reagents for immunostaining are not available, and even for AL amyloidosis, occasionally the light chain is not detected by immunostaining. Laser capture microdissection of Congo red-positive material followed by mass spectrometry should be performed if the type of amyloidosis is not evident by immunostaining (Picken 2015).

Most patients with AL amyloidosis will have evidence of a monoclonal light chain in the serum and/or urine. In contrast to multiple myeloma, the concentration of the light chain is often too low to be detected by serum or urine protein electrophoresis but is usually detectable by immunofixation electrophoretic studies. Additionally, an elevated free kappa or lambda light chain is usually evident

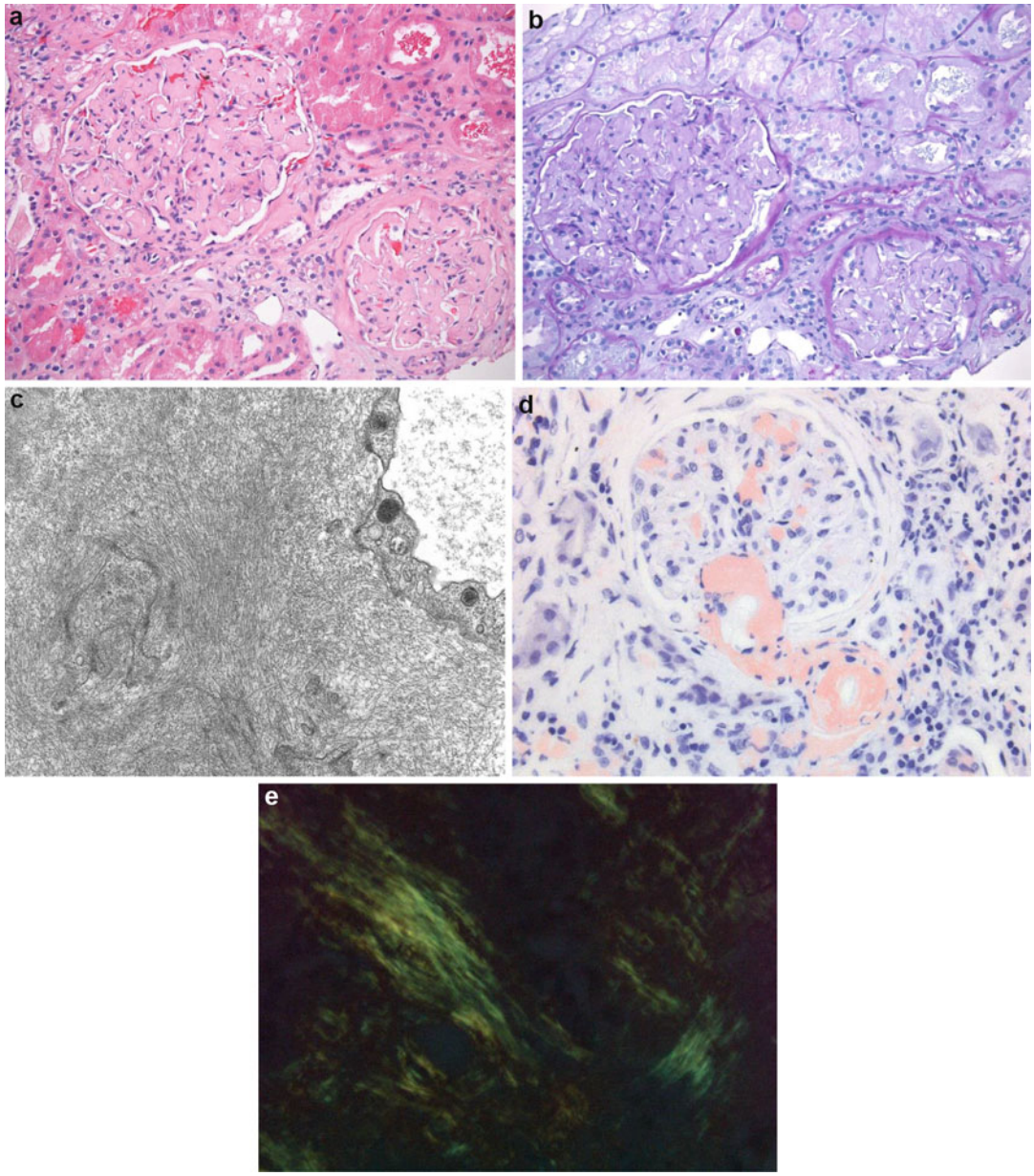

Fig. 1 Glomerular amyloid deposition is characterized by variable expansion and distortion of the mesangium and capillary walls with amorphous material staining lightly eosinophilic (**a**) and weak to negative on PAS (**b**). On electron microscopy (**c**), there are fine fibrils arranged in random orientations filling and replacing the mesangial matrix. To the right are an endothelial cell and a capillary lumen. (**d**) Congo red stain highlights amyloid deposits in vessel walls and glomerular mesangium. (**e**) Under polarized light, amyloid deposits stained with Congo red exhibit birefringence. (**a**, H&E 200×; **b**, PAS 200×; **c**, electron micrograph 20,000×; **d**, Congo red, light microscopy 400×; **e**, Congo red, polarizing microscopy 630×). (Figure provided by Matthew Palmer, M.D., Ph.D.)

by a nephelometric serum-free light chain assay. When renal function is impaired, the ratio of free kappa and lambda light chains rather than their absolute levels should be evaluated since free light chains are eliminated by glomerular filtration. A bone marrow biopsy usually reveals

plasma cells with lambda or kappa light chain restriction, but the percentage of plasma cells is normal or only slightly increased unless the patient has multiple myeloma.

Clinical Presentation

AL amyloidosis is a rare disease, with an estimated sex- and age-adjusted incidence of 10 per million person-years (Kyle et al. 1992). The disease is typically diagnosed in individuals over the age of 50 years but can also occur in young adults. The pathogenic light chain is of the lambda isotype in approximately 75% of patients with AL amyloidosis. In contrast, the paraprotein is usually of the kappa isotype in multiple myeloma (Falk et al. 1997).

The kidney is the most common site of amyloid deposition in AL amyloidosis although many patients have multiple organs or tissues affected. Most patients with renal involvement have proteinuria that is in the nephrotic range. Full-blown nephrotic syndrome with marked hypoalbuminemia and severe edema and hyperlipidemia is common. A minority of patients have amyloid deposition that spares the glomeruli. When amyloid is restricted to the tubulointerstitium or the vessels, patients have reduced GFR without significant proteinuria. Although the eGFR tends to be lower at presentation in such patients (Eirin et al. 2012), some have observed slower decline in kidney function among those without substantial glomerular involvement.

When evaluating a patient with AL amyloidosis affecting the kidneys, it is important to also consider extrarenal involvement because of the implications for management, complications, and treatment tolerability (Table 2). For example, hemodynamic alterations from cardiac involvement or autonomic nervous system involvement can underlie creatinine elevations, loss of muscle mass can confound creatinine-based estimation of glomerular filtration rate, and cardiac involvement is a relative contraindication to the use of certain medications such as calcium channel blockers (Siddiqi and Ruberg 2018).

Table 2 Clinical manifestations of AL amyloidosis

Site of involvement	Clinical manifestations
Kidney	Nephrotic syndrome; kidney failure
Heart	Restrictive cardiomyopathy; arrhythmias; sudden death
Liver	Hepatomegaly; elevated alkaline phosphatase
Autonomic nervous system	Orthostatic hypotension; diarrhea
Peripheral nervous system	Sensory neuropathy
Gastrointestinal tract	Bleeding; malabsorption
Vasculature	Jaw and/or buttock claudication, small vessel cardiac ischemia; ecchymoses, periorbital bruising; subconjunctival hemorrhage
Soft tissue	Macroglossia, submandibular gland enlargement; muscle pseudohypertrophy; subcutaneous nodules and plaques; arthropathy; carpal tunnel syndrome

Treatment of AL Amyloidosis

Anti-plasma Cell Therapies

Current treatment of AL amyloidosis is directed at the underlying clonal plasma cell (or, rarely, B lymphocyte) disorder. Prior to the late 1990s, the standard treatment was repeated cycles of orally administered melphalan and prednisone, both of which have activity against plasma cells. However, this treatment had to be administered for many months before an effect was apparent, it rarely resulted in elimination of the amyloidogenic light chain, and it increased survival from approximately 8 months to only 12–18 months (Skinner et al. 1996; Kyle et al. 1997). The introduction of high-dose melphalan with autologous stem cell transplantation (HDM/SCT) was an important advance because, although associated with substantial toxicity, this aggressive treatment results in eradication of the clonal plasma cells and amyloidogenic light chain in approximately 40% of patients (Skinner et al. 2004). The hematologic response to this treatment is durable, and the

median survival in one of the largest series was 6.1 and 13.2 years among all patients and among those with a complete hematologic response, respectively (Cibeira et al. 2011). Treatment-associated mortality decreased from approximately 14% to less than 5% as experience with HDM/SCT for AL amyloidosis increased and patient selection criteria evolved (Tsai et al. 2012).

Because of the substantial toxicities with HDM/SCT, particularly among those with cardiac involvement or poor functional status, and the development of new anti-plasma cell agents, alternatives to HDM/SCT are increasingly being used as first-line therapy for patients who are either not candidates for high-dose melphalan with autologous stem cell transplantation or who prefer a less intensive treatment approach. Bortezomib, a proteasome inhibitor that is typically administered with high-dose dexamethasone and low-dose cyclophosphamide, is reasonably well tolerated and has a rapid onset of action that allows for evaluation of response within a few months of starting treatment. Lenalidomide, an immunomodulating agent, is less well tolerated among patients with amyloidosis, and its efficacy is often not apparent until after many months of treatment, but it offers an alternative for patients who do not respond to or have important toxicities with HDM/SCT or bortezomib-based regimens. Daratumumab, an IgG1 kappa monoclonal antibody directed against the CD38 cell surface molecule on plasma cells, is starting to be used as second-line therapy for AL amyloidosis and appears to be well tolerated. The development of multiple new anti-plasma cell therapies has markedly expanded treatment options for patients with AL amyloidosis; however, in contrast to HDM/SCT, the durability of the hematologic responses with these agents is not yet established.

Anti-plasma cell therapies have renal-related issues that have implications for treatment selection and monitoring. While melphalan itself is probably not nephrotoxic, acute kidney injury is a frequent complication of treatment with high-dose melphalan and autologous stem cell transplantation (Fadia et al. 2003). Acute worsening of kidney function can occur during growth factor mobilization of stem cells or following administration of the high-dose melphalan either before or after development of cytopenias. Patients at highest risk for acute kidney injury (AKI) appear to be those with pre-existing renal impairment, substantial edema, cardiomyopathy, or hypotension. The AKI is usually reversible but sometimes results in long-term dialysis dependence. Bortezomib does not appear to cause renal impairment, and its dosing does not need to be adjusted for reduced kidney function. The major adverse effect of bortezomib is peripheral or autonomic nervous system toxicity that can be treatment-limiting. There have been a small number of reports of renal failure from thrombotic microangiopathy with carfilzomib, a second-generation proteasome inhibitor (Hobeika et al. 2014; Lodhi et al. 2015). Lenalidomide use has been associated with acute kidney injury of unclear etiology; this seems to occur more often in AL amyloidosis than in multiple myeloma (Specter et al. 2011). Lenalidomide clearance dependent on kidney function and the dose must be reduced in patients with renal impairment. Dexamethasone, administered in doses as high as 40 mg once per week, is usually a component of treatment regimens with proteasome inhibitors and immunomodulating agents. Dexamethasone dose reductions may be needed in patients with renal involvement because of its fluid-retaining effects.

Anti-amyloid Therapies

Amyloid fibrils are highly resistant to endogenous proteases and, as a result, remain in tissue even if production of the amyloidogenic protein is halted. Treatments that are designed to facilitate removal of tissue amyloid deposits are under development. One approach targets serum amyloid P protein (SAP), a member of the pentraxin family that is present in amyloid deposits of all types and protects amyloid fibrils from degradation. Depletion of circulating SAP using (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC), a small molecule

that binds to SAP, followed by administration of a fully humanized anti-SAP monoclonal antibody that binds to SAP in tissue amyloid deposits and triggers phagocytosis of the amyloid fibrils, has shown some promising results in studies of small numbers of patients (Pepys et al. 2002; Richards et al. 2015). An antibody directed against misfolded light chain aggregates is currently being studied in placebo-controlled trials of patients with AL amyloidosis with cardiac involvement (NCT02312206, NCT02632786) or renal involvement (NCT03168906#). Like the anti-SAP strategy, the anti-light chain antibody is expected to trigger endogenous mechanisms to clear the antibody light chain amyloid complexes (Gertz et al. 2016; Edwards et al. 2017).

Supportive Management

Supportive management of patients with AL amyloidosis and kidney involvement requires attention to volume status, hemodynamics, medication absorption, and nutritional status. Nephrotic patients typically require loop diuretics which often need to be given in high doses because of marked renal sodium avidity. Torsemide may be particularly effective if there is gastrointestinal mucosal edema, and the addition of a thiazide diuretic, such as metolazone, to inhibit distal sodium reabsorption, can enhance the effect of the loop diuretic. However, patients with AL amyloidosis may be particularly sensitive to the hemodynamic effects of diuresis particularly if there is autonomic nervous system or cardiac involvement. Midodrine, an oral alpha-1 agonist, and support stockings for patients with hypotension and peripheral edema, respectively, can improve diuretic tolerability and/or responsiveness. In the absence of hypotension, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be used for their proteinuria-lowering effect. Statins are often used for the hyperlipidemia that accompanies nephrotic syndrome, but they often do not result in normalization of lipid levels. Patients with cardiac amyloidosis are often placed on prophylactic anticoagulation because of the high rate of intra-atrial thrombus formation; however, anticoagulation is not typically used in these patients to prevent nephrotic syndrome-associated thrombosis.

Renal Response to Treatment

Elimination of the amyloidogenic light chain is accompanied by a progressive reduction in proteinuria in most patients. This was demonstrated initially among a group of 65 patients with AL amyloidosis and renal involvement who were treated with HDM/SCT (Dember et al. 2001). At 12 months after treatment, a "renal response" defined as a 50% reduction in 24-h urinary protein excretion with preservation of creatinine clearance occurred in 71% of the patients who had a complete hematologic response meaning that there was no evidence of a monoclonal light chain by examination of the serum, urine, and bone marrow. In contrast, among the patients who had persistence of the monoclonal protein, only 11% had a renal response at 12 months. Larger series with longer follow-up confirmed this relationship between hematologic response and renal response and found that the reduction in proteinuria continued beyond 12 months with normalization or near normalization of proteinuria in many of the patients who had a complete hematologic response (Skinner et al. 2004; Leung et al. 2005). Hematologic remissions induced by other anti-plasma cell treatments such as bortezomib also are often accompanied by gradual resolution of proteinuria. Improvement in GFR is unusual in AL amyloidosis-associated kidney disease, but kidney function, as assessed by serum creatinine, creatinine clearance, or GFR estimating equations, does remain reasonably stable in most patients who achieve a hematologic response. However, some patients have progressive loss of kidney function and ultimately need renal replacement therapy despite a hematologic response. Table 3 shows consensus criteria for hematologic, renal, and cardiac responses.

The reduction in proteinuria that occurs following eradication of amyloidogenic light chain production is not the result of clearance of tissue

Table 3 Response criteria for hematologic and organ response criteria for AL amyloidosis (adapted from Comenzo et al. 2012)

Hematologic	
Complete response	Normalization of serum FLC levels and ratio; no monoclonal protein evident by serum and urine IFE
Very good partial response	Reduction in dFLC to <40 mg/dL
Partial response	>50% reduction in dFLC
No response	Less than PR
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double) From PR, 50% increase in serum M protein to >0.5 g/dl or 50% increase in urine M protein to >200 mg/day (a visible peak must be present) Free light chain increase of 50% to >100 mg/l
Renal	
Response	Proteinuria decrease 50% (to ≤0.5 g/day) **and** renal function not worsened by 25% from baseline[a]
Progression	Proteinuria increase 50% (to ≥1 g/day) **or** 25% worsening of renal function[a]
Cardiac	
Response	NT-proBNP decrease (>30% and >300 ng/L decrease) if baseline NT-proBNP ≥650 ng/L **or** NYHA class response of ≥2 for patients starting with class 3 or 4
Progression	NT-proBNP progression (>30% and >300 ng/L increase) **or** cardiac troponin progression (≥33% increase) **or** EF progression (≥10% decrease)

Abbreviations: FLC, free light chain, IFE immunofixation electrophoresis, *dFLC* difference between the involved and uninvolved serum-free light chain, *CR* complete response, *PR* partial response, M monoclonal, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association, *EF* ejection fraction
[a]Measured by creatinine clearance or creatinine-based estimated glomerular filtration rate

amyloid as amyloid deposits are highly resistant to proteolytic degradation. Instead, the rapid reduction in proteinuria likely reflects either toxicity of amyloidogenic light chains or light chain aggregates or differential effects on proteinuria of new versus old amyloid deposition (Dember 2006, 2009).

Kidney Transplantation in AL Amyloidosis

Criteria for kidney transplantation for patients with AL amyloidosis-associated end-stage renal disease have not been established. Concerns about transplantation in this setting include the possibility of amyloid deposition in the transplanted kidney and the potential for poor outcomes related to pre-existing or new extrarenal amyloid disease. Several retrospective analyses found that outcomes following kidney transplantation were worse among patients with amyloidosis than those with other causes of ESRD (Pasternack et al. 1986; Bleyer et al. 2001; Sattianayagam et al. 2010; Pinney et al. 2013; Herrmann et al. 2011; Sawinski et al. 2017). However, a recently published analysis of US registry data found that outcomes were comparable between patients with amyloidosis and those with diabetes or advanced age (Sawinski et al. 2017). Studies of transplantation for amyloidosis have important limitations including an absence of information about the type of amyloidosis, the hematologic status for those with AL amyloidosis, and prior treatment. Additionally, several of these studies include patients transplanted during eras in which treatments for AL amyloidosis were much less effective than they are currently. The studies describing the clinical course prior to kidney transplantation show similar outcomes regardless of whether a hematologic response was achieved with HDM/SCT or other anti-plasma cell treatments but better outcomes among patients who

had achieved a complete or partial hematologic response rather than no hematologic response (Pinney et al. 2013; Herrmann et al. 2011). Amyloid recurrence in the kidney allograft has been reported, although its effect on graft loss is unclear (Sattianayagam et al. 2010; Herrmann et al. 2011; Sawinski et al. 2017). There is also limited information about the tolerability of anti-plasma cell therapies after kidney transplantation. Based on theoretical considerations as well as a few case reports, lenalidomide and other members of the immunomodulatory class of anti-plasma cell agents should be avoided because of a possible rejection-triggering effect (Meyers et al. 2013; Lum et al. 2017). Until more data are available, it seems reasonable to consider kidney transplantation for patients who have had a sustained hematologic response and limited extrarenal amyloid disease. For individuals with ongoing production of the amyloidogenic light chain or extrarenal disease with clinically apparent effects, renal transplantation should probably be avoided.

Summary

Renal involvement is common in AL amyloidosis and typically manifests as nephrotic syndrome and progressive loss of kidney function. Extrarenal amyloid disease can complicate the supportive management of nephrotic syndrome and can contribute to kidney function impairment. Currently available treatments aim to eradicate the underlying plasma cell clone, and newer approaches that target existing amyloid deposits are being studied. Treatment advances during the last two decades have changed AL amyloidosis from a uniformly fatal disease to a serious but treatable and manageable disorder for many patients.

Cross-References

▶ Lipoprotein Glomerulopathy, Non-AL Amyloidosis, LCAT, ING

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Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

34

Samar M. Said and Samih H. Nasr

Contents

Abstract

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a relatively recently described form of glomerulonephritis that mimics immune-complex-type glomerulonephritis on light microscopy and electron microscopy. However, by immunofluorescence, the glomerular deposits are monotypic, staining for a single light chain isotype and a single gamma heavy chain subclass, most commonly IgG3 kappa. PGNMID is classified as a monoclonal gammopathy of renal significance – lesion characterized by non-organized deposits in patients who do not have systemic lymphoma or multiple myeloma. Despite the monotypic nature of glomerular deposits, only a small subset of patients has a detectable serum monoclonal immunoglobulin, and hematologic malignancy is rare. Furthermore, PGNMID does not appear to represent a premyelomatous condition in most patients. The disease mainly affects adults and is slightly more common in females. Most patients present with nephrotic-range proteinuria and hematuria with or without renal insufficiency. Prognosis is variable, with nearly a quarter of patients progressing to ESRD within 2.5 years despite immunomodulatory therapy. Early recurrence in the renal allograft is observed in most patients. The pathogenesis of PGNMID remains elusive.

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PGNMID · Proliferative glomerulonephritis with monoclonal IgG deposits · Monoclonal gammopathy · IgG3 · Monoclonal gammopathy of renal significance · MGRS

Introduction

Glomerular diseases caused by monoclonal immunoglobulin deposition include light and heavy chain deposition disease, type 1 cryoglobulinemic glomerulonephritis, immunotactoid glomerulonephritis, light and heavy chain amyloidosis, and monoclonal fibrillary glomerulonephritis (Bridoux et al. 2015). In 2004, a novel form of glomerular injury related to monoclonal IgG deposition that could not be assigned to any of the above conditions was described and termed "proliferative glomerulonephritis with monoclonal IgG deposits" (PGNMID) (Nasr et al. 2004). On immunofluorescence (IF), the glomerular deposits were monotypic, staining for a single light chain isotype and a single gamma heavy chain subclass. However, light microscopy (LM) exhibited endocapillary proliferative or membranoproliferative glomerulonephritis, and electron microscopy (EM) revealed mostly granular electron-dense deposits, mimicking immune-complex glomerulonephritis. Since then, there have been two reported large series on PGNMID, one from Columbia University of 37 patients (Nasr et al. 2009) and one from the Mayo Clinic of 54 patients (Bhutani et al. 2015) and over 25 case reports or small series. The reported renal biopsy incidence of PGNMID ranged from 0.17% to 3.7% (Gowda et al. 2015; Nasr et al. 2009). It is eightfold rarer than AL amyloidosis and twice as rare as Randall type monoclonal immunoglobulin deposition disease, but more common than type 1 cryoglobulinemic glomerulonephritis and immunotactoid glomerulonephritis. In this chapter we will review the clinical renal and hematologic characteristics, pathologic features, diagnostic criteria, treatment, outcome, recurrence in the allograft, and potential pathogenesis of PGNMID. Of note, rare cases of proliferative glomerulonephritis with non-organized monoclonal IgM, IgA, or lambda light chain deposits have been reported (Bhutani et al. 2015) which will not be addressed in this chapter.

Demographic and Clinical Characteristics of PGNMID

PGNMID appears to be a glomerular-limited condition as no extraglomerular or extrarenal deposits have been described thus far in this form of glomerulonephritis. Patients with PGNMID typically present in their sixth to seventh decade of life with a median age of 56 years. Two thirds of patients are >50 years old and 17% are >70 years old at diagnosis. Rarely, PGNMID can affect children. There is a slight female predominance (female-to-male ratio of 1.2:1). The vast majority of reported patients were Caucasian. Most patients do not have clinical evidence of underlying infectious, autoimmune, or other systemic disease, although there have been few reported patients who had a history of carcinoma (of colon, anus, bladder, breast), infection (recent upper respiratory tract, HCV, HIV, parvovirus B19), or autoimmune disease (Sjogren's syndrome, autoimmune hemolytic anemia) (Nasr et al. 2009; Bhutani et al. 2015). Chronic hypertension and diabetes mellitus are present in 38% and 14% of patients, respectively.

Patients typically present with proteinuria, hematuria, and renal insufficiency. All patients have proteinuria (median 3.8 g/day, interquartile range 2–8.2), which is in the nephrotic range in 69% of patients, and about half have full nephrotic syndrome. Microhematuria is present in 77% of patients, whereas gross hematuria is rare, reported in <3% of patients. Two thirds of patients have renal insufficiency at presentation (median eGFR 36 mL/min/1.73 m^2 (interquartile range 20–50)), including 8% who require dialysis at the time of diagnosis. The mean serum albumin is 3.1 g/dL (range 1.1–4.9). Peripheral edema is present in 62% of patients. Serum cryoglobulin and rheumatoid factor are typically negative, without systemic manifestations of cryoglobulinemia. Hypocomplementemia is present in 21–27% of

patients (low C3 alone, low C4 alone, or low C3 and C4, with equal frequencies).

Hematologic Characteristics of PGNMID

Overall, only 19% to 27% of patients with PGNMID have a detectable circulating monoclonal immunoglobulin (MIg) by serum immunofixation (SIFE), which is more sensitive than serum protein electrophoresis (SPEP). In these patients, the MIg is detectable at presentation although rare patients with an initial negative SIFE develop positive SIFE on repeat testing as late as 3 years after presentation. Using the standard serum free light chain ratio (sFLCR) (range 0.26–1.65), sFLCR has comparable sensitivity to SIFE for the detection of MIg. Patients with abnormal sFLCR and those with positive SIFE for MIg do not overlap completely. In the abovementioned cohort by Bhutani et al. (2015), 50 patients were tested by sFLCR; 11 (22%) had abnormal sFLCR; and two thirds of these had negative SIFE. Together, SIFE and sFLCR detected MIg in 30% of patients. However, using the extended renal range of sFLCR (0.3–3.1), only one patient had abnormal sFLCR. Urine protein electrophoresis (UPEP) with immunofixation (UIFE) is less sensitive than the serum monoclonal protein studies in detecting the nephropathic MIg (detection rate 8–9%), and they are typically negative when the serum studies are negative.

The clone detection rate on bone marrow (BM) examination (including testing by immunohistochemistry and flow cytometry) is 19%, and it correlates with the results of SIFE and sFLCR. The nephropathic clone is detected in 100% of patients with positive SIFE and abnormal sFLCR, in 75% of patients with positive SIFE and normal sFLCR, in 17% of patients with abnormal sFLCR and negative SIFE, and in 0% in those with negative SIFE and normal sFLCR (Bhutani et al. 2015). The nephropathic clone is most commonly a plasma cell clone, and the percentage of monoclonal plasma cells is usually <10% of the BM cellularity. CD20-positive B-cell clones are less common and are most commonly chronic lymphocytic leukemia (CLL) clones. The above data suggests that BM biopsy is not informative in PGNMID patients with negative SIFE and normal sFLCR. Hematologic malignancy is rare in PGNMID, reported in 3–4% of patients, and includes CLL and multiple myeloma (Barbour et al. 2011; Nasr et al. 2009). One patient with concurrent AL amyloidosis involving the renal vessels with sparing of glomeruli has also been reported (Nasr et al. 2004).

Pathologic Features of PGNMID

The diagnostic criteria for PGNMID are listed in Table 1. On LM, the glomerular alterations are heterogeneous, with the majority of cases showing variable degrees of endocapillary hypercellularity and duplication of the glomerular basement membranes (GBM). The most frequent pattern of glomerular injury, seen in 55–68% of cases, is membranoproliferative glomerulonephritis (MPGN) characterized by diffuse and global duplication of the GBM with cellular interposition and mesangial expansion by increased mesangial cell number and matrix (Fig. 1a). Most of these cases also exhibit endocapillary hypercellularity, and some show segmental membranous features. The second most

Table 1 Diagnostic criteria for PGNMID

Immune deposit staining positive for gamma heavy chain (IgG), with negativity for alpha (IgA) and mu (IgM) heavy chains, indicating restriction to a single immunoglobulin class
Positive staining for a single gamma (IgG) subclass (IgG1, IgG2, IgG3, or IgG4), indicating restriction to a single IgG subclass
Positive staining for a single light chain isotype (kappa or lambda), indicating that the deposits are monotypic
Predominantly granular electron-dense deposits in mesangial, subendothelial, and/or subepithelial locations by EM, resembling immune complex type deposits
Absence of clinical or laboratory evidence of cryoglobulinemia

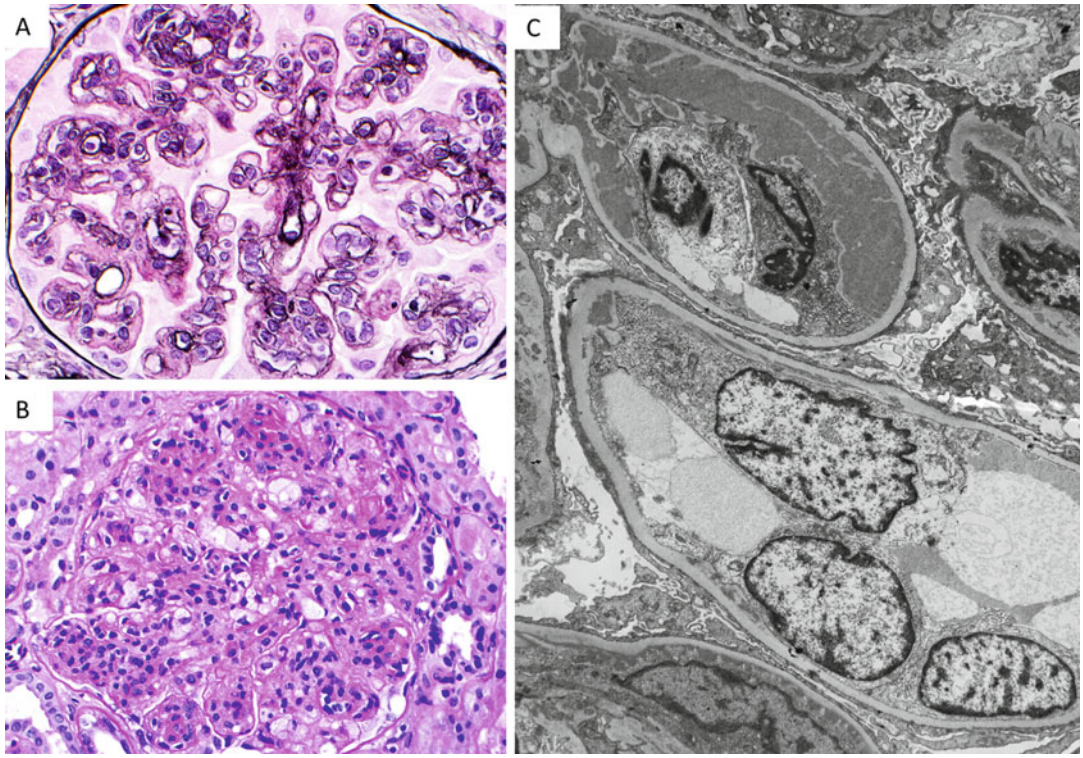

Fig. 1 (**a**) Membranoproliferative pattern of PGNMID. There is widespread duplication of the glomerular basement membrane associated with cellular interposition. The glomerulus also shows global mesangial and segmental endocapillary hypercellularity (silver stain). (**b**) Endocapillary proliferative pattern of PGNMID. The glomerulus shows global mesangial hypercellularity and endocapillary hypercellularity which segmentally occludes the glomerular capillary lumina (periodic acid-Schiff stain). (**c**) Electron microscopy in PGNMID. There are large granular subendothelial and mesangial electron-dense deposits without substructure. Podocytes display global foot process effacement

common pattern, seen in 20–35% of cases, is endocapillary proliferative glomerulonephritis, characterized by endocapillary hypercellularity and leukocyte infiltration causing luminal occlusion (Fig. 1b). Some of these cases have associated segmental membranoproliferative features, neutrophil infiltration, or segmental membranous features. A pure mesangial proliferative glomerulonephritis pattern, characterized by mesangial hypercellularity without endocapillary proliferative or membranoproliferative features, occurs in 3–13% of cases. A fourth histological pattern, encountered in 5% of cases, is predominantly membranous glomerulonephritis characterized by GBM thickening and global subepithelial deposits (Komatsuda et al. 2008; Guiard et al. 2011). Crescents are present in 18–32% of patients and are typically focal affecting <50% of glomeruli. Crescentic transformation of PGNMID has been reported after upper respiratory tract infection or treatment with filgrastim (Batal et al. 2016).

By IF, the monotypic deposits are seen exclusively in the glomeruli, localized mainly to the glomerular capillary wall and mesangium and generally have a granular texture. IgG is the only immunoglobulin deposited (Fig. 2). There is light chain isotype restriction, with sole positivity for kappa in 70–73% of cases and sole positivity for lambda in 27–30% of cases (Fig. 2). There is glomerular co-deposition of C3 in almost all cases and C1q in 55–64% of cases (Fig. 2). Staining for IgG1–4 subclasses shows monotypic deposits: IgG3 only in 60–68% of

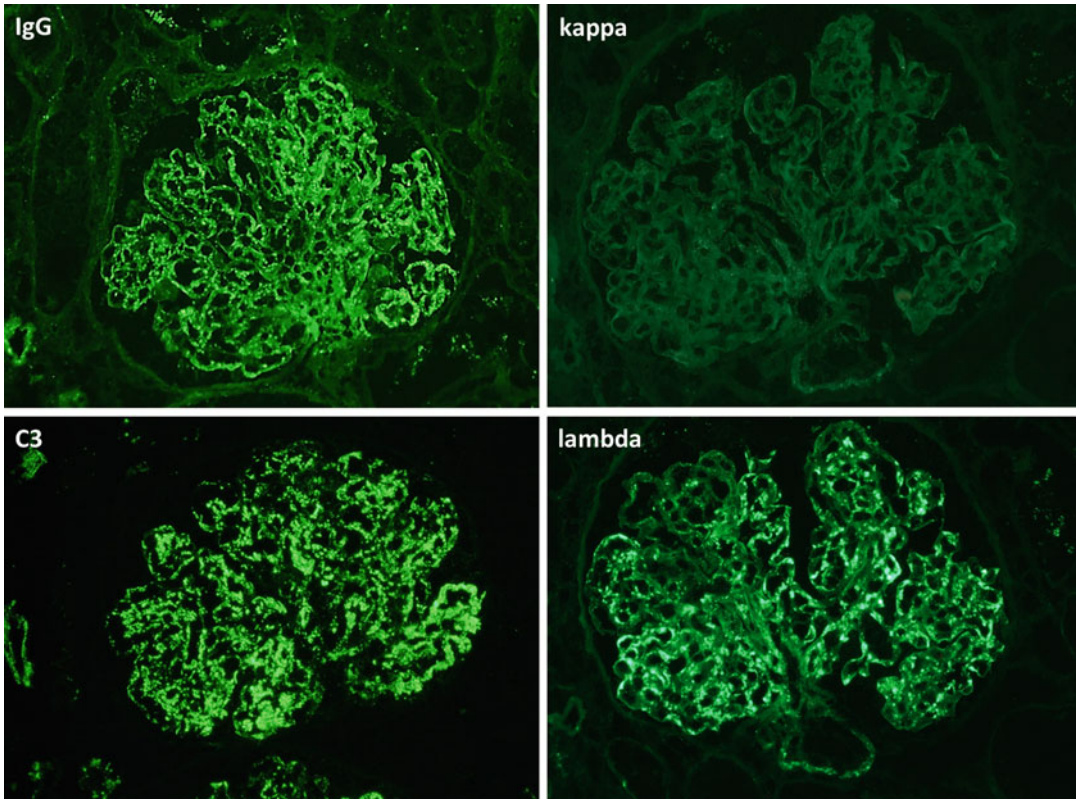

Fig. 2 Immunofluorescence in this case of PGNMID shows bright granular global mesangial and glomerular capillary wall positivity for IgG, C3, and lambda. The glomerulus is negative for kappa

cases, IgG1 only in 24–29% of cases, and IgG2 only in 3–16% of cases (Fig. 3). No case of PGNMID with monotypic IgG4 deposits has been reported so far.

On EM, the deposits are confined to the glomerular compartment, present primarily in the mesangium and subendothelial space (Fig. 1c). Subepithelial deposits are less frequent, seen in 17–57% of patients, and are segmental in most cases. In 70–81% of cases, the electron-dense deposits have a finely granular texture throughout, without substructure, resembling immune-complex-type deposits. In the remaining cases, the deposits are mostly granular, but with focally variegated texture. In a small subset of cases, ill-defined fibrils, microtubules, lattice-like arrays, or paracrystalline substructure can be seen involving a portion of otherwise granular deposits.

Treatment and Prognosis of PGNMID

In the absence of prospective, controlled studies, the optimal therapeutic regimen has not been established. Renin angiotensin system blockade and immunomodulatory (IM) therapy with steroids alone or in combination with other immunosuppressive agents, such as cyclophosphamide, mycophenolate mofetil, cyclosporine, rituximab, and bortezomib, have been used in PGNMID with variable results. In patients with stages 1 and 2 CKD, mild proteinuria (<1 g/day), and no histologic evidence of progression (glomerulosclerosis, crescents, interstitial fibrosis), symptomatic therapy only is advised (Fermand et al. 2013; Nasr et al. 2009). In patients with higher CKD stages, nephrotic range proteinuria, and/or histologic evidence of progression, IM is indicated. Clone-directed chemotherapy (such as cyclophosphamide

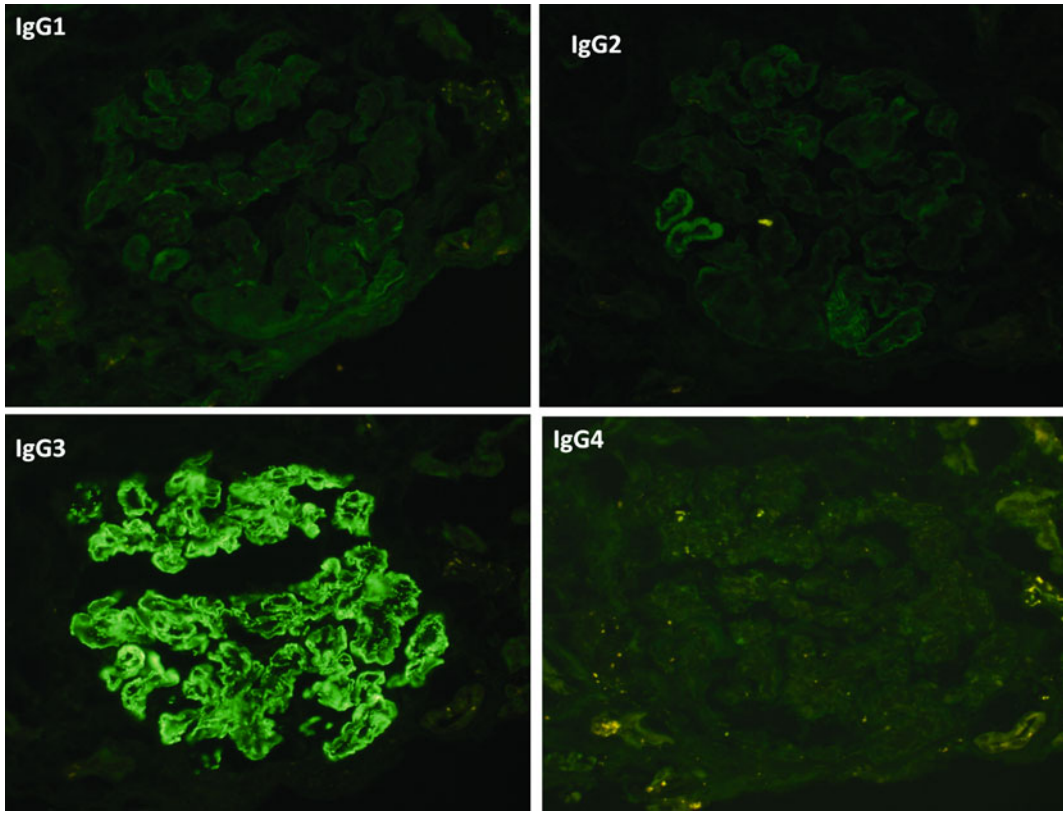

Fig. 3 Immunofluorescence staining for IgG subtypes in this case of PGNMID shows bright glomerular positivity for IgG3. The glomerulus is negative for IgG1, IgG2, and IgG4

and bortezomib or CyBorD (cyclophosphamide/bortezomib/dexamethasone)) should be the first line of treatment in the subset of PGNMID patients with a detectable BM nephropathic clone. In patients without a detectable nephropathic clone, the first line of therapy has not been established, but treatment with cyclophosphamide is a reasonable choice (Fermand et al. 2013; Bhutani et al. 2015). Anecdotal reports found rituximab to be effective, particularly in CLL-associated PGNMID in which the nephropathic clone is a CD20+ B cell (Barbour et al. 2011; Guiard et al. 2011).

Renal prognosis of PGNMID is variable. In the study by Nasr et al. (2009) in which follow-up (mean 30 months) was available on 32 patients, 38% had complete or partial recovery (reduction in proteinuria by at least 50% and to <2 g/d with stable renal function), 38% had persistent renal dysfunction, and 22% progressed to ESRD. Predictors of ESRD on univariate analysis were creatinine at biopsy, percentage of global glomerulosclerosis, and the degree of interstitial fibrosis, but not IM treatment or detection of circulating MIg. On multivariate analysis, higher percentage of glomerulosclerosis was the only independent predictor of ESRD. Only a single patient with negative SIFE at presentation subsequently had positive SIFE, and none of the patients with positive SIFE at presentation subsequently developed MM on follow-up, suggesting that PGNMID is not a precursor of myeloma in most patients (Nasr et al. 2009).

PGNMID in the Renal Allograft

Ten case reports or small series addressing recurrent PGNMID in the renal allograft have been recently reported (Albawardi et al. 2011;

Al-Rabadi et al. 2015; Nasr et al. 2011). The recurrence rate appears to be as high as 80% (Bhutani et al. 2015). Recurrent PGNMID in most patients develops in the first-year post transplant with an average time from transplant to recurrence of 4 months (range 3–13 months). Early detection is enhanced by the use of protocol surveillance biopsies. The recurrent disease manifests clinically with proteinuria, hematuria, and variable degrees of renal insufficiency. The monotypic deposits in the glomeruli of renal allograft and native kidneys are identical with regard to the IgG light and heavy chain isotype restriction (most commonly IgG3, rarely IgG1). As in PGNMID in the native kidneys, most patients do not have a detectable circulating MIg or hematologic malignancy. PGNMID may also develop de novo in the renal allograft (Albawardi et al. 2011). PGNMID in the allograft responds to early aggressive IM therapy including high-dose prednisone, cyclophosphamide, and rituximab, but disease relapse may occur after discontinuation of therapy. The impact of recurrence on the long-term graft survival remains to be determined.

Pathogenesis of PGNMID

The pathogenesis of PGNMID remains elusive. The absence of the underlying infectious, autoimmune, or other systemic disease in most patients and the light chain and heavy chain subclass restriction argue against antigen-antibody immune complex deposition and, instead, favor that monoclonal IgG is deposited in glomeruli as a free, noncomplexed immunoglobulin. Since the majority of patients do not have a detectable circulating MIg or underlying clonal cell population, in these cases PGNMID could arise in the course of normal immune responses. One hypothesis is that during an immune response, a clone of B cells or plasma cells proliferates and produces a monoclonal IgG molecule (particularly IgG3) with the ability to self-aggregate and rapidly deposit in glomeruli through entrapment and/or interaction with negatively charged glomerular constituents. The small quantity of this monoclonal IgG may elude detection by our standard SPEP/SIFE owing to its high avidity for the glomeruli and rapid aggregability favored by its intrinsic physical properties and glomerular sieving itself. In contrast to heavy chain deposition disease in which the CH1 constant domain is deleted, there is no detectable deletion in any of the constant domains in PGNMID (Nasr et al. 2004). The intact CH2 domain is essential for complement fixation.

IgG3, which comprises only 8% of IgG in the circulation, has several properties that allow it to be intrinsically "nephritogenic." IgG3 has the highest molecular weight among the IgG subclasses, making it more size restricted by the glomerular filtration barrier, has the unique physicochemical property of self-aggregability via Fc-Fc interactions, and has the greatest complement-fixing capacity, which could activate downstream inflammatory mediators that promote glomerular leukocyte infiltration and proliferation, leading to glomerulonephritis. These special properties of IgG3 may explain the overrepresentation of this uncommon serum subtype in patients with PGNMID and the universal glomerular co-deposition of C3.

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Immunotactoid Glomerulopathy

35

Meghan E. Kapp and Agnes B. Fogo

Contents

Abstract

Immunotactoid glomerulopathy (ITG) describes a glomerular lesion with specific ultrastructural features of organized deposits, most often microtubular and/or in parallel arrays, usually with monotypic immunoglobulin staining. It is diagnosed in the absence of cryoglobulinemia and is often associated with underlying lymphoproliferative disease, which results in production of the pathogenic paraprotein with subsequent renal deposition. Treatment of such underlying diseases has shown beneficial results in some patients.

Keywords

Immunotactoid glomerulopathy · Fibrillary glomerulonephritis · Organized deposits · Microtubular · Cryoglobulinemia · Lymphoproliferative disease · Mesangioproliferative · Membranoproliferative · Atypical membranous · Paraprotein

Introduction

Immunotactoid glomerulopathy (ITG) is a broadly, but not universally accepted distinct morphologic entity within the spectrum of nonamyloidogenic renal disease with organized deposits (Bridoux et al. 2002; Iskandar et al. 1992; Rosenstock et al. 2003; Alpers 1992, 1993; Fogo et al. 1993; Schwartz et al. 2002; Korbet et al. 1991). This entity is rare, occurring in approximately 0.1% of native kidney biopsies, and most commonly shows

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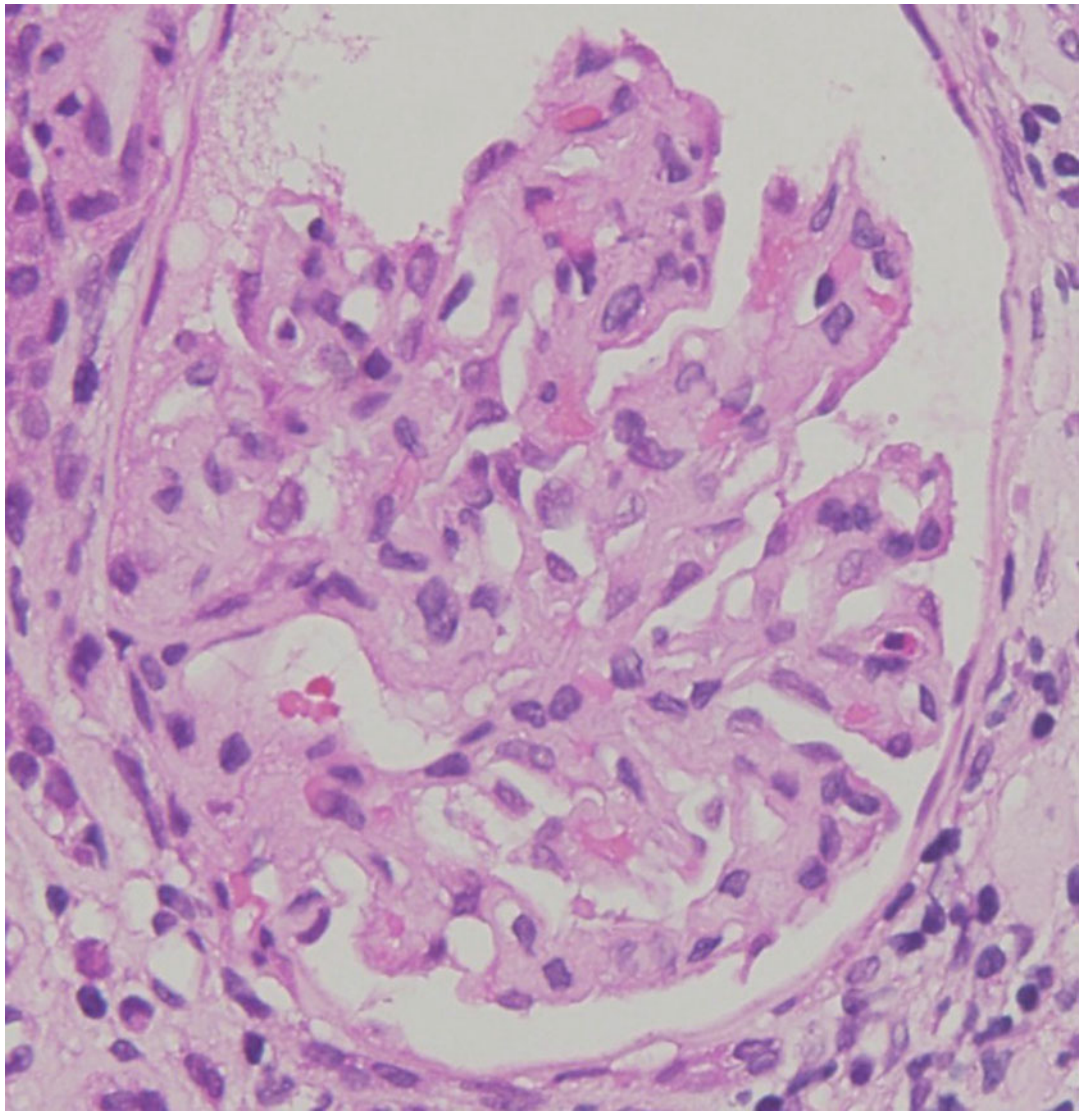

Fig. 1 Glomerular lesions may present with a mesangioproliferative pattern of injury showing expansion of mesangial matrix and cellularity. Additional findings include membranoproliferative or atypical membranous patterns (hematoxylin and eosin 64×)

a membranoproliferative-type pattern of renal injury by light microscopy with characteristic microtubule formation by electron microscopy. Immunotactoid glomerulopathy tends to be associated with paraprotein production in the setting of chronic lymphocytic leukemia (CLL) and related B cell lymphomas. No randomized trials for treatment have been conducted; however, case reports show some success with targeting the underlying B cell neoplasm.

Clinical Manifestations

Immunotactoid glomerulopathy occurs in an older (average 62 years), predominantly Caucasian population, with equal incidence in men and women. It presents most commonly with nephrotic syndrome, though hematuria, hypocomplementemia, and renal insufficiency are also seen (Fogo et al. 1993; Pronovost et al. 1996). Notably, patients with

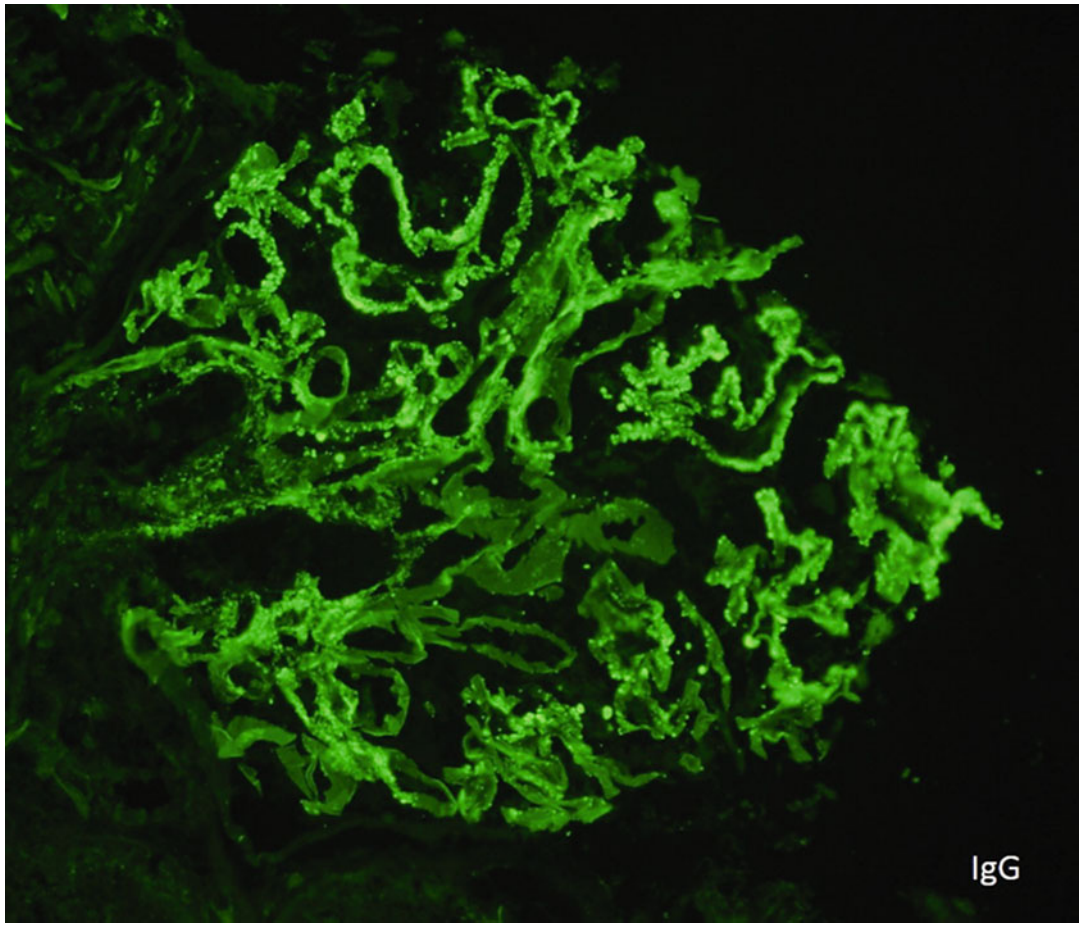

Fig. 2 IgG dominant staining in a granular global capillary loop pattern in a case of ITG presenting as an atypical membranous glomerulopathy (anti-IgG immunofluorescence, 40×)

immuntactoid glomerulopathy have a greater propensity for an underlying lymphoplasmacytic disorder when compared to fibrillary glomerulonephritis patients, another entity with organized, but randomly arranged fibrils. Thus, two-thirds of patients have a preceding, concomitant, or subsequent circulating monoclonal paraprotein and/or lymphoplasmacytic malignancy identified.

The causal relationship between chronic lymphocytic leukemia (CLL) or related B cell lymphomas to the development of ITG is supported by immunofluorescence studies, which demonstrate monotypic glomerular deposits which matched the isotype in the patient's serum and/or lymphocyte cytoplasm (Bridoux et al. 2002). Furthermore, mass spectrometry studies have shown the deposits to be comprised of immunoglobulins, monotypic light chains, complement factors of classical and terminal pathway, and a small amount of serum amyloid P component, consistent with deposition of monotypic immunoglobulins and activation of classical and terminal pathway of complement (Sethi et al. 2013; Nasr et al. 2012).

Kidney Abnormalities

Histology

The glomerular lesions by light microscopy show a mesangioproliferative or membranoproliferative (in about half), or atypical membranous pattern (in about a third) with a moth-eaten appearance on silver stain, as the deposits resist impregnation by

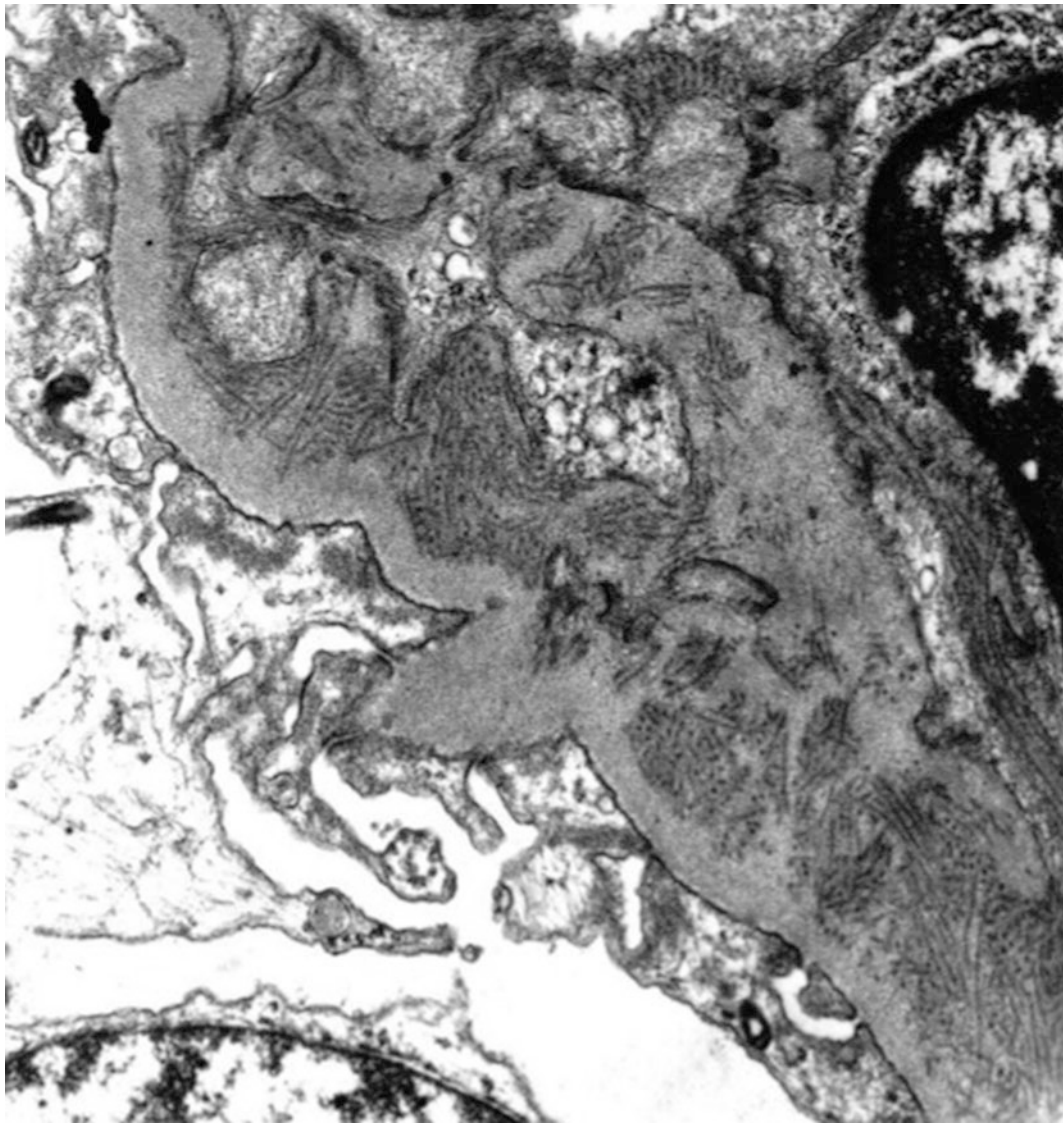

Fig. 3 Moderate to marked mesangial deposits with well-developed large (25–50 nm) microtubular structures are evident. These structures are focally organized with parallel bundles. There is occasional cellular interposition (transmission electron microscopy, 8000×)

silver. Crescents are rare, in contrast to fibrillary glomerulonephritis, which has crescents in a third of cases. The kidney is negative for amyloid by Congo red stain. Immunofluorescence most commonly shows monoclonal staining for IgG and C3 without C1q, and the majority of cases are reported to be IgG kappa-restricted. IgG1 subclass is the most common with no cases of IgG4 reported in one series (Bridoux et al. 2002), in contrast to fibrillary glomerulonephritis, which is typically polytypic IgG4. Additional cases with staining for IgM have been reported. The defining characteristic ultrastructural findings are straight to slightly curved microtubules measuring >30 nm in diameter, often aligned in intersecting stacks of parallel arrays. The diagnosis can only be made with certainty when cryoglobulinemia has been ruled out, as similar organized deposits

may occur in cryoglobulinemia glomerulonephritis, especially if it is type I monoclonal. Fibrillary glomerulonephritis does not show microtubular substructure or parallel array organization, and most cases of fibrillary glomerulonephritis exhibit polyclonal staining on immunofluorescence microscopy.

Treatment and Prognosis

Due to the paucity of cases, no randomized trials for therapy have been conducted. Hematologic consultation should be initiated to identify an underlying B or plasma cell clone, and if identified, clone-specific treatment should be initiated. Treatment with varying immunosuppression, including corticosteroids, or added alkylating agents, resulted in complete or partial remission of nephrotic syndrome in the majority of patients in one study of 14 patients (9 of whom had an associated lymphoma) (Bridoux et al. 2002). Patient survival at 54 months was 71.4%. While prognosis may be better in immunotactoid glomerulopathy than in fibrillary glomerulonephritis (Fogo et al. 1993), these patients tend to have inferior survival on dialysis, though renal transplant outcomes have been shown to be acceptable (Mallett et al. 2015). Known to recur in allografts, treatment of immunotactoid glomerulopathy in one renal transplant recipient with an increase in immunosuppressive therapy, including plasma exchange, methylprednisolone, cyclophosphamide, and cyclosporine, was successful in decreasing both serum creatinine and proteinuria (Carles et al. 2000). Another patient unresponsive to conventional therapy showed reduction and stabilization of serum creatinine level with utilization of Rituximab, an antibody to CD20 positive B cells, although proteinuria persisted (Sathyan et al. 2009) (Figs. 1, 2, and 3).

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Waldenstrom Macroglobulinemia

36

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Contents

Abstract

Waldenström's macroglobulinemia (WM), also called lymphoplasmacytic lymphoma, is a rare hematologic disorder associated with a monoclonal immunoglobulin M protein (IgM) that infrequently involves the kidney. Renal manifestations are primarily glomerular abnormalities related to paraprotein deposition, but direct infiltration of the neoplastic hematopoietic cells may also be seen. Treatment is mandatory after the diagnosis of WM in symptomatic patients due primarily to complications of hyperviscosity, but no standard approach for therapy has been described. An exciting advancement in the understanding of the pathogenesis of WM is the discovery of a somatic mutation in the myeloid differentiation primary response gene 88 (MYD88) gene resulting in activation of Bruton's tyrosine kinase and leading to survival of the neoplastic cells. This also serves as a point of therapy as a novel drug, ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has shown great response in the treatment of WM.

Keywords

Waldenström's macroglobulinemia · Lymphoplasmacytic leukemia · IgM · Monoclonal protein · Bruton's tyrosine kinase · MYD88 · Hyperviscosity · Pseudothrombi · Paraprotein · Kidney

Introduction

Waldenström's macroglobulinemia (WM) was first described by Jan Gosta Waldenstrom in 1944 in two patients affected by retinal hemorrhages, mucocutaneous bleeding, increased numbers of lymphoid cells in the bone marrow, lymphadenopathy,

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normochromic anemia, and thrombocytopenia in the absence of bone pain and with normal bone radiographs, and thus not showing classic signs of multiple myeloma. By modifying the Ostwald viscometer, Waldenstrom demonstrated an increased serum viscosity in both patients and found that the plasma precipitate was formed by a large amount of a homogeneous giant globulin-like molecule, and that the serum gelled at 7 °C, suggestive for cryoglobulin (Kyle and Anderson 1997). These findings represent the foundation of the more modern WHO definition of WM given: a lymphoplasmacytic lymphoma associated with a monoclonal immunoglobulin M protein (IgM). Renal disease is more rare than in multiple myeloma and is related to the paraprotein and/or tissue infiltration by the underlying lymphoplasmacytic neoplasm.

Clinical Manifestations

WM is a rare hematological disorder, accounting for 2% of all hematological malignancies (Salviani et al. 2014). The incidence of the disease is approximately 6.1 cases per million with a predilection for Caucasian men (2:1 Caucasians vs. African American ethnicity, and 2:1 men vs. women) in their sixth-seventh decades (Herrinton and Weiss 1993). The monoclonal overproduction of IgM can cause different clinical manifestations related to tumor infiltration (cytopenias, lymphadenopathy, and hepatosplenomegaly), autoantibody production (IgM can act as an autoantibody against nerve components resulting in neuropathy and against red blood cells inducing hemolytic anemia), monoclonal protein accumulation in the circulation (cryoglobulinemia type I and II and hyperviscosity syndrome), monoclonal protein accumulation in tissues (kidney, gastrointestinal tract, and skin), as well as weakness, recurrent bleeding, and fatigue (Gnemmi et al. 2012). Due to the high molecular weight of IgM, about 10–30% of patients develop hyperviscosity syndrome, often with rouleaux formation, i.e., aggregation of RBCs seen on peripheral blood smears. The hyperviscosity syndrome occurs when serum IgM level exceeds 3 g/dl. Symptoms may include changes in vision and mental status, tinnitus, decreased hearing, headaches, and optic fundal hemorrhages. Some patients may also have precipitation of the IgM with exposure to cold and experience symptoms of cryoglobulin, including Raynaud's phenomenon (see ▶ Chap. 37, "Cryoglobulinemic Glomerulonephritis, Type I") (Crawford et al. 1985).

Renal disease in WM is a rare event as compared with patients with multiple myeloma, because the amount of urinary free light chain is usually small and hypercalcemia secondary to an osteolytic process is uncommon. Mild nonselective proteinuria and hematuria are the most common renal manifestations. Some patients manifest volume depletion due to the increased plasma oncotic pressure. Proteinuria is detected in 30–35% of Waldenström's macroglobulinemia patients, with 10–15% of patients showing proteinuria with a monoclonal Bence-Jones component (Argani and Kipkie 1964). Nephrotic syndrome is rare and usually secondary to amyloidosis, which can be seen in about 20% of patients with WM. Patients may have pyuria and hematuria; however, gross hematuria is rare, and usually occurs in patients with bleeding diathesis due to hyperviscosity syndrome.

Acute renal failure can be a consequence of occluded vessels by circulating IgM or massive renal infiltration by neoplastic B cells. Rarely, infiltration by the malignant cells can create a mass effect, with tubular injury and occasional acute kidney injury (Grossman et al. 1977). Renal insufficiency is unusual with about 15% of patients showing impaired renal function (Morel-Maroger et al. 1970), and 3% of patients developing renal failure (Kyle and Garton 1987).

Currently, renal complications are decreasing in patients with WM due to improved therapies.

Kidney Abnormalities

Histology

Despite the uncommon renal manifestations, there is a wide variety of WM-related renal pathology, particularly glomerular abnormalities, related to direct infiltration by the malignant cells and/or to

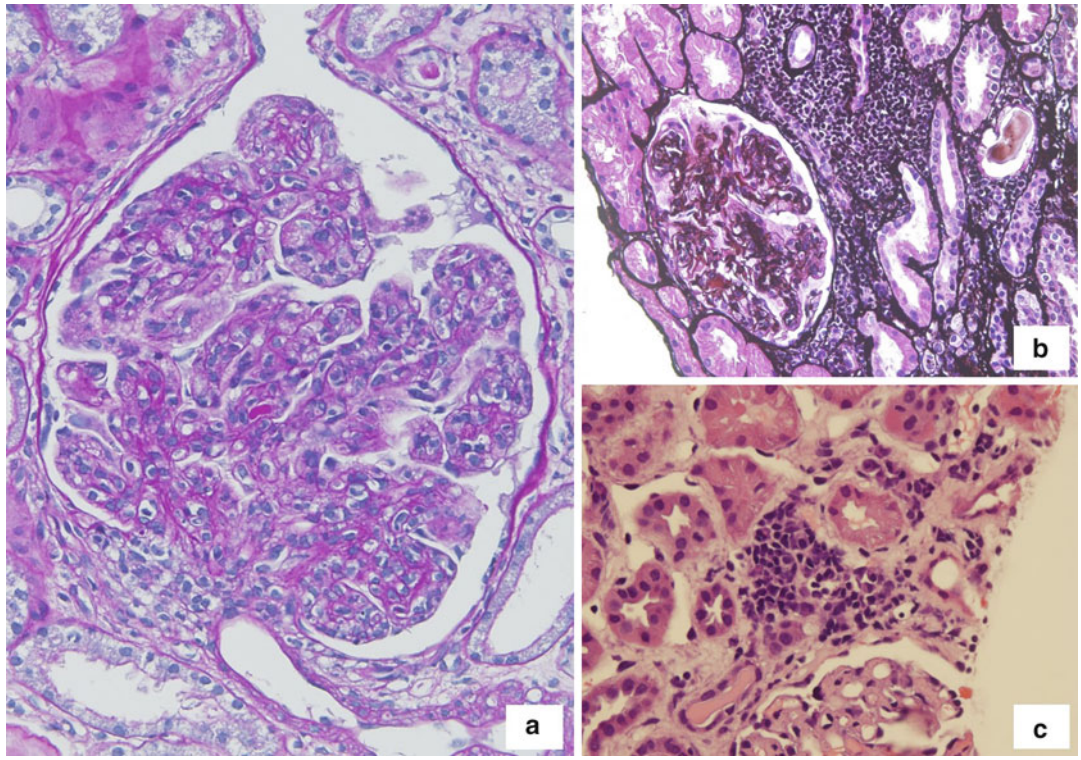

Fig. 1 The most common glomerular lesion is due to subendothelial deposits of the associated paraprotein with intraluminal PAS positive pseudothrombi. Reaction to the subendothelial deposits includes segmental endocapillary hypercellularity and glomerular basement membrane double contours (**a**, periodic acid-Schiff 40×). In addition to the glomerular lesions, infiltration of the interstitium by the neoplastic hematopoietic cells can also be seen with small monomorphic lymphocytes (**b**, Jones methenamine silver 40×), and plasma cells with dysplastic features including enlarged size, binucleation, and Dutcher bodies (**c**, hematoxylin and eosin 64×)

the abnormal monoclonal protein. The most common glomerular lesion is due to extensive subendothelial deposits composed of large intracapillary aggregates of monoclonal IgM that stain negative for fibrin, which often occlude the capillary lumens and are thus so-called pseudothrombi. In 7–20% of patients, the monoclonal protein can have cryoglobulin properties, with strongly PAS-positive cryo-plugs in glomerular capillaries (Fig. 1). Other renal abnormalities have also been rarely described including membranous nephropathy, minimal change disease, and thrombotic microangiopathy (Vos et al. 2016).There is not a direct correlation between the aberrant proteins produced by the WM clone (IgM and light chains) and other renal pathologies. Neoplastic lymphoplasmacytic cells may be present in the interstitium. The characteristic inclusions of immunoglobulin in the malignant cells can be visualized as so-called Dutcher or Russell bodies, in nuclei and cytoplasm, respectively (Dutcher and Fahey 1959). Plasma cells may also be atypical or binucleate.

By immunofluorescence studies, there is IgM dominant or codominant clonal staining, most commonly with kappa, in a granular to coarsely chunky glomerular capillary wall and mesangial pattern (Fig. 2). Arterioles and arteries can also show IgM staining, and deposits of IgM may also be present in the tubulointerstitium. In some patients, the deposits included all immunoglobulins, complement C3, C4, C1q, and both kappa and lambda with numerous electron dense deposits present in the mesangium and glomerulus in subendothelial or occasionally subepithelial location, without organized

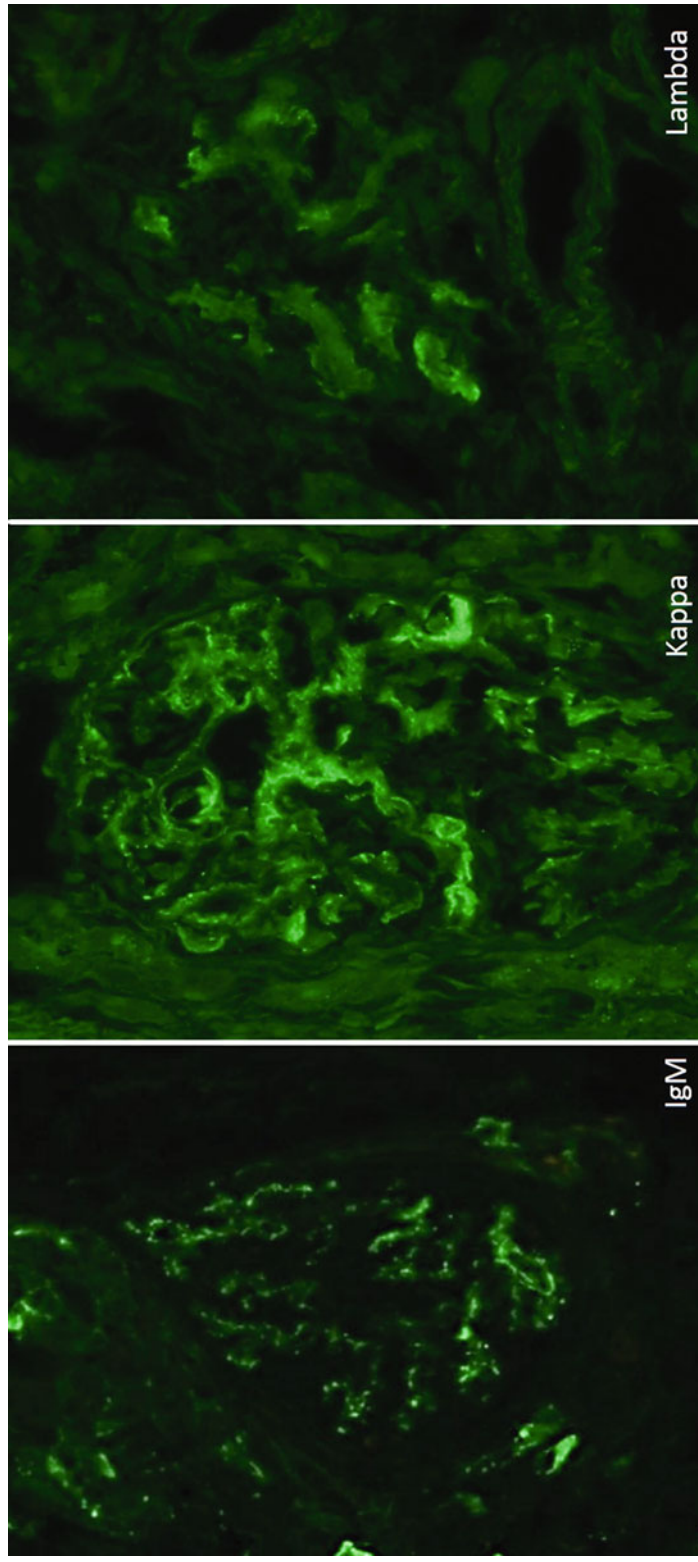

Fig. 2 Immunofluorescence (40×) shows kappa-restricted IgM dominant staining in a granular to chunky global capillary loop and segmental mesangial pattern

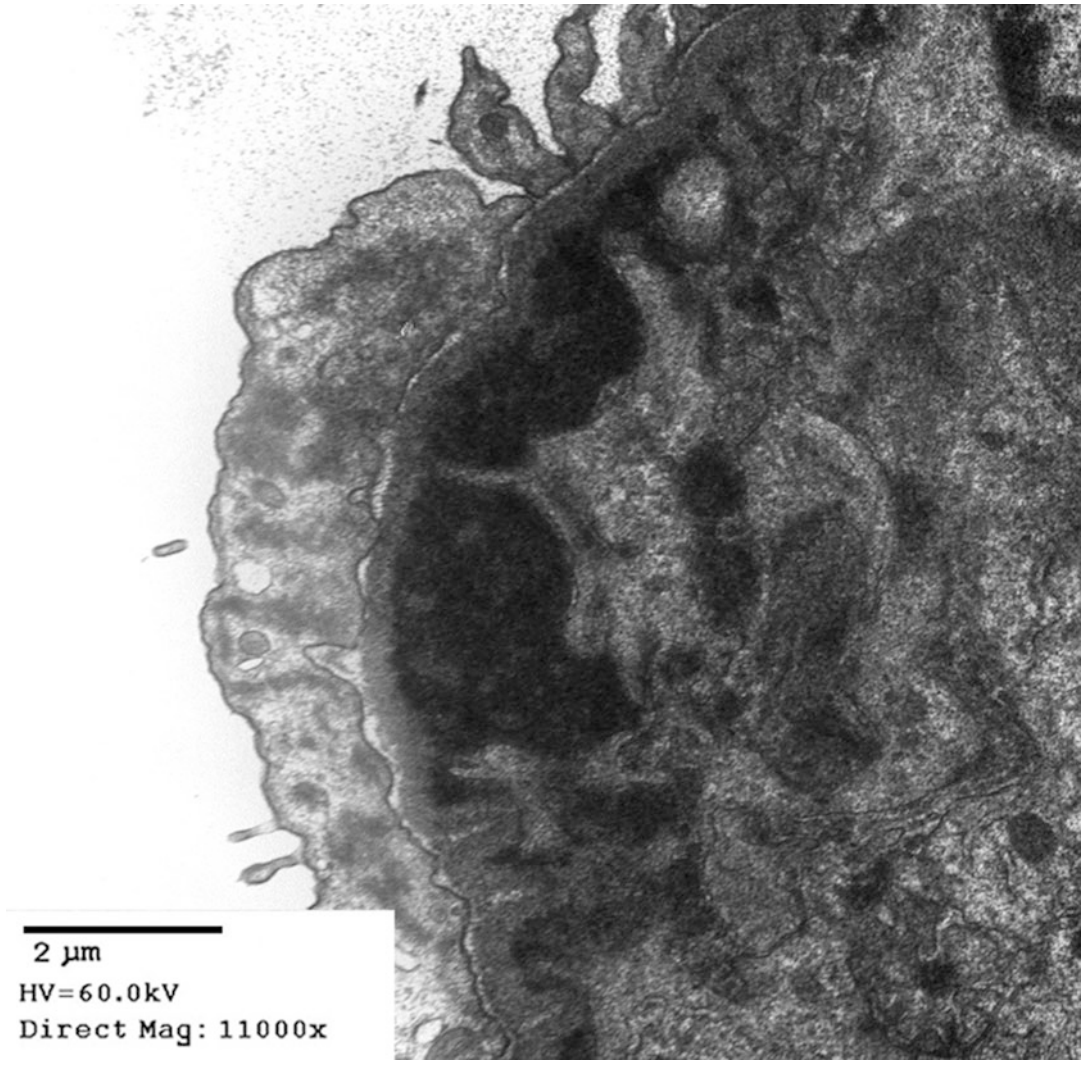

Fig. 3 Electron microscopy shows amorphous subendothelial deposits and cellular interposition with overlying extensive footprocess effacement

substructure (Castro et al. 2008). Of note, other hematopoietic diseases with monoclonal IgM may show a similar spectrum of lesions, and thus these deposits are not pathognomonic of Waldenström's macroglobulinemia. When intraluminal pseudothrombi are present, these stain strongly for IgM.

Electron microscopy confirms large amorphous subendothelial deposits (Fig. 3), with short fibrillary or even microtubular substructure in those with a cryoglobulin component.

In contrast to the more common mixed cryoglobulinemic glomerulonephritis, there is little if any inflammatory reaction to the deposits, and they are monoclonal by IF instead of showing the mixed pattern typical in type II and type III cryoglobulinemia. Type 1 cryoglobulinemia is differentiated from WM based on integrated assessment of all clinicopathologic data.

The monoclonal IgM may also cause monoclonal immunoglobulin amyloidosis, which may occur as an isolated lesion, or with deposits as

described above, with or without parenchymal infiltration by malignant cells. The amyloidosis may rarely be monoclonal heavy chain IgM μ deposits or more commonly monoclonal light chain (AL amyloid) (Audard et al. 2008; Forget et al. 1966). Amyloid deposits manifest as pale acellular cotton-candy like deposits in the mesangium, and may extend to the capillary loops and involve arterioles/arteries and the interstitium. When capillary loops are involved, long feathery spikes are present segmentally on Jones' silver stain. Congo red stains show bright red staining and apple-green birefringence under polarized light. Immunofluorescence shows the clonal staining, most commonly with kappa light chain. Electron microscopy shows randomly arranged nonbranching fibrils, 9–11 nm, characteristic of amyloid. Patients with AL amyloid due to WM occasionally also show involvement of other tissues by amyloid, such as liver, spleen, and adrenal glands (Forget et al. 1966).

Etiology, Treatment, and Prognosis

Treatment is mandatory after the diagnosis of WM in symptomatic patients due to complications such as hyperviscosity and elevated risk of venous thrombosis; however, there is no standard approach to therapy (Shaheen et al. 2012). Most of the time, the presence of renal complication and/or the diagnosis of specific renal pathologies by kidney biopsy represent a potential indication to start a personalized clinical management and treatment choice (Sayed et al. 2015).

Plasma exchange may be very useful in patients with renal failure, hyperviscosity syndrome, or symptoms of antibody-related damage. In most patients, plasma exchange is utilized with concomitant chemotherapy to suppress the underlying neoplastic load. Oral alkylating agents, together with steroids, purine nucleoside analogs, or rituximab, a monoclonal antibody directed against the malignant B-cells, have been used. More recent trials have also looked at proteasome inhibitors including bortezomib, with 21 of 27 patients in one small trial responding with decreased IgM (Vijay and Gertz 2007). In some patients with repeated kidney biopsy after therapy, deposits of IgM disappeared (Lindstrom 1980). In addition, treatment with the mTOR inhibitor, everolimus, has shown response in about 70% of patients (Treon et al. 2016). Stem cell transplant is less frequently used, due to the relatively indolent nature of the underlying lymphoid neoplasm.

New insights into the underlying etiology of WM is now leading to new drug approaches. More than 90% of WM patients have a somatic mutation in the myeloid differentiation primary response gene 88 (MYD88) causing a substitution of leucine to proline at position 265. MYD88 is an adapter protein and allows Toll-like receptors (TLR) to mediate innate immune responses, and interaction with interleukins-1 receptors-associated kinases (IRAKs), with downstream effects on nuclear factor-kappa B, a key transcription factor. In WM patients, a gain of function mutation in MYD88 results in activation of Bruton's tyrosine kinase and increased survival of the malignant cells. A novel drug, ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, acts by forming a covalent bond with a cysteine residue in the BTK active site and was approved by the FDA in January 2015 for use in WM. Trials have shown a response rate of 62% (Castillo et al. 2016; Yang et al. 2013).

Survival of patients with Waldenstrom macroglobulinemia is affected by several features at presentation, with worse prognosis with male sex, age >60 years, anemia, and neutropenia. The median survival for all patients is 5 years, but in cases in which amyloidosis complicates WM (Dimopoulos and Alexanian 1994), it is drastically reduced to 28 months or less in those patients with cardiac involvement at time of presentation (Gertz et al. 1993). While patients with renal injury related to WM have a shorter survival compared to patients without renal complication, gastrointestinal hemorrhage is the most common cause of mortality.

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Cryoglobulinemic Glomerulonephritis, Type I

37

Shunhua Guo and Agnes B. Fogo

Contents

Abstract

Type I cryoglobulinemic glomerulonephritis is a lesion caused by cryoglobulins composed of monoclonal immunoglobulins IgG, IgA, or IgM. It is classically caused by underlying lymphoproliferative diseases, and nephropathy occurs in about 30% of patients of patients with type I cryoglobulinemia. The most common histology seen on light microscopy is membranoproliferative glomerulonephritis, and immunofluorescence microscopy shows deposits of a single monoclonal immunoglobulin component. Electron microscopy shows subendothelial, occasional intramembranous, and mesangial deposits with a short microtubular or short fibrillary substructure, often >30 nm in diameter. Therapy is aimed at treating the underlying lymphoproliferative condition and reducing cryoglobulins and the resultant inflammatory effects.

Keywords

Cryoglobulinemia · Type I · Monoclonal immunoglobulin · Membranoproliferative glomerulonephritis · Microtubular · Subendothelial deposits · Cryo-plugs · IgG · IgM · Lymphoproliferative disease

Introduction

Cryoglobulins are immunoglobulins that precipitate in the cold and are categorized as types I to III. Type II and III cryoglobulinemia are mixed cryoglobulins with monoclonal IgM (type II) or

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polyclonal IgM (type III) with rheumatoid factor activity and, in addition, polyclonal IgG. The majority of cases of cryoglobulinemia are composed of mixed cryoglobulins (about 80% of total cryoglobulin cases), which are most often associated with chronic hepatitis C virus or other infections and autoimmune disorders. In contrast, type I cryoglobulinemia is a relatively rare entity, which makes up about 10–20% of cases of cryoglobulinemia (Harel et al. 2015). The population incidence is about 1:1,000,000. It is characterized by a single monoclonal immunoglobulin and is classically caused by underlying lymphoproliferative diseases (Alpers and Smith 2008).

Etiology

Type I cryoglobulinemia is related to an underlying B cell or plasma cell lymphoproliferative disorder in 60% of patients, including multiple myeloma, chronic lymphocytic leukemia, Waldenström's macroglobulinemia, and other lymphoproliferative disorders such as non-Hodgkin's lymphoma (Payet et al. 2013; Arora et al. 2016). Waldenström's macroglobulinemia is a lymphoproliferative disorder with monoclonal IgM paraproteinemia. Cryoglobulinemia can be present in 8–18% of Waldenström's macroglobulinemia patients. In the remaining 40% of cases, in which a definitive etiology may not be found after a thorough evaluation, the monoclonal immunoglobulin is usually IgM (70%), with less frequent cases of IgG or IgA.

Clinical Presentation and Epidemiology

Hyperviscosity can occur due to high levels of circulating monoclonal cryoglobulin, leading to physical obstruction of vessels. In addition, non-obstructive damage may be mediated by the deposits and subsequent inflammatory vasculitis. Manifestations include cutaneous involvement in 58% in one series (Néel et al. 2014), sometimes with acrocyanosis, severe Raynaud phenomenon with digital ulceration or necrosis, purpura, livedo reticularis, retinal hemorrhage, arterial thrombosis, and neuropathy. Kidney disease is less frequent than in type II or III cryoglobulinemia. Nephropathy occurs in about 30% of patients, with nephrotic syndrome in about 70%, and acute kidney injury in about 75%. Patients typically have microscopic hematuria and RBC casts. C3 levels are decreased in 36% of patients, while C4 levels are decreased in 81%. Erythrocyte sedimentation rate is markedly increased in type 1 cryoglobulinemia. About 45% of patients with type I cryoglobulinemic glomerulonephritis do not have extrarenal symptoms at presentation (Terrier et al. 2013).

Detection of cryoglobulins can be challenging. Blood samples must be collected in warm tubes at 37 °C without anticoagulants. After warm clotting and centrifugation (at 37 °C), serum is kept at 4 °C for 7 days and observed for formation of cryoprecipitate. The cryoprecipitate is then washed and warmed to 37 °C, quantified, and subjected to analysis by immunofixation for classification (Brouet et al. 1974). Cryocrit levels are markedly higher in type I cryoglobulinemia (>70% usually, >5–10 mg/dL) than in type II or III mixed cryoglobulinemia.

Histology

Patients most often have a membranoproliferative glomerulonephritis pattern with diffuse endocapillary hypercellularity with monocytes and occasionally also neutrophils. The glomeruli often have a lobular accentuation with cellular interposition and deposits, causing double contours of the capillary loops by silver stain (Fig. 1). Cryo-plugs (previously called hyaline thrombi) may be observed in the lumen of glomerular capillaries and are strongly positive by PAS stain.

Immunofluorescence microscopy shows immune deposits of a single monoclonal immunoglobulin component (Fig. 2). Either monoclonal IgM or IgG has been reported in varying frequencies in type I cryoglobulinemia (40–70% for IgM versus 60–30% for IgG in large series (Harel et al. 2015; Néel et al. 2014). However, in patients with type I cryoglobulinemia and kidney

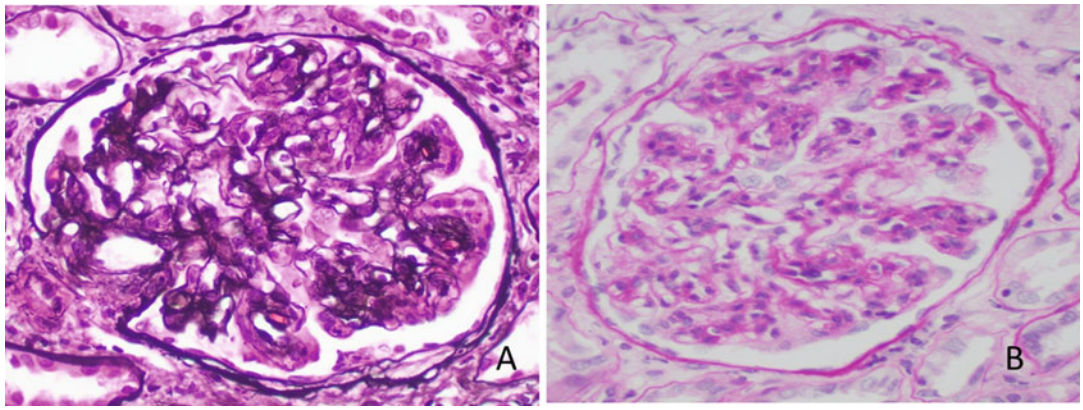

Fig. 1 Glomeruli show lobular accentuation with cellular interposition and diffuse endocapillary hypercellularity with monocytes ((**a**), Jones' silver methenamine, ×40; (**b**), periodic acid Schiff, ×40)

disease, monoclonal IgG is much more common (11/13 patients) in one series (Harel et al. 2015). Further, renal disease was more common in type I cryoglobulinemia patients with IgG versus IgM, 11/38 versus 2/26, respectively (Harel et al. 2015). In addition, overall disease severity appears to be worse in those with IgG type I cryoglobulinemia. The monoclonal protein light chain component is usually kappa light chain. Further characterization as IgG3 kappa was reported in two cases (Karras et al. 2002). Monoclonal IgM deposition can present in patients with Waldenström's macroglobulinemia (mostly IgM kappa). Complement components C3 or C1q may or may not be present. The deposits are irregular, chunky capillary loop and mesangial in distribution.

Less commonly, a thrombotic microangiopathy is diagnosed. Vasculitis is uncommon in type I cryoglobulinemia, in contrast to mixed cryoglobulinemia. However, occluding vascular lesions may result in tissue infarcts or hemorrhage. Cryoglobulinemic vasculitis may be seen in the arterioles, interlobular arteries of the kidney or extrarenal organs, or cutaneous blood vessels, with intimal cryoglobulin deposits of the vessel wall. In rare cases, transmural necrotizing arteritis may be seen. Infiltrate by the underlying hematopoietic neoplastic cells may also occur.

Electron microscopy shows subendothelial, intramembranous, and mesangial deposits, which may have a short microtubular or short fibrillary substructure, often >30 nm in diameter (Fig. 3). Cellular interposition is frequently observed, which is due to interposition of cytoplasmic processes of monocytes or mesangial cells between endothelial cells and glomerular basement membranes with new basement material immediately under the swollen endothelial cells.

Treatment

The goal of therapy is to treat the underlying lymphoproliferative condition and reduce cryoglobulins and the resultant inflammatory effects. Therefore, when organ involvement (such as vasculitis, renal disease, progressive neurologic findings, or disabling skin manifestations) is present, a hematologic workup must be conducted to identify the underlying B or plasma cell clonal disorder and therapy initiated that targets this clone. Plasmapheresis is indicated for severe or life-threatening complications related to in vivo cryoprecipitation or serum hyperviscosity. Concomitant/subsequent use of high-dose corticosteroids and cytotoxic agents is recommended for reduction of rebound phenomenon of immunoglobulin production. Cryofiltration is used to precipitate the cryoglobulins by cooling the patient's plasma to selectively remove cryoglobulins and then reinfuses the rewarmed plasma to the patient, thus reducing the need for replacement of fluid.

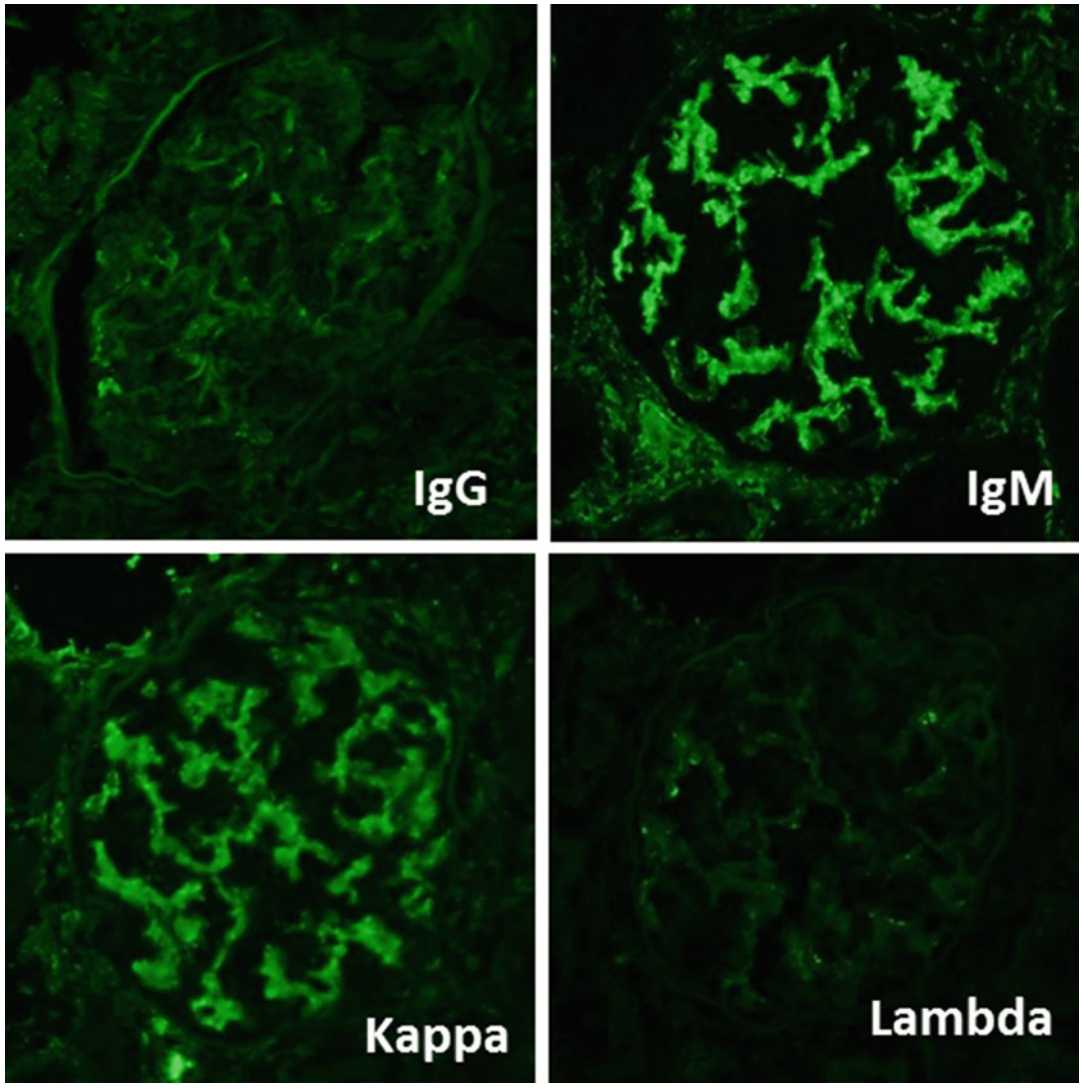

Fig. 2 There is trace granular focal segmental mesangial staining for IgG (**a**) and lambda (**d**) (0–3+ scale) and 2+ diffuse global granular mesangial and capillary loop staining for IgM (**b**) and kappa (**c**) (all 40×)

In case of detected specific hematological malignancy, the treatment is dictated by the nature of the underlying disease with the aim of inducing hematological remission. Treatments included alkylating agents, rituximab, thalidomide or lenalidomide, and bortezomib (Harel et al. 2015). In cases of IgM monoclonal cryoglobulinemia in Waldenström's macroglobulinemia, rituximab, a monoclonal anti-CD20 antibody directed to plasma cells, is often used (Néel et al. 2014).

Treatment directed against the specific MYD88 mutation in Waldenström's macroglobulinemia patients is now used in this group (see ▶ Chap. 36, "Waldenstrom Macroglobulinemia"). In addition, cryoglobulinemia "flare" has also been described occurring after treatment with rituximab for Waldenström's macroglobulinemia. Therefore pre- and posttreatment monitoring of the cryoglobulin level is advised in these patients (Olson et al. 2016).

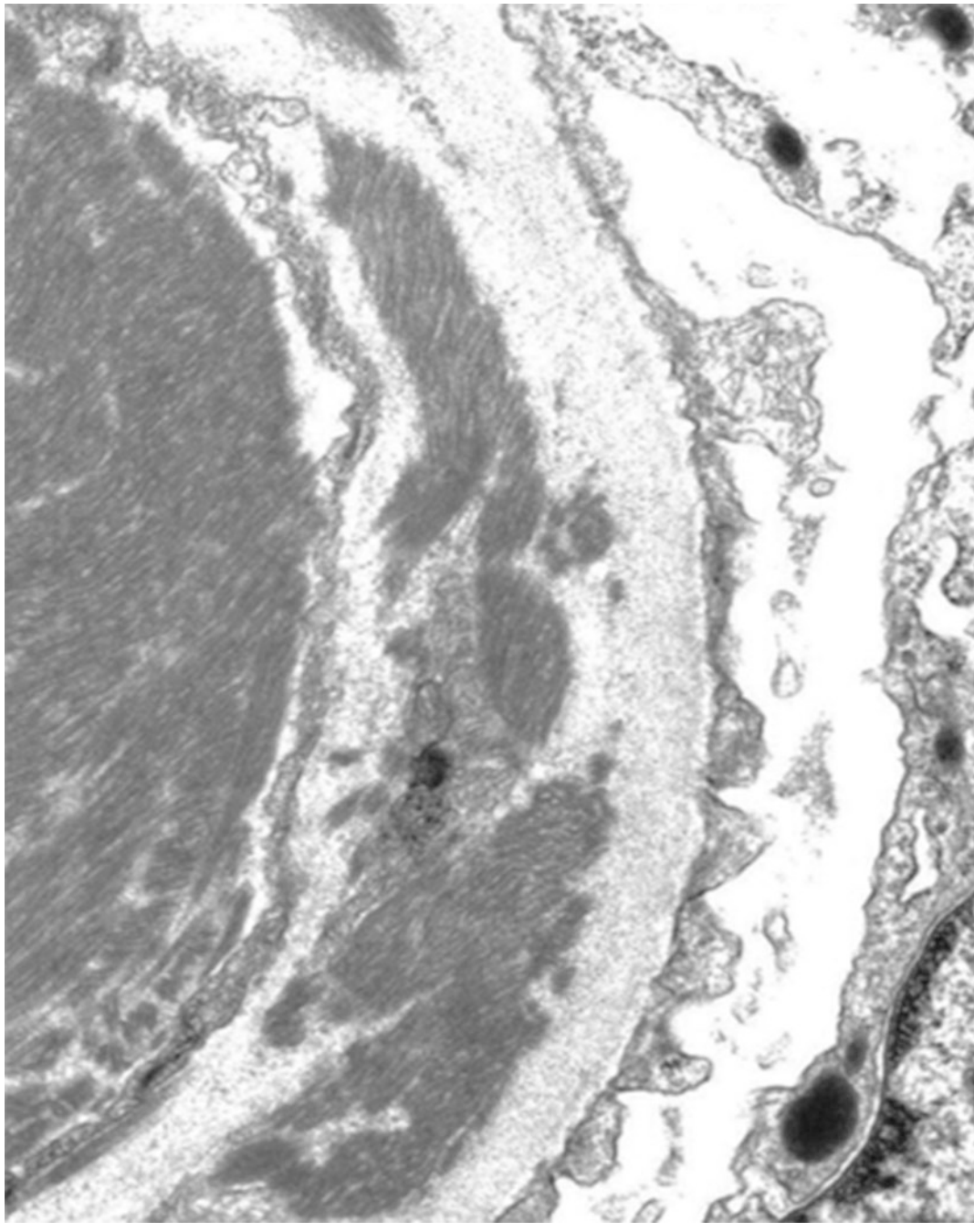

Fig. 3 Electron microscopy shows subendothelial and intraluminal deposits with microtubular and fibrillary substructure. Cellular interposition is also present with cytoplasmic processes seen between endothelial cells and glomerular basement membranes and intermingled with the deposits (transmission electron microscopy, ×8000)

Prognosis

The clinical course of monoclonal cryoglobulinemia with renal involvement is dependent on the hematological response of treatment of the underlying lymphoproliferative disorder. Survival rates are reported of 97% at 1 year, 94% at 5 years, and 87% at 10 years. In one report, 5 years after biopsy, 49% of patients had died or needed regular dialysis treatment; after 10 years, this proportion increased to 64% (Schmitt et al. 1990).

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Light Chain Deposition Disease

38

Andrea Kattah and Nelson Leung

Contents

Abstract

Monoclonal immunoglobulin deposition disease (MIDD) is a rare disorder characterized by the aberrant production and deposition of light and/or heavy chain immunoglobulins by clonal B-cell or plasma cell populations, resulting in multisystemic organ dysfunction. Renal disease is the most common initial disease manifestation, but other organs, such as the heart, lungs, liver, peripheral nerves, and skin, can be involved. Patients often present

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with nephrotic syndrome, hypertension, and an impaired glomerular filtration rate. Renal biopsy classically reveals nodular glomerulosclerosis on light microscopy, with non-congophilic, monotypic immunoglobulin deposits along the tubular and glomerular basement membranes by immunofluorescence and powdery and granular deposits on the basement membrane by electron microscopy. MIDD can be associated with multiple myeloma but may also be associated with a monoclonal gammopathy of renal significance, aparaprotein disorder of the kidney in patients who do not meet criteria for systemic lymphoma or multiple myeloma. The pathogenesis is related to an underlying clonal cell B or plasma cell population, the amount and primary structure of the abnormal light or heavy chain, as well as the interaction of the immunoglobulin with the local tissue environment. Treatment includes systemic chemotherapy and autologous stem cell transplantation to reduce the production of abnormal immunoglobulins. Bortezomib-based regimens have shown promise as a first-line therapy in MIDD. Renal transplantation has shown variable results due to the risk of recurrent disease.

Keywords
Monoclonal immunoglobulin deposition disease · Light chain deposition disease · Monoclonal gammopathy · Nephrotic syndrome

Introduction

Monoclonal immunoglobulin deposition disease (MIDD) is a disorder caused by the deposition of monoclonal immunoglobulin proteins as granular, non-congophilic material in many visceral tissues, leading to a spectrum of disease manifestations due to end-organ dysfunction. Patients with MIDD almost always present with renal dysfunction, and therefore, nephrologists are often involved in the initial evaluation and diagnosis of this multisystemic disease. Light chain deposition disease (LCDD) is the most common subtype of MIDD and is characterized by the deposition of monoclonal light chains. This disorder was first described by Randall et al. in the 1970s, and therefore, the deposits in MIDD are sometimes referred to as Randall-type (Randall et al. 1976). Other less common variants of MIDD include heavy chain deposition disease (HCDD) and light and heavy chain deposition disease (LHCDD).

Epidemiology

MIDD is a rare disease and there is limited data on its incidence in a population-based setting. A study on incident ESRD patients in France, using the Renal Epidemiology and Information Network (REIN), found that of the 63,340 incident ESRD patients from 2002 to 2011, 1462 (2.3%) patients had ESRD related to monoclonal gammopathy (defined as AL amyloidosis, LCDD, or myeloma cast nephropathy), and LCDD was the cause in 334 cases (0.5% of all patients) (Decourt et al. 2016). In general, affected individuals are in the sixth decade of life, and men are affected more often than woman in a 2:1 ratio (Pozzi et al. 2003; Heilman et al. 1992; Lin et al. 2001). The true degree of association of MIDD and multiple myeloma is unclear given the varying criteria used for the diagnosis of multiple myeloma in several studies. The incidence of multiple myeloma in patients with LCDD has been reported as anywhere between 25% and 65% (Buxbaum et al. 1990; Buxbaum and Gallo 1999; Lin et al. 2001; Pozzi et al. 1995, 2003; Nasr et al. 2012a). However, when newer criteria for multiple myeloma are used, the percentage is closer to 20–25%. On the other hand, patients with multiple myeloma have a 5–22% lifetime incidence of LCDD. The incidence of multiple myeloma in patients with HCDD and LHCDD may be slightly lower, 29% and 50%, respectively, in a one case series (Nasr et al. 2012a). The remainder of affected individuals may have fewer than 10% plasma cells on bone marrow biopsy, rarely another lymphoproliferative disorder, or no discernible hematologic disorder by conventional criteria.

Pathogenesis

The central pathogenetic factor in MIDD is the aberrant production of monoclonal immunoglobulins by plasma cell or B-cell clones that deposit in an amorphous (Randall-type) pattern. MIDD is part of the larger family of disorders known as monoclonal gammopathies of renal significance (MGRS), a classification scheme first proposed in 2012 (Fig. 1) (Leung et al. 2012a). This family of disorders includes renal diseases associated with monoclonal immunoglobulins, but with a hematologic profile that does not meet criteria for systemic lymphoma or multiple myeloma (Leung et al. 2012a; Merlini and Stone 2006). Some affected individuals with MIDD may have no demonstrable paraprotein on serum or urine protein electrophoresis, demonstrating that very low levels of immunoglobulins are still capable of causing significant renal impairment (Pozzi et al. 2003).

The pathogenesis of MIDD is related to the primary structure of the immunoglobulin protein, the amount of protein produced by a specific B-cell or plasma cell clone, the environment in which the immunoglobulin is presented, and the reaction of the cells in that environment. Several large case series have shown that patients with multiple myeloma have a worse outcome than patients who would currently be classified as having MGRS, and this may be related to the amount of protein produced by the malignant clone (Buxbaum and Gallo 1999; Pozzi et al. 2003; Montseny et al. 1998). There are patients, however, with rapidly progressive MIDD in the absence of multiple myeloma, suggesting that other factors besides the absolute clonal cell burden and amount of immunoglobulin that dictates the severity of disease (Short et al. 2001). The current theory is that the structural properties of monoclonal immunoglobulins, in combination

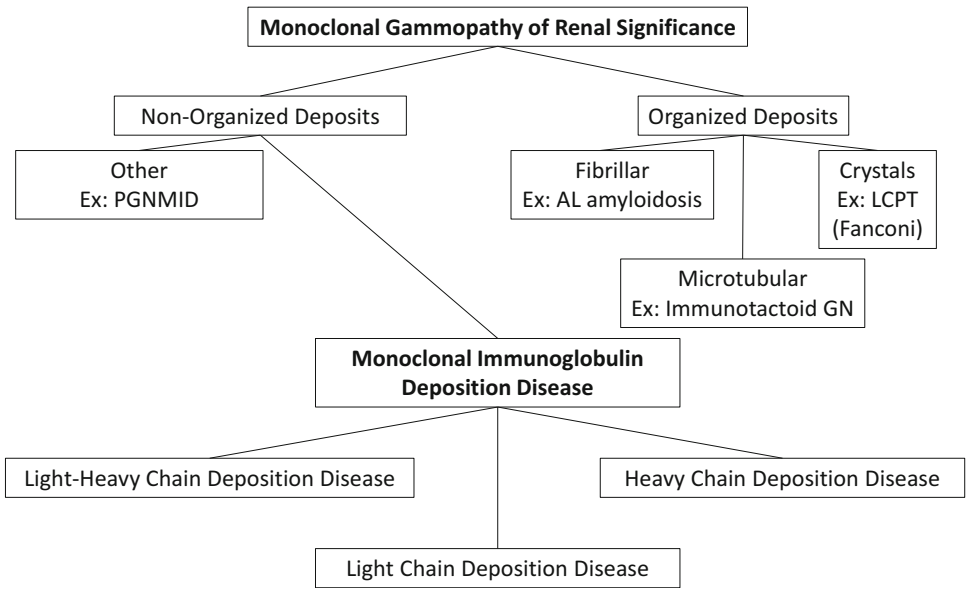

Fig. 1 Proposed classification of monoclonal gammopathy of renal significance (*MGRS*). The first breakdown is between organized and non-organized deposits. Organized deposit MGRS diseases include diseases with crystal deposits (light chain proximal tubulopathy (*LCPT*) and crystal-storing histiocytosis), fibrillar deposits (light chain (*AL*) amyloidosis and fibrillary glomerulonephritis) and microtubular deposits (immunotactoid glomerulonephritis (*GN*), cryoglobulinemic glomerulonephritis (Type I and II), and glomerulonephritis with organized microtubular monoclonal Ig deposits). Non-organized, or granular, deposits characterize the remaining diseases, including monoclonal immunoglobulin deposition disease (*MIDD*), proliferative glomerulonephritis with monoclonal Ig deposits (*PGNMID*) and Waldenstrom macroglobulinemia. MIDD includes light chain deposition disease, heavy chain deposition disease, and light-heavy chain deposition disease

with local factors such as inflammatory cytokines other host factors, influence the type and severity of disease. Below is a description of the proposed pathogenesis of LCDD and HCDD.

LCDD

In LCDD, the primary structure of the light chain likely determines how it deposits in the body. The kappa light chains in LCDD that have been sequenced are more likely to be of the V-region subtype, of which VκIV seems to be overrepresented, though κI-IV have been described (Vidal et al. 1999; Denoroy et al. 1994; Hassoun et al. 2008). There is no specific structural motif or residue that has been shown to be responsible for the pathogenicity of these proteins; however, certain consistent features have emerged. First, the amino acid substitutions derive from somatic mutations, as opposed to germline mutations. Second, the substitutions most commonly occur in the complementarity determining region (CDR) (Vidal et al. 1999). Third, the mutations described in both kappa and light chains are more likely to introduce hydrophobic residues, which may disturb protein-protein interaction and cause destabilization of the protein, resulting in protein deposition in tissues (Decourt et al. 1998; Vidal et al. 1999; Rocca et al. 1993). The predisposition to aggregation can be demonstrated in a murine model of LCDD, in which transfected mice with vectors containing kappa light chain sequence from a human subject with LCDD of the VκIV subtype showed light chain deposition in the kidney (Khamlichi et al. 1995b). Lastly, posttranslational modification has been implicated in creating pathologic light chains, as the isolates of kappa light chains from some patients with LCDD have mutations that generate new N-glycosylation sites (Cogne et al. 1991; Ganeval et al. 1984). The combination of the new hydrophobic residues and N-glycosylation sites may predispose the light chains to deposit in the basement membranes of involved tissues (Ronco et al. 2006).

The mesangial cell also likely plays a significant role in the pathogenesis of this disease. As shown in a series of in vitro studies by Herrera et al. mesangial cells are integral to the deposition of excess extracellular matrix (ECM) proteins that characterize the pathologic lesion of nodular glomerulosclerosis (Herrera et al. 1999; Keeling and Herrera 2005, 2009). In one of the initial studies, cultured mesangial cells were incubated with light chains from patients with either amyloidosis, MCN or LCDD (Herrera et al. 1999). The authors demonstrated that mesangial cells cultured with amyloid light chains eventually decreased ECM production to below control levels and at the same time increased collagenase activity. In contrast, mesangial cells cultured with LCDD light chains proliferated, promoted excess ECM formation, and reduced collagenase activity. This process resulted in mesangial nodules consistent with nodular glomerulosclerosis. Transforming growth factor β (TGF-β), a profibrotic cytokine, is present in the glomeruli of patients with LCDD and may also induce the production of tenascin, a component of the mesangial ECM that is increased in pathologic conditions of the kidney (Herrera et al. 1994; Truong et al. 1994). Tenascin is degraded by the matrix metalloproteinase (MMP) 7. In the same in vitro model described above, the culture media from mesangial cells incubated with LCDD light chains showed a marked reduction in MMP-7 levels in comparison to those incubated with amyloid light chains (Keeling et al. 2005), as well as an increase in TGF-β and platelet-derived growth factor β (Keeling and Herrera 2009). These experiments suggest that there is some intrinsic feature of the light chain itself that promotes or inhibits ECM production, alters regulation of ECM breakdown by MMPs and collagenase, and thereby produces different pathologic entities.

HCDD

HCDD was first described as a distinct entity in 1992 by Tubbs et al. (1992) The heavy chain in HCDD is more likely to be of the γ class (Lin et al. 2001; Nasr et al. 2012a), with some rarer cases of the α subtype (Alexander et al. 2011) and only one published case of the μ subtype (Liapis et al. 2000). In most reported cases of γ-HCDD, there is a deletion of the first constant (CH1) domain

(Aucouturier et al. 1993; Yasuda et al. 1995; Kambham et al. 1999; Moulin et al. 1999), resulting in a truncated protein. One theory as to the mechanism of disease is that as these proteins lack the CH1 portion, they cannot bind to the heavy chain binding protein (BiP) in the endoplasmic reticulum (Knittler and Haas 1992) and therefore are secreted into circulation rather than being degraded (Soma et al. 2004). There also may be amino acid substitutions in the CDRs and framework regions that can change the property of the heavy chain, making it more likely to deposit in tissues (Khamlichi et al. 1995a; Kambham et al. 1999). A recent study using a transgenic mouse model of HCDD used a heavy chain from a HCDD patient and selectively expressed this human HC in mouse B and plasma cells (Bonaud et al. 2015). The inserted heavy chain had the characteristic deletion of the CH1 domain and produced a truncated monoclonal heavy chain. The transgenic mice developed HCDD and treatment with bortezomib decreased the number of renal deposits. The authors were further able to demonstrate that the truncated heavy chain increased the sensitivity of plasma cells to bortezomib via the terminal unfolded protein response pathway.

Further insight into the pathogenesis of HCDD can be gained by further subtyping the heavy chain. There have been reports of γ1–4 subtypes (Soma et al. 2004; Tubbs et al. 1992; Aucouturier et al. 1993; Kambham et al. 1999). All of the γ3 subtypes and the majority of the γ1 subtypes are associated with low serum complements and deposition of C1q and C3 on immunofluorescence (Soma et al. 2004). The cases of γ4-HCDD and the one case of γ2-HCDD, however, did not have low serum complement or deposition of C3 and C1q. This is consistent with current understanding of the classical pathway of the complement system, where IgG3 binds C1q most avidly, followed by IgG1 and IgG2 (Miletic and Frank 1995). IgG4 is unable to activate the classical pathway. In a review of all the cases reported of γ-HCDD, 11/19 patients had hypocomplementemia, as opposed to the five reported cases of α-HCDD, where no patients had hypocomplementemia (Alexander et al. 2011). Interestingly, in all cases of α-HCDD, crescents were observed on light microscopy. As crescents are relatively rare in MIDD, this feature highlights the subtle but real pathogenic differences between all the subtypes of MIDD based on the characteristics of the deposited immunoglobulin.

In patients with LHCDD, the heavy chains that have been studied have also been truncated, as in HCDD, and the light chains have similar properties to the light chains described above (Buxbaum 2001). Therefore, it seems that the phenotype of LHCDD is truly due to the combined deposition of both the aberrant immunoglobulin polypeptides. However, more research into the properties of the various immunoglobulins in MIDD may help explain the varied pathologic and clinical features of these different subtypes. Promising animal studies will hopefully give further insights into the pathogenesis of MIDD and perhaps even direct future treatment strategies.

Histology

The diagnosis of MIDD is often made by renal biopsy as renal dysfunction is the most common initial disease manifestation. MIDD has several distinct findings on light microscopy, IF, and EM. On light microscopy, the most common pattern is nodular glomerulosclerosis. The mesangial matrix expansion is typically periodic acid-Schiff (PAS)-positive, which can appear indistinguishable from diabetic glomerulosclerosis. It is typically poorly argyrophilic, however, and so this can be a clue from the light microscopy that the biopsy may be a case of MIDD (Fig. 2). The presence of nodular glomerulosclerosis is seen in approximately one-third to two-thirds of renal biopsies (Pozzi et al. 1995, 2003; Gokden et al. 2007; Nasr et al. 2012a). Tubular basement membrane thickening is a common finding and may be present is up to 87% of cases of LCDD (Pozzi et al. 2003; Confalonieri et al. 1988) though some authors have reported the presence of this feature to be variable (Nasr et al. 2012a; Lin et al. 2001). Tubular atrophy and interstitial infiltration can also be seen (Heilman et al. 1992; Confalonieri et al. 1988). Some biopsies may have membranoproliferative features and an inflammatory pattern of injury, with crescents being reported in some

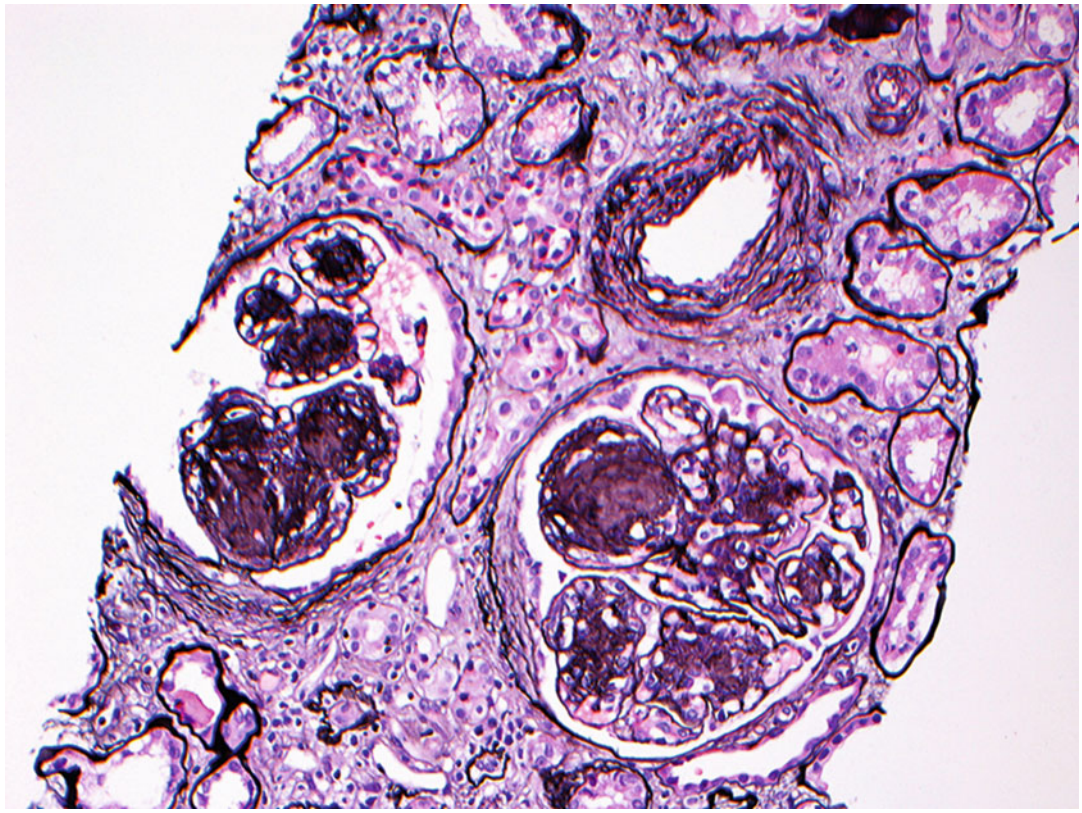

Fig. 2 By light microscopy, a glomerulus shows nodules that are poorly argyrophilic (silver stain)

cases (Chang et al. 2005; Strom et al. 1994; Nasr et al. 2012a; Alexander et al. 2011).

Immunofluorescence is essential for diagnosis, as it is the most sensitive technique for diagnosis (Pozzi et al. 2003; Buxbaum and Gallo 1999; Nasr et al. 2012a). In LCDD, the light chains are more commonly kappa than lambda (Heilman et al. 1992; Pozzi et al. 2003; Herrera et al. 1994; Lin et al. 2001). Lambda light chains account for only 10–30% of cases of LCDD (Fig. 3). A case series by Nasr et al. of 64 patients with MIDD reported that 84% of LCDD patients and 67% of LHCDD had a kappa light chain present on IF (Nasr et al. 2012a). The most common site of basement membrane deposition is the tubule, followed by the glomerulus and then the blood vessel (Buxbaum and Gallo 1999). Electron microscopy demonstrates granular, "powdery," electron-dense deposits along outer aspect of the tubular basement membrane and the inner side of the glomerular basement membrane, as well as in the mesangium (Fig. 4) (Confalonieri et al. 1988; Nasr et al. 2012a). There are rare cases of MIDD in which electron-dense deposits are present on EM and the IF is negative, which is why both modalities are necessary to confirm the diagnosis. The discrepancy between IF and EM is more common in patients with coincident myeloma cast nephropathy (MCN) (Pozzi et al. 2003; Gokden et al. 2007).

The heavy chain in both LHCDD and HCDD is more likely to be of the γ subtype with immunofluorescence revealing monotypic IgG staining. The staining pattern and deposits on electron microscopy are otherwise indistinguishable from LCDD. All IgG subclasses (1–4) have been reported and there are also rare cases of IgA-HCDD (Kambham et al. 1999). A case of IgD heavy chain deposition disease was recently reported (Royal et al. 2015). In this case report,

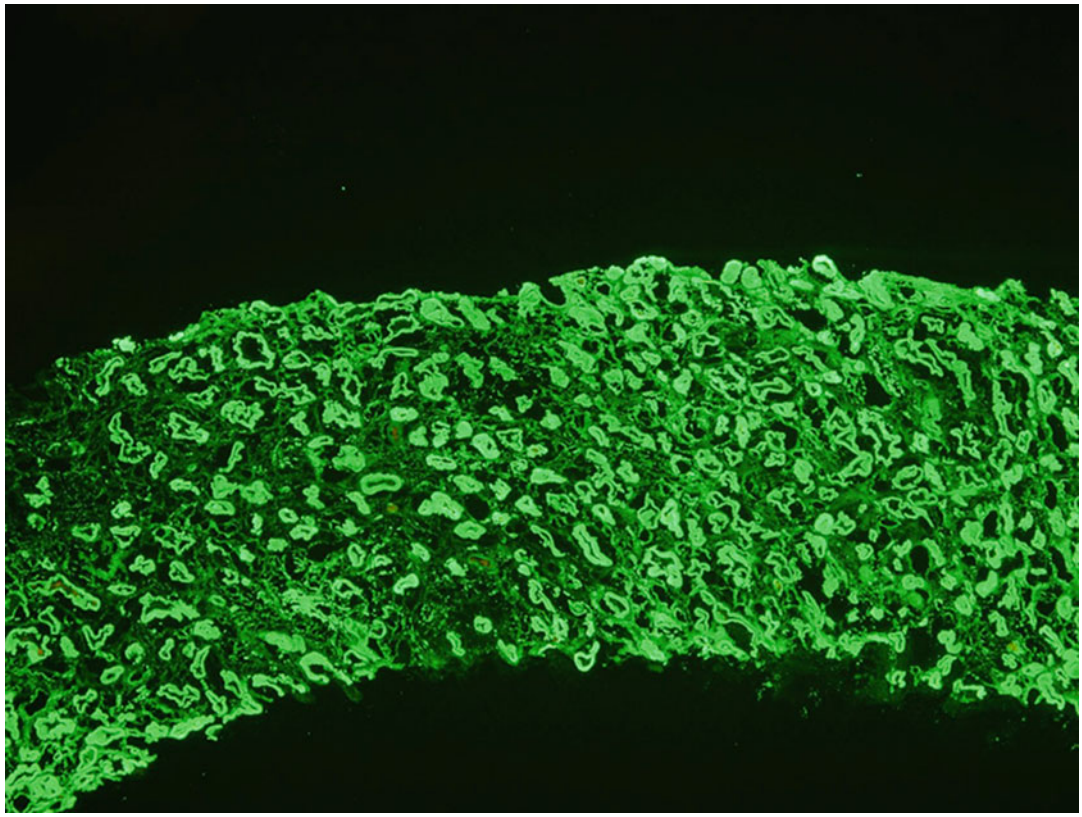

Fig. 3 By immunofluorescence, a stain shows bright linear tubular basement membrane staining for lambda light chain in this case of lambda light chain deposition disease. Staining for kappa light chain and other immunoreactants was negative

the authors describe a man who presented with nephrotic syndrome, and the renal biopsy was negative for immunoglobulins on routine IF, but EM demonstrated electron-dense deposits along the basement membrane. Using laser microdissection and mass spectrometry, they were able to demonstrate the presence of IgD in the glomerular deposits. Mass spectrometry is not routinely used in the diagnosis of MIDD, though may be useful in atypical cases, similar to its role in the diagnosis of amyloidosis (Sethi et al. 2012).

Monoclonal immunoglobulins are capable of causing many different disease processes in the kidney, even within the same individual. MIDD may co-occur with amyloidosis and myeloma cast nephropathy. Pozzi et al. reported a case series of 63 patients in which 3% had amyloidosis on renal biopsy (Pozzi et al. 2003). Another small case series described three patients with features of both LCDD and AL in renal tissue and demonstrated the presence of congo red positivity, diagnostic of AL, together with light chain deposits along the basement membranes, consistent with LCDD (Jacquot et al. 1985). They also demonstrated both types of deposits in other involved tissues, such as the skin, liver, heart, and lung. The authors concluded that the same light chain was capable of forming either the fibrillar deposits of AL or the non-fibrillar, granular deposits of LCDD, depending on environmental factors.

MIDD may also occur in the presence of myeloma cast nephropathy in patients with multiple myeloma. In a case series of 34 patients with MIDD by Lin et al. the biopsies with both myeloma cast nephropathy and LCDD had significant

Fig. 4 Electron micrograph of a tubule shows finely granular electron dense deposits along the tubular basement membrane

tubular injury, with less severe glomerular disease and less significant deposition of light chains along the basement membranes (Lin et al. 2001). The clinical features and outcomes of these patients were more consistent with cast nephropathy than with pure MIDD. In another case series of 23 patients with LCDD and cast nephropathy, the glomeruli appeared normal in two-thirds of cases and nodular glomerulosclerosis was present in only three biopsies (Gokden et al. 2007). Again, the pathology was most notable for the tubular damage with light chain casts, and the diagnosis of LCDD was made only by IF. Approximately one-third of cases did not demonstrate electron-dense deposits on electron microscopy. In a published series of 190 patients from the Mayo Clinic with multiple myeloma, 41 patients had MIDD, of which five had concurrent cast nephropathy and two had concurrent AL amyloidosis (Nasr et al. 2012b). Features of myeloma cast nephropathy, LCDD, and amyloidosis have also been described in a single patient with a monoclonal IgG kappa on serum immunofixation (Lorenz et al. 2010).

MIDD is truly a systemic disease and immunoglobulin deposition may be seen in many other organs, including the heart, lung, and liver. Myocardial tissue demonstrates smooth, diffuse, and uniform staining in a perimuscular pattern (Buxbaum and Gallo 1999; Buxbaum et al. 2000). In lung tissue, there can be a more patchy deposition of eosinophilic material in alveolar walls, small airways, and vessels, with marked giant cell reaction. Similar to the renal biopsy findings, immunofluorescence shows either light or heavy chains within the basement membranes of these organs, and electron microscopy demonstrates coarse

extracellular granular deposits (Colombat et al. 2006; Bhargava et al. 2007). Liver biopsy shows diffuse staining of the basement membranes, outlining the liver cell cords (Buxbaum and Gallo 1999).

With treatment, there may be regression of the underlying nodular glomerulosclerosis and disappearance of the deposits (Komatsuda et al. 2000; Harada et al. 2010). A case report describes a 53-year-old woman with LCDD, who presented with nephrotic syndrome and nodular glomerulosclerosis on biopsy, received chemotherapy and an autologous stem cell transplant and achieved remission of her underlying disease. She then developed nephrotic syndrome 6 years later, with a new IgG lambda monoclonal gammopathy (Copeland et al. 2003). On repeat biopsy, she had IgG heavy chain (AH) amyloidosis and no evidence of the prior nodular glomerulosclerosis. This case demonstrates the emergence of a second clone after autologous stem cell transplant but also shows the reversibility of the glomerular lesion with effective treatment of the underlying disorder. Other authors, however, have reported persistence of light chain deposits after chemotherapy and remission of underlying disease (Royer et al. 2004; Firkin et al. 2004).

Laboratory Studies

Serum protein electrophoresis (SPEP) is positive only in approximately 25% of cases, but the majority of patients have an identifiable monoclonal protein by immunofixation in either the serum or urine, at a rate of 73–78% and 79–90%, respectively (Pozzi et al. 1995, 2003; Heilman et al. 1992; Katzmann et al. 2009). As light chains are concentrated in the urine, UPEP and urine immunofixation may be a more sensitive test than serum studies. It is important to note that approximately 10% of patients have no monoclonal protein detected by immunofixation, emphasizing the need for more sensitive tests, in addition to routine IF on kidney biopsy.

Quantifying the ratio of kappa/lambda light chains, known as the serum free light chain (SFLC) ratio, aids in the diagnosis of amyloidosis, MIDD, and other plasma cell dyscrasias. More recent evidence suggests that the SFLC ratio is more sensitive than urine immunofixation for the diagnosis of a light chain clone in the evaluation of MGRS (Fulton and Fernando 2009). It should be noted that the absolute levels of light chains and the ratio of kappa/lambda light chains can be altered in the setting of acute renal impairment and a reference range for ratio of 0.37–3.1 has been suggested (as compared to 0.26–1.65 in healthy individuals) (Hutchison et al. 2008; Yadav et al. 2015). SFLC may also correlate with disease activity and can be followed during the course of treatment (Brockhurst et al. 2005; Kastritis et al. 2009).

In patients with renal disease and proteinuria due a suspected monoclonal protein, an SPEP and UPEP with immunofixation, SFLC assay, and urinary albumin level should be checked. In MIDD and AL amyloidosis, patients will usually have a markedly abnormal SFLC assay and will have a high urinary albumin, indicating true nephrotic disease and not simply Bence Jones proteinuria. In fact, some suggest that the high level of urinary albumin "buries" the free light chain in the urine and the UPEP may be less likely to be positive in these cases (Gertz et al. 2002). In patients with cast nephropathy, they will have a markedly abnormal SFLC assay but will have elevated urinary light chains by UPEP and low urinary albumin (Hutchison et al. 2012). A study evaluating the urinary albumin excretion (UAE) patterns in patients with biopsy-proven monoclonal gammopathy-related kidney diseases found that the%UAE on urine protein electrophoresis was able to discriminate cast nephropathy (%UAE: 7%) from other renal diseases, including amyloidosis (%UAE: 70%), LCDD (%UAE: 55%), and acute tubular necrosis (%UAE: 25%) (Leung et al. 2012b).

Clinical Presentation

The clinical presentation of MIDD depends on the organ systems involved and therefore can have a wide variety of signs and symptoms (Table 1). Renal disease is the most common initial

Table 1 Summary of clinical characteristics of light chain deposition disease

Kidney	Renal insufficiency
	Nephrotic syndrome
	Proteinuria
	Microscopic hematuria
	Hypertension
Heart	Restrictive cardiomyopathy
	Congestive heart failure
	Cardiac arrhythmias
Lung	Interstitial lung disease
	Pulmonary nodules
	Cystic lung disease
Liver	Hepatomegaly
	Transaminase elevation
	Fulminant hepatic failure
Nervous system	Peripheral neuropathy
	Focal brain lesions
	Seizures
	Retinal vasculopathy

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manifestation of MIDD, with nephrotic syndrome, hypertension, and impaired GFR being the most frequent presentations (Buxbaum et al. 1990; Buxbaum and Gallo 1999; Pozzi et al. 1995, 2003; Lin et al. 2001; Nasr et al. 2012a). Extrarenal disease may occur and can involve the heart, lungs, liver, and peripheral nerves, but most clinically important is the heart (Buxbaum and Gallo 1999; Buxbaum et al. 2000). These are described further below.

Renal Manifestations

Most patients with MIDD come to medical attention due to elevated plasma creatinine and/or proteinuria (Buxbaum et al. 1990). The usual presentation is nephrotic syndrome and progressive loss of renal function, though some patients will have slowly progressive disease without significant proteinuria (Sicard et al. 2014). Approximately 90% of individuals have an elevation in serum creatinine at time of biopsy (Pozzi et al. 1995; Buxbaum et al. 1990; Lin et al. 2001; Nasr et al. 2012a), and 50% will have nephrotic range proteinuria (Heilman et al. 1992; Pozzi et al. 1995). Patients with HCDD may be more likely to present with nephrotic syndrome than patients with LCDD (Cohen et al. 2015). Patients with multiple myeloma-associated MIDD present with acute renal failure much more commonly and are more likely to need dialysis at presentation (Lin et al. 2001). Hypertension is often present, in contrast to AL where patients are usually hypotensive (Buxbaum et al. 1990). Table 2 demonstrates additional clinicopathologic correlates of LCDD, LHCDD, and HCDD, respectively.

Cardiac Manifestations

Cardiac disease can be present in up to 80% of cases of MIDD (Buxbaum and Gallo 1999). As patients often primarily present with renal involvement and many of the associated symptoms may be ascribed to the renal dysfunction, the exact prevalence of cardiac dysfunction is hard to quantify. In a review of patients with confirmed cardiac LCDD by biopsy or autopsy, the most common clinical manifestations were arrhythmia, congestive heart failure, and conduction disease (Buxbaum and Gallo 1999). Transthoracic echocardiography (TTE) in general will have evidence of diastolic dysfunction and decreased compliance, consistent with a restrictive cardiomyopathy (Nakamura et al. 2002). In a series of five patients with cardiac LCDD, of whom only four had TTE available, all demonstrated increase in LV wall thickness and preserved ejection fraction (50–85%), as well as low voltage (Buxbaum et al. 2000). Arrhythmias were common in this group, including atrial fibrillation, atrial flutter, and AV conduction delays. One patient had ventricular tachycardia. These clinical and echocardiographic characteristics are very similar to cardiac amyloidosis and other infiltrative cardiomyopathies.

Pulmonary Manifestations

The pulmonary manifestations of MIDD are somewhat heterogeneous and immunoglobulin deposits may be confined to the lung without

Table 2 Clinical and pathologic features of MIDD based on data from three large case series (Lin et al. 2001; Nasr et al. 2012a; Pozzi et al. 2003)

	LCDD	HCDD	LHCDD
Light microscopy			
Nodular glomerulosclerosis	+++/+	++++	+++/+
Global glomerulosclerosis	+	+	+
TBM thickening	V	V	V
GBM thickening	NS	NS	NS
Crescents	+	+	+
Tubular atrophy/interstitial fibrosis	V	V	V
Immunofluorescence			
Anti-light chain on TBM	++++		++++
Anti-heavy chain on TBM		++++	++++
Anti-light chain on GBM	++++		++++
Anti-heavy chain on GBM		++++	++++
Electron microscopy			
Granular deposits along TBM	++++	++++	++++
Granular deposits along GBM	++++	++++	++++
Mesangial deposits	+++	++++	++++
Clinical features			
Creatinine at diagnosis (mg/dl)	3.8–4.0	4.8–5.6	3.1–5.3
Nephrotic range proteinuria (>3 g/day)	++	+++/+	+/+
Nephrotic syndrome[a]	+	+++	+/+
Hypertension	++++	++++	+++/+
Diagnosis of multiple myeloma[b]	+++	++/+	+/+
+SPEP and immunofixation	++/+	+++/+	++++
+UPEP and immunofixation	+++/+	+++/+	++++

+ = 1–25%, ++ = 25–50%, +++ = 50–75%, ++++ = >75%, values separated by/have range that span two quartiles. *NS* not significant, *V* variable range

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[a]Definition of nephrotic syndrome – nephrotic range proteinuria with hypoalbuminemia and peripheral edema

[b]Definition of multiple myeloma in Nasr et al.: renal MIDD plus ≥10% monoclonal plasma cells in BM and monoclonal protein identified in serum and/or urine, Lin et al.: renal MIDD plus at least one of the following: (1) positive BM biopsy, (2) presence of osteolytic lesions, (3) hypercalcemia with positive SPEP/UPEP or (4) ≥10% BM plasmacytosis with low quantitative serum immunoglobulins and Pozzi et al. according to major and minor diagnostic criteria of multiple myeloma and not otherwise specified

systemic involvement (Rho et al. 2009). The most commonly described symptoms are dyspnea and mild cough. Patients may be asymptomatic with only radiologic evidence of disease. In cases of LCDD, patients can present with nodules composed of light chains that can be either peripheral or endobronchial (Buxbaum and Gallo 1999; Khoor et al. 2004). One case report describes a patient with multiple nodules on PET-CT concerning for multifocal malignancy who subsequently underwent wedge resection and was found to have LHCDD (Makis et al. 2010). Patients with diffuse interstitial disease due to LCDD have a worse prognosis and are more likely to have an underlying plasma cell disorder (Bhargava et al. 2007). A few patients with cystic lung disease, consistent with the radiographic appearance of lymphangioleiomyomatosis, have also been described (Colombat et al. 2006).

Hepatic Manifestations

Patients with MIDD often have hepatomegaly and modest enzyme elevations, but synthetic dysfunction is uncommon (Buxbaum and Gallo 1999).

There are rare cases of fulminant hepatic failure and subsequent death due to LCDD (Casiraghi et al. 2000; Michopoulos et al. 2002). There have not been any case reports of LHCDD or HCDD resulting in significant liver disease.

Neurologic Manifestations

Peripheral neuropathy can be present in 20% of cases (Buxbaum and Gallo 1999). As paraproteins cannot cross the blood-brain barrier, central nervous system disease is rare; however, a few cases of LCDD in the brain have been described, with seizures being the most common presentation (Popovic et al. 2007; Fischer et al. 2006; Pantazis et al. 2010). In all cases, there were collections of lymphocytes, either reactive or malignant, in the brain parenchyma that were the likely source of light chains, though one patient was subsequently found to have a monoclonal gammopathy in the serum. In one case, high levels of IgG were detected in the cerebrospinal fluid (Pantazis et al. 2010). A case of LHCDD in the skeletal muscle of patient with bilateral compressive optic neuropathies due to accumulation of the immunoglobulins has also been described (Zakrzewski et al. 2010).

Skin

In HCDD, several cases of cutis laxa have been described (Alexander et al. 2011; Harrington et al. 2008; Tan et al. 2003). Cutis laxa is a rare skin condition characterized by loss of elastic fibers in the dermis, resulting in loose skin. It can be congenital or has been described in association with an urticarial reaction, suggesting an immune-mediated mechanism (Highet 1980; Gupta and Helm 2002). Immunofluorescence performed on skin biopsies in HCDD patients do demonstrate immunoglobulin deposition on elastic fibers (Harrington et al. 2008).

Natural History of MIDD

The natural history of MIDD is variable and is dependent on the presence or absence of clinical multiple myeloma. It is well established that patients with multiple myeloma and LCDD, the most common form of MIDD, have a more rapid renal deterioration and shorter survival (Pozzi et al. 1995, 2003; Lin et al. 2001; Buxbaum and Gallo 1999). In a retrospective study of 63 patients with LCDD by Pozzi et al. (2003), 88% of whom received some form of treatment, the median survival was 4 years and the death rate was 17.5 per 100 patient-years. Renal survival was 67% at 6 months and 31% at 8 years. The authors found that factors associated with worse overall survival, as well as renal survival, were presence of multiple myeloma and symptomatic extrarenal disease. Factors associated with worse renal outcomes alone were presence of cast nephropathy and acute renal failure or rapidly progressive disease (Zand et al. 2015).

In a larger retrospective review of 118 patients with multiple myeloma and renal disease, Montseny et al. (1998) looked at the outcomes of patients with LCDD, AL, and MCN. In this series, 22 patients had LCDD, and the incidence of LCDD was distributed evenly among the different stages (1–3) of multiple myeloma, as opposed to AL, which was present mostly in stage 1 multiple myeloma and MCN which was present in stage 3 multiple myeloma. The LCDD patients had a median survival of 36 months, versus 24 months in AL and 12 months in MCN. Once HD was initiated, patients with LCDD had a survival of 48 months versus 22 months in AL and 6 months in MCN. The predictors of survival in this study were age less than 70, low serum calcium, and low serum creatinine.

In the case series by Nasr et al. (2012a) of 64 patients with MIDD where 56 patients had available data on follow-up, 32 patients (57%) were treated with chemotherapy and 11 (34%) progressed to ESRD over a mean follow-up of 34 months. Sixteen patients underwent autologous stem cell transplantation (ASCT). Despite these interventions, 39% progressed to ESRD and another 4% had worsening renal function, with a mean renal survival of 64 months for all patients with MIDD. There was no statistical

difference in renal survival for LCDD, LHCDD, and HCDD. The mean patient survival was 90 months, also with no statistical difference between the different MIDD subtypes. In those patients who died (32%), the mean time from biopsy to death was 18 months. A study from the United Kingdom of 53 patients with LCDD reported a median renal survival of 5.4 years and patient survival of 14 years. In this study population, there was a strong association between the hematologic response to chemotherapy and renal outcomes – most of the patients who had a partial or no hematologic response developed ESRD (Sayed et al. 2015). Both of these studies are encouraging in that there is an overall trend of better renal and overall survival, likely due to more effective therapy.

A study by Decourt et al. specifically evaluated the outcomes of patients with ESRD due to monoclonal gammopathies, including amyloidosis ($n = 267$), LCDD ($n = 334$), and myeloma cast nephropathy ($n = 861$), after they initiate dialysis, using a registry of incident dialysis patients in France from 2002 to 2011 (Decourt et al. 2016). The median survival of patients with LCDD after dialysis initiation was 18.4 months (95% CI 14.9–24.1), as compared to 28.9 months in amyloidosis patients and 16 months in cast nephropathy patients. The survival rates at 1, 3, and 5 years in LCDD patients were 59%, 37% and 26%, respectively. Only 4.5% of patients were listed for transplantation and 3.3% underwent transplantation; in contrast, 7.5% of amyloidosis patients were listed for transplant and 6.4% were transplanted.

Notably, cardiac disease is an important source of mortality in this population. Cardiac insufficiency, arrhythmia, or sudden death can be the cause of death in approximately 20% of cases (Montseny et al. 1998; Pozzi et al. 2003). Other causes of death include cachexia, GI bleeding, and infection (Buxbaum et al. 1990; Montseny et al. 1998). In the study by DeCourt et al. the main causes of death in the patients with monoclonal gammopathy on dialysis, including the patients with LCDD, were progressive malignancy and cardiovascular events (Decourt et al. 2016).

Treatment

The long-term outcomes associated with the treatment of MIDD are somewhat difficult to characterize, as it is a rare disease, and there have been several different chemotherapeutic regimens tried over the years. Just as the treatment of multiple myeloma has been undergone a large shift with the use of proteasome inhibitors and autologous stem cell transplantation, there has been a parallel shift in the treatment of MIDD with some promising results.

Patients in early studies who received chemotherapy for LCDD often received alkylating agents, most often melphalan, and prednisone in varying amounts, and showed some modest improvements in survival (70% survival at 5 years), as well as some improvement in renal parameters including proteinuria and creatinine (Heilman et al. 1992). The main determinant of how well patients responded was how severe their renal dysfunction was at initiation of chemotherapy. Multidrug chemotherapy with regimens such as vincristine, doxorubicin, and dexamethasone (VAD) has also been tried with some improvement in survival and progression of renal disease (Montseny et al. 1998; Pozzi et al. 2003). However, one study observed a worsening in renal function and development of extrarenal symptoms in some patients treated by conventional chemotherapy (Pozzi et al. 1995).

More encouraging results have emerged with the use of high-dose chemotherapy and ASCT. Several retrospective studies of patients with MIDD and multiple myeloma who have received high-dose chemotherapy and ASCT have shown promising results in terms of regression of disease, improvement in survival, and durability of renal allografts. In the first study by Royer et al. (2004), 11 patients with LCDD or LHCDD were described who received variable amounts of chemotherapy prior to undergoing mobilization with G-CSF or cyclophosphamide, high-dose melphalan, and ASCT. There was a reduction in the level of monoclonal immunoglobulin in eight of ten patients and six achieved complete response (CR). Extrarenal manifestations improved mainly in the patients with CR, and the renal response

was somewhat variable – some stabilized, some improved, but the nephrotic syndrome did regress in the three patients who had it at presentation. It should be noted that aside from the expected side effects of neutropenic fever, nausea, and mucositis, two of the dialysis patients had severe encephalopathy after receiving high-dose melphalan. In terms of relapse, three patients had recurrence of their myeloma at 24–30 months, but none developed extrarenal manifestations. Only one patient underwent renal transplant and had no recurrent disease, though the length of follow-up is not stated.

Similar results were found in the study by Hassoun et al. (2008) that looked at seven patients with MIDD and multiple myeloma five with LCDD, one with LHCDD, and one with light chain proximal tubulopathy who received melphalan and ASCT. Of the seven patients, six achieved CR with normalization of the free light chain ratios, and proteinuria improved in the four patients who did not start dialysis. Of the three patients who were dialysis dependent, two underwent transplantation and had normal creatinine clearance at 14 and 45 months. Another retrospective review by Telio et al. had similar results in terms of hematologic CR, but seven of eight patients had a greater than 50% improvement in serum creatinine from baseline (Telio et al. 2012). A prospective study done at Boston University Medical Center (Weichman et al. 2006) of patients with MIDD included six patients – five with LCDD and one with light chain proximal tubulopathy, some of whom had already received chemotherapy – and treated them with high-dose melphalan and ASCT. The follow-up was much shorter, median of 12 months, but results were also encouraging with five of six patients achieving CR, a 75% reduction in proteinuria, regression of septal thickness in the patient with cardiomyopathy, and only one patient with the severe side effect of encephalopathy. There is one case report of a patient with LCDD on dialysis who improved to the point of being able to come off dialysis after treatment with ASCT, but this is not the standard course (Firkin et al. 2004).

Bortezomib, a proteasome inhibitor developed for the treatment of multiple myeloma, has recently been used in patients with LCDD and HCDD. Table 3 shows a summary of case series using bortezomib-based therapy for MIDD, either alone or in combination with high-dose melphalan and ASCT. The definitions of hematologic response, renal response, and the lengths of follow-up differ significantly between series. The largest retrospective series, consisting of 49 patients with MIDD treated with bortezomib, was reported by Cohen et al. in 2015 (Cohen et al. 2015). The series included 35 patients with LCDD, 12 patients with HCDD, and 2 patients with LHCDD, all of whom received bortezomib-based therapy, which was first line in 77.5% of cases. Bortezomib was given most commonly in combination with dexamethasone (BD, $n = 25$) and cyclophosphamide and dexamethasone (CyBorD, $n = 18$). The overall hematologic response, as measured by SFLC ratio, was 91%, and renal response was achieved in 26 patients (defined as 50% decrease in proteinuria in the absence of a reduction in eGFR >25% or an increase in serum Cr of ≥0.5 mg/dl), with no difference in the response of patients with LCDD, HCDD, or LHCDD. The best predictor of renal response in multivariate models was whether the difference in involved and uninvolved serum free light chains after therapy was less than 40 mg/l. In this larger series, there was no difference in outcomes (hematologic or renal) in patients that underwent melphalan/ASCT therapy after induction therapy with bortezomib as compared to those who received bortezomib-based therapy alone. However, in some of the case series, a few patients are reported that had a relapse in proteinuria after stopping bortezomib therapy. This suggests that if ASCT is not pursued, prolonged therapy with bortezomib may be needed to maintain remission (Kastritis et al. 2009; Patel et al. 2014).

Kidney transplantation in patients with MIDD has had somewhat discouraging results. The majority of patients have had recurrence of the MIDD posttransplantation, despite treatment with chemotherapy and reduction in paraprotein levels prior to transplant, according to a review of the

Table 3 Summary of case series describing bortezomib-based therapy for monoclonal immunoglobulin deposition disease

Study	Patients included	Treatment	Hematologic response	Renal response	Adverse events
Kastritis et al.	4 pts. with LCDD	BD, followed by melphalan/ ASCT	Induction: 2 patients had CR and 2 had >50% decrease in light chain	After ASCT: 3 patients with only trace proteinuria at 10–18 months follow-up	Peripheral neuropathy
	None with MM		Melphalan and ASCT: 3/4 patients -> all 3 with CR	No ASCT: proteinuria recurred in 1 patient after stopping BD	Orthostatic hypotension
					Increase in LFTs
					Constipation
Jimenez-Zepeda et al.	6 pts. with LCDD	BD vs. dexamethasone alone, followed by melphalan and ASCT	Induction: 4/6 with PR and 2/6 with stable disease	All patients had a decrease in proteinuria by >50% at 6 months post-ASCT, none with ESRD	Peripheral neuropathy
	1 with MM		Melphalan and ASCT: 6/6 ->4 patients with CR, 1 with near CR and 1 with PR	Patients on BD vs. dex alone: median time to kidney response 3 months vs. 6 months	
Tovar et al.	3 pts. with LCDD	BD, followed by melphalan and ASCT	Induction: 1 with CR, 1 with PR, 1 with no response	1 patient able to come off dialysis, but with persistent proteinuria, 1 patient with no renal improvement and had transplant, 1 with minimal proteinuria at follow-up	Not mentioned
	1 with MM		Melphalan and ASCT: 3/3 ->2 with CR and 1 with VGPR		
Minarik et al.	3 pts. with LCDD	CyBorD or BD	Induction only: rapid hematologic response with normalization of SFLC ratios at 6 months in 3/3	1 patient with improvement in proteinuria and creatinine, 2 patients with stable disease but persistent renal impairment at 12 months	Peripheral neuropathy
	1 with MM				Respiratory infections
					Diarrhea
Patel et al.	3 pts. with HCDD	BD, followed by lenalidomide in 1 patient	Induction only: 1/3 patients with normalization of SFLC ratio	Resolution of nephrotic syndrome and improvement in kidney function in 3/3, 1 patient with recurrent proteinuria after discontinuation of bortezomib	Peripheral neuropathy
	None with MM				
Cohen et al.	49 pts. with MIDD	Bortezomib-based therapy, 13 patients treated with melphalan/ ASCT	Induction: 91% response rate, 31 patients with CR ($n = 5$) and VGPR ($n = 26$)	Improvement in proteinuria without worsening of renal function in 53% at median follow-up of 54 months	Peripheral neuropathy in 12.5%
	35 with LCDD, 12 with HCDD, 2 with LHCDD		Melphalan/ASCT: no difference in hematologic or renal response or time to progression	2 patients with LCDD had renal transplant	

LCDD light chain deposition disease, *HCDD* heavy chain deposition disease, *LHCDD*, light heavy chain deposition disease, *MM* multiple myeloma, *BD* bortezomib-dexamethasone, *CyBorD* cyclophosphamide-dexamethasone-bortezomib, dexamethasone, *ASCT* autologous stem cell transplant, *CR* complete response, *VGPR* very good partial response, *PR* partial response, *SFLC* serum free light chain, *LFTs* liver function tests, *ESRD* end-stage renal disease

literature by Short et al. (2001). In this group of patients, six of seven patients had a recurrence and four of seven patients died after renal transplant, with disseminated myeloma and sepsis being the most common causes of death. Another case series by Leung et al. (2004) looked at the outcomes of seven patients with LCDD who received kidney transplants, three of whom had received chemotherapy with an alkylating agent and prednisone prior to transplant. These patients also had poor outcomes – three patients had early acute cellular rejection, two required allograft nephrectomy, and five patients (71%) had recurrent disease in the allograft at a median time of 33 months. Median survival was 12 years after diagnosis, 6 years after transplant, and 3.6 years after recurrence. Overall survival was worse than age-matched kidney transplant recipients without LCDD. As some patients seem to have early and somewhat aggressive recurrence of their disease, it raises the concern of the effect of immunosuppression on the natural history of MIDD. In the UK study of 53 patients with MIDD, seven patients underwent renal transplantation and three of these grafts failed – two due to recurrent disease and one due to rejection (Sayed et al. 2015). Bortezomib has been used to treat recurrent MIDD in the allograft with success in a few case reports (Kuppachi et al. 2016; Kaposztas et al. 2009; Moiz et al. 2014). The success of transplant remains to be seen, as there are still very few patients described. In light of the improved renal outcomes in patients who achieve hematologic remission, it makes sense to try to achieve hematologic remission prior to pursuing transplantation in this high-risk population.

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Myeloma Associated Glomerular Disease

39

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Abstract

Multiple myeloma is a plasma cell malignancy characterized by the presence of a monoclonal gammopathy, lytic bone lesions, hypercalcemia, anemia, and/or renal impairment. Renal impairment is common and most frequently occurs in the form of light chain cast nephropathy. However, in addition to cast nephropathy, the kidney can also sustain injury to the glomerulus, tubules, interstitium, and the vessels by other mechanisms, with glomerular lesions being most common. The focus of this chapter will be on the spectrum of glomerular lesions associated with multiple myeloma.

Keywords

Multiple myeloma · Glomerular · Amyloidosis · MIDD · Light chain · MGRS

Introduction

Multiple myeloma (MM) is a malignancy of the plasma cell accounting for about 10% of hematological malignancies. (Kyle et al. 2003) The definition of MM has changed over the years. Initially, MM was defined as >5% bone marrow plasma cells with a circulating monoclonal gammopathy. (Kyle 1978) Later, it required a monoclonal (M)-spike of >3 g/dl or >10% clonal bone marrow plasma cells along with one of the myeloma-defining events: hypercalcemia (C), renal impairment (R), anemia (A), and lytic bone lesions (B) now known as the CRAB criteria. Recently, three additional criteria (clonal bone marrow plasma cell percentage ≥60%, involved to uninvolved serum free light chain ratio ≥100 and >1 focal bone or bone marrow lesions on magnetic resonance imaging) were added to the definition (Rajkumar et al. 2014). These new criteria recognize conditions that are high risk of progressing to active MM. The inclusion of these new criteria allows for earlier initiation of treatment which could help prevent the development of end-organ damage that is associated with significant morbidity and mortality for these patients.

Renal Pathology in Multiple Myeloma

Renal impairment is common in patients with multiple myeloma. Depending on the definition, up to 40% of patients are found to have abnormal renal function at the time of diagnosis with 10–15% requiring dialysis (Dimopoulos et al. 2010). Previously, renal impairment was defined by a serum creatinine (Scr) >2 mg/dl, but a revised definition now uses an estimated glomerular filtration rate (eGFR) cutoff of <40 ml/min/1.73 m2 (Rajkumar et al. 2014). In addition, only cast nephropathy is considered a myeloma-defining event. This is because unlike the other renal lesions that are seen in MM, cast nephropathy is nearly always associated with high tumor burden. While a diagnosis by renal biopsy is ideal, this cannot always be performed in clinical practice (Ecotiere et al. 2016; Leung 2016). In these situations, two characteristics are helpful to distinguish cast nephropathy from other lesions. These are high serum free light chain (sFLC) levels (>50 mg/dl) and a low urinary albumin excretion especially when it is <10% of total proteinuria (Leung et al. 2012b).

In addition to cast nephropathy, a number of additional lesions have been described on kidney biopsies from patients with MM (Fig. 1). In an autopsy series, 48% of the patients were found to have one or more renal lesions. Of these, 66.7% had cast nephropathy, 22.2% had immunoglobulin light chain (AL) amyloidosis, and 11.1% had monoclonal immunoglobulin deposition disease (MIDD) (Ivanyi 1990). Two patients had more than one pathological features. One patient had MIDD and cast nephropathy and the other had

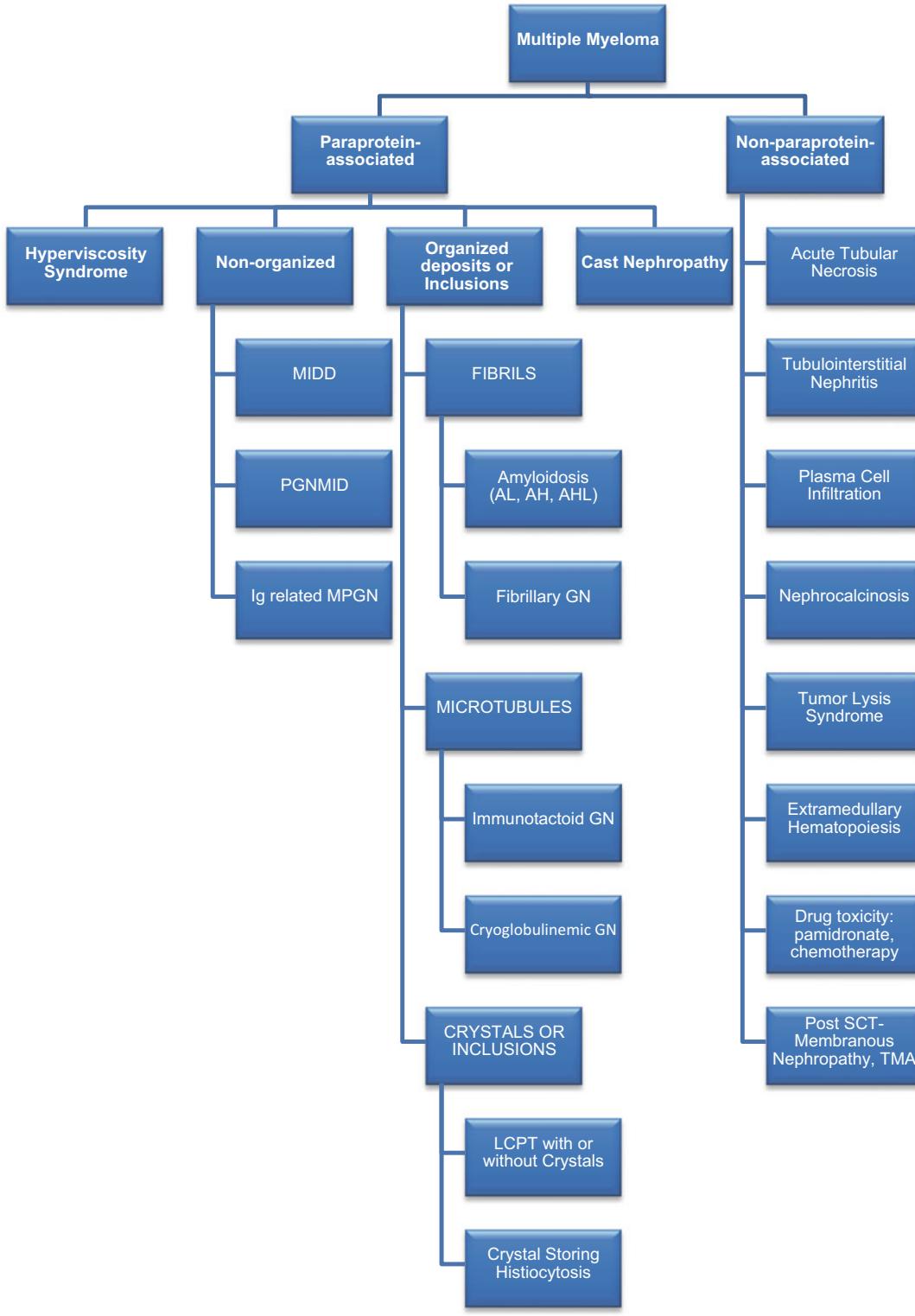

Fig. 1 (continued)

MIDD with AL amyloidosis. In a series of 42 patients with MM who underwent a kidney biopsy, cast nephropathy was found in 47.6%, while immunoglobulin (AIg) amyloidosis was found in 7.1% (Pasquali et al. 1987). Interstitial nephritis was noted in 16.6% and acute tubular necrosis was seen in 7.1%. In a larger series of 190 patients with MM who underwent a kidney biopsy, paraprotein-associated pathology was identified in 73% of the patients, while 25% were considered to have non-paraprotein-associated lesions (Nasr et al. 2012c). The most common paraprotein-associated lesion was myeloma cast nephropathy (33%) followed by MIDD (22%) and amyloidosis (21%). The most common non-paraprotein-associated lesions were acute tubular necrosis (ATN, 9%), hypertensive arteriosclerosis (6%), and diabetic nephropathy (5%). In a study of highly selective patients for cast nephropathy (elevated sFLC and low urinary albumin excretion), 58.6% had only cast nephropathy, and 17.1% had AL amyloidosis, 8.6% with MIDD, 1.4% with light chain proximal tubulopathy with Fanconi syndrome, 4.3% with MIDD and cast nephropathy, 1.4% with AL amyloidosis and cast nephropathy, and 1.4% with arteriolosclerosis (Ecotiere et al. 2016).

While all of these renal lesions can be seen in patients with MM, it is clear that having overt multiple myeloma (i.e., a high plasma cell burden) is not a prerequisite for renal involvement by the pathogenic paraprotein (Solomon et al. 1991; Paueksakon et al. 2003). Mice injected intraperitoneally with Bence Jones protein from patients with multiple myeloma with renal involvement were found to develop lesions similar to the human subjects. In order to more accurately describe the hematologic condition, the term monoclonal gammopathy of renal significance (MGRS) was introduced (Leung et al. 2012a). The MGRS encompasses paraprotein-mediated kidney damage in patients who do not meet criteria for overt multiple myeloma or systemic lymphoma. MGRS establishes the link between low-grade plasma cell or B-cell lymphoproliferative disorders with the renal conditions. The new designation allows better classification and study of these diseases (Bridoux et al. 2015; Leung et al. 2012a). It also allows for clone-directed therapy to be used (Fermand et al. 2013; Hogan and Weiss 2016).

It is important to recognize that MM or plasma cell clones are not the only clones that can produce nephrotoxic monoclonal immunoglobulin (MIg). In fact, the pattern of renal involvement is generally determined by the characteristics of the pathogenic MIg and not the clone. A recent study of IgM secreting lymphoproliferative disorders which included Waldenström macroglobulinemia (WM), MGRS and other low-grade lymphoma found the most common renal lesion to be AL amyloidosis (31.4%), followed by cryoglobulinemic glomerulonephritis (14.3%), membranoproliferative glomerulonephritis (11.4%), intracapillary monoclonal IgM deposits (2.9%), MIDD (2.9%), and ATN (2.9%) (Chauvet et al. 2015). A study in patients with WM with kidney biopsy reported similar findings with 25% AL amyloidosis, 23% cryoglobulinemic glomerulonephritis, 18% lymphoplasmacytic lymphoma infiltration, 9% MIDD, 9% cast nephropathy, as well as 7% thrombotic microangiopathy, 5% minimal change disease, 2% membranous nephropathy, and 2% crystal storing tubulopathy (Vos et al. 2016). Interestingly, there were also cases of cast nephropathy (14.3%) and light chain proximal tubulopathy with Fanconi syndrome 8.6%). A variety of renal lesions was also reported in patients with chronic lymphocytic leukemia (CLL). These included membranoproliferative glomerulonephritis (MPGN, 20%), CLL infiltration (12%), AL amyloidosis (7%), cast nephropathy (7%), as well as minimal change disease (10%), membranous nephropathy 4%, and thrombotic

Fig. 1 Renal diseases in multiple myeloma. *AH* immunoglobulin heavy chain, *AHL* immunoglobulin heavy and light chain, *AL* immunoglobulin light chain, *GN* glomerulonephritis, *Ig* immunoglobulin, *LCPT* light chain proximal tubulopathy, *MIDD* monoclonal immunoglobulin deposition disease, *MPGN* membranoproliferative glomerulonephritis, *PGNMID* proliferative glomerulonephritis with monoclonal immunoglobulin deposits, *SCT* stem cell transplant, *TMA* thrombotic microangiopathy

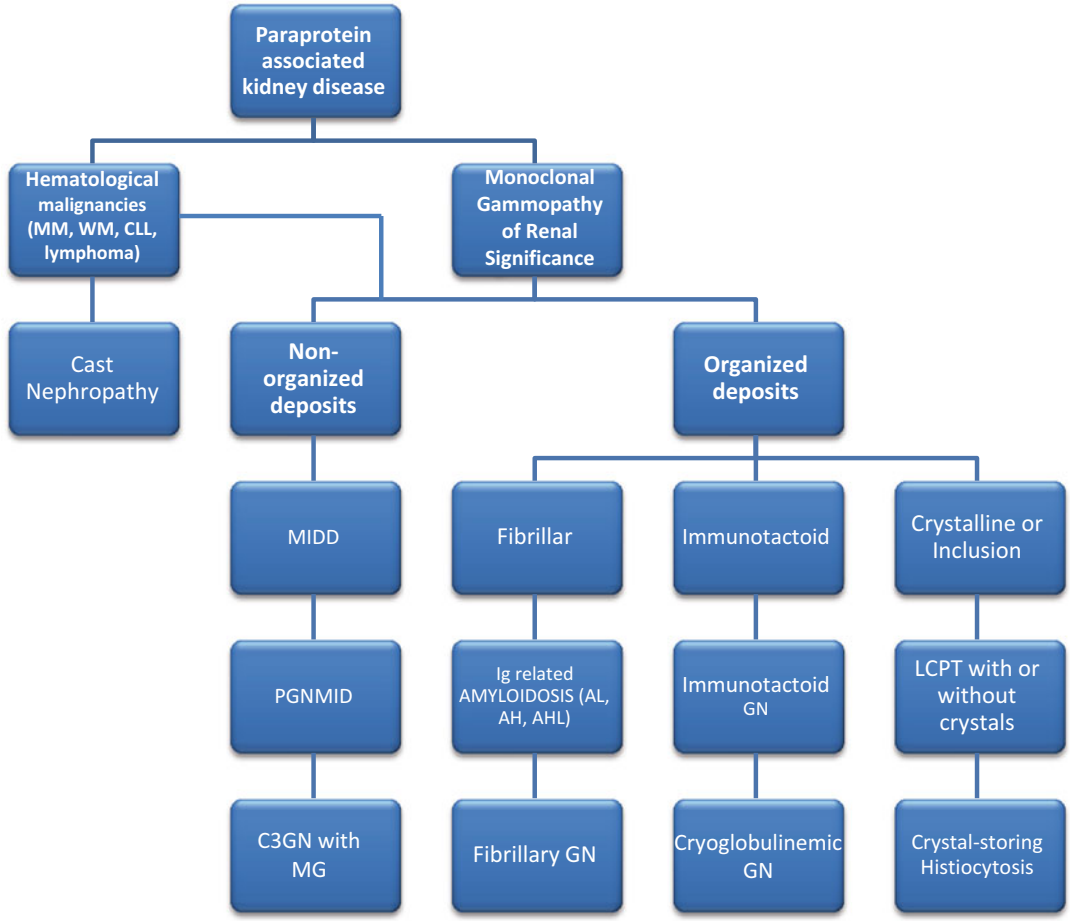

Fig. 2 Paraprotein associated kidney diseases. *AH* immunoglobulin heavy chain, *AHL* immunoglobulin heavy and light chain, *AL* immunoglobulin light chain, *CLL* chronic lymphocytic leukemia, *GN* glomerulonephritis, *Ig* immunoglobulin, *LCPT* light chain proximal tubulopathy, *MIDD* monoclonal immunoglobulin deposition disease, *MG* monoclonal gammopathy, *MM* multiple myeloma, *PGNMID* proliferative glomerulonephritis with monoclonal immunoglobulin deposits, *WM* Waldenström macroglobulinemia

microangiopathy (12%) (Strati et al. 2015). These studies clearly indicate that some renal lesions do occur more commonly in the setting of certain clonal diseases. For example, cast nephropathy is most common in MM, while AL amyloidosis is more common in WM, and MPGN is most common in CLL. However, no lesion is exclusive to any clonal disorder. This reinforces the hypothesis that the renal lesion is determined by the MIg rather than the clone itself.

A number of different schemes have been devised to classify renal lesions associated with paraproteinemia. They all have their advantages and disadvantages. The International Kidney and Monoclonal Gammopathy Research Group recommends the classification based on ultrastructural characteristics of the deposits (Fig. 2) (Bridoux et al. 2015). The lesions are first categorized by whether the deposits are organized or non-organized. Organized deposits are further subdivided into fibrillar, immunotactoid, or crystalline. The non-organized deposits category represents three groups of diseases: monoclonal immunoglobulin deposition disease (MIDD), proliferative glomerulonephritis with

monoclonal immunoglobulin deposits (PGNMID), and C3 glomerulonephritis with monoclonal gammopathy.

Mechanisms of Kidney Injury in Multiple Myeloma

Multiple myeloma mainly exerts its nephrotoxic effects via the overproduction of MIg. MIg can be separated into monoclonal free light chain (FLC), monoclonal intact immunoglobulin (Ig), and monoclonal heavy chain which is often truncated. Monoclonal FLC was first described by Henry Bence Jones in 1846 and has since been named Bence Jones protein (Hutchison et al. 2012). Normally, about 500 mg of polyclonal FLCs are produced daily in excess of the heavy chain. A portion is catabolized by the reticuloendothelial system, but the majority undergoes glomerular filtration and subsequent catabolism in the proximal tubules. This system is highly efficient, and only about 1–10 mg of polyclonal FLCs end up in the urine daily. In multiple myeloma, free light chain synthesis is ramped up to a considerable extent, overwhelming the capacity of the multiligand endocytic receptor complex of the proximal tubule. As a result, high concentrations of FLC are present in the loop of Henle and distal tubule where normally little FLC exists. Elevated concentrations of certain monoclonal FLC with affinity toward Tamm-Horsfall protein (THP) can bind and precipitate THP, resulting in obstructive casts (i.e., cast nephropathy). FLC can also cause damage by depositing in the kidney. It can be deposited in fibrillar form (i.e., amyloidosis), amorphous form (i.e., light chain deposition disease (LCDD) variant of MIDD), or crystalline form (i.e., light chain proximal tubulopathy (LCPT) Fanconi syndrome).

Monoclonal intact immunoglobulins can also be nephrotoxic, but they do not cause cast nephropathy because they are too large to be filtered by the glomerulus. Instead, they are deposited in the glomerulus resulting in PGNMID, immunotactoid glomerulonephritis, and monoclonal fibrillary glomerulonephritis. They are also responsible for light-heavy chain deposition disease (LHCDD) and light and heavy chain (ALH) amyloidosis. The rarest monoclonal immunoglobulin deposition disease occurs in the setting of a pathogenic heavy chain. These immunoglobulin heavy chains are often truncated so they are unable to bind the immunoglobulin light chain. They can be seen in heavy chain deposition disease (HCDD) of MIDD and heavy chain (AH) amyloidosis. HCDD and AH amyloidosis are quite rare compared to other forms of MIDD and immunoglobulin (AIg) amyloidosis. Finally, MIg can also cause kidney disease via the activation of complement, with kidney biopsies showing C3 glomerulonephritis. In this setting, the monoclonal immunoglobulin is not typically seen in the kidney biopsy.

AL Amyloidosis in Multiple Myeloma

AIg amyloidosis is most common form of glomerular disease in MM (Said et al. 2013). Three variants of AIg amyloidosis exist: AL, ALH, and AH amyloidosis (Nasr et al. 2013). By far, AL amyloidosis represents the majority of cases of AIg amyloidosis, and thus most of the discussion will focus on AL amyloidosis. Although 10% or more bone marrow plasma cells can been seen in up to 40% of patients with AL amyloidosis, only ~15% meet the definition of MM (Kyle and Gertz 1995). In a study of over 1000 patients with MM, 1% was diagnosed with AL amyloidosis prior to the diagnosis of MM, 3% were diagnosed within 30 days of diagnosis of MM, and 2% were diagnosed during the course of MM (Kyle et al. 2003). Patients who have both MM and AL amyloidosis have a worse prognosis than patients with AL amyloidosis or MM alone. This has not changed despite modern therapies (Kyle and Bayrd 1975; Kourelis et al. 2013).

Kidney is one of the most commonly involved organs in AL amyloidosis. These patients present with proteinuria and renal insufficiency, although rarer manifestations including Fanconi syndrome with renal tubular acidosis and nephrogenic diabetes insipidus from amyloid deposits around the proximal tubules and collecting ducts have been reported (Kyle and Gertz 1995). In one study,

70% of patients presented with proteinuria (Kyle and Gertz 1995). The median proteinuria was 1.2 g/d, and nephrotic range proteinuria was noted in half of the patients with proteinuria. A more recent study of 407 patients found the median proteinuria was 6.7 g/d with nephrotic range proteinuria in 68% of patients. There was no significant difference among patients with AL, AH and ALH amyloidosis (Nasr et al. 2013). The reason for the differences is unclear as both of these studies were performed at the same institution but at different time periods. Proteinuria in AL amyloidosis is mainly albuminuria which differs from cast nephropathy which is mostly Bence-Jones proteinuria (Leung et al. 2012b). Renal impairment is seen in 50% patients with a median serum creatinine (Scr) of 1.2 mg/dl. Patients with Scr > 2.0 mg/dl ranged from 20% to 26%. In a large combined Italian/German study, end-stage renal disease (ESRD) was present in 4–5% of patients at diagnosis, with ESRD occurring in 15% of the Italian patients and 31% of the German patients after treatment began (Palladini et al. 2014). The reason for the difference could not be explained by the first- or second-line therapy. A separate study found that ESRD developed mainly in patients who presented with renal involvement. Over a median follow-up of 11 years, 42% of patients with renal involvement vs 5% without renal involvement at presentation developed ESRD (Gertz et al. 2009). In this study, hypoalbuminemia was also a significant risk factor for progression to ESRD. The prognosis of patients with ESRD has improved significantly over the years. In a cohort of patients studied between 1994 and 1997, the median survival after starting dialysis was 11 months (Gertz et al. 2009). A more recent study of patients between 1987 and 2008 found the median survival has extended to 39 months after development of ESRD (Pinney et al. 2011).

In the kidney, AL Amyloidosis has a characteristic appearance on light microscopy. Amyloid appears as eosinophilic deposits that is periodic acid-Schiff (PAS) stain negative and silver stain negative. AL deposits can be found in all three compartments in particular the vascular compartment. The deposits can range from minimal to massive. In about 5% of cases, the deposits are limited to the vascular compartment. Unlike the usual amyloidosis patients, these patients present mainly with progressive renal insufficiency often with little or no proteinuria (Eirin et al. 2011). Under polarized light, apple-green birefringence of the Congo red stain is required for the diagnosis of all amyloidosis. This is confirmed by the presence of randomly arranged solid fibers of 8 to 12 nm in diameter seen on electron microscopy (EM). However, typing of the amyloid requires immunofluorescence (IF) studies which should demonstrate light chain restriction in AL and ALH and heavy chain restriction in ALH and AH. In cases where light or heavy chain restriction cannot be clearly demonstrated, proteomic analysis by mass spectrometry should be performed since familial amyloidosis has been reported in patients with monoclonal gammopathy of undetermined significance (MGUS) or myeloma (Leung et al. 2012c; Lachmann et al. 2002).

Laboratory testing for AL amyloidosis should include tests for monoclonal gammopathy, kidney function tests, liver function tests, as well as cardiac biomarkers. These will help determine extrarenal involvement particularly the heart which has the most impact on prognosis (Dispenzieri et al. 2004). Monoclonal protein testing differs from that required for MM since these patients often have low plasma or B-cell clonal mass and low levels of circulating monoclonal protein. Compared to MM, the sensitivity of serum protein electrophoresis is 66% in AL amyloidosis vs 88% in MM (Katzmann et al. 2009). Serum immunofixation improves the sensitivity to 74%. The addition of serum free light chain assay to serum protein electrophoresis and immunofixation can detect a monoclonal gammopathy in over 97% of patients. The serum free light chain assay is not only important diagnostically, it is also a key biomarker for assessment of response to therapy (Kumar et al. 2011). Although urine protein electrophoresis does not improve the monoclonal protein detection rate, it is used to measure renal response (Katzmann et al. 2009; Palladini et al. 2014).

AL amyloidosis can be particularly fatal with cardiac involvement. Patients with renal only involvement have significantly better prognosis, but they are at risk for ESRD. Median survival as high as 6.3 years has been reported in patients

treated with autologous stem cell transplantation (ASCT); however, patients with advance cardiac involvement are at high risk for treatment-related mortality (TRM), and alternative treatment should be sought (Cibeira et al. 2011; Gertz et al. 2010). Recently, hypoalbuminemia (<2.5 g/dl) and low eGFR (<40 ml/min/1.73 m^2) have been found to be risk factors for development of acute renal failure and TRM during autologous stem cell transplant independent of cardiac biomarkers (Leung et al. 2016). Interestingly, the risk returns to baseline if a patient is on stable hemodialysis prior to the stem cell transplant. The combination of melphalan and dexamethasone has been shown to be effective and to have a significantly lower TRM than ASCT for patients with advanced cardiac involvement in a randomized trial, but its slower time to response still leave the sickest patients without a viable option (Gertz 2010; Jaccard et al. 2007; Lebovic et al. 2008; Palladini et al. 2007). Melphalan is also not preferred if there is significant renal impairment. Small studies have shown promising results with bortezomib-based therapies which have a more rapid response time (Mikhael et al. 2012; Venner et al. 2012), and bortezomib does not require renal dosing adjustment. However, the early success has not been universally repeated (Palladini et al. 2015). Larger trials are needed to evaluate the true efficacy of bortezomib-based therapies. Regardless of therapy, patients who achieves at least a very good partial response (VGPR) hematologically or >90% reduction of the pathologic serum FLC are more likely to have preservation and improvement of their renal amyloidosis (Palladini et al. 2014; Pinney et al. 2011). Achieving a renal response is an independent marker of treatment success (Leung et al. 2005a).

Kidney transplantation in patients with true MM is controversial. Since MM is not a curable disease currently, relapse is inevitable. This poses a risk for recurrence of the paraprotein-associated renal lesion if that was the cause of the ESRD (Goel et al. 2011). In addition, death due to progression of disease is another major consideration especially for patients with cardiac involvement in AL amyloidosis. Fortunately, with the introduction of novel agents, patient survival has been increasing (Kumar et al. 2008). Small studies have shown that immunosuppression used in kidney transplantation does not appear to promote the progression of MGUS to MM (Naina et al. 2012). Since these patients will likely require chemotherapy at some point, they are susceptible to over-immunosuppression and infection (Humphrey et al. 1975). Recurrence of AL amyloidosis does occur in the renal allograft if the disease is not in complete response prior to kidney transplantation (Leung et al. 2005b). However, due to the slow nature of its recurrence, successful kidney transplantation had been reported in patients that were treated either prior or after kidney transplantation (Herrmann et al. 2011; Pinney et al. 2013). Treatment of the AL amyloidosis after kidney transplant does impose a risk of injury to the renal allograft (Leung et al. 2009). Therefore it is preferred to successfully treat the AL amyloidosis prior to kidney transplantation.

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN), which is also known as mesangiocapillary glomerulonephritis (GN), is a pattern of injury that is commonly seen in MM and MGRS and is characterized by mesangial expansion often due to hypercellularity, glomerular basement membrane (GBM) double contouring, and duplication. Historically, MPGN was classified by the location of the deposits on EM (e.g., Type I, II, and III). Type II was also known as dense deposit disease and was known to involve complement, while the etiologies of Type I and III overlapped significantly. As a result, this classification was unhelpful in clinical practice and even less in research regarding etiology or treatment. More recently, a new classification system was introduced based on the IF microscopy. The first step is to assess for the presence of immune complexes (Sethi and Fervenza 2012). If immune complexes are present, the immunoglobulin should be identified as either monoclonal or polyclonal. MIg would suggest MGRS or myeloma-associated GN, while polyclonal is due to etiologies such as autoimmune connective tissue disorders, infections, or other

malignancies. If immunoglobulin deposits are not present, complement deposits should be sought. Dominate C3 staining (without immunoglobulin deposits) is characteristic of C3 glomerulopathy which can be further divided into C3 GN and dense deposit disease. Finally, if neither immune complexes nor complement is present, the differential includes thrombotic microangiopathy (Masani et al. 2014). The new IF classification of MPGN allows for a more etiology-based classification system with the hope of improving treatment determination and research into the different diseases that presents with the MPGN pattern.

Monoclonal Immunoglobulin Deposition Disease

MIDD is a group of kidney diseases characterized by the non-organized deposition of MIg or its components. The deposits are amorphous or granular and non-Congophilic. It is often referred to as Randall-type deposits in reference to Dr. Randall who first reported nodular glomerulopathy in non-diabetic myeloma patients (Randall et al. 1976). Kidney involvement is nearly universal and is the dominant clinical presentation. Extrarenal manifestations have been reported in the heart, liver, and even brain (Nasr et al. 2012b). The three subtypes are determined by the immunoglobulin component that is deposited. LCDD is characterized by monoclonal immunoglobulin light chain deposits, where light-heavy chain deposition disease (LCHDD) involves the entire immunoglobulin. The rare is heavy chain deposition disease (HCDD) which is characterized by truncated immunoglobulin heavy chain often missing the CH1 portion. For more detailed discussion, please refer to the chapter on monoclonal immunoglobulin deposition disease.

Proliferative Glomerulonephritis with Monoclonal IgG Deposits

PGNMID is a GN characterized by deposits of intact immunoglobulin. The most common immunoglobulin is IgG_3 kappa which accounts for 50% of cases (Nasr et al. 2011a). Another 15% of cases are due to IgG_3 lambda. Since then, IgM and IgA subtypes have been described (Bhutani et al. 2015). The most common pattern of injury is MPGN with endocapillary hypercellularity (Nasr et al. 2011a). The true incidence of PGNMID is not known (Nasr et al. 2009; Bridoux et al. 2015). PGNMID tends to occur in low-level clonal disorders. Less than 3% of patients meet criteria for MM (Nasr et al. 2011a). In fact, $< 30\%$ of patients have a detectable circulating monoclonal protein by serum immunofixation and serum free light chain assay (Bhutani et al. 2015). Patients with positive serum or urine immunofixation are most likely to have a detectable clone in the marrow. When a clone can be identified, they are plasma cell in 50%, B-cell including CLL in 30% and lymphoplasmacytic (WM) 20% of cases. Patients with neither a positive immunofixation nor an abnormal FLC ratio are unlikely to have a clone identifiable by current techniques. Despite that, multiple myeloma have developed in patients who were initially negative for monoclonal protein or plasma cells in the marrow several years later (Herrmann et al. 2015). Risk of recurrence is very high with PGNMID often occurring within 4 months of kidney transplantation (Albawardi et al. 2011; Nasr et al. 2011a).

Immunotactoid Glomerulonephritis

Immunotactoid glomerulonephritis is characterized by non-cryoglobulin, Congo red-negative deposits of large thick-walled microtubules (Bridoux et al. 2015). The median age at diagnosis is 60 (Bridoux et al. 2002; Nasr et al. 2012a). In one series, male patients were more common with a male to female ratio of 10:4, while it was 50:50 in another. A third series found 83% of the cases were female (Rosenstock et al. 2003). Majority are associated with a monoclonal gammopathy, and roughly 38% of patients with immunotactoid glomerulonephritis have an associated hematologic malignancy. The most common of these is CLL which has been

reported as high as 50% in some series (Rosenstock et al. 2003; Nasr et al. 2012a; Bridoux et al. 2002). Multiple myeloma makes up 13% of patients and the rest have MGRS (Nasr et al. 2012a; Bridoux et al. 2002). Typical clinical presentation includes proteinuria, nephrotic syndrome, and microhematuria. Proteinuria is heavy with median daily urinary excretion of 6 to 11 g/d (Bridoux et al. 2002; Nasr et al. 2011a; Rosenstock et al. 2003). Majority of patients presents with renal insufficiency (50–83%) with a median Scr at presentation of 1.5–2.1 mg/dl.

Fibrillary Glomerulonephritis

Fibrillary glomerulonephritis (FG) is another glomerular disease that is associated with MM and MGRS. However, unlike the other lesions discussed which are always associated with clonal disorders, majority of FG are the result of polyclonal immunoglobulins (Alpers et al. 1987; Nasr et al. 2011b). Patients with fibrillary glomerulonephritis usually present in their mid-1950s (53–57 years) (Nasr et al. 2011b; Bridoux et al. 2002; Rosenstock et al. 2003). Monoclonal gammopathy is found in 15–17% of patients in two series but none in another series. In one series, 9% of patients had multiple myeloma (Nasr et al. 2011b). IgG is most common in the polyclonal subtype, mostly IgG_4 and IgG_1 (Rosenstock et al. 2003; Javaugue et al. 2013). The presence of a monoclonal gammopathy does increase the risk of recurrence and allograft loss in these patients (Czarnecki et al. 2009). Rare extrarenal manifestations such as pulmonary hemorrhage have also been reported (Masson et al. 1992).

Cryoglobulinemic Glomerulonephritis

Cryoglobulinemia is a rare complication of multiple myeloma but is more common in lymphoproliferative disorders. In a large series of noninfectious cryoglobulinemic glomerulonephritis from France, only 1 out of 80 was secondary to MM (Zaidan et al. 2016). In MM, this is typically manifested as a type I cryoglobulinemia where the cryoglobulin is a monoclonal IgG or IgA. Occasionally an IgM myeloma can produce a type II cryoglobulin but IgM myelomas are rare. In a review of 14 patients (7 patients and 7 cases from the literature) with type I cryoglobulinemia and MM, only 1 of the 14 had a monoclonal IgM (Payet et al. 2013). The rest were monoclonal IgG with about equal distribution for κ and λ. Another review of 20 (2 patients plus 18 cases from the literature) cases of cryoglobulinemic glomerulonephritis again found only 3 were due to monoclonal IgM, while the rest had monoclonal IgG (Karras et al. 2002). In this review, majority of the monoclonal proteins were IgG_κ. Renal manifestations usually occur in 20–25% of type I cryoglobulinemia (Ramos-Casals et al. 2012; Karras et al. 2002). In the previous series of 14 patients, 4 (29%) had renal involvement.

C3 Glomerulonephritis Associated with Monoclonal Gammopathy

C3 glomerulonephritis (C3GN) is a proliferative GN characterized by glomerular deposition of complement component usually secondary to dysregulation of the alternative pathway (Larsen et al. 2015). C3GN is a subset of C3 glomerulopathy which also includes dense deposit disease. By light microscopy, C3GN often demonstrates pattern of mesangioproliferative or membranoproliferative or endocapillary glomerulonephritis. C3GN is characterized by bright C3 staining on IF. By definition, no significant immunoglobulin deposits should be present by IF. Two studies have reported the presence of monoclonal gammopathy in patients with C3GN (Bridoux et al. 2011; Zand et al. 2013). In one study, 10 of 32 patients were found to have a monoclonal gammopathy (Zand et al. 2013). This is much higher than the percentage predicted by epidemiology. Patients with C3GN with monoclonal gammopathy tend to be older than C3GN patients without monoclonal gammopathy (64 vs 31 years, respectively), but there are some overlaps. Bone marrow

evaluation in nine patients found MGUS in five, CLL in one, and no identifiable clone in three patients. No complement mutation was found in either series of patients although risk allele for Factor H polymorphism was found in three patients. Two patients had a positive C3 nephritic factor (C3nef). In another study, direct complement activation by the monoclonal protein was demonstrated but in majority of case the link between the monoclonal protein and C3 glomerulonephritis remains to be determined (Meri et al. 1992).

Rare Entities

Extramedullary Hematopoiesis

In advanced stage of hematologic disease, extramedullary hematopoiesis can be a cause of renal failure and nephrotic syndrome (Alexander et al. 2015). Hematopoietic cells are pushed out of the bone marrow by the hematologic neoplasm forcing them to settle in other organs. This is most often encountered in patients with myeloproliferative disorders, but cases have been reported in MM. Patients present with severe renal impairment (mean Scr = 2.9 mg/dl) and heavy proteinuria (mean proteinuria 7.9 g/d). Cells from all three lineages of hematopoiesis are characteristically present in the kidney. The infiltrates are concentrated in the interstitial space often resulting in acute tubular injury. Patients with MM often have other myeloma-related lesions such as MIDD and cast nephropathy. In addition to the demonstration of hematopoietic cells in the kidney, mesangial sclerosis and even focal segmental glomerulosclerosis can be demonstrated. Prognosis both from renal and overall survival standpoint is generally poor for these patients as they often represent refractory disease.

Crystalline Podocytopathy

In addition to the proximal tubular cells, monoclonal light chain can also be deposited in the podocytes. Unlike patient with light chain proximal tubulopathy (Fanconi syndrome) where proteinuria is generally mild, these patients present with acute kidney injury and massive proteinuria (8–14 g/d) (Akilesh et al. 2014; Nasr et al. 2006). Podocytes are swollen and the glomeruli are globally sclerotic and collapsed. In one case this was attributed pamidronate, but similar findings were described in another in which no bisphosphonate was given. In both patients, crystals of kappa light chain were also seen in the proximal tubules. In one case, coexisting cast nephropathy was present.

Crystalglobulinemic Glomerulonephritis

This is a rare complication of multiple myeloma where occlusion of blood vessel occurs as a result of crystalline deposition of monoclonal proteins (Gupta et al. 2015; Ball et al. 1993). It is sometimes called cryocrystalglobulinemia because the crystals can be seen precipitating out of cooling serum in vitro (Dotten et al. 1976). Typically, the crystals result in thrombosis of peripheral vessels resulting in digital ischemia and purpuric/petechial rashes. In some cases, occlusion of visceral vessels can occur. In the kidney, monoclonal light chain crystals may be seen occluding the glomerular capillary tuft and even into the intralobular arteries (Gupta et al. 2010). In severe cases, segmental and lobar arteries can be occluded (Leung et al. 2010). Electron microscopy may show electron-dense crystals with a substructure composed of parallel linear arrays with periodicity.

Other Glomerulopathies Observed in Multiple Myeloma

Collapsing FSGS with Pamidronate Therapy

Pamidronate and other bisphosphonates are used to prevent pathologic fractures, treat hypercalcemia, and may also provide benefits to the treatment of MM (Terpos and Rahemtulla 2004). Collapsing focal segmental glomerulosclerosis

(FSGS) has been reported as a complication of high-dose, intravenous bisphosphonate use especially with pamidronate. In a case series of seven patients who developed the collapsing variant of FSGS after exposure to pamidronate, six patients had a diagnosis of multiple myeloma (Markowitz et al. 2001). However, others have shown focal segmental glomerulosclerosis lesions in patients who had not received bisphosphonate including patients with just MGUS (Dingli et al. 2005). In some case, the monoclonal protein can be seen deposited in the kidney, thus suggesting a direct role of the monoclonal gammopathy.

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C3 Glomerulopathy

40

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Contents

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Abstract

C3 Glomerulopathy (C3G) defines a group of complement-mediated renal diseases that share specific features identifiable on kidney biopsy the hallmark of which is C3 dominance on immunofluorescence by at least two orders of magnitude greater than any other immunoreactant; electron microscopy is also specific. These features should prompt a thorough evaluation of the complement system that covers four domains: 1) genetic drivers of disease; 2) acquired drivers of disease; 3) biomarker profiling; and, 4) tests of complement function. The

aggregate picture afforded by these studies provides insight into disease status and can guide treatment. Although optimal disease-directed treatment has not be determined, most patients should receive angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker for their anti-proteinuric and nephro-protective effects. The value of anti-cellular immune suppression to target T and/or B cells is controversial. The role of complement abnormalities has focused attention on anti-complement therapies as potential treatments and it is well documented that some, but not all, patients respond to eculizumab with elevation of soluble C5b-9 being a potentially useful marker of a responder to this terminal pathway blocker. No specific data are available to inform decisions surrounding transplantation. The development of novel complement inhibitors is a high priority for these patients.

Keywords
C3 glomerulopathy · Dense deposit disease · C3 glomerulonephritis · Complement dysregulation · alternative pathway

Introduction

C3 Glomerulopathy (C3G) defines a group of complement-mediated renal diseases that share specific features identifiable on kidney biopsy. These features should prompt a thorough targeted evaluation of the complement cascade in affected patients. The hallmark of C3G is reflected in the nomenclature – on immunofluorescence (IF), C3 must be identified and scored at least two orders of magnitude higher than any other immuno-reactant. Electron microscopy (EM) is also specific; it must resolve deposits that can range in density from light to extremely dark and in location from within the pars densa of the glomerular basement membrane (GBM), to subendothelial, subepithelial, and intramesangial. The light microscopic (LM) findings, in contrast, are nonspecific and include a number of patterns of injury that range from membranoproliferative (MPGN) in 65–70% of cases to a spectrum of mild glomerular abnormalities, which with time can progress to irreversible crescentic scarring. Laser microdissection and mass spectrometry of C3G glomeruli have identified within the hallmark deposits, complement proteins, their breakdown products, a large variety of other serum proteins, and often, small amounts of immune complex, reflecting a disease process driven by complement dysregulation (Fig. 1) (Sethi et al. 2012).

Two major subgroups of C3G are recognized: C3 Glomerulonephritis (C3GN) and Dense Deposit Disease (DDD) (Fig. 2) (Sethi et al. 2012). Both subgroups share the IF criteria required to diagnose C3G – C3 positivity at least twofold greater than any other immunoreactant – but are differentiated by their EM findings. In C3GN, the EM deposits are light in color and often have the appearance of fluffy grey clouds within mesangial cells or as light, amorphous subendothelial or subepithelial humps. By comparison, in DDD the deposits are very dark and intramembranous and have been described as "sausage-shaped" or like Chinese calligraphy (Smith et al. 2011; Fakhouri et al. 2010; Servais et al. 2007; Pickering et al. 2013).

The glomerular C3 deposition reflects dysregulation of the alternative pathway of the complement cascade, (Nester and Smith 2013a) and while the importance of distinguishing C3GN and DDD by EM remains unclear, there is evidence that response to therapy and outcome of the two subtypes of C3G may be different (Xiao et al. 2014). This chapter has four goals: (1) to review the complement cascade, an understanding of which informs the pathogenesis of C3G; (2) to describe the evaluation of the C3G patient; (3) to present available treatment options; and finally, (4) to offer specific targets to ensure that care for these patients will improve.

The Complement Cascade

Triggering Complement Activity

The complement cascade is the cornerstone of innate immunity (Fig. 3). Comprised of over 45 proteins, it serves as one of the first lines of defense in an immune response. Its three initiating

a

		DDD	C3GN
Signs and Symptoms at Diagnosis	Average age of onset	14 years	30 years
	Proteinuria	91%	76%
	Hematuria	84%	88%
	Hypertension	54%	38%
	Nephrotic Syndrome	38%	27%
Acquired Drivers	C3 nephritic factors identified	80%	50%
Renal Failure	10 year progression to ESRD	50%	25%
	Receive kidney transplant	38%	18%
	Recurrence of disease after transplant	70%	60%

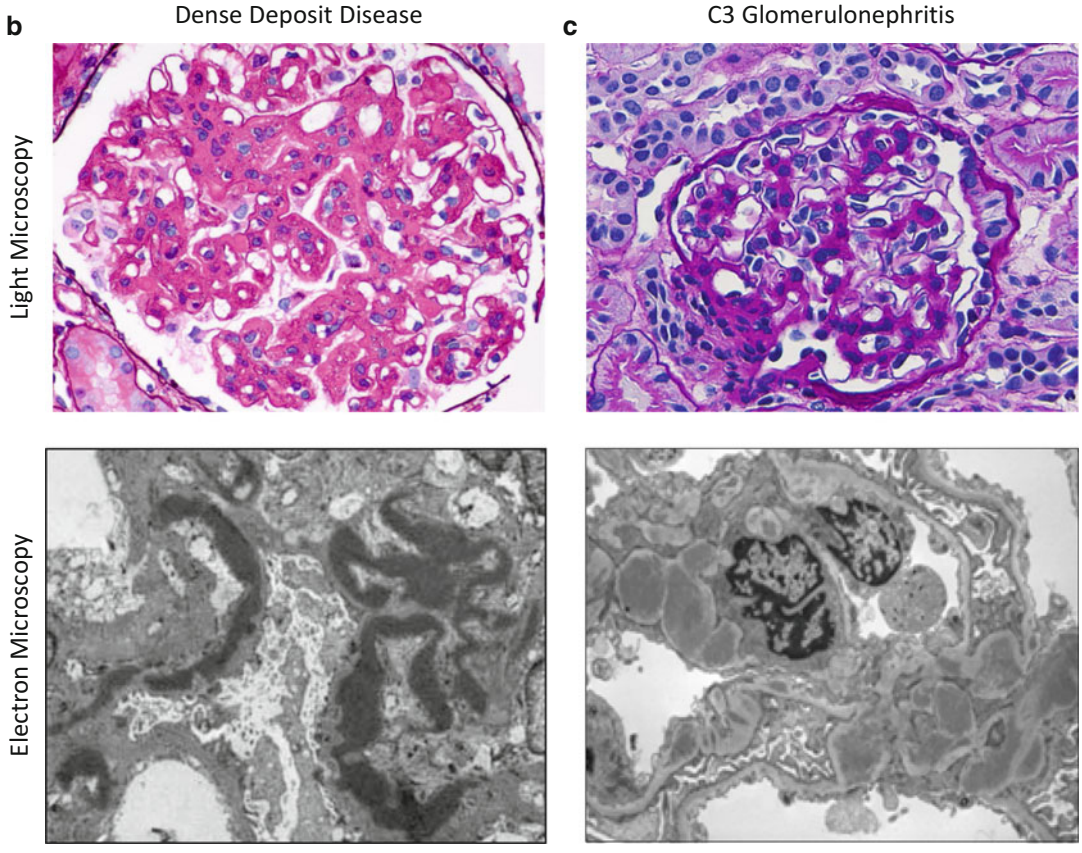


Fig. 1 (**a**) DDD and C3Gn are subtypes of C3G that progress to end-stage renal failure in a significant number of patients. Disease also recurs post-transplant highlighting the urgent need for a disease-specific treatment. (**b**) and (**c**) show the light and electron microscopic (EM) findings on biopsy in DDD and C3GN. Note the characteristic and disease-defining differences on EM (Medjeral-Thomas et al. 2014b; Servais et al. 2012; Lu et al. 2012)

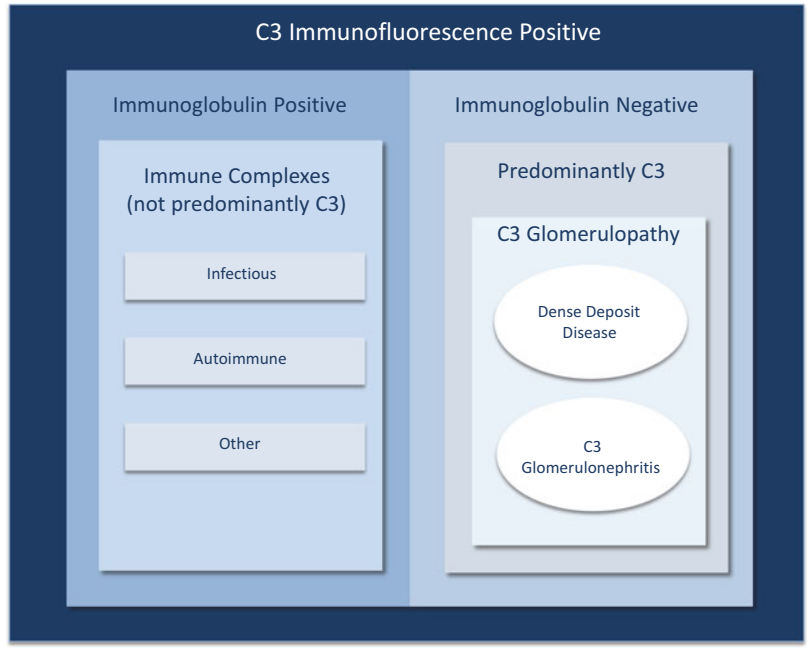


Fig. 2 C3G is identified using immunofluorescence (IF) to detect the presence of C3 in a renal biopsy. If C3 is detected, the pattern of injury can be further classified by identifying the presence of other immune complexes. If the presence of C3 is at least two-fold higher in magnitude than any other immuno reactant, the findings are consistent with C3G. EM can further refine the diagnosis as either DDD or C3GN (see Fig. 1) (Fakhouri et al. 2010)

pathways – the classical, lectin, and alternative – trigger and amplify any incipient complement reaction, leading to a coordinated anaphylatoxic, cell lytic, and inflammatory response (Walport et al. 2001). Several proteins acting at multiple points in the complement cascade regulate the location, duration, and magnitude of the response.

Activation of the classical and lectin pathways (CP and LP) generally requires immunoglobulin or carbohydrate, respectively, usually reflecting the presence of a pathogen. The CP is activated when C1q binds immunoglobulin on the surface of a pathogen, while the LP is initiated when a mannose-binding lectin recognizes pathogen-specific mannose-containing carbohydrates. Both pathways lead to formation of serine proteases that cleave C3 and are therefore known as C3 convertases. The C3 convertase of the CP and LP is C4b2a. It amplifies the initial complement response by cleaving C3 into C3a and C3b. The former is a potent anaphylatoxin, while the latter contains a reactive thioester that binds covalently and indiscriminately to neighboring proteins on cell surfaces or in the circulation, amplifying complement activity (Walport et al. 2001).

Activation of the alternative pathway (AP) is different. Rather than being dependent on protein recognition (CP, immunoglobulins; LP, carbohydrates), AP activity occurs spontaneously, albeit at a low level, reflecting properties of a reactive thioester in C3 that undergoes continual hydrolysis. This process, known as "tick-over," converts a small fraction of the circulating C3 into $C3_{H2O}$, which associates with factor B to form $C3_{H2O}Bb$, another C3 convertase capable of cleaving C3 to C3a and C3b (Law and Dodds 1997).

Common to both the C4b2a and $C3_{H2O}Bb$ proteases is their ability to generate additional C3b, which sustains and amplifies the complement response. In the presence of factor B massive amounts of C3bBb are formed, a powerful C3 convertase that cleaves all available C3 into C3a and C3b. The C3b that is generated (1) indiscriminately binds to cells, targeting them for opsonization; (2) forms more C3bBb to sustain and amplify the complement response; and (3) associates with extant C3bBb to generate a new protease, C3bBbC3b, that cleaves C5. By cleaving C5 to C5a and C5b, this C5 convertase triggers the terminal complement response. C5a, like C3a, is an anaphylatoxin, while C5b associates with C6, C7, C8, and C9 to form membrane attack complex (MAC), a lytic complex that destroys cells (Müller-Eberhard 1985).

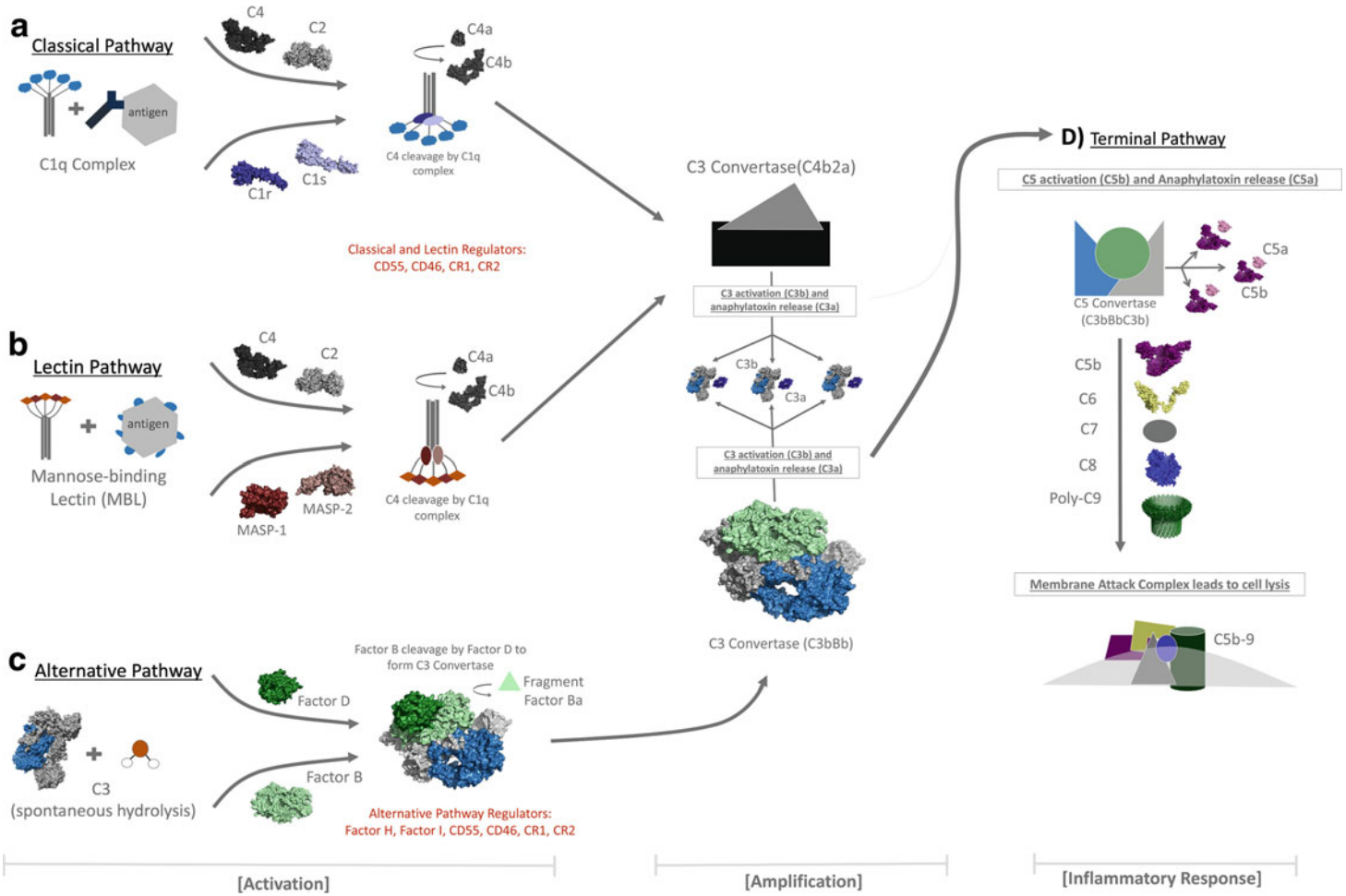


Fig. 3 Complement can be activated through three pathways. (**a**) The classical pathway (CP) is triggered when the serum C1 complex (C1q, C1r and C1s) interacts with antibody-antigen complexes. The induced conformational change in the C1 complex activates the C1s and C1r serine protease subunits, which cleave C4 to generate a reactive C4b that covalently binds to the surface in close proximity of the C1. Bound C4b binds C2 and renders it accessible for C1-mediated proteolysis. The formed complex, C4b2a, is the CP C3

Inadequate regulation of complement activity underlies several ultra-rare renal diseases, one of which is C3G (Mayilyan 2012)

Regulating Complement

Regulation of complement activity is a complex multifaceted process. In general, complement regulators can be considered fluid phase, membrane bound, or complement-receptor regulators (Zipfel and Skerka 2009). Because C3G is specifically associated with dysregulation of the AP, an understanding of the regulation of this pathway is critical to understanding the etiology and progression of the disease.

The most important regulator of complement in the fluid phase is factor H (FH), a protein built on a motive of 20 short consensus repeats (SCRs, also called complement control modules, CCMs, or sushi domains). FH controls C3 convertase by accelerating the decay of existing C3bBb (decay accelerating activity, DAA), inhibiting the conversion of C3bB to C3bBb, and acting as a cofactor for factor I-mediated breakdown of C3b into iC3b (Lachmann and Muller-Eberhard 1968). Its fours N-terminal SCRs bind C3b and are important for fluid-phase control of complement activity, while its two C-terminus SCRs serves as a target recognition domain for the surface of host cells, thereby preventing unwanted C3-mediated damage on self-surfaces. This duality makes FH as both a fluid phase *and* membrane bound regulator (Józsi and Zipfel 2008). Complement factor H-like 1 (FHL1), an alternative splicing variant of FH, contains only the first seven SCRs of FH and plays a role in fluid phase AP regulation. Because it lacks the C-terminal host-recognition domain of FH, FHL1 does not bind well to self-surfaces; however, some bacteria have developed methods of acquiring FHL1 as a decoy to evade host complement activity (Fig. 4) (Zipfel and Skerka 1999).

Cell-membrane-bound complement regulators include decay accelerating factor (DAF, also known as CD55), membrane cofactor protein (MCP, also known as CD46), complement receptor 1 (CR1), and complement receptor 2 (CR2, also known as CD21). Apart from their location on the surface of host cells, these proteins also differ from fluid-phase regulators by their ability to regulate complement components from any pathway. Membrane-bound regulators control not only AP convertases, but also the convertases formed by CP and LP activity (Zipfel and Skerka 2009).

Terminal complement activity is inhibited by MAC-inhibitory protein (MAC-IP). Also known as membrane-inhibitor of reactive lysis (MIRL), protectin, and CD59, this protein is attached to cells through a glycophosphatidylinositol (GPI) anchor and prevents C9 polymerization, a requisite process for MAC formation. Viruses such as HIV and cytomegalovirus incorporate CD59 into their viral envelope to prevent complement-mediated lysis (Watts et al. 1990)

Fig. 3 (continued) convertase (Perry et al. 2013; Croll and Andersen 2016; Budayova-Spano et al. 2002). (**b**) The lectin pathway (LP) recognizes carbohydrates on the surface of bacteria. Like the CP, the LP leads to the formation of a C4b2a C3 convertase (Harmat et al. 2004; Gingras et al. 2011; Milder et al. 2006; Mortensen et al. 2015). (**c**) The alternative pathway (AP) is spontaneously activated by the hydrolysis of C3 in a process known as 'tick over'. Tick over leads to formation of a pro-convertase complex C3bB, which in the presence of the protease factor D is activated into C3bBb, the C3 convertase of the AP. Note that regardless of the method of activation (CP, LP or AP), once a C3 convertase is formed, C3bBb is central to the amplification step (Bajic et al. 2013; Forneris et al. 2010). (**d**) Amplification culminates in triggering of the terminal complement cascade, which begins with the formation of the C5 convertase (C3bBbC3b). This convertase cleaves C5 to generate activated C5 (C5b). Its association with C6, C7, C8, and a poly C9 complex leads to formation of the membrane attack complex (MAC), which initiates cell lysis. Co-incidental to this process, the activation of both C3 and C5 releases anaphylatoxins (C3a and C5a, respectively), which contribute to the overall inflammatory response of the complement system (Dudkina et al. 2016; Lovelace et al. 2011; Colley et al. 1999; Aleshin et al. 2012) (Models are not available for structures represented as geometric shapes.)

Evaluating the Patient with C3G

The underpinning of C3G is dysregulation of the AP of complement, either genetic or acquired. Complement dysregulation can be quantitated by measuring the levels of complement proteins and their cleavage products in the serum, a process known as complement biomarker profiling, and by assessing activity of the complement system through a number of functional assays. Because of the complexity of the system, a *comprehensive* evaluation is required to generate a composite picture of the site and degree of abnormal activity. Detailed studies are completed that cover four domains: (1) genetic drivers of disease, (2) acquired drivers of disease, (3) biomarker profiling, and (4) tests of complement function. The *aggregate* picture afforded by these studies can provide insight into the disease status of a patient with C3G and can guide treatment.

Drivers of Disease

Genetic Drivers of Disease

Several families segregating well-studied pathogenic variants (mutations) in complement genes or novel fusion proteins definitively implicate complement dysregulation in the pathogenesis of C3G. In addition, comprehensive genetic studies show that up to 40% of C3G patients are enriched for rare and/or novel variants in both C3 convertase and AP regulator genes. Many patients carry multiple variants, suggesting a complex and multifactorial genetic contribution to disease (Abrera-Abeleda et al. 2011). At the molecular level, the impact of these variants is often unclear (they are typically called variants of uncertain significance, VUSs), a limitation reflecting the implausibility of completing functional studies on every VUS. As an alternative, molecular modeling often can be used to demonstrate the impact of these variants on protein structure, and by inference, their impact on function and/or regulation of C3 convertase activity (Bu et al. 2016).

Most C3G patients also carry specific haplotypes of several complement genes. These "risk" alleles are associated with increased C3 "tick over" but whether this increase in basal spontaneous activation is germane to disease is not clear (Abrera-Abeleda et al. 2011; Sethi et al. 2012a). To date, a good genotype-phenotype understanding of C3G is lacking.

Especially germane to C3GN is the *CFHR* family of genes named sequentially *CFHR-1* to *CFHR-5* (Fig. 4). The exceptionally abundant regions of high sequence homology across this gene family reflect ancestral gene duplication

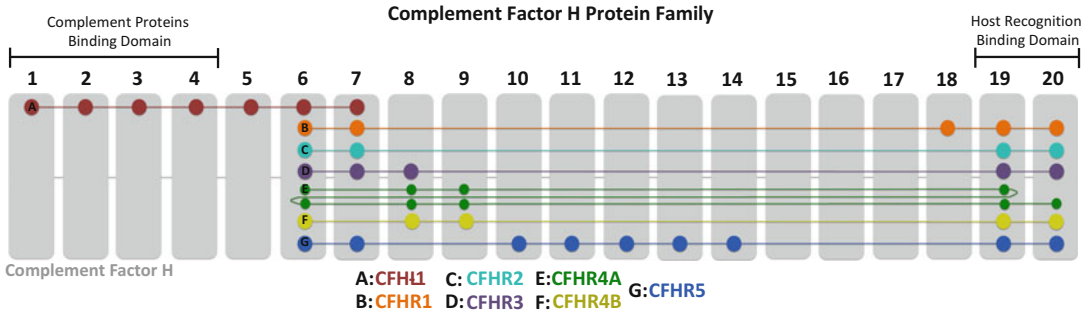


Fig. 4 The Factor H protein family shows high sequence, structure and functional homology. Shown is the relationship between the Complement Factor H-Related proteins (FHR1-5) and Factor H. Factor H is comprised of 20 short consensus repeat (SCRs, also known as sushi domains or complement control modules (CCM)), which are represented as gray rectangles. CFH Like-1 (FHL1) is a splice variant of FH and with the exception of 4 carboxy-terminal amino acids, has 100% sequence identity to FH. The proteins in the FHR family, of which there are 5, have from 4 to 9 SCRs. Each individual SCR is most similar to specific SCRs of FH, as indicated by their position in the gray rectangles. The Factor H protein family is integral to complement control. Mutations in the *CFH* gene and genetic rearrangements in the *CFHR* gene family have been identified in families with C3G (Zipfel et al. 2002)

events and make this genomic region prone to rearrangement by nonallelic homology recombination (NAHR) (Józsi and Zipfel 2008; Zipfel et al. 2002). For example, a common *CFHR* copy number variation (CNV), the homozygous deletion of *CFHR3-CFHR1*, is a known *risk factor* for atypical hemolytic uremic syndrome but is *protective* against DDD and age-related macular degeneration (Zipfel et al. 2007).

Several *CFHR2-CFHR5* rearrangements have been reported that create novel genes and lead to C3GN (Malik et al. 2012; Medjeral-Thomas et al. 2014a). The general mechanism underlying disease pathogenesis is a dominant gain-of-function property of encoded novel proteins that alters normal formation of heteromeric FHR protein complexes. Formation of abnormal FHR protein complexes is favored and protein combinations are formed that typically do not exist. These abnormal complexes impair complement regulation and lead to disease (Goicoechea de Jorge et al. 2013)

Acquired Drivers of Disease

The most commonly identified acquired drivers of disease are autoantibodies to C3bBb known as C3 nephritic factors (C3Nefs). These immunoglobulins stabilize membrane-bound and fluid-phase AP C3 convertase, protecting it from normal regulatory mechanisms and increasing its half-life up to tenfold (Spitzer et al. 1969; Mold and Medof 1985). As a result, AP activity is greater and serum C3 is consumed. C3Nefs are detected in up to 80% of patients with DDD and are often associated with exceedingly low plasma C3 levels. The trigger for their development is not known (Nester and Smith 2013a; Daha et al. 1976). They are less frequently seen in patients with C3GN (Fig. 5).

C5Nefs or autoantibodies that stabilize C5 convertase (C3bBbC3b) are also highly likely to exist, although their presence is technically difficult to validate because of the challenge associated with building C5 convertase. In fact, recent evidence suggests that a preassembled C5 convertase may not exist. Rather, current data suggest that C5 binds to C3b and in so doing, may induce a substantial conformational to C3b that leads to C5 cleavage by C3bBb (Jore et al. 2016).

In a small percentage of C3G patients, autoantibodies to FH, FB, and C4b2a (the C3 convertase of the CP) are reported (Blanc et al. 2015; Strobel et al. 2010; Chen et al. 2011; Tanuma et al. 1989; Seino et al. 1990; Halbwachs et al. 1980)

Biomarker Profiling and Tests of Complement Function

Biomarker Profiling

Biomarker profiling is an important tool that provides insight into the ongoing disease process. Patients with both C3GN and DDD have low C3 serum levels, reflecting overconsumption of C3 driven by C3 convertase formation and amplification. FB cleavage products (Bb and Ba) often validate C3 convertase activity, with low levels of plasma FB and high levels of Bb consistent with ongoing C3 convertase activity. To quantitate activity of the terminal complement pathway, C5 through C9 levels can be measured. With increased C5 convertase activity, C5 levels are lowered and C5a levels are increased; levels of soluble C5b-9 (sC5b-9) are also elevated (Pickering et al. 2013; Zhang et al. 2014).

Biomarker differences provide added information. Both properdin and sC5b-9 are more frequently altered in C3GN than in DDD (Xiao et al. 2014). Reduction of the former is consistent with increased stabilization of the C3 convertase, C3bBb, potentiating the formation of more C3bBb and increasing the likelihood of C5 priming and cleavage, thus elevating levels of sC5b-9. These differences may have clinical relevance, as elevation of sC5b-9 and the implied deregulation of the terminal complement pathway would suggest that terminal complement blockade might be beneficial as a treatment strategy (Nester and Smith 2013b). Conversely, in the absence of indication of terminal activity, more proximal complement control would be predicted to be beneficial. Unfortunately, interlaboratory differences in sC5b-9 measurements confound our difficulty to assess the value of this assay (Bu et al. 2015).

When detailed biomarker data are obtained, they are predictive of the underlying pathology (DDD vs. C3GN) in over 90% of cases. In

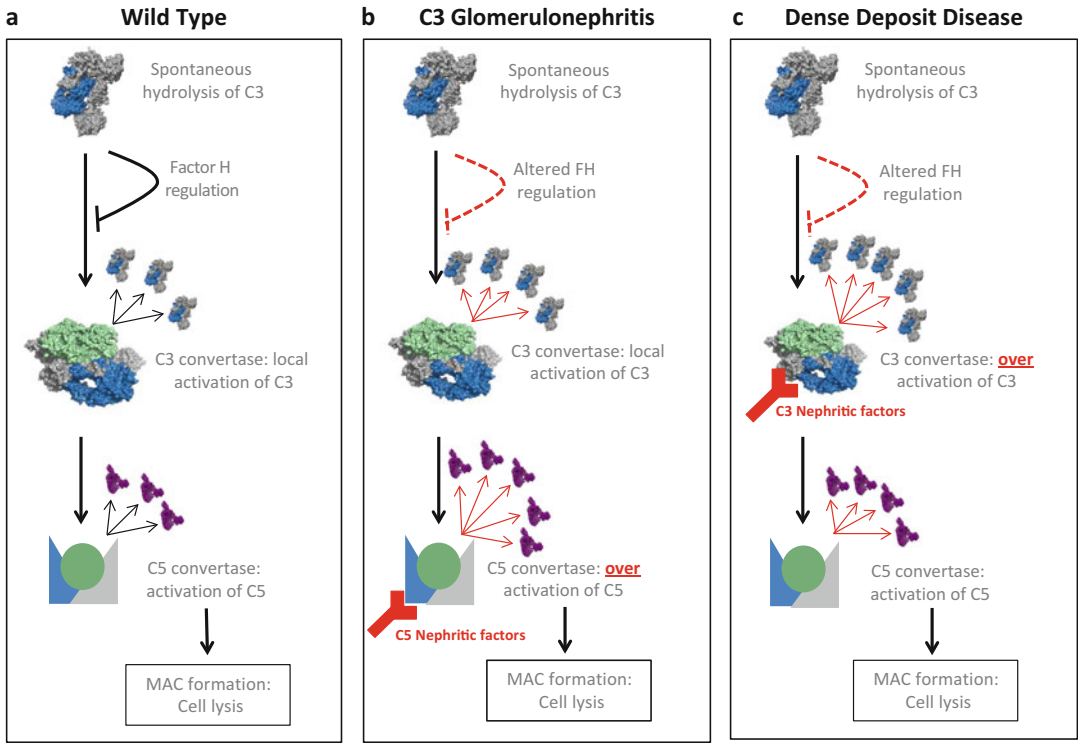


Fig. 5 The alternative pathway (AP) plays a central role in C3G. (**a**) Normally, AP activity is finely controlled by Factor H (see Fig. 4) and other proteins collectively known as Regulators of Complement Activation (RCA). In C3G, uncontrolled AP activity occurs in the fluid phase and in the glomerular microenvironment, secondary to dysregulation of the C3 and C5 convertases (see Fig. 3). (**b**) and (**c**) While a complete understanding of C3G is lacking, biomarker and functional data support the existence of important differences between DDD and C3GN in the relative degree of dysregulation of these two convertases. In DDD, C3 convertase dysregulation tends to be greater than C5 convertase dysregulation, while in C3GN, the reverse is true. Autoantibodies to C3bBb (C3 nephritic factors) and C3bBbC3b (C5 nephritic factors) have been identified in both DDD and C3GN patients. These acquired drivers of disease lead to C3G by prolonging the half-life of convertases, shielding them from normal regulatory mechanisms. The trigger that leads to autoantibody formation is not known (Xiao et al. 2014; Forneris et al. 2010; Aleshin et al. 2012).

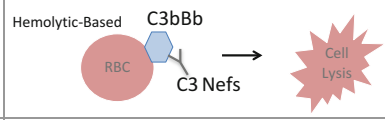
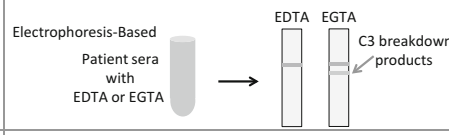
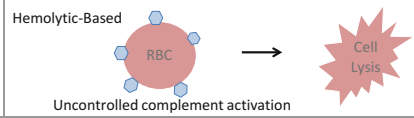
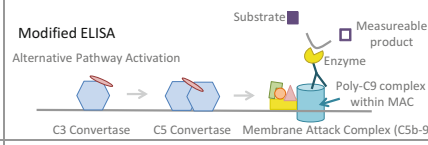
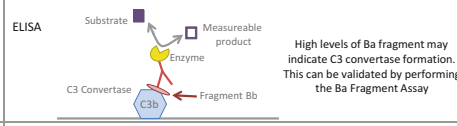
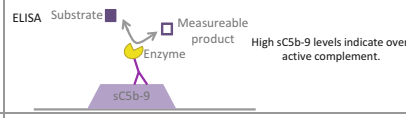
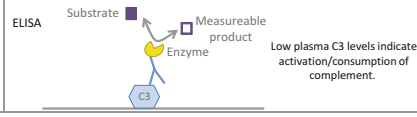
aggregate, biomarker data support an important difference between DDD and C3GN. As a general rule, the difference is reflected in differential activity of the C3 and C5 convertases. In DDD, C3 convertase dysregulation is greater than C5 convertase dysregulation, while in C3GN the reverse is true (Fig. 5) (Xiao et al. 2014)

Tests of Complement Function

Several assays of complement activity should be included in the patient evaluation (Table 1). These assays provide an overview of the entire complement system (CH50, APH50) or specific portions therein. Expert interpretation of the assays is required in the context of the biomarker data, genotypic data, and autoantibody data. For example, a C3Nef-positive patient with DDD and massive consumption of C3 can have a normal hemolytic assay (false negative) secondary to the lack of substrate (C3) in the assay.

Clinical presentation often manifests as proteinuria, hematuria, edema, hypertension, and fatigue (Xiao et al. 2014; Medjeral-Thomas et al. 2014b). If C3G is suspected, functional testing, biomarker profiling, genetic testing, and testing for the presence of acquired drivers should be

Table 1 Functional Assays are vital to proper diagnosis and treatment of a patient. Acquired drivers, complement pathway activity, and biomarkers should be considered along with genetic screening to make informed clinical decisions. (**a**) There are two methods to test for the presence of C3 nephritic factors. The hemolytic approach uses sheep erythrocytes as non-activators of complement. The Electrophoresis-based approach detects C3 breakdown products and infers the presence of C3 nephritic factors. (**b**) Complement pathway activity can be measured with either hemolytic or ELISA-based methods. These assays measure the degree of dysregulation in the patient's serum, but does not elucidate the driver(s) of dysregulation. (**c**) Biomarker assays help determine where the dysregulation is occurring. The Bb Fragment assay measures the presence of cleaved Factor B and determines how often the C3 convertase is forming, the sC5b-9 assay determines the activity of the C5 convertase, and the plasma C3 levels indicate the level of C3 consumption (Zhang et al. 2014)

Assay	(Patient) Input	Methodology	Readout
C3 Nephritic Factors	IgG		Hemolysis
C3 Nephritic Factors	Serum		iC3b
Hemolytic Assays of Complement Activity	Serum		Hemolysis
Alternative Pathway Functional Assay (APFA)	Serum		Immunofluorescence
Complement Bb Fragment	Serum		Immunofluorescence (Ba Fragment of Factor B)
Soluble C5b-9	Serum		Immunofluorescence (sC5b-9)
Complement C3 Plasma Level	Serum		Immunofluorescence (Plasma C3)

completed and analyzed together in order to create a unified understanding of a patient's disease profile. While disease progression is not yet fully understood, the degree of complement dysregulation and genetic background can predict the likelihood of continued deterioration of kidney function and are helpful in considering treatment options. The course of disease varies greatly with approximately 50% of patients progressing to ESRD within 10 years of diagnosis, while in others renal function remains relatively stable with conservative treatment (Nester and Smith 2013a; Sethi et al. 2012b)

Treating the C3G Patient

Supportive Treatment

Optimal disease-directed treatment for C3G has yet to be determined and as a consequence a variety of therapies are in use. Most patients should receive angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blocker (ARB) for their well-documented anti-proteinuric and nephro-protective effects. Although this treatment is not disease-specific, from the limited data offered from the French C3G Cohort, their use is associated with better renal survival ($P<0.0001$). Similarly, lipid-lowering agents are likely to be useful as needed in C3G (Servais et al. 2012).

The role of plasma therapy is controversial. The use of plasma exchange in a 15-year-old girl with C3Nefs was successful in removing these autoantibodies from the circulation when DDD recurred in her allograft; however, thrice weekly plasma exchange was required to keep C3Nefs levels down and that was not sustainable (Kurtz and Schlueter 2002). In comparison, in patients with *CFH* mutations, the use of plasma infusion to compensate for loss of function in FH has been successful (Licht et al. 2006)

Cellular Immune Therapy

The use of anticellular immune suppression in C3G to target T and/or B cells should be beneficial by: (1) limiting the anaphylatoxic effects of C3a and C5a, (2) inhibiting immune cell reaction and inflammation, and (3) reducing antibody production. However, results are far from clear. Medjeral-Thomas et al. describe a cohort of 80 C3G patients (21 with DDD; 59 with C3GN) with a 10-year renal survival less than 50%. Twenty-nine percent (29%) of these patients progressed to end-stage renal disease (ESRD) after a median follow-up of 28 months, with no differences in renal outcome between DDD and C3GN patients. Thirty-two of these patients received immuno-suppressive treatment, either with corticosteroids alone (22 patients) or other drugs (10 patients), and by univariate and multivariate analysis these treatments failed to predict the occurrence of ESRD (Medjeral-Thomas et al. 2014b).

Servais et al. reviewed 85 patients with C3G (29 with DDD; 56 with C3GN). Also included were 49 patients with membranoproliferative glomerulonephritis type 1. The 10-year renal survival in the entire cohort was 63% without differences between groups, although when the analysis was restricted to adult patients, those with DDD had a poorer prognosis than the other two groups. Immuno-suppressive treatment did *not* improve renal survival (Servais et al. 2012).

In contrast, a retrospective study by the Spanish Group for the Study of Glomerular Diseases (GLOSEN) has reported that immuno-suppressive treatment significantly lowers the number of patients who progress to ESRD. The study cohort was comprised of 60 patients in whom a complete registry of treatments was available over a median follow-up period of 47 months. Forty patients received immuno-suppressive treatment (22 with corticosteroids and mycophenolate mofetil, 18 with other immuno-suppressive treatment regimens such as corticosteroids alone or corticosteroids plus cyclophosphamide). Outcomes were compared to 20 patients who did not receive immuno-suppressive treatment. The number of patients developing ESRD was significantly lower among treated as compared to untreated patients (3 vs. 7 patients, respectively), with no patient in the corticosteroids plus mycophenolate mofetil group doubling their serum creatinine or developing ESRD, as compared with 7 (significant) and 3 (not significant), respectively, patients treated with other immuno-suppressive treatment regimens. Renal survival (100%, 80% and 72% at 5 years) and the number of patients achieving clinical remission (86%, 50% and 25%) were significantly higher in patients treated with corticosteroids plus mycophenolate mofetil as compared to patients treated with other immunosuppressive regimens and untreated patients, respectively.

Although a prospective study is needed, these results suggest that immuno-suppressive treatment, and in particular the combination of corticosteroids plus mycophenolate mofetil, may be

beneficial in the treatment of C3GN (Rabasco et al. 2015).

Anticomplement Therapy

As data have accumulated to support the central role of complement abnormalities in the pathogenesis of C3G, attention has focused on anticomplement therapies as potential treatments. Animal models predict an anticomplement response, and several case reports support the utility of anti-C5 therapy in at least a subset of C3G patients. In the single trial to date using eculizumab for the treatment of C3G (open-label, proof-of-concept, efficacy-and-safety study), Bomback et al. treated 3 DDD patients (one with a renal transplant) and 3 C3GN patients (two with renal transplants) with eculizumab every other week for 1 year. All had proteinuria >1 g/d and/or acute kidney injury (AKI) at enrollment. Genetic and complement function testing revealed a pathogenic variant in *CFH* and *MCP* in one subject each and C3Nefs in three subjects.

After 12 months of therapy, two patients showed significantly reduced serum creatinine (DDD patient #1 and C3GN patient #3), one patient had a marked reduction in proteinuria (DDD patient #3), and one patient with stable laboratory parameters had histopathologic evidence of improvement (C3GN patient #3). In all patients with elevated soluble C5b-9, treatment normalized terminal pathway activity. The authors concluded that some but not all patients respond to eculizumab and that an elevation of soluble C5b-9 could be a potentially useful marker of a responder (Bomback et al. 2012)

Transplant

No specific data are available to inform decisions surrounding transplantation in C3G, and recommendations are based on expert opinion and limited case reports. A *comprehensive* evaluation of the complement system should be part of the pretransplant evaluation to provide insight into the degree of ongoing complement activity and to potentially guide treatment options (e.g., the use of eculizumab). Disease recurs in 70–90% of allografts within 5 years, with an allograft failure rate of ~50% (Pickering et al. 2013; Medjeral-Thomas et al. 2014b; Lu et al. 2012). This bleak outlook speaks to the necessity for new complement-targeting therapies for these patients.

The Future for C3G Patients

The development and trial of novel complement inhibitors is a *high priority* for C3G patients. These trials must enroll well-phenotyped patients, with biopsy classification into DDD and C3GN cohorts. In all patients, a detailed genetic and functional evaluation of the complement cascade must be obtained prior to therapy, with interval complement studies during treatment to interpret the anticomplement effect of new drugs. In addition, our understanding of C3G must continue to evolve. The mechanisms of control complement in unique microenvironments pertinent to C3G like the glomerular endothelial pores require in-depth study and may offer new insights into C3G and its treatment.

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Hemolytic Uremic Syndrome

41

Christine B. Sethna and Shari Gurusinghe

Contents

Abstract

Shiga-toxin producing *E. coli*-hemolytic uremic syndrome (STEC-HUS) is a rare condition defined by the prodrome of STEC-associated diarrhea followed by the triad of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury (AKI). *E. coli* 0157: H7 is the most common cause of STEC-HUS, but other bacteria trigger HUS as well. Only a small portion of those with STEC infection will go on to develop HUS. Ground beef, water sources, unpasteurized foods, contaminated fruits and vegetables, and person-to-person contact are the vehicles of transmission. Toxin released from the bacteria enters the blood stream where it binds to receptors in the endothelium of kidney and blood vessels, leading to platelet-thrombi, anemia, and vascular injury. The diagnosis is confirmed by evidence of STEC or toxin in the stool and thrombocytopenia, hemolytic anemia (presence of schistocytes, low haptoglobin, elevated

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lactate dehydrogenase) and AKI. Treatment is primarily supportive, although newer treatments such as eculizumab have been recently tried. The prognosis is generally good and most patients recover. The mortality rate is less than 5%; however, 30% are left with long-term sequelae. The pathogenesis, clinical presentation, diagnosis, treatment, and prognosis are presented in detail in this chapter.

Keywords

Thrombotic microangiopathy (TMA) · Hemolytic uremic syndrome (HUS) · Diarrhea-associated HUS · Typical HUS · Shiga-toxin producing *E. coli* (STEC) · German outbreak · Eculizumab

History

In 1898, Kioshi Shiga was the first to describe that *Shigella dysenteriae* type 1 was the pathogen that caused epidemic dysentery (Shiga 1898). Over the next century, researchers came to discover that the bacteria released a protein with endotoxic activity that targeted the vascular endothelium, named "shiga-like toxin" that later became known as "shiga-toxin (Stx)." In 1977, Konowalchuk and colleagues found that certain strains of *E. coli* released proteins that were cytotoxic to vero cells and thus were named "verotoxins" (Konowalchuk et al. 1977). It was later realized that Stx and verotoxin described the same proteins.

Hemolytic uremic syndrome was first reported in 1955 by Gasser et al. in a case-series of five Swiss children with small-vessel renal thrombi, thrombocytopenia, and hemolytic anemia (Gasser et al. 1955). In 1968, even before knowledge of STEC, Barnard and Kibel speculated that enteric *E. coli* infections might be the trigger for HUS (Kibel and Barnard 1968). In 1975, Kaplan et al. postulated that a HUS outbreak was likely due to an environmental factor such as an infectious agent (Kaplan et al. 1975). It was not until 1983 that the connection between HUS and STEC was confirmed. Karmali et al. reported in *The Lancet* cases of HUS with cytotoxin-producing *E. coli* cultured in the stool (Karmali et al. 1983). They published a report in 1985 that described six serogroups of *E. coli*, including 0157:H7, that were associated with HUS (Karmali et al. 1985). Since then, multiple outbreaks of HUS due to *E. coli* 0157:H7 have been described. In 2011, a large outbreak in Germany with *E. coli* O104:H4 showed that enteroaggregative *E. coli* (EAEC) could also cause HUS after acquiring the capacity to produce Stx.

Classification

Thrombotic microangiopathy (TMA) describes the pathologic finding of arteriolar thrombi associated with intimal swelling and fibrinoid necrosis of the vessel wall that is present in both HUS and thrombotic thrombocytopenic purpura (TTP) (Trachtman 2013; Mele et al. 2014). Previously, these two terms were used interchangeably and there was much debate as to whether HUS and TTP should be regarded as two distinct disorders or whether they should be considered as two manifestations of the same syndrome (Pollock et al. 2008). Although HUS and TTP have different mechanisms of pathogenesis, they are difficult to distinguish solely on clinical presentation, as patients with HUS have demonstrated extrarenal organ dysfunction. Additionally, patients with TTP have often developed kidney injury. The development of new pathophysiological mechanisms allowed for these syndromes to be distinguished by molecular features (Noris et al. 2012). Patients with TTP have been shown to have decreased levels of ADAMTS13, due to autoantibodies that inhibit its activity or ADAMTS13 gene defects. ADAMTS13 is a plasma metalloprotease, which results in the cleavage of the von Willebrand factor and reduced levels of this enzyme results in increased activation of platelets and thrombosis in arterioles and capillaries (Noris et al. 2012; Cataland and Wu 2013) (see ▶ Chap. 43, "Thrombotic Thrombocytopenic Purpura, Genetic and Secondary").

The current definition of HUS includes a packed-cell volume less than 30%, evidence of erythrocyte lysis on a peripheral-blood smear, a

serum creatinine that is higher than the age specific upper limit, and a low platelet count (less than 150 × 10^9/L) (Tarr et al. 2005).

Traditionally, HUS has been classified as "diarrhea positive (D+)" or "diarrhea negative (D−) HUS" where D+ HUS was associated with "typical HUS" and D− HUS was associated with "atypical HUS (aHUS)." However, this classification system is flawed as 25–30% of aHUS cases are triggered by diarrhea (Canpolat 2015).

HUS is currently classified as STEC-HUS (or typical HUS), atypical nonfamilial HUS and atypical familial HUS. Typical HUS is triggered by STEC, while atypical nonfamilial HUS occur secondary to infections, medications, or disease such as HIV infection, cyclosporine, and systemic lupus erythematous, respectively. Approximately, 5% of atypical, nonfamilial HUS cases are due to neuraminidase-producing *Streptococcus pnuemoniae*. This entity is categorized as either pneumococcal-HUS or neuraminidase-associated HUS (Mele et al. 2014). Familial atypical HUS is predominantly associated with genetic anomalies in complement regulatory proteins (Kelleher et al. 1996; Lapointe et al. 1999; Tarr et al. 2005; Trachtman 2013).

Epidemiology

STEC is responsible for 90% of pediatric HUS cases with a reported annual incidence of 2–3 cases per 100,000 children, thereby meeting the official rare disease designation (Canpolat 2015). Children under the age of 5 years old are the most susceptible population with a peak incidence of six cases per 100,000 children. Girls have been found to be affected more frequently than boys and it affects all racial and ethnic groups, although the incidence is lower among African Americans (Cheung and Trachtman 2014). Studies have found that there is a rough correlation between distance from the equator and HUS frequency within the northern hemisphere (Cummings et al. 2002; Jernigan and Waldo 1994; Tarr and Hickman 1987; Thomas et al. 1993). Although STEC-HUS occurs globally, countries with less developed medical services have reported higher rates of incidence (Keir 2015). Some studies have found that rural populations in the United States are at higher risk of *E.coli* O157:H7 infection than urban populations (Crump et al. 2002; Haack et al. 2003). Additionally, seasonal variation occurs as it is more commonly observed in warmer months (Boyce et al. 1995).

Particular regions in South America have reported much higher rates of STEC-HUS, especially Argentina, where there is a five- to tenfold difference in incidence compared to North America. STEC-HUS is endemic in Argentina and is the leading cause of AKI in children. It is also one of the most common causes of chronic kidney disease (CKD) where 20–80% of all pediatric kidney transplants have been due to STEC-HUS (Palermo et al. 2009). Interestingly, in Mexico, there have been no reported cases of *E.coli* O157:H7-induced HUS or hemorrhagic colitis. When analyzing serum and maternal milk samples from a sample of Mexican adults and infants, Navarro et al. found that 69% of these samples contained antibodies against the O157 lipopolysaccharide (LPS), indicating that this may be an explanation as to why there have been no reports of *E.coli* O157:H7-associated diseases (Navarro et al. 2003).

Cases of STEC-HUS may be sporadic or clustered in epidemic outbreaks. One of the largest outbreaks to date occurred in Northern Germany in 2011 when 3816 patients were infected by *E.coli* O104:H4 resulting in 845 patients developing HUS and 54 deaths. Initially, *E.coli* O157:H7 was believed to be responsible for the outbreak. However, it was later discovered that the highly antibiotic resistant, enteroaggregative strain *E.coli* O104:H4 was responsible. Interestingly, almost all of the affected individuals were adults (~90%) with a median age of 42 years and most individuals were of a high socioeconomic status (Canpolat 2015; Borgatta et al. 2012). Two-thirds of affected individuals were women and a larger number of young to middle-aged women were affected compared to previous epidemics (Borgatta et al. 2012; Mele et al. 2014). Other European countries were also affected during this outbreak including Austria, Czech Republic, Denmark, France, Greece, Luxembourg, Netherlands, Norway, Poland, Spain, Sweden, and the

United Kingdom (Borgatta et al. 2012). As demonstrated by the Northern German outbreak, there has been an increasing prevalence of non-O157 serotypes responsible for the development of STEC-HUS including the O8, O26, O45, O103, and O145 strains (Johnson et al. 2006).

Recently, there have been two multistate outbreaks occurring within the United States. In 2016, 46 individuals were infected by *E.coli* O121 or O26 of whom 13 were hospitalized and 1 developed HUS. The median age of infected individuals was 18 years old, and 80% of affected individuals were female. The source was identified to be flour produced by the General Mills facility in Kansas City, Missouri. As a result of the outbreak, General Mills issued a flour recall (CDC 2016a). Another recall was issued for alfalfa sprouts produced by Jack & The Green Sprouts of River Falls. Eleven individuals were infected by *E.coli* O157, none of whom developed HUS (CDC 2016b).

The gastrointestinal tract of cattle has been deemed to be the most important reservoir of STEC. However, *E.coli* has also been isolated from deer, sheep, goats, horses, dogs, birds, and flies (Mele et al. 2014). The transmission of STEC generally occurs through the consumption of contaminated food where most foodborne outbreaks have been due to consumption of ground beef and unpasteurized milk (Canpolat 2015). Therefore, the high incidence of STEC-HUS in Argentina may largely be explained by their extensive cattle farming and heavy meat consumption (Mele et al. 2014). Over the past few years, there have been a growing number of STEC infections due to contaminated fruits and vegetables (Canpolat 2015). Fresh produce including romaine lettuce, ready-to-eat salads, apple cider, and unpasteurized apple juice have accounted for several STEC infections (CDC 2016b; Mele et al. 2014). Although contamination in produce may be due to cross-contamination from meat products, direct contamination from wild or domestic animals may also be responsible (Mele et al. 2014). The 2006 spinach outbreak in North America had dramatically higher rates of hospitalization (51%) and HUS (16%). The strain responsible was an emerging subpopulation of the O157:H7 serotype that acquired critical microbial virulence factors that likely contributed to the more severe disease. The particular clade associated with this outbreak has been shown to have a higher frequency of carrying both the stx2 and stx2c genes within its genome. However, this is not the sole contributing factor and the basis for its increased intrinsic virulence is not fully understood (Manning et al. 2008). Additionally, the large outbreak in Germany was traced to fresh sprouts produced in a farm located in Lower Saxony (CDC 2016b). The European Food Safety Authority reported that fecal-contaminated fenugreek seeds from an exporter in Egypt were responsible for the outbreak. This demonstrated that sprouts pose a significant hazard as trace amounts of bacteria present in seeds may multiply during germination resulting in the production of large amounts of toxins (Mele et al. 2014).

STEC O157 infections have also occurred from the consumption of contaminated water. In October 1992, thousands of individuals in Swaziland were infected by *E.coli* O157 after drinking untreated river water, which contained washed up carcasses of cattle (Isaacson et al. 1993). Direct transmission from one person to another including from mother-to-baby and animal-to-human has also been observed (Canpolat 2015). Unfortunately, person-to-person transmission generally occurs in settings of vulnerable populations such as daycare and chronic care facilities (Mead and Griffin 1998).

Microbiology

E.coli O157:H7 is the most common strain that causes STEC-HUS (Tarr et al. 2005). However, non-O157:H7 serotypes are becoming an increasingly prevalent cause of HUS. These serotypes include the O111:H8, O103:H2, O123, O26, O145, and O104:H4 (Mele et al. 2014). From 2000 to 2010, the incidence of infection caused by non-O157 serotypes has increased from 0.12 per 100,000 to 0.95 per 100,000, respectively. This increase in incidence is largely due to an increase in the number of clinical laboratories that utilize culture-independent tests, as currently

there is no selective agar that isolates non-O157 strains. In a population-based surveillance conducted by the Foodborne Diseases Active Surveillance Network, O26, O103, O111, O121, O45, and O145 serotypes accounted for 83% of all reported non-O157 STEC isolates (Gould et al. 2013). It is important to note that certain clades of *E.coli* O157:H7 have developed increased virulence and resistance to multiple antibiotics including streptomycin, sulfisoxazole, and tetracycline (Mora et al. 2005). Therefore, the usage of antibiotics in the treatment of STEC-HUS is not recommended.

E.coli O157:H7 is best detected on a sorbitol, not lactose, containing MacConkey-agar plate. Contrary to most *E.coli*, serotype O157:H7 cannot ferment sorbitol, and therefore, it forms colorless colonies when incubated on a sorbitol-MacConkey agar plate overnight, thereby allowing for its easy detection (Slutsker et al. 1997). Commercial and culture-independent tests that detect shiga toxins are particularly useful for identifying non-O157: H7 serotypes (Gould et al. 2013). It is recommended that both a sorbitol-MacConkey agar plate and a Stx identification assay performed on the broth culture of the stool are used for diagnostic purposes. (Slutsker et al. 1997).

Stx1 and Stx2, both of which are 70-kDa AB5 holotoxins, are two of the main toxins produced by enterohaemorrhagic *E.coli* (EHEC). The single 32-kDa A subunit of Stx binds noncovalently to five 7.7-kDa B subunits (Cimolai 1990). Both Stx1 and Stx2 are closely related to the shiga toxin (Stx) produced by *Shigella dysenteria* (Basu and Tumer 2015). Genetic studies have found that the amino acid sequence of Stx1 is almost identical to Stx, as both toxins only differ by one to zero amino acids (Weinstein et al. 1988; Takao et al. 1988). On the other hand, Stx1 and Stx2 are antigenetically distinct and only 56% of their amino acid sequences are identical (Weinstein et al. 1988). These differences in their primary sequences may result in different mechanisms of action in the pathogenesis of STEC-HUS.

E.coli also produces other factors, which may be pathogenic to humans. Intimin is another relevant, virulent toxin that has been shown to assist E.coli in its adhesion to epithelial cells in vitro and in animal models (Jerse et al. 1990). StcE, an inhibitor of the C1 esterase inhibitor, subtilase cytotoxin and cytolethal distending toxin are other toxins that may cause the clinical manifestations of an infection with STEC (Janka et al. 2003; Lathem et al. 2002; Paton et al. 2004). *E.coli* O113:H21 has been shown to produce cytolethal distending toxin (Paton et al. 2004). The identification of new virulence factors are likely to be identified as research continues in this field.

Pathogenesis

Upon colonization of the intestinal mucosa, STEC induces destruction of the brush border villi resulting in bloody diarrhea (Donnenberg et al. 1993). Following adhesion to the intestinal epithelial cells, STEC releases Stx, which crosses the gastrointestinal epithelium through a transcellular mechanism. However, the exact mechanism of its transportation is still unclear (Mele et al. 2014). Erythrocytes, neutrophils, and platelets have all been implicated in the carriage of Stx to the peripheral vasculature (Cheung and Trachtman 2014; Keir 2015). In 60% of patients, neutrophil-associated Stx has been detected in the bloodstream. Studies have demonstrated that levels of neutrophil-bound Stx correlate with the amount of kidney injury (Brigotti et al. 2011). The toll-like receptor 4 (TLR4) has been identified as the receptor that binds both shiga toxin 1 (Stx1) and shiga toxin 2 (Stx2) in human neutrophils, as treatment of neutrophils with TLR4 agonists and antagonists resulted in the displacement of Stxs (Brigotti et al. 2013). While circulating through the blood stream, Stx targets cells expressing the globotriaosylceramide (Gb3) receptor, a glycolipid cell surface receptor (Noris and Remuzzi 2009). It has been hypothesized that TL4 has a reduced affinity for Stx compared to Gb3. Therefore, once Stx arrives at an organ expressing the Gb3 receptor, such as the kidney, it detaches from the circulating cells and binds to the B subunit of the Gb3 receptor (Keir 2015). Although STEC-HUS affects every organ, the density of the Gb3 receptor among the vascular beds determines the

organ's susceptibility to the toxin (Trachtman et al. 2012; O'Loughlin and Robins-Browne 2001). Stxs predominately affect the kidney and the brain as these organs highly express this receptor (O'Loughlin and Robins-Browne 2001). Within the kidney, the glomerular endothelial cells are the main target; however, Stxs have been found to bind to podocytes, mesangial cells, and proximal tubules (Chaisri et al. 2001).

The B subunits of Stx direct the toxin towards cells expressing the receptor while the A subunit contains the enzymatic activity. The A subunit is responsible for endothelial damage that occurs during the pathogenesis of HUS as well as damage to DNA, activation of the apoptotic program, endoplasmic reticulum stress response, and more (Brigotti et al. 2013). Although both Sx1 and Stx2 share similar sequences, both toxins have been shown to result in varying degrees of damage. *E.coli* strains that solely produce Stx2 are generally more virulent compared to strains that produce Stx1 alone (Mele et al. 2014).

After binding to the target cell, the toxin is endocytosed and undergoes retrograde transport to the endoplasmic reticulum thereby escaping lysosomal degradation (Johannes and Romer 2010; Spooner and Lord 2012). Once in the endoplasmic reticulum, Stxs disintegrate into its alpha and beta subunits. Ultimately, it results in cell death and apoptosis by inhibiting ribosomal protein synthesis (Keir 2015). This causes damage to endothelium resulting in the release of thrombin and high levels of fibrin (Cheung and Trachtman 2014). In mouse models, the manganese cation has been demonstrated to have protective effects by interfering with the intracellular trafficking of Stx thereby resulting in its degradation (Mukhopadhyay and Linstedt 2012).

Low levels of Stx have been shown to induce a broad inflammatory response, which includes a ribotoxic stress response and promotion of a prothrombotic state in the microvasculature (Mele et al. 2014). Stxs have also been shown to alter endothelial cell expression of inflammatory mediators such as chemokines, chemokine receptors, and cell adhesion molecules all of which favor leukocyte recruitment (Morigi et al. 1995; Petruzziello-Pellegrini et al. 2012; Zoja et al. 2002). Stxs have also been shown to directly activate platelet and inflammatory cells and enhance endothelial tissue factor activity (Karpman et al. 2001; Van Setten et al. 1996).

Stxs have also been shown to play a role in the complement system. Low levels of C3 along with increased levels of C3b, C3c, and C3d (C3 breakdown fragments) have been detected in a subset of patients with STEC-HUS (Koster et al. 1984; Robson et al. 1992). In vitro, Stxs has been shown to inhibit complement regulators. Stxs can bind to complement factor H (CFH) and CFH-related protein 1 (Poolpol et al. 2014). It specifically binds to the membrane-binding domains of CFH, therefore inhibiting its regulation on cell surfaces. This phenomenon is similar to the one seen in aHUS patients who have loss of function mutations in the CFH gene (Pickering et al. 2007). Additionally, Stx has been shown to activate the complement system through the alternative pathway (AP) resulting in the formation of C3a and C3b deposits (Keir 2015). A retrospective study of 17 children with STEC-HUS found high levels of Bb and sC5b-9 in each of the patient's plasma (Thurman et al. 2009; Trachtman et al. 2006). This evidence indicates that activation of the AP occurs via the C5b-9 assembly (Mele et al. 2014).

In mice models, Stx-induced activation of the complement system via the AP was found to be associated with podocyte damage (Locatelli et al. 2014). As previously mentioned, the activation of the complement system due to Stx exposure generates C3a and C3b (Morigi et al. 2011). When injecting experimental mice with a Stx2/LPS (lipopolysaccharide) solution, C3 deposits were observed on their glomeruli and podocytes. Interestingly, no C3 glomerular deposits were detected in mice deficient for factor B ($Bf^{-/-}$), a zymogen which contains the AP C3 and C5 convertases' catalytic activity. Wild-type (WT) mice were found to have significantly reduced number and density of podocytes per glomerulus than $Bf^{-/-}$ mice demonstrating that the deposition of C3 is associated with podocyte loss. There were no significant differences in the density and number of podocytes between the $Bf^{-/-}$ mice and controls. Ultrastructural damage such as the focal

effacement of the podocyte foot processes was observed in WT mice. In addition, after the injection of Stx2/LPS, there was an increase in expression of integrin-linked kinase (ILK) followed by the upregulation of Snail and downregulation of nephrin and α-Actinin-4 in podocytes. α-Actinin-4 is a F-actin associated protein that contributes to the maintenance and stabilization of podocytes. Weak staining for ILK was detected in the glomeruli of the $Bf^{-/-}$ mice demonstrating the importance of complement activation in ILK upregulation and subsequent intracellular signal dysregulation. Therefore, activation of the AP and the generation of C3a in response to Stx exposure increase ILK expression ultimately leading to podocyte damage and loss (Locatelli et al. 2014).

Additionally, findings have indicated that Stxs may directly activate complement. Endothelial cells pretreated with Stx and then exposed to human serum, demonstrated increased expression of the membrane adhesion molecule, P-selectin, and increased C3 activation (Morigi et al. 2011). P-selectin cleaves C3 into C3a and C3b and the production of C3a further increases P-selectin expression while decreasing thrombomodulin expression triggering thrombosis (Rosales et al. 2012; Morigi et al. 2011). Additionally, these microvascular endothelial cell lines were found to have C3 deposits. Upon exposure to whole blood, pretreated endothelial cells with Stx1 had a larger surface area covered by thrombi compared to cells that were solely preexposed to medium. The addition of the complement inhibitor, soluble complement receptor type 1, sCR1 fully abolished this effect (Morigi et al. 2011). Additionally, a P-selectin blockade substantially decreased C3 deposition on endothelial cells and thrombus formation in vitro, demonstrating the significant role P-selectin plays in this process (Gasser et al. 1955).

In addition to complements, several other inflammatory mediators have been identified that are involved in the pathogenesis of STEC-HUS. For instance, patients with STEC-HUS have been found to have elevated plasma levels of TNF-α and IL-6 (Cheung and Trachtman 2014). In addition, isolated monocytes from children with STEC-HUS that were exposed to Stx1 produced IL-1β, IL-6, IL-8, and TNF-α via a LPS independent pathway. In an experimental mice model of STEC-HUS, exposure to a TNF-α inhibitor was found to reduce renal and central nervous system damage (Isogai et al. 2001). Furthermore, when preincubating human endothelial cells with TNF-α or IL-1, an increase in Gb3 synthesis was observed. As the Gb3 receptor is the main target of Stx, an increase in Gb3 synthesis was followed by an increase in Stx1 binding (Van De Kar et al. 1992).

Several chemokines also play an essential role in the development of STEC-HUS. Increased expression of chemokine receptor 4 (CXCR4) and stromal-derived factor-1 (SDF-1) was observed after treating human microvascular endothelial cells to Stx2. SDF-1 along with its receptor CXCR4 regulate stem cell mobilization, angiogenesis, and inflammatory cell infiltration. Children who developed STEC-HUS from an *E.coli* O157:H7 infection have higher plasma levels of SDF-1 and CXCR4 than children whose enteritis resolved. Inhibition of the CXCR4/SDF-1 complex was found to be associated with decreased endothelial activation and organ injury (Cheung and Trachtman 2014; Petruzziello-Pellegrini et al. 2012). In addition, monocytes from children with STEC-HUS were found to have increased expression of the chemokine receptor (CCR) 1, CCR2, and CCR5 (Ramos et al. 2012). CCR1 knockout mice that were treated with Stx1 were found to have fewer monocytes and neutrophils infiltrating the kidneys along with increased survival. Ramos et al. also observed a correlation between CCR expression and HUS severity (Ramos et al. 2012).

Chiyoda et al. discovered that the addition of Stx2 to human bone marrow or cord blood culture cells results in the formation of macrophage-granulocyte colonies. This implies that Stx2 may induce granulocytosis in the peripheral blood by indirectly or directly stimulating bone marrow cells (Chiyoda et al. 2002). Patients with STEC-HUS were found to have a tenfold increase in the level of granulocyte stimulating factor and leukocytosis as well as higher levels of absolute polymorphonuclear (PMN) cells and monocyte counts (Proulx et al. 2002; Buteau et al. 2000). During

the early stages of STEC-HUS, PMN infiltrates the kidneys (Palermo et al. 1999). Although PMN clearance is expected in 2–3 weeks, a high level of PMN at diagnosis is associated with a poor prognosis (Cheung and Trachtman 2014).

Clinical Findings

The clinical course of STEC-HUS begins with infection of the gastrointestinal tract with STEC. The incubation period between ingestion of the organism and the onset of diarrhea is 2 to 12 days, with a median of 3 days (Riley et al. 1983; Bell et al. 1994). Bloody diarrhea is present in 57–90% of cases and develops 1–3 days after the onset of watery diarrhea (Gerber et al. 2002; Ostroff et al. 1989). Visual inspection of stool for blood is not adequate as many laboratory workers fail to detect blood in the submitted samples (Slutsker et al. 1997). The greatest risk for person-to-person transmission of bacteria is during the diarrheal phase, which typically lasts for 1 week. The bacteria can continue to shed in the stool for weeks after the infection (median 21 days). Symptoms during this phase include fever, abdominal pain, and vomiting. Between 5 and 15% of cases of STEC, gastroenteritis will develop into HUS at around 5 to 13 days after diarrhea onset, with a median of 1 week (Wong et al. 2000). Risk factors for developing HUS after STEC enteritis include leukocytosis, early presentation to care, age less than 10 years, and use of antibiotics and antimotility agents (Wong et al. 2000; Bell et al. 1997).

Of the triad of HUS, thrombocytopenia usually presents first, followed by hemolytic anemia, and then AKI. The platelet count can be severely low; however, petechiae and purpura rarely are present. Microangiopathic hemolytic anemia is present with hemoglobin levels usually less than 8 g/dL. Fragmented red blood cells in the form of schistocytes and helmet cells are found on peripheral smear. Additionally, lactate dehydrogenase (LDH) and bilirubin are elevated, haptoglobin is decreased, and the Coombs test is negative. AKI severity is variable, ranging from mild disease to oligo-anuria with requirement for dialysis. Published series since the 1990s have reported that dialysis was required in 19–90% of cases (Garg et al. 2003). The urinalysis may show hematuria with red blood cell casts and proteinuria. There may also be significant leukocytosis with elevated fibrinogen and prolonged PT. Hypertension is often present due to volume overload and activation of the renin-angiotensin-aldosterone system. Upon resolution of HUS, a rising platelet count is usually the first sign of recovery. Anemia may be prolonged and is the last to recover.

Extrarenal manifestations of STEC-HUS are common. Neurological complications such as irritability, confusion, stroke, seizure, and coma are present in 20–28% of cases (Nathanson et al. 2010). Cerebral microvascular thrombi, ischemia–hypoxia, or direct damage by Stx are the proposed mechanisms of damage. Severe central nervous system involvement portends a poor prognosis with increased risk of mortality. Cardiopulmonary involvement is present in 10% of cases presenting as cardiac dysfunction, heart failure, myocardial infarction, and pleural effusion. Gastrointestinal complications include intestinal perforation, necrosis, strictures, rectal prolapse, gallstones, and pancreatitis.

Evaluation

The diagnosis of STEC-HUS is made clinically based on a prodrome of diarrhea with evidence of STEC infection followed by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and AKI. In some instances, diarrhea may not be present at the onset of HUS and the diagnosis is confirmed by positive STEC stool culture. Stool sent for culture can come from rectal swab or stool samples. Stx can also be detected in the stool. Additionally, polymerase chain reaction (PCR) can detect Stx genes (Gerritzen et al. 2011) and serology may test for anti-Stx antibodies (Chart and Jenkins 1999).

TMA is confirmed by a platelet count less than 150,000/mm^3 and evidence of hemolysis (anemia, elevated LDH, elevated bilirubin, low haptoglobin, negative Coomb's test). A blood smear

should be reviewed by a hematology specialist for the presence of schistocytes or helmet cells. If TTP is a consideration, ADAMTS13 should be sent. It is within normal range in STEC-HUS.

Kidney biopsy is rarely indicated unless the diagnosis is questionable, especially because of the risk of bleeding. The microvascular lesion of HUS consists of fibrin thrombi and microthrombi in the glomerular loops with vessel wall thickening and endothelial swelling.

The differential diagnosis of STEC-HUS includes non-STEC-HUS (complement-associated HUS, *strep. pneumoniae* HUS, medication-related HUS), as diarrhea present in 50% of non-STEC HUS cases. *Strep. pneumoniae* HUS makes up 5–15% of all cases of HUS in childhood (Copelovitch and Kaplan 2008). Patients most commonly present after pneumonia with effusion, but HUS may also occur with meningitis, bacteremia, and sinus infections. Compared with STEC HUS, *strep. pneumoniae* HUS typically has a more severe clinical course and poorer outcomes with higher incidence of end-stage renal disease and mortality. It can also often times be difficult to clinically differentiate STEC-HUS from TTP. Ulcerative colitis, other bacterial gastroenteritis, and appendicitis can mimic abdominal symptoms during the diarrheal phase. The diagnostic triad of HUS can also be seen in disseminated intravascular coagulation, sepsis, and vasculitis.

Treatment

Supportive Care

Inpatients infected with STEC should be isolated to prevent further transmission of the bacterium (Bender 2005). Although there has been significant investigation on the usage of antibiotic treatments postinfection, this is not recommended.

There are no proven therapies for the treatment or prevention of STEC-HUS and management is primarily supportive care. Management is focused on restoration and maintenance of adequate fluid balance, correction of metabolic and electrolyte disturbances, transfusions, blood pressure control, nutritional support, and renal replacement therapy (RRT). In addition, management of extrarenal manifestations, such as neurologic sequelae, gastrointestinal colitis/perforation, cardiac dysfunction, and pulmonary complications, may require targeted treatment with the aid of subspecialty consultation.

Fluid management has traditionally centered on fluid restriction and avoidance of volume overload. However, recent evidence suggests that dehydration, especially early on in the disease course, can increase blood viscosity thereby favoring the formation of thrombi and decreased blood flow leading to more severe disease course and outcomes (Ardissino et al. 2015; Balestracci et al. 2012). Early volume expansion with sodium-containing intravenous fluids has been shown to mitigate organ tissue damage possibly by improving organ perfusion, minimizing ischemia, preventing glomerular tubular imbalance, and maintaining tubular flow. Ardessino et al. demonstrated that a group of children with STEC-HUS who received volume expansion with normal saline to increase body weight by 10% at disease presentation had lower central nervous system involvement, less need for RRT and intensive care support, shorter length of stay, and improved long-term outcomes when compared to historical controls who were fluid restricted (Ardissino et al. 2015). Once volume replete, the goal of fluid management is to maintain adequate effective circulating volume while avoiding fluid overload. Established AKI with oliguria (< 1.0 ml/kg/hr in infants, <0.5 ml/kg/hr in children) or anuria (<0.2 ml/kg/hr) after volume administration requires fluid restriction because increased fluid administration and positive fluid balance are associated with increased mortality in AKI (Goldstein et al. 2005; Payen et al. 2008). To maintain euvolemia, intravenous fluids may be administered at the rate of insensible losses (~1/3 "maintenance fluid") plus replacement of ongoing losses in equivalent volumes. Patients should be monitored carefully for signs of fluid overload with strict recording of daily inputs, outputs, and weights. A trial of diuretics may be used to manage volume overload (KDIGO). Diuretics may convert oliguric AKI to

nonoliguric AKI; however, its use should not be continued if there is no response.

Renal replacement therapy is frequently required during the acute phase of STEC-HUS. Indications for dialysis in STEC-HUS are the same as for all other causes of AKI (e.g., severe metabolic acidosis unresponsive to bicarbonate therapy, electrolyte disturbance despite medical therapy, fluid overload unresponsive to diuretics, and uremic complications such as pericarditis and encephalopathy). For STEC-HUS, RRT is also recommended to start when there is oliguria for 72 h or anuria for 24 h (Schulman and Kaplan 1996). RRT modalities include peritoneal dialysis (PD), intermittent hemodialysis (HD), and continuous renal replacement therapy (CRRT). The choice of dialysis modality depends on the age, size, comorbidities of the patient, availability of access placement, and expertise of the institution. Some earlier studies favored the use of PD over HD for STEC-HUS due to the improved clearance of plasminogen-activator inhibitor type 1, a protein thought to be involved in the pathogenesis of HUS (Bergstein et al. 1992). However, there is no evidence suggesting a benefit for one modality over the other. In cases of severe gastrointestinal involvement, PD may not be an option although its successful use has been described (Grisaru et al. 2011).

Frequent blood work is needed to monitor kidney function, hemoglobin/platelet count, and electrolytes. Support with blood products may be required during the course of STEC-HUS. Packed red blood cell (PRBC) transfusions are given as needed for anemia, generally for hemoglobin levels <6–7 g/dl. Hemoglobin should not be targeted to normal range because the increased volume may lead to cardiopulmonary volume overload and hypertension. If the patient is on dialysis, PRBCs may be given during treatment to minimize complications of volume overload and hyperkalemia. Platelet transfusions should be avoided if possible as they may favor microthrombi formation by increasing platelet consumption (Harkness et al. 1981); however, platelets are indicated in the setting of active bleeding or during an invasive procedure. Electrolyte disturbances such as hyperkalemia, hyperphosphatemia, and acidosis are frequent and are managed similarly to those with other causes of AKI.

Management of hypertension in HUS includes correction of volume overload and use of antihypertensive medications. Calcium channel blockers are a safe first-line choice for the treatment of hypertension. Although the mechanism of hypertension in HUS may include activation of the renin-angiotensin-aldosterone (RAAS) system, RAAS blockade should be avoided in the acute phase due to the risk of worsening renal perfusion, lowering the glomerular filtration rate, and hyperkalemia. For those with long-term sequelae of HUS such as hypertension or proteinuria, RAAS blockade is the treatment of choice (Van Dyck and Proesmans 2004).

Nutritional support that provides adequate energy and protein is essential in the care of AKI due to STEC-HUS. Potassium, sodium, and phosphate should be restricted in the diet. In addition, nonsteroidal anti-inflammatory agents and other nephrotoxins should be avoided. Dosing of medications should be adjusted for renal dysfunction.

Specific Therapies

Many different therapies have been trialed for the treatment of STEC-HUS. There is no evidence of benefit for any of the following therapeutic options: antibiotics, antimotility agents, plasma infusion, plasmapheresis, antiplatelet drugs, intravenous immunoglobulin G, corticosteroids, anticoagulants, fibrinolytic agents, and oral administration of a shiga toxin-binding agent. However, the use of eculizumab has received recent attention.

Antibiotics and Antimotility Drugs

The use of antibiotics and anti-motility agents in STEC-HUS are not recommended. Antibiotics during the diarrheal phase of STEC-HUS provide no benefit in preventing progression of disease and may potentially increase the risk of HUS. In vitro studies have shown that antibiotics cause bacterial lysis thereby liberating Stx and

also induce increased production of toxin (Walterspiel et al. 1992). Antibiotics do not decrease the duration of gastrointestinal symptoms (Bell et al. 1997) but analysis of the German outbreak found that those who took antibiotics had decreased duration of pathogen shedding in the stool (Nitschke et al. 2012; Vonberg et al. 2013). There is evidence that antibiotics lead to a higher rate of HUS, although a meta-analysis of 1896 cases from studies of variable quality failed to confirm this association. However, when the studies of lower quality were excluded from the meta-analysis, there was a significantly higher risk of HUS with antibiotic administration (Freedman et al. 2016). In the German outbreak, antibiotic use demonstrated a protective effect, with a reduction in seizures, death, abdominal surgeries, and carriage time (Menne et al. 2012).

Antimotility agents, such as anticholinergic drugs and narcotics, have also been associated with an increased risk of development of HUS (Bell et al. 1997). One study demonstrated an increase in central nervous system complications with antimotility use with no difference in duration of diarrhea (Cimolai et al. 1992).

Plasma Infusion and Plasmapheresis

Although proven to be efficacious in TTP and complement-mediated HUS, evidence for the benefit of plasma infusion with fresh frozen plasma (FFP) and plasma exchange in STEC-HUS is limited and therefore not recommended. One controlled trial demonstrated benefit of FFP infusions with lower serum creatinine and proteinuria at 1- and 6-month follow-up compared to the no FFP group, (Loirat et al. 1988) while another controlled trial and case-control study failed to show a difference in outcomes between the two groups (Rizzoni et al. 1988).

Plasmapheresis has been used in severe cases of HUS and those with central nervous system complications, but there are no controlled trials in children. A study of adults with STEC-HUS demonstrated lower mortality in the group treated with plasmapheresis versus the conservatively treated group (Dundas et al. 1999). However, plasmapheresis demonstrated no benefit during the German outbreak (Menne et al. 2012; Kielstein et al. 2012).

Eculizumab

There is evidence of activation of the complement system by the alternative pathway early in the course of STEC-HUS (Morigi et al. 2011; Thurman et al. 2009). Therefore, there is rationale for the use of eculizumab, a monoclonal antibody to complement factor C5, as a potential treatment of STEC-HUS. The first report of eculizumab for this indication was in three young children requiring dialysis with severe neurologic symptoms during the German outbreak in 2011. The neurologic status and platelet count improved quickly after the initial dose of eculizumab and all were able to come off dialysis within 16 days (Lapeyraque et al. 2011). A couple of small case series also described benefit of eculizumab in patients with severe neurological involvement during the outbreak (Delmas et al. 2014; Pape et al. 2015). However, beyond severe neurological involvement, the utility of eculizumab is questionable. Loos and colleagues reported on 90 children who were treated in Germany; 13 children were given eculizumab, 17 received plasmapheresis, while the rest received supportive care. Seventy-one percent of the patients (64/90) required renal replacement therapy and 23/90 (26%) had neurologic symptoms. Outcomes were comparable regardless of treatment (Loos et al. 2012). Similarly, a study of 298 adults during the outbreak demonstrated no benefit in 67 patients treated with eculizumab compared to supportive care (Menne et al. 2012).

The dosing of eculizumab is similar to the treatment protocol of complement-mediated HUS with additional doses dependent on clinical response. Given the prohibitive cost of the drug and questionable efficacy, further evaluation of eculizumab in a randomized clinical trial is needed before a recommendation can be made for its use in this disease.

Other

There have been several other treatments that have been proposed for STEC-HUS, none of which have proven to be beneficial. Some these include

antithrombotic agents (heparin, prostacyclin, urokinase) (Loirat et al. 1984; Van Damme-Lombaerts et al. 1988), fibrinolytics (streptokinase) (Diekmann 1980), intravenous IgG (Robson et al. 1991), steroids (Menne et al. 2012), and oral toxin binding agents (Synsorb-Pk) (Trachtman et al. 1993). Potential future treatments that require further exploration include immunoadsorption (Greinacher et al. 2011), recombinant thrombomodulin (Honda et al. 2013), anti-shiga toxin antibodies (Mukherjee et al. 2002; Mejias et al. 2016), and human mannose-binding lectin inhibitor (Ozaki et al. 2016).

Prevention

Ultimately, the best course of action to prevent the development of STEC-HUS is to reduce the risk of infection. When an outbreak occurs, infected individuals should be isolated in order to minimize person-to-person transmission (Queensland Health 2013). The Health Protection Agency in the United Kingdom (UK) has issued several guidelines to reduce such transmissions including microbial screening of individuals who have been in close contact with infected individuals, assurance of adequate hygiene, implementation of environmental controls and supervised hand washing com (APHL STEC Work Group 2012; Infections 2004). Proper hand washing with soap and water is essential to preventing the acquisition and spread of STEC, thereby decreasing the risk of HUS. It is also important to stringently manage pediatric cases of acute bloody diarrhea. Children with proven STEC infections should stay at home until the diarrhea has passed for at least 48 h (Thomas and Elliott 2013). Recommended measures after a school or daycare STEC outbreak include a prompt assessment of the school's eating and food preparation areas as well as bathrooms, the isolation of high risk and symptomatic children until microbiological clearance, institutional reinforcement of hygienic practices, and revision of food preparation procedures as needed (Bender 2005).

There is no conclusive evidence that demonstrates that antibiotic treatment of STEC enteritis prevents HUS (Bender 2005). A prospective study of 71 children, who were infected with *E.coli* O157:H7, found that antibiotic treatment increased the risk of developing HUS (Wong et al. 2000). Other studies have inconclusive results where antibiotic treatment either did not increase the risk or prevent the development of HUS (Safdar et al. 2002). The use of antibiotics may select for resistant strains. Meng et al. have demonstrated that certain strains of *E.coli* O157:H7 have developed antibiotic resistance, where 34% of the bacterial isolates from cattle were found to be resistant (Meng et al. 1998). Many *E.coli* O157:H7 strains have also developed multiple resistance patterns (Mora et al. 2005). As contaminated food products have been responsible for many STEC outbreaks, especially ground beef, several guidelines have been issued to prevent this from occurring. Mince meat or hamburgers should be cooked to a temperature of 70°C. It is essential that a food thermometer is used while cooking hamburgers, as the color of the meat does not serve as a reliable marker. Additionally, the ingestion of undercooked hamburgers poses a significant risk of infection (Thomas and Elliott 2013).

The World Health Organization (WHO) has also issued several guidelines on the preparation of food, which emphasizes that hands as well as all food preparation equipment and areas should be thoroughly cleaned. Additional WHO guidelines include: raw and cooked food items should be stored separately and different equipment should be used for the handing of both items. This will help reduce the risk of cross-contamination. Food items should be cooked and reheated at a temperature of 70°C or greater and they should be refrigerated no later than 2 h after being stored at room temperature. Frozen food should not be thawed at room temperature and cooked food should be kept hot at a temperature of 60°C or greater (WHO). The Center for Disease Control and Prevention (CDC) also advises to avoid the consumption of unpasteurized milk, dairy products, and juices. Additionally, water from swimming pools, paddling pools, lakes, or rivers should not be swallowed (CDC 2016c). Following the large *E.coli* O157:H7 outbreak in

2006 due to contaminated spinach, new guidelines were issued to prevent contamination when processing fresh-cut produce (Thomas and Elliott 2013).

As animals, especially cattle, have been the source of many STEC outbreaks, several investigations have been conducted to prevent animal carriage. Animal vaccinations as well as the manipulation of animal feeds and farm practices have been proven to reduce animal carriage of STEC (Thomas and Elliott 2013). The supplementation of animal feeds with probiotics and chlorate has been effective in reducing fecal *E.coli* O157 load (Sargeant et al. 2007). Certain farm practices, including the solarization of soil, retaining animals in the original herd, and providing dry bedding have also been proven to be effective in reducing *E.coli* O157:H7 levels (Thomas and Elliott 2013).

In addition to the interventions mentioned above, public health campaigns are essential to raise awareness on the risk factors and preventative measures for STEC infection. Individuals should be educated on proper hygiene and sanitary measures as well as proper food preparation early on, not only when an outbreak occurs. On January 4, 2011, the Food Safety Modernization Act (FMSA) was signed into law by President Obama, with the goal of shifting focus from the response to contamination to its prevention. The FMSA provides the FDA with the right to issue mandatory recalls of all food products. Additionally, the FDA now has the legislative mandate to require the usage of thorough, prevention controls for applicable facilities. Additionally, the FDA will be implementing innovative inspection approaches to ensure compliance. In regard to imported food items, importers are now required to perform risk assessments of foreign suppliers and verify that their suppliers are maintaining adequate safety controls. The FDA has also established Good Manufacturing Practices for animal foods as well as science-based standards for produce farming and processing. Many of these rules have been recently implemented during 2015 and 2016; hopefully, these policies will reduce the frequency of STEC outbreaks (FDA 2016).

Outcomes

STEC-HUS is a self-limited disease with resolution beginning 1–2 weeks after the onset of disease. Outcomes have improved in recent years due to advances in supportive care and the overall prognosis is favorable. Deaths due to central nervous system insults, electrolyte abnormalities, sepsis, gastrointestinal injury, and cardiopulmonary events have been described, but they are rare. Mortality rates are reported to be 1–4% during the acute episode. Leukocytosis, hemoconcentration, dehydration, and oligoanuria increase the risk of mortality in the acute setting (Oakes et al. 2006).

While most patients recover completely, about 30% are left with long-term sequelae, mostly related to the kidney. Long-term outcomes include proteinuria (15–30%), hypertension (5–15%), CKD (9–18%), end-stage renal disease (3%), and neurologic symptoms (4%) (Rosales et al. 2012). Risk factors for development of long-term kidney damage include prolonged anuria, severity of the acute illness, and need for dialysis.

It is recommended that a patient be followed for at least 5 years after HUS to monitor for the development of late sequelae. The first morning urine protein:creatinine ratio should be monitored for the development of proteinuria. One may also consider following urine microalbumin. Blood pressure should be obtained at each health encounter and 24-h ambulatory blood pressure monitoring considered, even if clinic blood pressure is normal, as masked hypertension and blood pressure abnormalities have been discovered after long-term surveillance (Krmar et al. 2001). Serum creatinine should be followed regularly.

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Hemolytic Uremic Syndrome, Genetic

42

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Abstract

The nomenclature of atypical hemolytic uremic syndrome (aHUS) has undergone an evolution as rapid as the scientific understanding of the field during the last decade. Identification of many underlying genetic causes has increased understanding of the major mechanisms of disease. These defects principally, but not exclusively, involve the alternative pathway of complement. Important differences among the specific defects have impact on disease management, and clinical genetics plays a key role in that process. Untreated, aHUS frequently leads to end stage renal disease or death. Fortunately, understanding the major disease mechanisms has allowed development of effective treatment options.

Keywords

Hemolytic uremic syndrome · Complement · Alternative pathway · Hemolytic anemia · Thrombocytopenia · Thrombotic microangiopathy · Factor H · Eculizmuab · Plasmapheresis · Plasma exchange

Introduction

Hemolytic uremic syndrome (HUS) is form of thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. As understood from "uremic" in its designation, the most common organ to be injured by HUS is the kidney but other organs are also frequently involved and in fact sometimes the kidney is relatively spared. The hemolytic anemia is characterized by intravascular red blood cell fragmentation producing schistocytes and by a parallel process leading to thrombocytopenia which can be detected by peripheral blood smear examination. Other forms of TMA such as thrombotic thrombocytopenic purpura (TTP) can present in a very similar clinical manner, and these require careful consideration as the underlying etiology of the process and treatment may differ (Loirat et al. 2016; Nester et al. 2015; George and Nester 2014).

The several types of TMA can be classified in several ways, including by clinical syndrome, as secondary to a coexisting disease or condition, or related to certain infections (Fig. 1) (Loirat et al. 2016). The subjects of this chapter are those forms of HUS in which specific genetic abnormalities predispose to HUS. Commonly referred to as "atypical HUS (aHUS)," the majority of identified individual cases are due to defects that allow for increased activity in the alternative pathway of complement. The typical form of HUS, secondary to STEC infection, is discussed in this chapter.

Epidemiology and Clinical and Manifestations

Both typical and atypical HUS can present at any age. Both will manifest the cardinal laboratory features of HUS (hemolytic anemia, thrombocytopenia, uremia) though the degree of each is variable. Hypertension is very frequent in both except when hemodynamic shock prevails. Therefore, basic hematological and biochemical evaluations as well as a careful physical examination with evaluation of blood pressure are essential for diagnosis. Either typical or atypical HUS can present with multisystem disease involving the CNS, intestine, and other organs; arteriolar and arterial thrombosis may result from progressive microvascular disease and cause large scale ischemia in any organ.

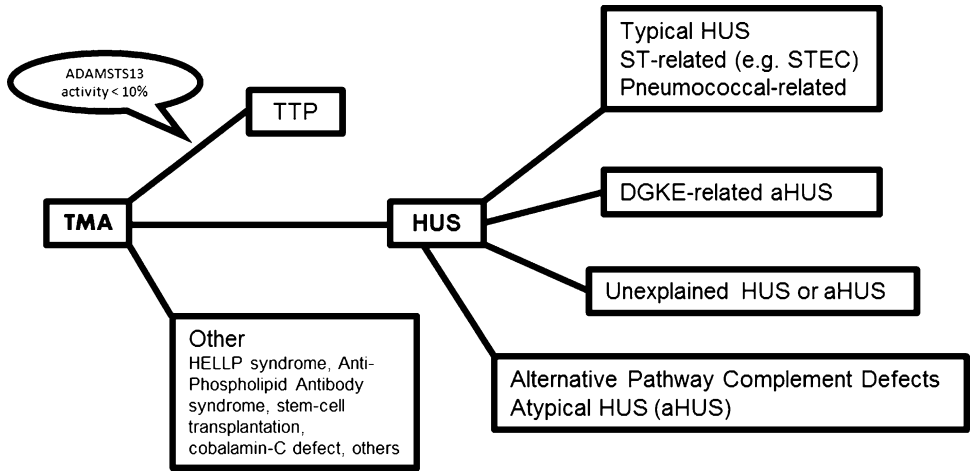

Fig. 1 Basic diagnostic flow chart: *TMA* thrombotic microangiopathy, *TTP* thrombotic thrombocytopenic purpura, *HUS* hemolytic uremic syndrome, *ST* Shiga-toxin, *STEC* ST enteropathogenic *E. coli*, *DGKE* diacylglycerol kinase epsilon

Though exact figures are unclear, aHUS is an "ultra-rare" disease, its incidence estimated between 0.1 and 2 per million population (Loirat and Fremeaux-Bacchi 2011). Re-emphasizing that aHUS can occur at any age, the most frequent age of onset is in very young children, usually under age 2 years. Cumulatively, however, most cases actually manifest in adulthood (Fremeaux-Bacchi et al. 2013). While there is no predominance by sex in childhood, it has been reported and widely accepted that adult cases occur in a female:male ratio of 3:1 perhaps because pregnancy is a potent trigger in susceptible individuals (Fremeaux-Bacchi et al. 2013; Greenbaum 2016).

Clinical features including disease occurring in non-summer months, non-synchronous HUS in a family member, recurrent disease, a prolonged relapsing/remitting or indolent course of illness, or onset prior to age 6 months are strongly suggestive of aHUS. Diarrhea, or indeed any other infectious trigger, is not an infrequent finding and therefore the terminology "diarrhea positive" or "diarrhea negative" to denote typical versus atypical HUS is no longer considered a useful approach to classify this disease.

Unlike typical HUS, in cases of aHUS, the platelet count may present at greater than 30 G/L, and in some cases greater than 150 G/L. In fact, up to 15–20% of cases have subclinical and fluctuating or relapsing/remitting hematological parameters over a prolonged period of time such that the presenting sign may be unexpected such as hypertension, proteinuria, or reduced renal function. In some patients with disorders of the AP of complement regulation, serum C3 or CH50 may be low, but these tests should not be considered sensitive enough to diagnose or exclude aHUS. Many patients have depressed ADAMSTS13 concentrations, but generally not to below 10% (which is characteristic of TTP). One study has documented that these partial deficiencies in aHUS patients are commonly associated with genetic variation in the gene encoding ADAMTS13, contributing to a permissive background to manifest TMA (Feng et al. 2013).

Untreated, the outcomes of aHUS are historically poor, with the majority developing ESRD and with significant mortality. Improved recognition and treatment options developed recently, and described below, have drastically changed these outcomes for the better. While the presenting episode remains potentially very severe and some cases respond less, the majority of patients can now expect to achieve remission and preserved renal function.

Pathological Findings of aHUS

Atypical HUS is characterized by glomerular capillary wall thickening from endothelial cell swelling and accumulation of material between the endothelial cells and the basement membrane. There is direct endothelial damage resulting in capillary thrombosis from platelet and fibrin thrombi occlusion. In the early stages there is mesangial lysis that later is replaced by sclerotic changes. Fibrin and fibrinogen deposits form in the glomeruli, mesangium, and vessel walls. Complement and immunoglobulin deposits may also be found in the capillaries (Kavanagh et al. 2013).

Extra-renal involvement may affect any organ system, including the CNS, pancreas, colon, and heart leading to severe clinical sequelae in some cases (Hirt-Minkowski et al. 2010). There is essentially no discernable difference in histopathology between aHUS and typical HUS.

Pathogenesis of aHUS

Disorders of the Alternative Pathway of Complement

As noted, the majority of patients with aHUS have a defect in the regulation of the alternative pathway (AP) of complement. The complement system forms part of the innate immunity and consists of plasma proteins, membrane-bound receptors, and membrane-deposited components. These interact with one another for a primary purpose of fighting infection, particularly encapsulated bacteria such as *N. Meningitidis*.

For the purpose of discussing aHUS, a discussion of complement must center on the AP. There are three pathways for complement activation: the AP, the classical pathway triggered largely by antibody, and the lectin pathway triggered by molecules expressing mannose residues. These pathways converge and overlap, principally at the level of the C3 convertases. C3 convertases are formed in different ways by each pathway but ultimately lead to activation of C5 and onward to formation of the membrane attack complex (MAC). This molecular assembly mediates the toxic end action of the system upon its target. Many so-called intermediates generated as fragments during sequential proteolytic activation of factors have important function. For example C3a and C5a are potent inflammatory mediators and C3b helps with opsonization of pathogens and removal of immune complexes (Murphy 2008; Noris and Remuzzi 2013; Picard et al. 2015).

The AP is continuously active at low levels, termed "tickover" which results from spontaneous hydrolysis of C3 by water and Factor B (Fig. 2). Following an additional "triggering" event (such as infection) the AP amplification loop can increase the activity of this system tremendously. This highlights the need for tight regulation of the pathway to avoid promiscuous tissue injury by terminating the additional complement activity when it is no longer required.

The initiated and spontaneous activation of the complement system is controlled by regulated proteins at different levels of the cascade in order to limit the response and terminate the process after the triggering event is resolved. Many cases of aHUS (Table 1) result from defects in these regulatory molecules or defects in effector complement proteins that reduce their ability to be regulated. In addition, there is also interaction between the complement system and the intrinsic coagulation/anticoagulation system and there are cases of aHUS that stem from defects at the level of this interaction (Table 1).

Noncomplement-Related Pathogenesis of aHUS

Other genetic causes of aHUS are related to mutation of diacylglycerol kinase epsilon (DGKE) and deficiencies in Cobalamin C, discussed below. The mechanisms by which these defects lead to HUS is less clear than for the defects in the AP of complement.

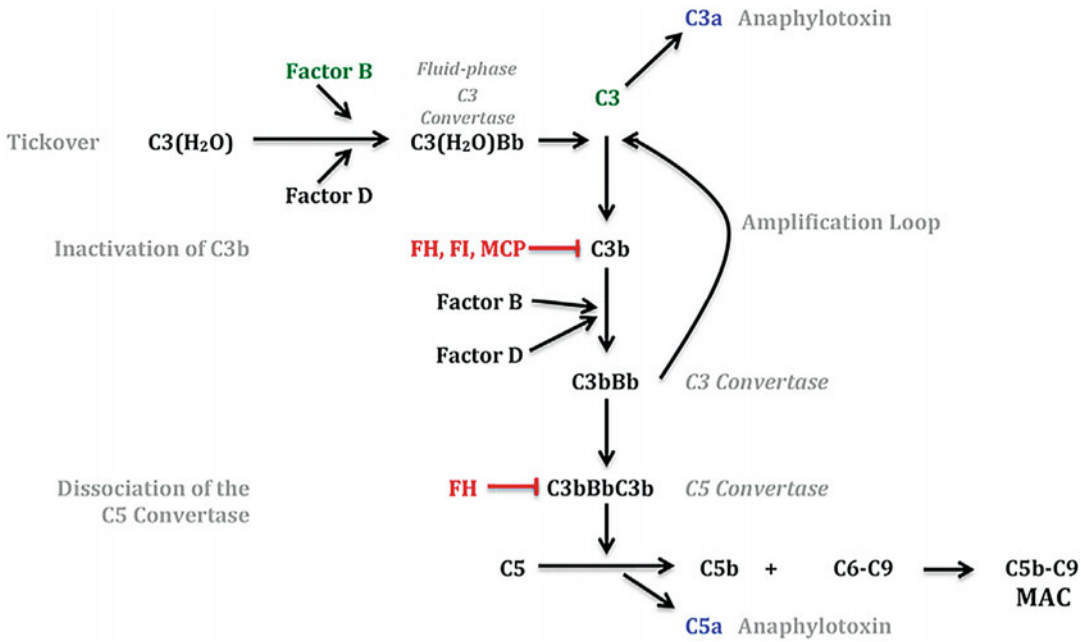

Fig. 2 A simplified diagram of the AP of complement: The AP pathway is normally active at a continuously low level termed "tickover" and is amplified in the presence of certain microbes and other triggers. The cascade undergoes amplification at several points and leads to formation of the membrane attack complex (MAC) as well as multiple intermediates with anaphylactic and other activities in the fluid phase as well as on native and exogenous cell membranes. (Figure reproduced from Nester et al., "Atypical aHUS: State of the art" with permission).

Genetic Basis of aHUS

Genetic variants can be classified as benign, likely benign, a variant of uncertain significance (VUS), likely pathogenic, or pathogenic (Richards et al. 2015). Dysregulation of the AP was the first recognized and the most common etiology of aHUS; in turn, genetic abnormalities affecting this pathway were the first to be elucidated. Inactivating ("loss-of-function") mutation in genes encoding for Complement Factor H, Factor I, and membrane cofactor protein as well as activating ("gain-of-function") mutation in C3 and factor B are all described and permit inappropriately intense or prolonged activation of the APC. In addition, acquired antibodies to complement factor H are well described and cumulatively account for a significant proportion of cases. These are almost always linked to mutation in CHFR proteins though the mechanism by which these genetic changes lead to the production of antibodies remains unclear (Durey et al. 2016; Gurjar et al. 2018). Defects in thrombomodulin also lead to abnormal AP activity. Mutations in DGKE and deficient cobalamin C are also reported but are quite infrequent (Berger 2016). It is also relevant to note that while specific genes are discussed separately, a certain proportion of patients manifest more than one pathogenic mutation, and a larger number of patients manifest combinations of pathogenic mutation and permissive common risk variants, and genetic alterations of uncertain significance (Goodship et al. 2017; Bresin et al. 2013). The above noted high frequency of common risk variants of ADAMSTS13 encountered in patients with aHUS is a good example of this issue (Feng et al. 2013).

Atypical HUS and C3 glomerulopathy have much in common and their clinical presentations can overlap. Over time, however, most cases are defined as one or the other largely on the basis of differing hematological parameters. Not surprisingly, there is also overlap in the genetic drivers

Table 1 Complement related causes of aHUS

Location	Name	Function	Effect of mutation
Plasma	Factor H (FH)	Binds C3b displacing Bb Cofactor for FI	Loss of function
	Factor I (FI)	Cleaves C3b with FH, MCP, CR1	Loss of function
	Factor B (FB)	Key effector protein in AP	Gain of function Less susceptible to cleavage and breakdown of C3 convertase
	C3	Key effector protein in AP	Gain of function Less binding to MCP Increased binding to FB
	CFHR family	FH like functions	Loss of function Hybrid proteins Competitive binding with FH
	FH antibodies	Associated with autoimmunity found with *CFHR3-CFHR1* deletion	Binds FH *CFHR3-CFHR1* deletion also found in 3% of healthy people
Membrane Bound	Membrane cofactor protein (MCP)	Membrane protein that promotes C3b inactivation	Loss of function
	Thrombomodulin (THBD)	Increases H cofactor activity Activates (Thrombin activatable fibrinolysis inhibitor) TAFI- mediated C3a and C5a activation	Loss of function

of disease in these two disease groups. This remains a very active area of research, with recent studies continuing to document both the similarities and differences in the patterns of genetic defects, their location within individual genes, and how these in turn differentially affect complement regulation on surfaces, in fluid phase, and with regard to binding sites (Osborne et al. 2018).

Gene Mutations in Complement Regulatory Proteins (Nester et al. 2015; Loirat and Fremeaux-Bacchi 2011; Noris and Remuzzi 2013; Kavanagh and Goodship 2010; Malina et al. 2012)

Mutations in Factor H (FH)

Factor H is circulating serum protein produced mainly in the liver, though also produced in quantitatively much smaller amounts by circulating lymphocytes, monocytes, dendritic cells, and in glomerular tissue on a "local" basis. It is formed of 20 short consensus repeat (SCR) domains, with an N-terminal SCR that forms the regulatory domain and a C-terminal SCR that forms the recognition terminal. The N-terminal competes with Factor B and accelerates the decay of the C3 convertase. FH also acts as a cofactor for Factor I-mediated inactivation of C3b. The gene encoding for FH is located in the RCA (regulators of complement activation) locus in chromosome in 1q32 and is the most frequently mutated gene in aHUS, identified in ~25% of all cases and in 40% of familial cases. Majority of the mutations are heterozygous and are located in the exons encoding the C-terminal domain of the protein. These mutations may not result in a quantitative deficiency of factor H, but instead normal levels of abnormal protein. In other cases, such as stop or nonsense mutations, FH levels may be drastically reduced.

Mutations in Factor I (FI)

Factor I is a regulatory plasma serine protease also synthesized mainly in the liver. FH has a modular structure consisting of a heavy chain that contains two low density lipoprotein

receptor domains, a CD5 domain, and a module only found in FI and complement proteins C6 and C7. FI inactivates C3b to iC3b and this into further fragments in the presence of cofactors including FH, and complement receptor 1 (CR1), MCP or von Willebrand factor. The gene encoding for FI is located on chromosome 4q25. Approximately 40 heterozygous mutations in FI have been reported corresponding to about 12% of aHUS cases. Depending on the nature of the mutation, plasma C3 concentration is decreased in 20–30% and CFI concentration in one third of affected individuals.

Mutations in Factor B (FB)

Factor B is a zymogen with a major role for amplification of the alternative pathway. FB is cleaved into factors Ba and Bb; and facilitates binding of Bb with C3 to form the active C3 convertase. With its formation, C3 convertase achieves a key threshold in the pathway of AP activation; regulation (inactivation) of C3 convertase is promoted by decay accelerating factor, CRI, and FH. The gene encoding FB is located in chromosome 6p21.3. Mutations in FB responsible for aHUS result in a gain of function by increasing the stability (and therefore activity) of C3 convertase via resistance to decay. FB mutations are uncommon, accounting only up to 4% of aHUS cases. Affected individuals have a permanent activation of AP with very low C3 and normal or low FB concentration. It is likely some of the mutations of FB in aHUS patients are either not pathogenic or only permissive, based on functional studies, acting in concert with associated mutations in the few cases reported (Osborne et al. 2018).

Mutations in Membrane Cofactor Protein (MCP/CD46)

MCP is a membrane cofactor protein expressed by most cells including leukocytes which serves as a cofactor for FI to degrade C3b and C4b. The MCP gene is located in within the RCA gene cluster on chromosome 1q32 and account for up to 15% of aHUS. MCP mutation is characterized by decreased MCP cell surface expression and less frequently the expression is normal but functionally inactive. Affected patients may present with normal C3 levels but about 1/4 to 1/3 of cases do have decreased levels; this often occurs when another complement-related mutation coexists. When MCP is defective, the most relevant cell surface involved in aHUS is the endothelial lining of the microvasculature of the kidneys. When affected individuals undergo kidney transplant, the graft and its endothelium is protected by expression of its intrinsic MCP. While post-transplant recurrence of aHUS is therefore unlikely in cases due to MCP mutation (in the absence of additional pathogenic defects in fluid-phase proteins), it is believed that recipient vascular cells do migrate into the graft, rendering the endothelium partially chimeric and variably susceptible to the effects of deficient MCP (Fremeaux-Bacchi et al. 2007).

C3 Mutations

C3 is abundant in plasma and its hydrolysis causes activation of the AP leading to the generation of C3 convertase. This reactions are regulated by cofactors including FH and MCP increasing the rate of dissociation of the convertase or serving as cofactor for FI to cleave C3b. The gene encoding for C3 is located on chromosome 19 and mutations in this gene account up to 10% of aHUS. In such cases, there is indirect gain of function by decreasing the ability of C3 to bind to the regulator MCP, with enhanced capacity of FB to bind C3b, resulting in greater formation of C3 convertase. Such patients present with low C3 levels in 70–80% of cases.

Antibodies Against Complement Factor H

Antibodies against FH (anti-FH) is an acquired dysfunction of FH but in a sense may be considered a complement mutation because it is highly

associated with rearrangements or deletions of FH-related proteins (typically homozygosity for delCFHR3-CFHR1) (Loirat and Fremeaux-Bacchi 2014). Interestingly, the deletion itself is not uncommon, found in up to 9% of healthy individuals in several populations studied; the mechanism leading to the association remains unclear. Anti FH Ab accounts for approximately 5–10% of cases of aHUS.

Thrombomodulin Mutations

Thrombomodulin (THBD) is a transmembrane glycoprotein expressed on vascular endothelial cells. Interacting with both the coagulation cascade and complement system, this protein facilitates activation of protein C and enhances thrombin-mediated activation of plasma procarboxypeptidase B, which inactivates C3a and C5a. THBD downregulates the AP by accelerating FI-mediated activation of C3b in the presence of cofactors. THBD mutations result in decreased function and account for 3% of cases of aHUS.

Noncomplement-Related Genetic Causes of aHUS

DGKE Mutation

The DGKE gene encodes diacylglycerol kinase-epsilon, an intracellular lipid kinase that phosphorylates diacylglycerol (DAG) to phosphatidic acid. DGKE is expressed in endothelium, platelets, and podocytes, and its mutation has been associated with aHUS in infants.

It is believed that the mechanism stems from loss of DGKE in endothelial cells, leading to endothelial cell damage and death, with a resulting microvascular prothrombotic consequence (Nester et al. 2015; Vieira-Martins et al. 2016). DGKE mutation is particularly frequent among infants (age $<$ 1 year) with aHUS; it accounts for 27% of sporadic cases and up to 50% of familial cases in that age group (Lemaire et al. 2013). While patients do not respond to anti-complement therapy, posttransplant recurrence risk appears to be very low. Recently, as with defects in the APC, the spectrum of renal disease due to DGKE has been extended beyond aHUS to include proliferative forms of GN, suggesting heterogeneity of effects (Azukaitis et al. 2017).

Cobalamin Deficiency Associated HUS

Cobalamin C disease is caused by a mutation in the gene encoding for the methylmalonic aciduria and homocystinuria type C protein (MMACHC). It is suggested that in Cobalamin deficiency–associated TMA, the hyperhomocysteinemia induces endothelial damage, leading to platelet aggregation and an induced procoagulant state with formation of microthrombi. Affected patients most commonly present in the newborn period with vomiting, poor sucking, failure to thrive, lethargy, hypotonia, and laboratory features of HUS/TMA (Beck et al. 2017).

Diagnostic Approach

The age, clinical presentation, and baseline laboratory should guide the diagnostic approach. It is critical to rule out infectious etiology (STEC-HUS or pneumonia-associated HUS) with bacterial and stool cultures. Cobalamin deficiency should be suspected in neonates and infants with supporting systemic findings including homocystinuria and methylmalonic aciduria. ADAMTS13 activity below 10% is consistent with primary or acquired TTP; testing for anti-ADAMTS13 antibodies can be helpful but it is important not to rule out aHUS with ADAMTS13 levels which are reduced, but greater than 10%. In many cases, it will not be clear whether a patient has typical HUS, aHUS, or another type of TMA during the acute presentation of the illness; regardless, in such cases empiric treatment must not be delayed pending clarification. When possible, it behooves clinicians to save plasma from the acute (as yet untreated) setting for future measurements that may clarify the diagnosis.

In suspected aHUS, thorough evaluation of the AP system is warranted. This can include plasma

C3 which is widely available; measurement of FH, FI, FB levels may also be done but as noted earlier, normal levels do not rule out aHUS and abnormal levels can be found in other conditions. Assessment for antibodies to FH and genetic testing, where available, should be performed for affected individuals. While these results do not inform initial diagnosis or guide acute therapy, the findings may be important for longer-term treatment, prognostication, and genetic counseling.

Treatment

Often, the first episode of aHUS an individual experiences will require treatment while the diagnosis remains suspected but not proven. Typical HUS, TTP, and other conditions like hemophagocytic syndromes, disseminated intravascular coagulation, and acute hemolytic anemia of other causes can remain in the differential diagnosis without impeding empiric treatment of aHUS while further diagnostic testing continues. Indeed, many of these conditions share some common treatment approaches.

The treatment of aHUS requires an experienced clinical team and supportive capacity typically available in tertiary care hospitals. The potential for rapid AKI with need for dialysis, as well as multiple organ pathology including CNS, cardiac, pulmonary, and GI systems must be respected. Untreated, the mortality rate and rate of renal failure is very high. In the immediate support of patients, red blood cell transfusion is often required, while platelet transfusion is generally reserved for those about to undergo a procedure with a high risk of bleeding, as there remains a clinical perception, somewhat controversial, that platelets may worsen the TMA by providing further substrate to create microthrombi.

Plasma Therapy

Historically, this was considered first line treatment; despite a lack of definitive studies, there was considerable observational evidence of benefit in many cases. Retrospective analysis supports the fact that plasma exchange (PE) in patients with aHUS can remove mutant FH, FI, FB, C3, and anti-FH antibodies, while plasma product replacement (in conjunction with PE or in isolation) can restore more normal protein levels. Following its definition as a cause of aHUS, patients with MCP gene mutation proved exceptions to this necessity with up to 90% of episodes resolving without the need for such treatment; this difference is believed to be the case because MCP is membrane-bound not in the fluid phase (Loirat et al. 2016; Loirat and Fremeaux-Bacchi 2011; Loirat et al. 2012).

Because plasma therapy is available relatively widely and quickly, and especially when eculizumab (discussed below) is not available or its administration is unavoidably delayed, plasma therapy can still be recommended. This treatment should begin as quickly as possible, at least within 24 h of presentation or when the empiric ("working") diagnosis of aHUS is recognized. Plasma exchange, rather than plasma infusion, is often recommended so as to enable larger volumes of plasma to be provided while reducing the risk of volume overload and severe hypertension especially in patients with AKI. Among infants or others in whom placing appropriate vascular access can itself present significant risk, plasma infusion may be used as a temporizing measure.

Plasma therapy should be performed daily until the platelet count, hemoglobin, and LDH normalize and renal function improves. Some patients may respond in less than a week and then tapering the frequency of treatment may be possible at that point. Maintenance therapy should be guided by frequency of relapses and the identified complement anomaly. While rapid institution of plasma therapy may be of benefit, it is also very important to consider the acute risks of PE including infusion reactions, hypotension or hypertension, altered coagulation profile, hypocalcemia, and anemia with additional requirement for blood transfusion, as well as catheter-related thrombosis and infection. As noted, placement and use of extracorporeal circuits can be life-threatening in hemodynamically unstable infants and children.

Chronic plasma therapy may help to gain control the acute episodes of aHUS, as well as to

prevent (as maintenance therapy) future episodes. Nonetheless, retrospective study has demonstrated that there is incomplete protection and that over time, a significant proportion of individuals with aHUS treated in this manner will continue to experience some amount of ongoing aHUS activity, accompanied by declining renal function and elevated risk of end stage kidney disease.

Eculizumab

Eculizumab is a humanized monoclonal antibody that inhibits terminal complement activity Eculizumab prevents C5 cleavage and formation of C5a, reducing the C5a pro-inflammatory and the toxic consequences of uncontrolled formation of the MAC. In the USA, the FDA approved eculizumab for the treatment of aHUS in 2011. Initial studies were widely viewed as demonstrating that eculizumab resulted in definitive remission of most cases of aHUS as well as superiority to plasma therapy (Legendre et al. 2013). Currently, eculizumab remains the only agent approved for aHUS, though newer generations of this treatment and alternative agents are in active development.

Eculizumab has been shown to be effective in patients with aHUS with or without detectable complement mutation, although it is not effective in cases due to DGKE mutation. Where early use of eculizumab was reserved for cases resistant to plasmatherapy, it should be considered standard of care in all phases of illness. Prompt empiric use in suspected cases of aHUS is indicated since outcomes after prompt treatment are superior than with delayed treatment (Yuksel et al. 2016). Even in cases where prompt diagnosis or treatment was delayed or not possible, administration of eculizumab has been shown to improve renal function over chronic periods of use, with some chronically dialysis-dependent patients regaining a degree of renal function. Treatment is also demonstrated to be effective in preventing or treating posttransplant aHUS recurrence, depending on the etiology. Patients with MCP mutation do not require and those with DGKE mutations do not benefit from eculizumab therapy. Certain uncommon variations in C5 complement reduce efficacy as well (Nishimura et al. 2014).

Due to inhibition of complement activity, eculizumab increases the risk of serious and fatal infection by encapsulated bacteria principally including *N. meningitidis*, but also *S. pneumoniae* and *H. influenza*. Other infections like respiratory tract infections, urinary tract infections, as well as viral syndromes have been reported in 23% to up to 42% of patients taking eculizumab. Antimeningococcal vaccination must be used, and vaccination for the other mentioned pathogens is extremely important as well. Because vaccination takes at least 2–4 weeks to achieve protective titers, prophylaxis with penicillin or other appropriate agent is required when eculizumab is required acutely (Benamu and Montoya 2016). Some clinicians will choose to use both vaccination as well as chronic antibiotic prophylaxis in all patients for concern of waning immunity on in particular for fear of impaired vaccine response. This concern may be particularly valid for example in a patient with a kidney transplant under immunosuppression or for infants whose vaccine responses may be incomplete.

Transplantation Considerations

Ideally, treatment of aHUS should prevent end-stage kidney disease. However, there are patients who suffered kidney failure before effective treatment was available or in whom it could not be delivered effectively. In other patients, the diagnosis of aHUS was not recognized and may only come to light after kidney failure or after transplantation when the disease may recur. Thus, the need to manage kidney transplantation for patients with aHUS remains highly relevant.

Achieving a good outcome after any of type of transplantation requires the best practices of "routine" surgical and perioperative management like dialysis, plasma exchange, central catheter management, posttransplant anticoagulation, and immunosuppression. Historically, many individuals suffering from aHUS and kidney failure remained dialysis-dependent for very long

periods, in some cases many years. Severe TMA with medium-sized and large vessel involvement is also not uncommon in aHUS even in cases where dialysis is not required. Prior to transplant surgery in such individuals, it is important to use imaging to carefully assess the central vasculature for unsuspected occlusions in order to identify both occluded as well as appropriate sites for transplant vessel anastomosis.

Like other inheritable causes of renal disease, living-related donor evaluations for individuals suffering from aHUS also require additional care. The individual genetic evaluation of each case is therefore of high importance and should be required before a related donor be accepted. In some cases, the potential donor may have risk of aHUS in addition to transmission of risk to the recipient.

Posttransplant recurrence and less frequently, de novo occurrence, of aHUS may occur. In a patient with recognized aHUS undergoing transplantation, the optimal approach requires an assessment of whether the patient's condition had been or will be responsive to eculizumab. In cases where recurrence is most likely, such as mutation in CFH, CFB, or CFI, the transplantation protocol must include preoperative eculizumab followed by regular treatment for prevention of aHUS. The surgical procedure of transplantation, along with the relative ischemia of the graft and its reperfusion are themselves potential triggers for aHUS. Unavailability of chronic eculizumab in any case should be considered a relative contraindication to transplant because other options such as observation alone or use of plasma therapy are more likely to result in graft loss and morbidity.

Unexpected aHUS following transplantation should be evaluated and treated in the same way as disease in the native kidneys. Such an occurrence usually indicates the original cause of ESRD was aHUS though there are exceptions. Posttransplantation aHUS in individuals with transplantation of other solid organs should also be evaluated as with aHUS in nontransplanted individuals. In addition to the simple fact that liver failure and transplantation surgery with reperfusion injury are potentially large triggers of aHUS, the possibility of "inheriting" a specific risk factor is evident. In one case, a donor had an asymptomatic CFH mutation and the recipient an unknown MCP defect which together permitted aHUS at a later date (Brown et al. 2012). The de novo occurrence of aHUS following stem cell or marrow transplantation is more common than for solid organs and may be unrelated to the mechanisms of aHUS discussed in this chapter. However, it is now well-described that TMA in such patients can and often does result from the same pathophysiological pathways described above. Thus, a similar, though modified, diagnostic and therapeutic approach will apply; importantly, clinicians may need to evaluate the genetic factors of both the graft and the recipient host.

As described earlier in the chapter, FH, FI, FB, and C3 are circulating proteins mainly produced in the liver, explaining the high recurrence rate of disease after isolated kidney transplant in patients with mutations leading to defects in these proteins. On the other hand, MCP and DGKE mutations are widely expressed, so a kidney transplant from a healthy donor not only restores kidney function but also represents local gene therapy by allowing expression of normal protein in that kidney. Also discussed above, individuals with the latter defects should not be considered totally immune from relapse following transplantation. Not only are multiple simultaneous genetic defects possible but exceptions do occur, for example, via evolution of recipient microchimerism in grafts of patients with MCP mutation which render the recipient susceptible to recurrence (Fremeaux-Bacchi et al. 2007).

Among patients with mutations in genes encoding for hepatically synthesized and circulating complement proteins, combined liver-kidney to cure patients with aHUS and end-stage kidney disease, or isolated liver transplantation to cure patients with aHUS with preserved renal function, may be considered (Saland et al. 2009; Saland 2014). This approach carries some important risks and also some potential benefits, which must be considered carefully for each patient. A perioperative strategy to approach transplant in the same manner as isolated kidney transplant in order to prevent aHUS recurrence is required,

Table 2 Observational frequencies of various mutations responsible for aHUS, percent of cases of ESRD and transplant recurrence (if untreated). (Reproduced from Nester et al., "Atypical aHUS: State of the art" with permission)

Gene	Frequency of mutations (%)	Native kidney outcome ESRD (%)	Transplant kidney outcome risk of recurrence (%)
CFH	24–27	52–65	80–90
MCP	5–9	6–63	15–20
C3	2–8	43–67	40–50
CFI	4–8	17–83	70–80
CFB	<1–4	70	[a]
THBD	5	23	[a]
CFHRS	<1–4	[a]	[a]
DGKE	<1	[a]	[a]
CFHR	3–10	[a]	[a]
FH Autoantibody	3–6	[a]	[a]

[a]Insufficient data, registry data pending

namely, using perioperative eculizumab or intensive plasma exchange. While this option predated eculizumab and has largely been supplanted, given its potential for cure, it should not be discarded as an option, but given its risks, it should also be reserved for cases where eculizumab is not available, strong patient preference, or in the uncommon scenario in which eculizumab is not effective (Coppo et al. 2016). Use of liver transplantation to cure aHUS should not be considered for patients with no evidence of gene mutations, patients with isolated MCP or DGKE mutation, anti FH-autoantibodies, or in the small minority of patients with mutations in a hepatically synthesized product (like FH or FI) but in whom affected family members (or themselves) have undergone successful isolated kidney transplantation (Table 2).

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Thrombotic Thrombocytopenic Purpura, Genetic and Secondary

43

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Contents

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a clinical entity caused by deficiency of the ADAMTS13 protease, either due to hereditary deficiency or autoantibody formation. ADAMTS13 deficiency results in the persistence of ultralarge von Willibrand factor (vWF) multimers in the blood, which cling to the endothelial surface, resulting in the deposition of platelet-rich vaso-occlusive thrombi. Occlusion and mechanical shearing caused by these thrombi result in the clinical manifestations of thrombocytopenia, microangiopathic hemolytic anemia, renal injury, neurologic manifestations, and fever. TTP is an extremely rare disease, with incidence of approximately 3 per million people in adults, and 1 per 10 million in children. While mortality rates in the past reached as high as 90–100%, the advent of effective treatment, most notably with corticosteroids and plasma exchange therapy, has resulted in a significant improvement in outcomes, with survival rates of 70–90%.

Keywords

Thrombotic microangiopathy (TMA) · Thrombotic thrombocytopenic purpura (TTP) · ADAMTS13 · Plasmapheresis

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Introduction

Thrombotic thrombocytopenic purpura (TTP), first described in Moschcowitz 1924 by Eli Moschcowitz, is a clinical entity caused by a deficiency in ADAMTS13, the protease responsible for cleaving von Willibrand factor (vWF). It is a form of thrombotic microangiopathy (TMA), a family of diseases characterized by endothelial injury and microthrombus formation. Other diseases in this family include hemolytic-uremic syndrome (HUS), drug-induced TMA, and pregnancy-associated diseases such as HELLP (hemolysis, elevated liver function tests, and low platelets). TTP is often idiopathic, although certain precipitating conditions such as malignancy, HIV infection, lupus, post-transplant state, and HIV infection have been described.

TTP is a rare disease, with an incidence of approximately three cases per million in adults, and even lower frequency of about 1 per 10 million in children (Reese et al. 2013). TTP in children is often the result of congenital ADAMTS13 deficiency, whereas in adults is generally the result of acquired deficiency due to the development of autoantibodies.

TTP is characterized by hemolytic anemia, thrombocytopenia, acute kidney injury (AKI), fever, and neurologic symptoms (Amorosi and Ultmann 1966), although the presence of this classic pentad has decreased in frequency as more effective treatments have been discovered, allowing earlier management of the disease (Kremer Hovinga et al. 2010). The mainstays of effective treatment in acquired TTP are plasma exchange therapy as well as corticosteroids, whereas congenital TTP can be managed with plasma infusion without exchange. Although in the past TTP had extremely high mortality rates, the discovery of effective treatment protocols has resulted in improvements in survival rates.

This chapter will focus on idiopathic and congenital TTP. Other thrombotic microangiopathies such as typical and atypical HUS are discussed elsewhere.

Pathophysiology

TTP is a result of a deficiency of ADAMTS13, a member of the zinc metalloproteinase gene family which acts as a vWF-cleaving protease. The gene for ADAMTS13, which stands for A Disintegrin and Metalloprotease with a ThromboSpondin type 1 motif, member 13, is located on chromosome 9q34 and is expressed primarily in the liver (Levy et al. 2001). The function of ADAMTS13 is to cleave vWF multimers on the endothelial surface. vWF is a platelet-adhesive protein involved in coagulation and hemostasis. It is produced as ultralarge multimers by the endothelial cells and megakaryocytes and works primarily by binding to collagen and other proteins such as Factor VIII. It is degraded by ADAMTS13, thereby becoming inactive. Deficiency of ADAMTS13 results in the persistence of ultralarge vWF multimers, which can remain bound to the endothelial surface and can bind platelets (Moake et al. 1994; Fujikawa et al. 2001). Occlusion and mechanical shearing caused by these platelet-rich vaso-occlusive thrombi result in the clinical manifestations of thrombocytopenia, microangiopathic hemolytic anemia, renal injury, neurologic manifestations, and fever.

ADAMTS13 deficiencies may be congenital, due to mutations in the ADAMTS13 gene, or they may be acquired as a result of autoantibody formation. Congenital TTP, also known as Upshaw–Schulman syndrome (Upshaw 1978; Schulman et al. 1960), is inherited in an autosomal recessive pattern and results in a deficiency of ADAMTS13 (Furlan et al. 1998). Various mutations have been described and are associated with variation in clinical phenotype. Lotta et al. (2012) have shown that mutations associated with lower levels of residual ADAMTS13 activity were associated with earlier onset of disease activity, whereas less severe mutations may present during the teenage years or during pregnancy in affected females. It is thought that mutations in the highly conserved N-terminal domains may result in more severe mutations than those in C-terminal domains, as these are associated with lower residual ADAMTS13 activity and earlier age of onset.

Heterozygotes for ADAMTS13 mutations are carriers and are not thought to display any clinical phenotype (Levy et al. 2001). It is also possible that other genetic and environmental modifying factors are present which can alter the onset of clinical expression.

Acquired TTP is the result of autoantibody inhibitor formation. A study by Rieger et al. (2005) detected the presence of anti-ADAMTS13 IgG in 97% of those with ADAMTS13 levels <10%, whereas prevalence of this antibody was only 20% in those with ADAMTS13 activity >10%. The autoantibody neutralizes ADAMTS13, resulting in severe deficiency.

Epidemiology

Although TTP can present in childhood, it is primarily a disease of adults, with a standardized incidence rate more than 30-fold higher in than in children (Reese et al. 2013). The annual incidence in adults is about 3 cases per million adults per year, but only about 1 in 10 million per year in children under 18 years of age (Reese et al. 2013; Torok et al. 1995). TTP may be precipitated by various factors including drugs, HIV infection, malignancy, and lupus (Allford et al. 2003). It has a peak incidence in the third to fourth decades of life, has a female predominance, and is more common in blacks than whites (Reese et al. 2013).

Congenital TTP, also known as Upshaw–Shulman syndrome, is an autosomal recessive condition that can be due to homozygous or compound heterozygous mutations. Carriers do not appear to be affected. Disease severity is variable and depends on the genetic mutation present. Environmental factors and stressors may also play a role in time of presentation. These include factors that can also induce secondary TTP, including medications such as calcineurin inhibitors, antivirals, and hormonal contraceptives and replacement therapies, as well as infectious etiologies including HIV, enteropathic bacteria, and parvovirus (Kok et al. 2001). Hereditary TTP often presents in the neonatal or early childhood period, although it can present in the teenage years as well, and in many cases does not manifest until during pregnancy (Fujimura et al. 2011). The disease is extremely rare, with the Hereditary TTP Registry currently listing only 189 enrolled members from 18 countries, although this may be an underestimate (www.ttpregistry.net).

Presentation

TTP is characterized by a classic pentad of symptoms which includes microangiopathic anemia, thrombocytopenia, acute kidney injury (AKI), fever, and neurologic symptoms. In the era prior to initiation of effective treatment for TTP, when symptoms generally progressed and led to mortality, these five features could be found in approximately 88–98% of patients at time of diagnosis (Kremer Hovinga et al. 2010). However, current diagnostic criteria include primarily thrombocytopenia and anemia, with decreased frequency of fever, neurologic symptoms, and AKI to about 24–63% (Rock et al. 1991; Kremer Hovinga et al. 2010). Neurologic features vary and include headaches, altered behavior, seizure, and coma. Abdominal pain, a sign of GI ischemia, as well as serous retinal detachment has also been described (Torok et al. 1995). Renal impairment is often absent and, when present, is often less severe than in other forms of TMA, with some studies showing as low as 18% of cases having renal involvement (Shumak et al. 1995). Vesely et al. (2003) report a series of 65 patients, in which 53% had normal renal function and only 6% had renal failure.

Laboratory findings on presentation include signs of hemolytic anemia, with evidence of schistocytes on smear and elevation of LDH. Coombs testing is negative, as hemolysis is mechanical rather than immune-mediated. Thrombocytopenia must also be present, with platelet count below 150×10^9 per liter, although some studies have used the stricter criterion of $<100 \times 10^9$ per liter (Bell et al. 1991; Peyvandi et al. 2016). However, platelet counts are often much lower than this, with a median value of

11×10^9 per liter in a study using the Oklahoma TTP-HUS Registry (Kremer Hovinga et al. 2010). Coagulation studies are typically normal.

Diagnosis

Due to the urgency of initiating treatment, presumptive diagnosis of TTP is often made on clinical presenting features and readily available lab parameters as described above. Definitive diagnosis, however, relies on measurement of ADAMTS13 activity, which is severely reduced, often to <10%. Inhibitor (autoantibody) testing can also be performed. A table of diagnostic lab criteria for TTP is presented below (Table 1). Measurement of ADAMTS13 activity can be done using quantitative immunoblotting or a fluorogenic assay using FRETS-VWF73 substrate; the diagnosis of TTP is confirmed by detection of low level of ADAMTS13 activity, generally below 10% using either method (Reese et al. 2013). However, cases of clinically diagnosed TTP have been reported with normal levels of ADAMTS13 activity in the setting of low autoantibody titer, and these titers may rise over time in the setting of chronic immune system activation (Froehlich-Zahnd et al. 2012). Falsely normal ADAMTS13 levels may also be seen in patients who have received transfusions or plasmapheresis with plasma replacement prior to testing; therefore, it is important if possible to obtain serum samples prior to initiating these interventions. Levels >50% generally suggest against TTP as the underlying cause of clinical findings and are helpful in distinguishing TTP From other forms of TMA.

Table 1 Lab parameters in the diagnosis of TTP

Clinical lab findings	Anemia Thrombocytopenia ($<150 \times 10^9$/L) Elevated creatinine Schistocytosis Elevated LDH Coombs negative Coagulation studies normal
ADAMTS13 testing	Activity levels (<10%) Immunoblotting Fluorogenic assay Inhibitor testing Mixing studies ELISA Genetic testing

Testing for ADAMTS13 inhibitor can be done using a mixing study, in which patient plasma is mixed with normal plasma to detect inhibition of ADAMTS13 activity, or via ELISA to detect IgG against ADAMTS13. ELISA has been shown to detect autoantibodies in 95% of cases of idiopathic TTP (Scully et al. 2008).

Severe ADAMTS13 deficiency without detection of inhibitors is characteristic of hereditary TTP and can be confirmed via genetic testing. Genetic testing is available as part of the Hereditary TTP registry (www.ttpregistry.net). As noted above, genetic mutations are variable and different mutations may have variable clinical phenotypes. In hereditary TTP, ADAMTS13 deficiency is demonstrable even during periods of clinical remission (Fujimura et al. 2011).

Pathology

Although a kidney biopsy is not required for diagnosis and often may not be performed, TTP does have characteristic findings of a thrombotic microangiopathic process on renal biopsy. Biopsy findings in the early stages of disease show capillary wall thickening caused by endothelial cell swelling with deposition of fibrin and acellular material. Fragmented blood cells, platelet thrombi and fibrin accumulate and occlude the capillary loops, and fibrinoid necrosis and thrombosis of the afferent arteriole can be seen. Mesangiolysis, a loss of normal mesangial structure in the setting of apoptosis, may also be observed. As the disease progresses, myointimal proliferation of the arteries occurs, producing a characteristic swollen appearance termed mucoid intimal hyperplasia. Immunofluorescence shows fibrin and fibrinogen deposition in the glomerulus, mesangium, and vessel walls. As the disease progresses and glomerular collapse occurs, secondary tubular loss can also be seen (Fogo and Kashgarian 2012).

Management

Effective management strategies for TTP have resulted in dramatically reduced mortality. Management of acquired and hereditary forms of TTP differ, and treatment of acquired TTP is discussed first here.

Plasmapheresis is considered the most effective therapy and standard of care for management of TTP. Plasmapheresis is demonstrated to have benefit in acquired TTP. A comparison of plasma infusion versus plasmapheresis demonstrated increased response rate in patients treated with pheresis (Rock et al. 1991). While plasma infusion alone can replace the deficiency in ADAMTS13, it does not remove the autoantibody responsible for its destruction, for which pheresis is required. In addition, plasma infusion requires larger volumes, which may result in increased adverse events from volume overload. In the study by Rock et al. (1991), patients were treated with daily pheresis or plasma infusion until platelet count improved to $>150 \times 10^9$ per liter for two consecutive days and were then tapered over the next 2 weeks. Patients treated with plasmapheresis had a significantly lower death rate as compared to plasma infusion ($p = 0.036$). Plasma exchange for TTP should use fresh frozen plasma rather than albumin as replacement (Bell et al. 1991), in order to replace the existing ADAMTS13 deficiency. Cryosupernatant, which lacks the largest vWF multimers and therefore may be thought to be most effective, has also been used, although data are mixed as to whether this results in superior outcomes as compared to FFP (Zeigler et al. 2001). Single-volume exchange is standardly used (approximately 40 mL/kg), and volume and/or frequency of administration may be increased if there is lack of clinical improvement (Allford et al. 2003).

Plasma exchange is typically given daily until clinical improvement is noted and lab parameters show normalization for 24–48 h (Bell et al. 1991). Use of less frequent plasma exchange has been associated with increased frequency of exacerbation. Some studies have continued with infusions of fresh frozen plasma after pheresis has been discontinued (Bell et al. 1991), and many centers taper plasma exchange sessions slowly rather than discontinuing abruptly (Allford et al. 2003).

Corticosteroids are considered a standard adjunct therapy in management of acquired TTP. They are thought to act via immunosuppressive mechanisms to reduce autoantibody production. Although there is a lack of clinical trials supporting its use, it is routinely used in treatment protocols (Allford et al. 2003; George 2010). Corticosteroids can induce remission in up to 30% of patients. (Allford et al. 2003). A trial comparing high dose (10 mg/kg) versus low dose (1 mg/kg) solumedrol found that remission rates were higher in those receiving the higher dose (Balduini et al. 2010). Patients with less severe neurologic findings may be treated with oral prednisone at lower dosing (Bell et al. 1991), with increase in steroid dosing if the platelet count does not normalize within 3–4 days (George 2010). After platelet recovery occurs, steroids are typically tapered over a few weeks. Although steroids alone may be effective in patients with minimal symptoms and no CNS involvement, those with more significant disease are generally treated with plasma exchange as well. A study of patients with TTP initially treated with glucocorticoids alone found no response in 44% of these patients; they were subsequently treated with plasma exchange with response in the majority (Bell et al. 1991).

While plasma exchange therapy and glucocorticoids represent the mainstays of TTP treatment, the addition of other agents may help improve survival and may play a role in management of refractory disease. Rituximab has been studied as an adjunct in addition to plasmapheresis and steroids. Rituximab, an anti-CD20 antibody, results in reduction of IgG autoantibodies against ADAMTS13. A study by Scully et al. (2011) compared patients treated with rituximab to historical controls and noted similar response rates and survival, with a significantly lower rate of relapse in the rituximab group. Treatment with rituximab was not associated with increased risk of infection or other serious adverse event. Although many centers reserve the use of Rituximab for refractory disease, a study by Westwood et al. (2013) showed that early administration of Rituximab, given within 3 days of

presentation, was associated with significantly reduced time to remission (12 vs. 20 days, $p < 0.001$), as well as significantly shorter hospital stay. A recent study by Page et al. (2016) found that patients treated with Rituximab in addition to plasma exchange and steroids had a significantly lower rate of relapse despite more resistant initial disease (13% vs. 43%, $p = 0.009$), with a 30% reduction in absolute risk of relapse. The most commonly used regimen for Rituximab in TTP is 375 mg/m^2, given once weekly for 4 weeks (Sayani and Abrams 2015). As more evidence is gathered, Rituximab may be added to the initial standard-of-care regimen for acquired TTP.

There is weak evidence for the use of stronger immunosuppressants such as cyclophosphamide (Stein et al. 2004; Zheng et al. 2003) and cyclosporine (Cataland et al. 2007) in refractory TTP. However, these are generally reserved for very refractory cases due to their side effect profile, including risk of drug-induced TMA with cyclosporine. Others have proposed the use of vincristine in refractory TTP (Bobbio-Pallavicini et al. 1994; Ferrara et al. 2002), which has been shown to result in platelet recovery by an unknown mechanism. Ziman et al. (2005) reported on 12 patients who were treated with vincristine in addition to plasmapheresis at the onset of disease and reported achievement in remission in all patients with no significant adverse effects. However, most published management strategies appear to favor Rituximab over other immunosuppressive options (Sayani and Abrams 2015).

Case reports of the use of bortezomib for relapsing TTP have been reported (Yates et al. 2014; Eskazan 2016); however, large-scale studies are lacking. Bortezomib is a protease inhibitor that may act by depleting residual plasma cells and also by inhibiting endocytosis of ADAMTS13 by inhibiting maturation of dendritic cells (Park et al. 2013).

Caplacizumab is an anti-von Willibrand factor antibody which inhibits the interaction between ultralarge vWF multimers and platelets. In a recent randomized controlled trial comparing caplacizumab to placebo, in addition to plasma exchange therapy and immunosuppressive medication, those receiving the antibody had a significantly reduced time to response (39% reduction in median response time, $p = 0.005$) (Catalan and Wu 2015, Peyvandi et al. 2016). However, relapses after cessation of treatment were more common in the caplacizumab group.

Other ancillary treatments such as splenectomy (Reynolds et al. 1976), and use of antiplatelet agents such as aspirin (Myers 1981; Rosove et al. 1982), have not been shown in studies to have consistent beneficial effect and are no longer routinely used. However, consistency in treatment recommendations are somewhat lacking, and some still recommend the use of low-dose aspirin once platelet levels have recovered due to a trend in reduced mortality (Bobbio-Pallavicini et al. 1997). Splenectomy has been reported in some studies to result in clear clinical deterioration (Bell et al. 1991); however, others have reported prompt clinical improvement with sustained 10-year remission rates of 70% (Kappers-Klune et al. 2005). However, due to the complicated nature of the surgery and risk of complications, splenectomy is infrequently used in the era of effective medical treatments (Sayani and Abrams 2015).

Supportive treatment including use of blood product transfusions may be needed. Although some studies have found an association between platelet transfusions and increased rates of arterial thrombosis (Harkness et al. 1981; Goel et al. 2015), a systematic review by Swisher et al. found no clear evidence of increased mortality or neurologic risk in patients who had received platelet transfusions (2009).

Hereditary TTP is managed somewhat differently and relies on plasma infusion. As no inhibitor is present and the deficient protein only needs to be replaced, plasma infusion alone is sufficient and plasma exchange is not required. During an acute exacerbation, daily infusions are given until the platelet count returns to normal (Barbot et al. 2001). Some patients who continue to have mild symptoms even during periods of relative remission may require chronic plasma infusion for prophylaxis, typically given every 2–4 weeks (Chintagumpala et al. 1992). Others routinely manage patients with hereditary TTP with prophylactic therapy even when no symptoms are present (von Krogh et al. 2016). For those not undergoing chronic prophylactic therapy, plasma infusions may be

required during times of acute stress, such as when undergoing surgical procedures and during pregnancy. There is a high risk of pregnancy loss with untreated congenital TTP during pregnancy; therefore, it is recommended that pregnant women with congenital TTP receive plasma infusion every 1–2 weeks until 6 weeks postpartum (Scully et al. 2014).

Recombinant ADAMTS13 is another potential treatment currently under investigation. Studies have shown that recombinant ADAMTS13 can normalize vWF activity by overcoming inhibitory autoantibodies (Plaimauer et al. 2015). A clinical trial of recombinant ADAMTS13 is now underway, and results of a phase 1 study showed that the treatment was well tolerated with no serious adverse events reported (Mannucci et al. 2013).

Prognosis

Untreated TTP has a mortality rate as high as 90% (Kremer Hovinga et al. 2010). Mortality has decreased with the advent of more effective treatment for TTP, with reports of survival rates of 70–90% reported after the use of plasma exchange was adopted (Rock et al. 1991; Kremer Hovinga et al. 2010). Analysis of the Oklahoma TTP-HUS Registry, which includes patients with both TTP and HUS for whom plasmapheresis was requested, demonstrated overall survival of 69% across a 2-year patient accrual period (Kremer Hovinga et al. 2010). In this study, patients with ADAMTS13 $<$ 10% (more likely to have idiopathic TTP than other causes of TMA) had a higher survival rate of 78% as compared to the overall group.

In an analysis of over 8000 patients admitted to the hospital with primary diagnosis of TTP (Goel et al. 2016), it was found that age greater than 60 years, arterial thrombosis, intracranial hemorrhage, renal failure, ischemic stroke, myocardial infarction, and having received platelet transfusions were all independent risk factors for mortality. This was similar to the mortality risk factors described by Benhamou et al. (2012) in their report of the French TMA Reference Center experience.

TTP often has a relapsing and remitting course. One study found relapse rates of 64% (Bell et al. 1991), most occurring shortly after the initial episode. Various definitions of relapse exist. In one study, the recurrence of thrombocytopenia within 30 days of cessation of plasma exchange was termed an exacerbation, whereas recurrence after 30 days was defined as relapse (Peyvandi et al. 2016). Other studies however have defined relapse as any recurrence of symptoms after initial response. In Bell et al. (1991), the cumulative incidence rate of relapse, defined as the occurrence of a new episode of TTP after the achievement of remission (no plasma exchange for 30 days), was 41% at 7.5 years.

Severity of ADAMTS13 deficiency, both during initial presentation and during remission, has been found to predict risk of relapse (Kremer Hovinga et al. 2010). Patients with more severe ADAMTS13 deficiencies were found to have higher rate of relapse and required more pheresis to achieve remission. In addition, male sex was found to be associated with increased risk of relapse. Most relapses have been found to occur within the first year after initial remission was achieved (Peyvandi et al. 2016). Patients who continued to have low ADAMTS13 levels during episodes of clinical remission were also noted to have a 3 times higher risk of recurrence (Peyvandi et al 2008).

In patients who survive an acute episode of TTP, long-term effects such as minor cognitive abnormalities have been reported (Kennedy et al. 2009; George 2009). A long-term follow-up of TTP survivors in the Oklahoma TTP-HUS registry found significantly higher rates of hypertension and depression as compared to the general population. In addition, patients with previous history of TTP appeared to die prior to their expected age of death, often from cardiac causes. Renal function was not significantly different as compared to the general population (Deford et al. 2013).

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Glomerular Diseases Associated with Malignancies

44

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Abstract

Glomerular diseases associated with malignancies remain rare. A wealth of glomerular lesions has been described in a variety of neoplasms, resulting from diverse pathophysiologic links. At variance with solid tumor-associated glomerulopathies for which the pathophysiology remains poorly understood, a molecular link can usually be demonstrated in hematologic malignancy-induced glomerulopathies. This chapter provides an update on epidemiology, pathophysiology, clinical presentation, and therapy of these paraneoplastic glomerulopathies. The usefulness of novel biomarkers, such as anti-phospholipase A2 receptor (PLA2R) antibodies and anti-thrombospondin domain 7A antibodies in membranous nephropathy or immunoglobulin-free light-chain ratio in paraprotein-related glomerulopathies, is emphasized. This chapter also covers rare types of glomerulopathies such as those encountered in patients with myeloproliferative neoplasms and glomerular metastases where glomerular involvement is directly linked to cancer cells. It will only briefly touch anticancer drug-induced glomerulopathies which are described in another chapter. One important aspect that we also discuss in this chapter relates to the concept of malignancy. Although visceral complications associated with benign cell proliferation such as monoclonal gammopathy of renal significance are by definition out of the scope of this chapter, they may have ominous and, so to speak, "malignant" consequences with life-threatening complications. It is remarkable that glomerular diseases associated with malignancy are often substantially improved by the cure of the proliferative disorder, which points to the importance of etiological investigations in patients with a glomerulopathy of unknown origin.

Keywords

Membranous nephropathy · Thrombotic microangiopathy · Amyloidosis · Hematologic malignancy · Lymphomas · Chronic lymphocytic leukemia · Myeloma · Waldenström macroglobulinemia · Monoclonal immunoglobulin deposition disease · Immunotactoid glomerulopathy

Introduction

Glomerular diseases associated with malignancies are not a new concept. Actually paraneoplastic glomerulopathy was first reported in 1922 by Galloway in a patient with Hodgkin's disease. Since then, the spectrum of paraneoplastic glomerulopathies has markedly expanded with the description of glomerular complications in a variety of solid epithelial tumors and hematologic malignancies. The term *paraneoplastic syndrome* refers to clinical manifestations that are not directly related to tumor burden, invasion, or metastasis but are caused by the secretion of tumor cell products such as hormones, growth factors, cytokines, and tumor antigens. The diagnosis of paraneoplastic glomerulopathy should rely on three strong criteria (Ronco 1999). First, a remission occurs after complete removal of the tumor by surgery, chemotherapy, or other treatments. Second, a renal relapse accompanies recurrence of the neoplasia. Third, a pathophysiologic link is established between cancer

and glomerulopathy. However, these criteria are not always gathered, and the evidence of a causal relationship between glomerulopathy and cancer may be blurred particularly in the case of solid tumors.

This chapter also covers rare types of glomerulopathies such as glomerular metastases and those encountered in patients with myeloproliferative neoplasms where glomerular involvement is directly linked to cancer cells. It will only briefly touch anticancer drug-induced glomerulopathies which are dealt with elsewhere and represent a new and expanding field with the dramatic progress of the cancer therapy and the development of a wealth of new drugs.

One important aspect that we also discuss in this chapter relates to the concept of malignancy. Although visceral complications associated with benign cell proliferation such as monoclonal gammopathy of renal significance (MGRS) are by definition out of the scope of this chapter, they may have ominous and, so to speak, "malignant" consequences. A good example is provided by light-chain amyloidosis caused by deposition of monoclonal light chains commonly produced by a plasma cell clone with benign features, which entails a more severe vital prognosis than low-mass myeloma.

Epidemiology

The prevalence of renal involvement in patients with cancer has been studied in autopsy and clinical series. In clinical series, the use of a low threshold of proteinuria and the detection of hematuria by qualitative dipstick tests have led to an overestimation of the prevalence (range, 7–34%), (Puolijoki et al. 1989). In autopsy studies, data are conflicting because of technical limits to postmortem study.

The prevalence of cancer in patients with glomerulopathy has been evaluated by few studies and varies from 3% to 23% (Ronco 1999). Compared with the general population, patients with glomerulopathy present an increased risk for cancer after the diagnosis of glomerulopathy as revealed by the analysis of the Danish Kidney Biopsy Registry which included all biopsies performed in Denmark since 1985 (Birkeland and Storm 2003). This study shows an increased risk by 2.4-fold during the first year and by 3.5-fold during the second year and until the end of the fourth one. However, this result was not confirmed at 5 years or thereafter. In the Tromsø study, albuminuria seemed to be a risk factor for cancer since patients with an albumin-to-creatinine ratio (ACR) in the highest quintile were 8.3- and 2.4-fold more likely to develop urinary bladder and lung cancers, respectively, than those with ACR in the lowest quintile (Jørgensen et al. 2008). This link between cancer and albuminuria may reflect the inflammatory process induced by neoplastic cells through elevated levels of cytokines responsible for an increased glomerular permeability. Nevertheless, it is difficult to assess the true prevalence of cancer among patients with a glomerular disease because of several bias: potential detection bias (e.g., in the case of membranous nephropathy in which patients are likely to be more aggressively screened for cancer), demographic characteristics of the population (e.g., membranous nephropathy and cancer tend to occur more frequently in the elderly and/or in heavy smokers), and the use of immunosuppressive agents to treat glomerular disease which may itself lead to subsequent malignancies (Cambier and Ronco 2012).

Solid Tumor-Associated Paraneoplastic Glomerulopathies

Membranous Nephropathy

Membranous nephropathy (MN) is a rare disease compared with cancer. Its annual incidence in adults worldwide is one new case per 100,000 per year (Maisonneuve et al. 2000). MN is the most common cause of the nephrotic syndrome in Caucasian adults, accounting for about 30% of cases, with a significant male preponderance and a peak incidence in the fourth and fifth decades. MN is an autoimmune disorder that targets the kidney glomerulus and more precisely the podocytes. It results from the formation of subepithelial immune deposits leading to complement activation at the podocyte surface, cell injury, and urinary protein loss (Fig. 1;

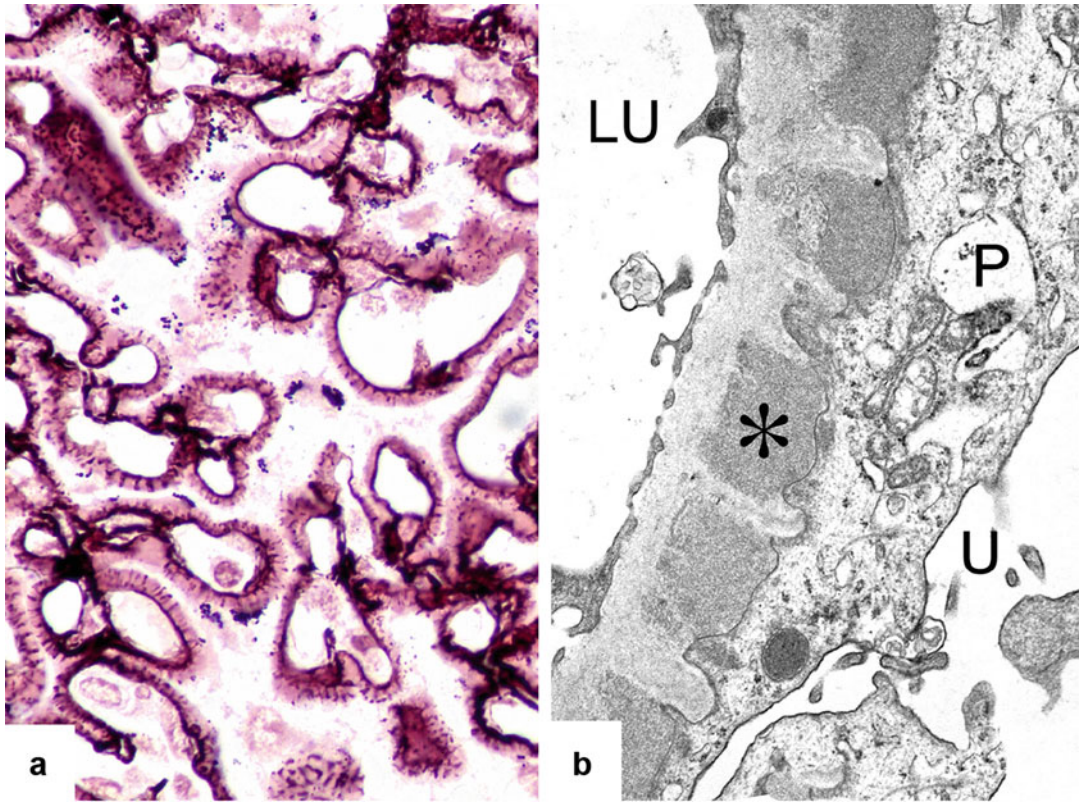

Fig. 1 (**a**) Type II MN with numerous spikes projecting from the epithelial side of the GBM. (Jones, ×500) (**b**) Diffuse subepithelial electron-dense deposits (*). (Uranyl acetate and lead citrate, ×29,000). *P*, podocyte; *Lu*, lumen; *U*, urinary space

Glassock 2010). Several podocyte antigenic targets have been identified such as neutral endopeptidase in the neonate (Debiec et al. 2002) and the phospholipase A2 receptor (PLA2R) (Beck et al. 2009) and the thrombospondin type 1 domain-containing 7A (THSD7A), (Tomas et al. 2014) in the adult; both PLA2R and THSD7A being colocalized within subepithelial deposits with IgG4. MN can be idiopathic or primary, without any identified cause (70–80% of cases), or secondary to a number of conditions such as hepatitis B, systemic lupus erythematosus, various drugs, and cancer.

The association between cancer and MN was first reported 50 years ago (Lee et al. 1966) and since then emphasized by several case series. The overall prevalence of cancer in patients with MN is estimated at 10% (Leeaphorn et al. 2014) and varies between 5% and 22% (Ronco 1999). Compared to idiopathic form, cancer-associated MN tends to occur later in the sixth to seventh decade with a mean age being 66 years at the time of cancer diagnosis. Malignancy is usually found within 12 months of the diagnosis of MN, and most of the cases (80%) are discovered at the time of or following the renal diagnosis. Nearly every known tumor has at some time been associated with MN, and, not surprisingly, the most common associations are with the more prevalent neoplastic diseases (Bacchetta et al. 2009). The vast majority (86%) of malignancies associated with MN are solid tumors, lung cancer being the most common, followed by gastrointestinal, prostate, and breast cancers. Hematologic malignancies are not rare, accounting for the remaining 14% cases. The occurrence of cancer is higher in a patient with MN than predicted from general population-based incidence, with a standardized incidence ratio ranging from 2.25 (Bjorneklett et al. 2007)

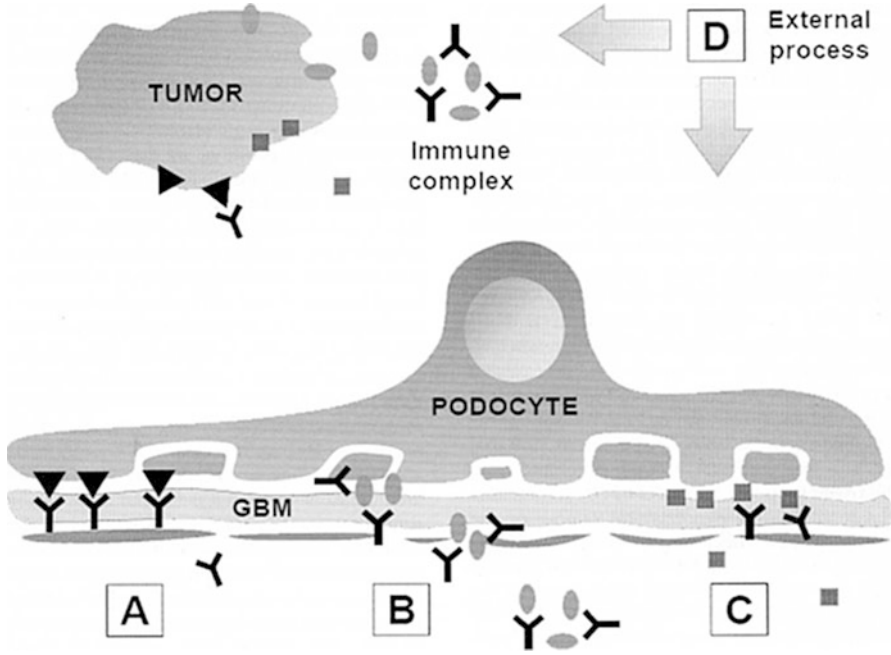

Fig. 2 Mechanisms by which solid tumors and MN may be linked. MN is defined by subepithelial deposits that form in the GBM beneath the foot processes of the glomerular visceral epithelial cell or podocyte. Antibodies may be generated against a tumor antigen identical to, or bearing an epitope similar to, an endogenous podocyte antigen, thereby leading to in situ immune complex formation. THSD7A is the first identified antigen shared by tumor cells and podocyte (*A*). Alternatively, shed tumor antigens may form circulating immune complexes that become trapped in the capillary wall (*B*). Complexes may initially form in a subendothelial location, dissociate, and reform in a subepithelial position. Tumor antigens also may, based on size and charge, become planted in a subepithelial location where they react with circulating antibodies at a later stage (*C*). Finally, extrinsic processes, such as infection with an oncogenic virus or altered immune function (*D*), potentially could cause both malignancy and MN (From Beck (2010), with permission)

to about 10 (Lefaucheur et al. 2006). The annual incidence of cancer continues to increase for more than 5 years after the histologic diagnosis of MN, suggesting that cancer susceptibility in case of MN persists for many years and warrants close follow-up. The risk of neoplastic disease in MN increases with age, heavy smoking, the use of cyclophosphamide, and if anti-PLA2R antibodies are not detected. These antibodies target a major podocyte antigen involved in the majority of adult idiopathic MN cases (Beck et al. 2009), and their absence is associated with a significant shorter malignancy-free survival and also a tenfold increase in cancer risk (Timmermans et al. 2013). Cyclophosphamide is frequently used in idiopathic membranous nephropathy, with a threefold rise of the risk for developing a cancer within 10–15 years after its use (van den Brand et al. 2014). However, several authors argue that the diagnosis of paraneoplastic glomerulopathy has been overemphasized and that strict criteria are requested for this diagnosis.

Several mechanisms can be involved in malignancy-associated MN (Fig. 2), but they are not yet fully elucidated (Beck 2010). Immune perturbations observed in cancer patients can increase the risk of MN by stimulating the production of antibodies against a tumor antigen identical to an endogenous podocyte antigen, leading to in situ immune complex formation. This mechanism of molecular mimicry has recently been illustrated by a patient presenting with carcinoma of the gallbladder and THSD7A-associated MN whose remission was obtained with chemotherapy alone (Hoxha et al. 2016b). THSD7A was newly expressed in the gallbladder carcinoma and also

in follicular dendritic cells of lymph nodes with metastatic infiltration suggesting that immunization against THSD7A could be a potential mechanism explaining the association between cancer and MN. The physiological role of follicular dendritic cells is to present stored antigen to maturing B cells leading to the formation of high-affinity antibodies. In cancer-associated MN, the expression of THSD7A by cancer and follicular dendritic cells could therefore induce the formation of autoantibodies against THSD7A, which in turn seem to be able to induce MN (Tomas et al. 2016). This mechanism has recently been strongly strengthened by the finding that malignancy is diagnosed in 20% of patients with THSD7A-associated MN within a median time of 3 months from the diagnosis of MN (Hoxha et al. 2016a). Alternatively, both tumor antigens and their respective antibodies can form immune complexes in blood and then become deposited in the glomeruli. However, the presence of tumor antigens (such as carcinoembryonic antigen, prostate-specific antigen, and melanoma antigens) and/or specific antibodies localized to the immune deposits seen in paraneoplastic MN has rarely been demonstrated (Ronco 1999).

Except for age (cancer-associated MN tends to occur later than idiopathic MN), clinical presentation (male predominance, hypertension, proteinuria, estimated glomerular filtration rate, serum albumin, stage of MN) of idiopathic MN and malignancy-associated MN is essentially the same (Lefaucheur et al. 2006). Therefore, determining whether MN is idiopathic or secondary to cancer remains challenging, but several clues (Table 1) can put on the track of a cancer (Cambier and Ronco 2012). First, half of the patients with cancer-associated MN without a diagnosis of malignancy at the time of renal biopsy present with cancer-related symptoms such as cough, urinary retention, night sweats, fever, or weight loss with an impairment of clinical condition (Lefaucheur et al. 2006). Second, as the nephrotic syndrome, cancer is a well-recognized risk factor for venous thromboembolism (VTE) (Lee and Levine 2003). Among the causes of nephrotic syndrome, MN presents the higher risk of VTE, especially when the serum albumin concentration is greatly depressed, with clinically apparent venous thromboembolic events occurring in about 7% of patients with MN in the largest cohort reported so far (Lionaki et al. 2012). Interestingly, 25% of the patients with malignancy-associated MN develop VTE (Lefaucheur et al. 2006), including deep vein thrombosis of the lower extremities and pulmonary emboli, which therefore should prompt the search for a cancer. No renal vein thrombosis has been observed in the patients with malignancy-associated MN. Third, >80% of the cases of idiopathic MN are associated with the presence of anti-PLA2R antibodies in the serum and/or with the expression of PLA2R in glomerular deposits (Ronco and Debiec 2015). In clinical practice, the immunofluorescence test and the ELISA are used for detection and quantification of circulating anti-PLA2R antibodies. Many studies (Du et al. 2014) have shown that these antibodies are specific (specificity of 99%) and sensitive (sensitivity of 78%) biomarkers of membranous nephropathy. In the absence of circulating antibodies, PLA2R antigen can still be detected in glomerular deposits (Debiec and Ronco 2011). Therefore, all patients with MN should be evaluated with a combined serological (antibody) and biopsy (antigen) analysis. Anti-PLA2R antibodies and/or PLA2R in glomerular deposits can be detected in a few cases of cancer-associated MN (Qin et al. 2011; Larsen et al. 2013), but these patients show a predominance of IgG4

Table 1 The acronym TIPS contains the clues for a more precise distinction between idiopathic and malignancy-associated membranous nephropathy (MN)

	Idiopathic MN (iMN)	*Malignancy-associated MN*
Thromboembolic disease	7.2%	25%
IgG subclass and Inflammatory cells per glomeruli	Mostly IgG4 ≤8 cells	Mostly IgG1 and IgG2 >8 cells
PLA2R antigen (kidney biopsy) and/or anti-PLA2R antibody (serum)	70–85%	Rare (probably a coincidence of cancer with iMN)
Symptoms associated with cancer	Absent	Present in about 50% at the time of biopsy

staining and persistent proteinuria despite curative treatment of the tumor, suggesting a coincidental occurrence of idiopathic MN with the "associated" disease. Currently, the detection of anti-THSD7A antibodies is only possible using Western blot, a technique that cannot be routinely used in clinical practice. However, a newly immunofluorescence test has been developed and show a 92% sensitivity and a 100% specificity compared with Western blot analysis in a large cohort of 1276 patients with MN (Hoxha et al. 2016a). In this cohort, the prevalence of anti-THSD7A antibodies seems to be low (2.6%) and increases to 10.5–12.4% in patients without anti-PLA2R antibodies. Compared with patients with PLA2R-associated MN, patients with THSD7A-associated MN had significantly more often malignancy, suggesting that a more intensive screening for the presence of a cancer may be warranted in those patients. Fourth, the study of IgG subclasses on kidney biopsy should be performed in all patients with MN. Indeed, in idiopathic MN, IgG4 is the predominant subclass of anti-PLA2R antibodies showing co-localization with the PLA2R antigen within the subepithelial immune deposits (Beck et al. 2009), whereas in cancer-associated MN, IgG1 and IgG2 seem to be the prevailing subclasses (Fig. 3; Murtas and Ghiggeri 2016). The absence of glomerular IgG4 deposition at an early stage may prompt to search for malignancy (Qu et al. 2012). Finally, in the absence of renal vein thrombosis, an evaluation of the number of inflammatory cells infiltrating the glomeruli is also of great value in separating malignancy-associated MN from idiopathic MN. The presence of more than eight inflammatory cells seems to strongly increase the likelihood of an underlying malignancy (Fig. 4; Lefaucheur et al. 2006). Many clues are therefore available to suspect malignancy-associated MN, but when utilized alone, none of them constitutes a definitive response. In a patient without cancer-associated symptoms and thromboembolism events, the presence of anti-PLA2R antibody in the serum or PLA2R antigen in the glomerular deposits, associated with a predominance of IgG4 deposits by immunofluorescence and few or no inflammatory cells in the glomeruli, is strongly suggestive for an idiopathic MN, and further investigations apart from routine examinations are not useful except in the presence of cancer risk factors. On the other hand, a search for cancer should be performed if anti-PLA2R antibody and PLA2R antigen are absent, or if IgG1 and IgG2 staining is prevailing, or in the presence of more than eight inflammatory cells per glomeruli. Further studies of larger cohorts are needed to establish whether anti-THSD7A antibodies can be considered at risk for malignancy. A stepwise approach could be proposed to search for malignancy (Table 2). If no malignancy is detected on initial screening, a close medical follow-up is mandatory because of the long-term risk for cancer occurrence, especially when cyclophosphamide is used with a cumulative dose exceeding 360 mg/kg.

As one might expect, the prognosis of patients with cancer-associated MN is poorer than that of patients without cancer, because of a lower renal survival and a higher probability of death (Lefaucheur et al. 2006). When MN is paraneoplastic, remission of the nephrotic syndrome occurs in patients who achieve tumor remission, emphasizing the importance of treating the tumor first of all.

Minimal-Change Disease

A variety of carcinomas has been reported in association with minimal-change disease (MCD), although MCD is more typical of lymphoproliferative disorders (Glassock 2003). Most of the time, the number of observations remain too small to support a strong causal relationship between cancer and MCD, except for thymoma.

Thymoma is a rare mediastinal tumor, frequently associated with a variety of paraneoplastic syndromes such as myasthenia gravis, systemic lupus erythematosus, polymyositis, pemphigus vulgaris, or autoimmune cytopenia. The association of glomerulopathy and thymoma remains rare, with renal involvement being reported in 2–10% of cases (Karras et al. 2005). The most frequently described type of glomerular disease is MCD, found in more than half of the cases with glomerular involvement (Fig. 5), suggesting a particular link between thymoma and MCD. Thymus is a primary lymphoid organ essential for the suppression of the

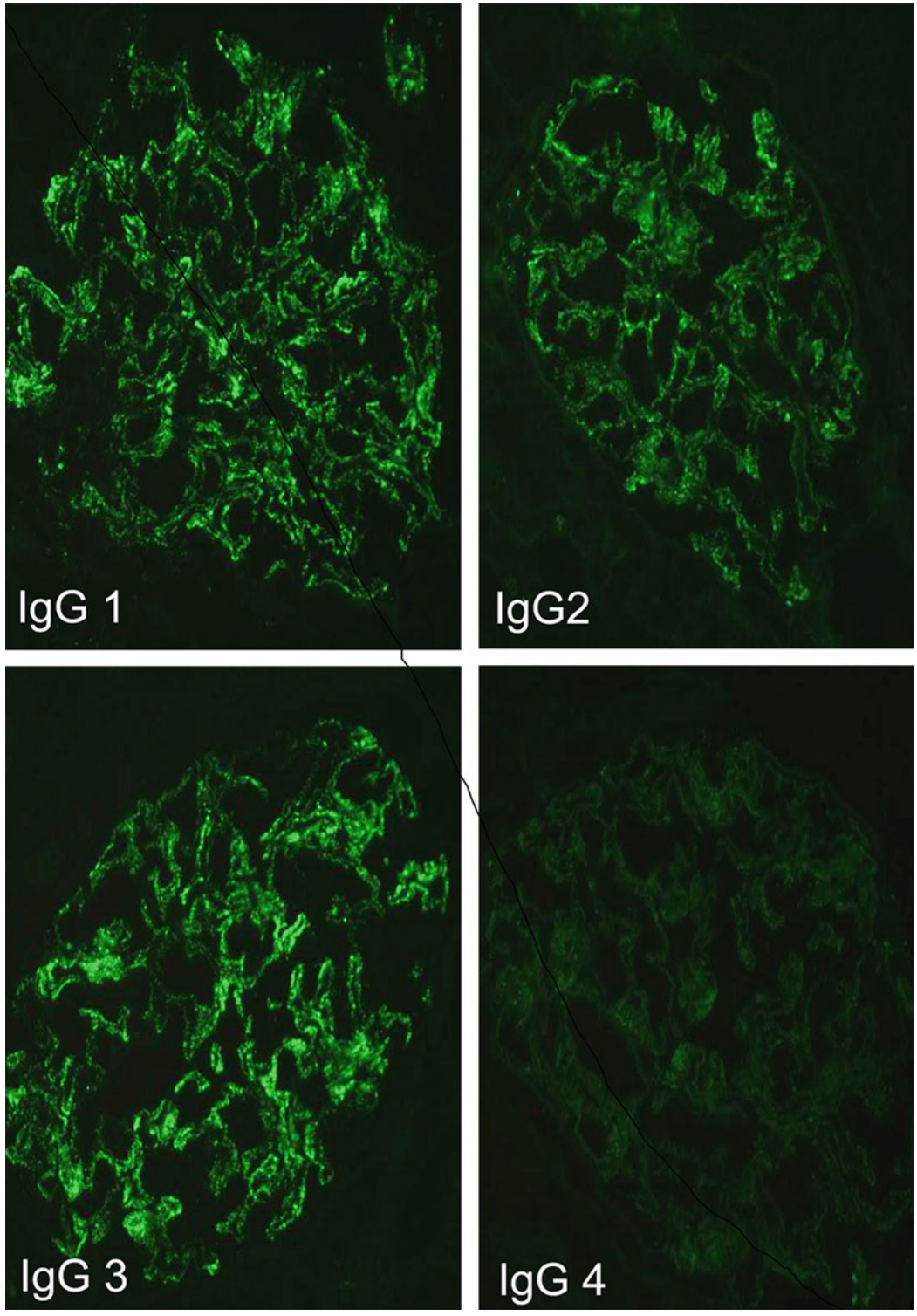

Fig. 3 In this cancer-associated MN, IgG subclass study shows staining for *IgG1*, *IgG2*, and *IgG3* but is negative for *IgG4* (Fluorescein, ×200)

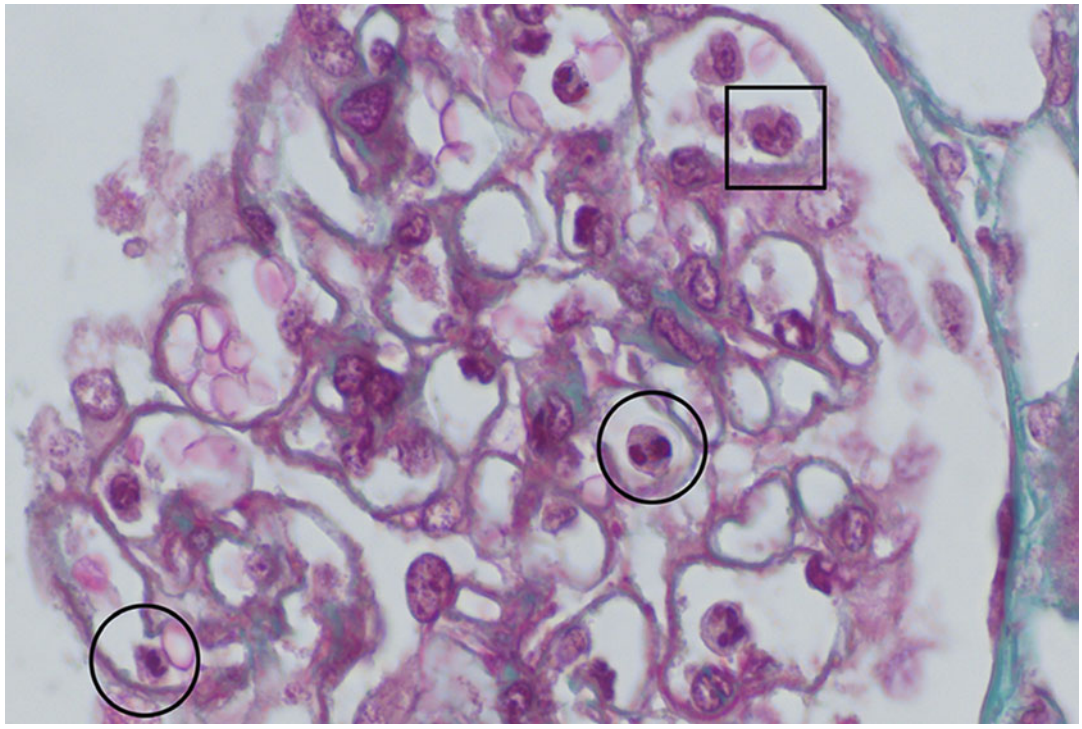

Fig. 4 In this cancer-associated MN, capillary wall is slightly thickened (type I MN). Inflammatory cells asre observed in the capillary lumen (neutrophils, *circle* and histiocytes: *square*) (Trichrome stain; ×400)

Table 2 Proposed stepwise approach to search for malignancy in patients with membranous nephropathy

Step 1	Identify specific cancer risk factors: Thromboembolic disease Absence of anti-PLA2R antibody or PLA2R antigen on kidney biopsy Presence of anti-THSD7A antibody or THSD7A antigen on kidney biopsy Absence of IgG4 or predominance of IgG1 and IgG2 More than 8 inflammatory cells infiltrating the glomeruli Search for personal (heavy smoker, chronic alcoholism, long-term immunosuppressive treatment, etc.) and hereditary cancer risk factors Careful physical examination including skin examination, search for lymph nodes, testicular palpation, throat, breast and rectal examination Standard biologic tests including prostate-specific antigen dosage Chest X-ray
Step 2 (in the presence of cancer risk factor)	Gastroscopy and coloscopy In women: breast ultrasonography +/− mammography, and gynecological examination Low-dose chest computed tomography in case of heavy smoker Consider Pet-CT because of its high sensitivity for cancer detection (Feng et al. 2016)
Step 3 (No malignancy detected on initial screening in at risk patients)	Close medical follow-up is mandatory because of the long-term risk for cancer occurrence

Abbreviations: PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing 7A

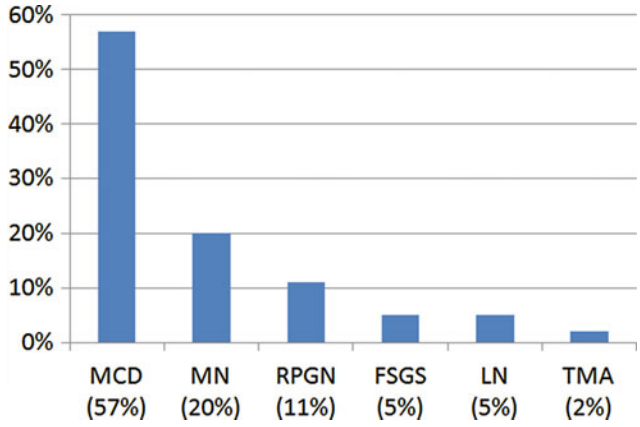

Fig. 5 Renal pathology findings in 56 patients presenting with thymic disease and glomerulopathy (From Karras et al. 2005 and Seguier et al. 2015). Abbreviations: *FSGS,* focal and segmental glomerulosclerosis; *LN*, lupus nephritis; *MCD*, minimal change disease; *MN*, membranous nephropathy; *RPGN*, rapidly progressive glomerulonephritis; *TMA*, thrombotic microangiopathy

immune response against autoantigens by selecting mature T lymphocytes through positive and negative selection. Patients with thymoma have disturbed lymphocytic populations as also found in the Buffalo/Mna rat model. This experimental model has been used to study the link between thymoma and glomerulopathy (Kato et al. 1983). Nephrotic syndrome appears at 1 month of age with MCD on renal pathology. Renal macrophage activation, T-cell infiltration, and the production of Th2-related cytokines (interleukin IL-10 and IL-13) precede the development of nephrotic syndrome in this model (Le Berre et al. 2005). The nephrotic syndrome is attenuated by the induction of T-regulatory (T_{REG}) cells that reduces renal macrophage and T-cell infiltration and also the production of Th2-type cytokines IL-10 and IL-13 (Le Berre et al. 2009), suggesting that the induction of T_{REG} cells could be a new potential therapeutic strategy for thymoma-associated MCD. Clinical characteristics of patients presenting MCD and thymoma are summarized in Table 3. In half of the cases, MCD occurs several months or even years after the diagnosis of thymoma. Myasthenia gravis is present in nearly half of the cases. Thymic pathology is consistent with malignant thymoma in the majority (92%), and renal function is frequently moderately impaired. Nearly all patients have been treated with corticosteroids, with complete and partial remission occurring in only 38% and 24% of the cases, respectively; this low response rate is quite unusual as compared to the most common cases of primary MCD. Regardless of nephropathy, prognosis of thymoma-associated nephropathy remains poor since 38% of patients will die from thymoma and 17% will develop end-stage renal disease.

Table 3 Clinical characteristics of patients presenting with MCD and thymoma

Mean age	51 years
Male to female ratio	1/1.4
Thymic pathology	Malignant thymoma, 92% Benign hyperplasia, 8%
Delay between thymoma and MCD	In 50% of the cases, MCD occurs several months or even years after thymoma (61 +/− 60 months)
Renal function	Mean serum creatinine, 1.69 mg/dl
Associated diseases	Myasthenia gravis, 46% Autoimmune cytopenia, 8% Lupus, 8% Polymyositis, 4% Pemphigus, 4%
Response to corticosteroids	Partial and complete remission, 62%

Adapted from Karras et al. (2005)

IgA Nephropathy and Henoch-Schönlein Purpura

The association between cancer and IgA nephropathy was first described more than 30 years ago

(Mustonen et al. 1984), with a predominance of solid tumors in the respiratory tract, the buccal cavity, and the nasopharynx. This association is almost only observed in patients aged 60 or older, emphasizing the importance to exclude such a cancer in an older patient developing an IgA nephropathy. The pathogenesis of cancer-associated IgA nephropathy might be explained by invasion of mucosa by tumor cells leading to the production of circulating IgA and their mesangial deposits. However, this association can be fortuitous or be strengthened by alcoholism, which is a well-known risk factor for both hepatopathy-induced IgA nephropathy and cancer of the upper respiratory tract.

In the recent years, renal cell carcinoma has been the most frequently reported cancer-associated IgA nephropathy. Treatment of the underlying tumor improves the IgA nephropathy, with regression of proteinuria and hematuria within 2–3 months after surgery (Magyarlaki et al. 1999).

Paraneoplastic Henoch-Schönlein purpura (HSP) has been associated both with hematologic malignancy and solid tumor (Pertuiset et al. 2000). Clinical characteristics of patients presenting with paraneoplastic HSP are summarized in Table 4. Most of the malignant neoplasms were solid tumors, with a lung cancer being found in 50% of the cases. Patients with malignancy were older and more likely to be male, with more frequent joint involvement and a lower frequency of prior acute infection than those without malignancy. In most of the cases, however, there was no conclusive evidence of a paraneoplastic HSP. Compared with age-matched controls, patients with HSP have an increased relative risk (5.25) for malignancy (Pankhurst et al. 2004). Among patients with HSP, cancer is the primary cause of mortality, accounting for 27% of deaths, but there is no correlation with immunosuppressive treatment (Pillebout et al. 2002).

Table 4 Clinical characteristics of patients presenting with paraneoplastic HSP

Mean age	59 years
Male to female ratio	8.5 (17/2)
Underlying malignancy	Hematologic malignancy, 37% Solid tumor, 63%
Time between HSP and malignancy diagnosis	Concomitant in 47% of the cases
Clinical presentation	Acute kidney injury, 26% Renal involvement, 84% Gastrointestinal involvement, 58% Joint involvement, 95% Cutaneous purpura, 100% IgA increase, 58%
Prognosis	Mortality, 50%

Adapted from Pertuiset et al. (2000)

Rapidly Progressive Glomerulonephritis

Several solid tumors including renal cell carcinomas and lung cancers have been associated with rapidly progressive glomerulonephritis and vasculitis (Bacchetta et al. 2009), with a prevalence of cancer between 7% and 9% (Whitworth et al. 1976; Biava et al. 1984). In patients with cancer, the occurrence of vasculitis can be explained by infections, drug reactions, or cryoglobulin deposits, a real paraneoplastic syndrome being rarely observed. Indeed, cancer seems to be more like a vasculitis triggering factor, and it is not yet established whether cancer removal alone treats the vasculitic process. Patients with solid tumor-associated vasculitis have more frequently peripheral neurologic involvement (Fain et al. 2007). Because long-term follow-up (up to 7 years) of patients with ANCA-associated vasculitis shows an incidence of treatment-related malignancy of 12.6% (Robson et al. 2015), the higher risk for developing malignancies in the patients with ANCA-associated vasculitis (relative risk of 6.02 compared to the general population) might be due, at least in part, to immunosuppressive medications (Pankhurst et al. 2004).

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is a multisystemic disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury resulting from ischemia (George and Nester 2014). Although the main pathological features are vascular damage, renal manifestations

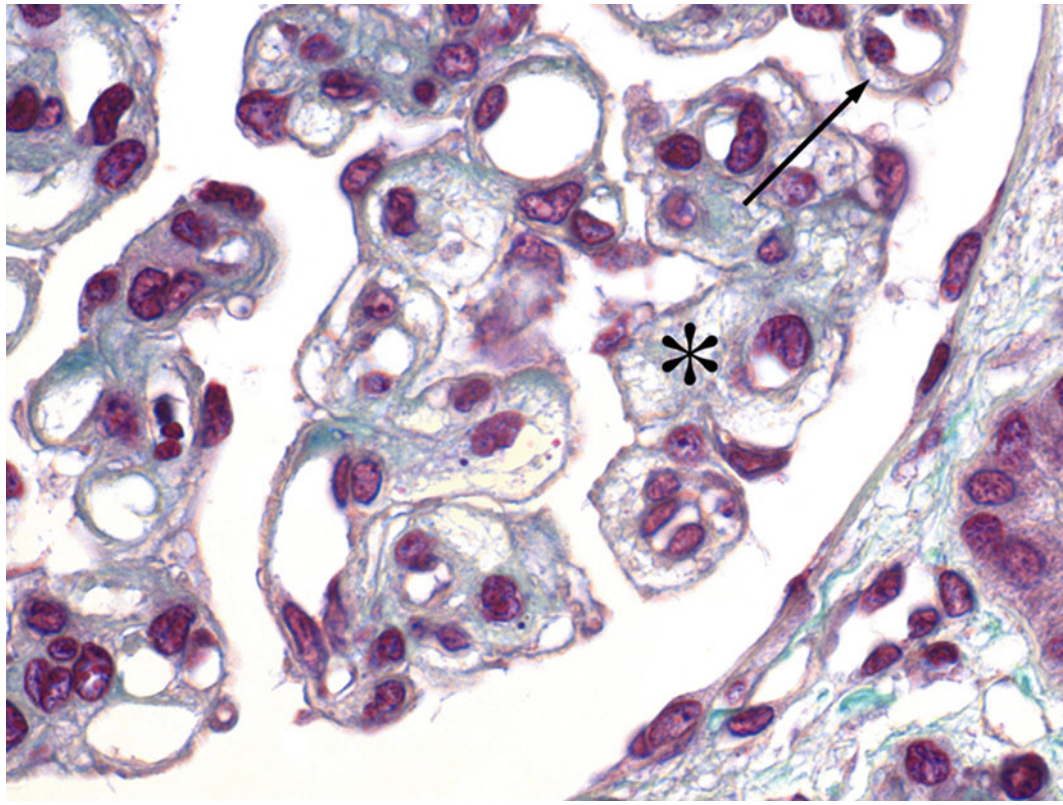

Fig. 6 Thrombotic microangiopathy without thrombi but with mesangiolysis (*), endotheliosis and clear subendothelial space (*arrow*). (Trichrome stain; ×700)

of TMA are essentially the same as those occurring with glomerulonephritis, such as hypertension, proteinuria, and hematuria (Fig. 6). TMA includes a broad spectrum of diseases including the thrombocytopenic thrombotic purpura (TTP), Shiga toxin-mediated hemolytic-uremic syndrome (HUS), and coagulation-, metabolism-, drug-, and complement-mediated TMA. TTP is the most common cause of TMA among adults without cancer. It results from the deficiency of ADAMTS13, a von Willebrand factor–cleaving protease, leading to large von Willebrand factor multimers and secondary platelet thrombi in small vessels.

In patients with cancer, TMA has been associated with several mucin-producing adenocarcinomas and disseminated malignancies and also with isolated invasion of the bone marrow by the tumor (Werner et al. 2007). There is no evidence that ADAMTS13 deficiency is involved in the pathogenesis of cancer-associated TMA which remains poorly understood. Several hypothetical mechanisms have been proposed: abnormal angiogenesis in the bone marrow induced by direct tumor invasion, leading to the release of ultra-large von Willebrand multimers, red blood cell fragmentation due to direct contact with microvascular tumor emboli, and production of mucin contributing to the endothelial dysfunction (Werner et al. 2007). TMA may also be caused by commonly used chemotherapy agents (see section "Drug-Induced Glomerular Disease") (Morton and George 2016). In the literature, TMA occurring in the setting of malignancy is also called cancer-related microangiopathic hemolytic anemia (CR-MAHA). Its incidence appears to range from 0.25 to 0.45 persons per million per year (Lechner and Obermeier 2012). Gastric carcinoma is the most common cancer (26.2%), followed by breast (21.4%), prostate (13.7%), and lung cancer (9.5%). TMA has also been reported in lymphoma

and other malignancies. In the large majority of patients (91.8%), the solid cancer is metastatic at the time of TMA. Although TMA is more frequently seen in patients with known metastatic cancer, it may also be the first sign of undiagnosed cancer. The distinction of these cases from TTP is essential to avoid inappropriate use of plasma exchange, which may have major complications. Whereas plasma exchange remains the first-line treatment for TTP, it has no known benefit for patients with cancer-induced or drug-induced TMA. The only effective treatment in these cases remains the control of the underlying malignant process and of hypertension. Signs of pulmonary TMA and hypofibrinogenemia seem to be more common in cancer-related TMA patients compared to patients with nonmalignant TMA. In the vast majority (81.1%), bone marrow infiltration with cancer cells can be documented by bone marrow biopsy (Lechner and Obermeier 2012). Patients presenting with cancer-associated TMA have a poor prognosis, the majority of them are dying within weeks of diagnosis.

AA-Type Amyloidosis

AA-type amyloidosis is found in approximately 3% of renal cell carcinomas, and conversely, these cancers account for 25–33% of all carcinomas associated with amyloidosis (Vanatta et al. 1983). The pathophysiology could involve an excess of IL-6 production by renal tumor cells, responsible for chronic inflammation. Remission of the nephrotic syndrome can be achieved by nephrectomy.

Glomerular Metastases

Intraglomerular metastasis (IGM) is a very rare entity, reported in 6–10% of secondary renal malignancies and in 3% of all disseminated cancers (Sridevi et al. 1999). Various types of malignancies have been reported, lung carcinomas being found in the majority (Ozluk et al. 2011). IGM can be observed in both intracapillary and extracapillary forms, the latter displaying crescentic lesions. Proteinuria and hematuria are common clinical manifestations, but acute kidney injury occurs very rarely. The pathogenesis of IGM is not fully known. Tumor cells can proliferate in the capillary lumen and then follow the same way as the urinary stream, leading to tubular obstruction and/or renovascular hemodynamic changes.

Hematologic Malignancy-Induced Paraneoplastic Glomerulopathies

While the pathophysiology of solid tumor-associated glomerulopathies remains poorly understood, a molecular link can usually be demonstrated in hematologic malignancy-induced paraneoplastic glomerulopathies apart from those related to Hodgkin's lymphoma where the pathophysiology remains uncertain. In most cases, the link is a monoclonal immunoglobulin (Ig) or a fragment thereof.

Hodgkin's Lymphoma

Two large, but old series have studied the prevalence of glomerulopathies in patients with Hodgkin's disease and showed that minimal-change disease (MCD) was found in 0.4% and AA amyloidosis in 0.1% of the patients (Franklin et al. 1972; Kramer et al. 1981). Other glomerulopathies have been associated with Hodgkin's lymphoma but remain anecdotal such as IgA nephropathy (Bergmann et al. 2005), focal and segmental glomerulosclerosis (Mallouk et al. 2006), membranous nephropathy (Eagen 1977), mesangiocapillary glomerulonephritis (Morel-Maroger Striker and Striker 1985), anti-glomerular basement membrane glomerulonephritis (Ma et al. 1978) and crescentic glomerulonephritis (Wolf et al. 2001).

The incidence of AA amyloidosis has decreased with improved modern treatments. At present, MCD is the most frequent Hodgkin's lymphoma (HL)-associated glomerulopathy, revealing the lymphoma in about 40% of cases and displaying a high frequency of steroid resistance (50%) and cyclosporine resistance (Audard et al. 2006). Remission of nephrotic syndrome occurs

simultaneously with effective treatment of Hodgkin's lymphoma whatever the therapeutic strategy, even without corticosteroids. Nephrotic syndrome usually relapses at the same time as lymphoma but remains highly responsive to specific treatment for the malignancy. MCD can occur at the time of lymphoma relapse even if it was initially absent, emphasizing the importance to evaluate proteinuria during the follow-up of classical Hodgkin's disease. Between-disease interval can be as long as 156 months. Patients with HL-associated MCD have a higher frequency of systemic symptoms and inflammatory syndrome compared to patients with HL alone. No particular subgroup of patients with HL seems to be at higher risk for MCD with respect to age, sex, or disease stage, except for HL exhibiting a mixed cellularity or the nodular sclerosing subtype which seem more frequently associated with MCD.

The pathophysiological link between MCD and HL may involve a cytokine response related to type 2 helper cells with increased IL-13 levels leading to foot process retraction and proteinuria (Lai et al. 2007). Another potential mechanism might be the activation of a new gene named for c-maf-inducing protein (*c-Mip*) (Grimbert et al. 2003). During primary nephrotic syndrome, it was shown that c-mip increased in the podocytes and turned off podocyte signaling by preventing the interaction of nephrin with the tyrosine kinase Fyn, thereby decreasing nephrin phosphorylation. Moreover, c-mip inhibited interactions between Fyn and neural Wiskott Aldrich syndrome protein and between Nck and nephrin, potentially accounting for cytoskeletal disorganization and the effacement of foot processes (Zhang et al. 2010). The potential involvement of c-mip in the pathogenesis of MCD in patients with HL is supported by the fact that c-mip was selectively induced both in podocytes and in Hodgkin and Reed-Sternberg cells in patients with HL-associated MCD but not in patients with isolated HL (Fig. 7; Audard et al. 2010).

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) represent the most frequent B-cell neoplasms in adults, usually diagnosed in patients aged more than 55 years. The diagnosis of CLL requires the presence of an increased lymphocytosis in the peripheral blood for more than 3 months, with evidence of monoclonality, whereas SLL usually presents clinically as lymphadenopathy and/or splenomegaly and is diagnosed on lymph node biopsy (Hallek et al. 2008).

The coexistence of CLL and nephrotic syndrome was first described in 1957 (Scott 1957). The prevalence of renal failure and/or nephrotic syndrome in patients with CLL or SLL is about 1% (Strati et al. 2015). A broad spectrum of kidney diseases is associated with CLL/SLL (Table 5), renal interstitial infiltration being found in up to 90% of CLL patients in autopsy series. CLL-associated glomerulopathies have rarely been reported, but they fulfill the three criteria of a paraneoplastic syndrome. First, they often reveal CLL with a simultaneous diagnosis of both diseases in about 50% of patients. Second, the control of hematologic disease improves glomerulonephritis, as illustrated by the first series of 13 cases demonstrating remission of the nephrotic syndrome with chlorambucil alone, a drug ordinarily not effective in membranoproliferative glomerulonephritis (MPGN) (Moulin et al. 1992). Third, the link between CLL and glomerulonephritis is the dysproteinemia (cryoglobulin or monoclonal component) produced by the B-cell clone, detected in about 40% of patients (Table 6). Such a high percentage contrasts with its low incidence in CLL without renal involvement (5–10%).

The most common lesions are MPGN (Fig. 8), followed by minimal-change disease (MCD) and membranous nephropathy (MN), which together account for more than half of the cases of CLL-associated glomerulopathies (Table 5). Several mechanisms may be involved. First, MPGN can be caused by cryoglobulinemia, predominantly a mixed type II cryoglobulin involving monoclonal IgM with rheumatoid factor activity and polyclonal IgG (Zaidan et al. 2016), although type I cryoglobulin composed of a single monoclonal immunoglobulin can also be implicated. Second, monotypic immunoglobulin deposits can occur in the absence of cryoglobulinemia and complement activation. Some patients present with features

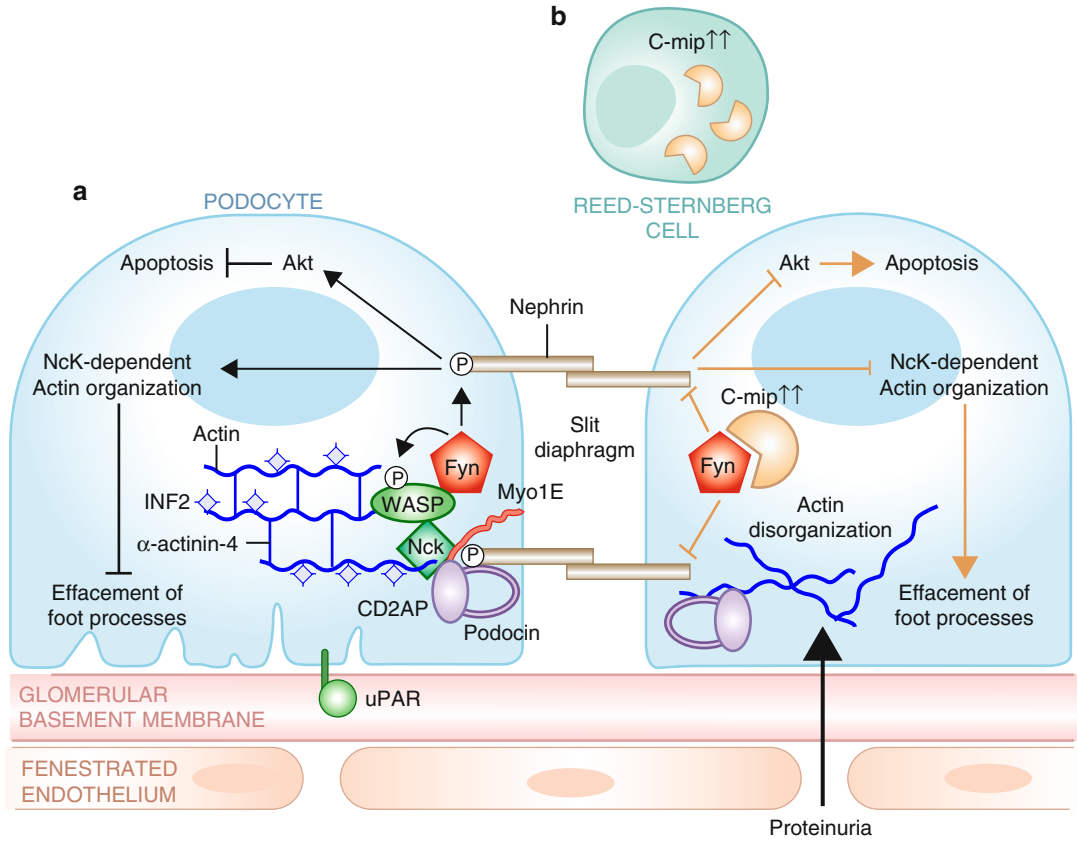

Fig. 7 Malignancy-induced MCD: hypothetical scenario for Hodgkin's disease. (**a**) Normal podocyte. The tyrosine kinase Fyn phosphorylates nephrin and WASP (Wiskott Aldrich syndrome protein) which is required for interactions between Nck and these proteins, therefore accounting for cytoskeletal organization. Moreover the phosphorylated nephrin interacts with several kinases such as Akt implicated in podocyte survival. (**b**) cHL-associated MCD. C-mip increases in Hodgkin and Reed-Sternberg cells and in the podocytes and turns off podocyte signaling by preventing the interaction of nephrin with Fyn, thereby decreasing nephrin and WASP phosphorylation. Moreover, c-mip inhibits interactions between Fyn and WASP and between Nck and nephrin, potentially accounting for cytoskeletal disorganization and the effacement of foot processes (From Cambier and Ronco (2012), with permission)

typical of monoclonal immunoglobulin deposition disease (MIDD, see section on "Plasma Cell Dyscrasias"), while others show an atypical form of MN or MPGN corresponding to an immunotactoid glomerulopathy (IT). At variance with MIDD in which the deposits display a non-organized granular pattern, deposits in IT are organized with a microtubular aspect and are restricted to the glomerulus. Similar organized deposits with microtubule formation were found in leukemic lymphocytes and glomeruli by Bridoux et al. who proposed the term "glomerulonephritis with organized microtubular monoclonal immunoglobulin deposition" (GOMMID) (Bridoux et al. 2002). Rare patients have a non-cryoglobulinemic proliferative glomerulonephritis with nonorganized monoclonal Ig deposits, a new entity described with the acronyme PGNMID (see section on "Other Dysproteinemia-Associated Glomerulopathies") (Nasr et al. 2004). At variance with MIDD where deposits predominate along tubular basement membranes and cell proliferation is usually mild or absent, PGNMID is a proliferative glomerulonephritis where deposits are confined to the mesangium and the glomerular basement membrane; hence, the term

non-Randall-type proliferative glomerulonephritis is also used to name this entity.

The clinical presentation of glomerulonephritis occurring in patients with CLL/SLL has been described in few studies (Table 6). Renal failure is the main indication for kidney biopsy (75% of the patients), whereas nephrotic syndrome accounts for 39% of the cases. The outcome of patients with CLL/SLL-associated glomerulonephritis has improved as illustrated by a decrease in the mortality rate from 67% in 1992 to 39% in the recent years (Table 6). This improvement results from earlier diagnosis and more potent chemotherapeutic regimens, including rituximab in association with cyclophosphamide. Rituximab-cyclophosphamide-dexamethasone (RCD) combination is emerging as a promising regimen irrespective of the glomerular pathologic pattern (Perry et al. 2014).

Table 5 Types of glomerulonephritis associated with chronic lymphocytic leukemia and small lymphocytic lymphoma (number of patients = 104)

Membranoproliferative glomerulonephritis (including immunotactoid glomerulonephritis, fibrillary glomerulonephritis, and proliferative glomerulonephritis with monoclonal IgG deposits)	37 (35.5%)
Minimal-change disease	13 (12.5%)
Membranous nephropathy	12 (11.5%)
Amyloidosis	7 (7%)
Thrombotic microangiopathy	6 (5.5%)
Infection-related glomerulonephritis	6 (5.5%)
Obesity-related focal and segmental glomerulosclerosis	6 (5.5%)
Unclassified	5 (5%)
Light-chain nephropathy	4 (4%)
Mesangial proliferative glomerulonephritis	3 (3%)
p-ANCA-associated crescentic glomerulonephritis	2 (2%)
Diabetic glomerulosclerosis	2 (2%)
Hypertension-related nephrosclerosis	1 (1%)

Adapted from Strati et al. 2015

Non Hodgkin's Lymphoma

The association of glomerular diseases with non-Hodgkin's lymphoma (NHL) has been rarely mentioned and described mostly in clinical cases (Dabbs et al. 1986; Da'as et al. 2001; Kowalewska et al. 2011), where various patterns of glomerulonephritis have been reported (Table 7). The most frequently observed glomerulonephritis is MPGN (sometimes caused by cryoglobulinemia) followed by minimal change disease (MCD).

Table 6 Clinical presentation of glomerulonephritis occurring in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma. N = number of patients, NA = not available

	Moulin et al. (1992) N = 13	Poitou-Verkinder et al. (2015) N = 15	Strati et al. (2015) N = 49	Li et al. (2014) N = 8	Total N = 85
Sex ratio (male to female)	8/5	9/6	34/15	7/1	58/27 (2.1)
Mean age (years)	65	65	63	61	63.5
Hypertension	NA	13/15	26/49	NA	39/64 (61%)
Renal failure	10/12	11/15	34/49	8/8	63/84 (75%)
Nephrotic syndrome	9/13	7/15	15/49	2/8	33/85 (39%)
Hematuria	NA	13/15	NA	7/8	20/23 (87%)
Monoclonal component	4/13	6/15	19/49	3/8	32/85 (38%)
Mortality rate	8/12 (67%)	6/15 (40%)	19/49 (39%)	3/7 (43%)	36/83 (43%) 28/71 (39%) without the series of Moulin et al.

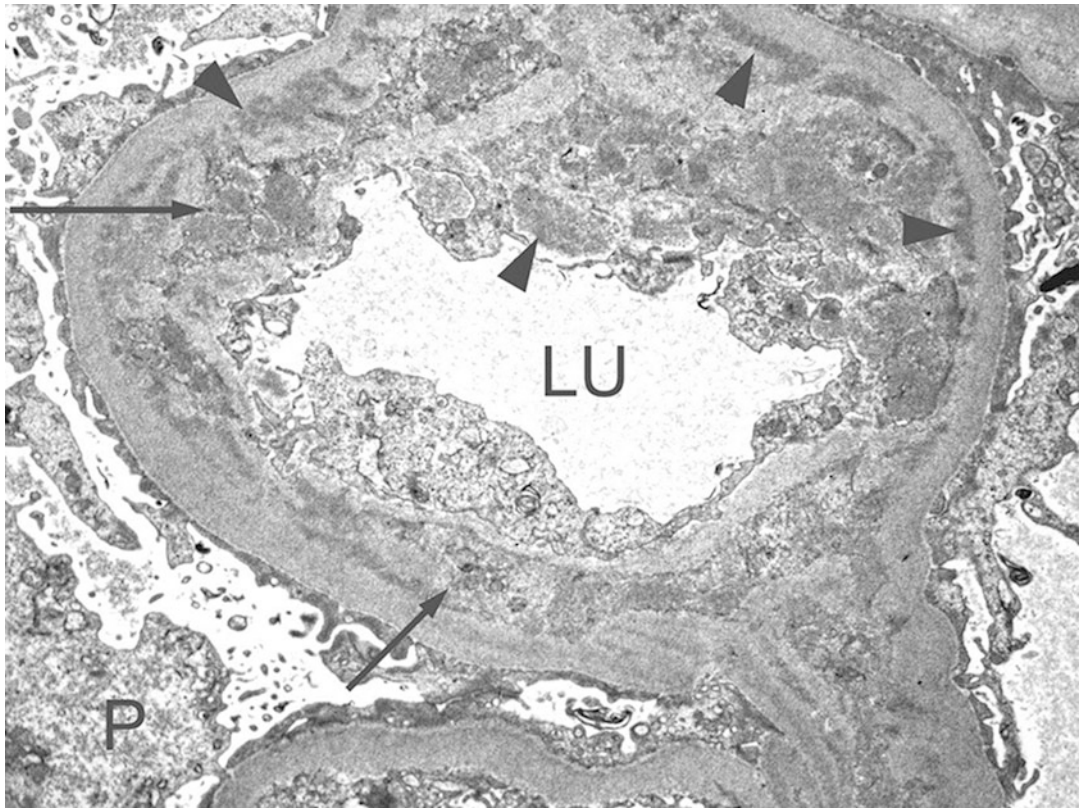

Fig. 8 Membranoproliferative glomerulonephritis. The capillary wall is thickened by interposed mesangial cells and by osmiophilic deposits. *Lu*, lumen; *arrow*, interposed cells; *arrow head*, deposit; *P*, podocyte (uranyl acetate and lead citrate, ×9700)

Table 7 Non-Hodgkin's lymphoma-related glomerulonephritis

Membranoproliferative glomerulonephritis +++
Minimal-change disease +++
Membranous nephropathy +
Focal and segmental glomerulosclerosis +
Mesangioproliferative glomerulonephritis +
IgA nephropathy +
Crescentic glomerulonephritis +
Immunotactoid glomerulonephritis +
AL amyloidosis +
Fibrillary glomerulonephritis +

+ and +++ refer to the frequency of the glomerulonephritis (Adapted from Dabbs et al. 1986; Da'as et al. 2001; Kowalewska et al. 2011, and Kofman et al. 2014)

MCD is a rare finding in the context of NHL, preferentially associated with B-cell lymphoma (Kofman et al. 2014). MCD occurs simultaneously in about half of the cases and is frequently complicated by acute kidney injury (AKI) due to acute tubular necrosis (ATN) and/or renal hypoperfusion; this unusual presentation leads to consider the possibility of underlying NHL in patients presenting AKI and MCD. MCD is frequently sensitive to steroids, but relapse is more frequent in patients treated exclusively by steroid therapy compared with those receiving both steroids and a regimen of chemotherapy. The pathophysiologic link between MCD and NHL may involve alterations in glomerular permeability related to the excessive production of inflammation cytokines.

Nephrotic syndrome associated with hemophagocytic syndrome (HPS) has been described in patients with NHL, predominantly T-cell lymphoma (Thaunat et al. 2006). HPS is characterized by fever, splenomegaly, and cytopenias as a consequence of the infiltration by macrophages phagocytizing hematopoietic elements in the bone marrow, lymph nodes,

liver, or spleen. AKI was present in all patients because of ATN and/or reduction of the glomerular filtration flow resulting from the massive collapse of glomerular tufts. Striking histologic features were described, with collapsing focal segmental glomerulosclerosis only in African patients while Caucasian patients presented MCD. The mechanism involved remains unknown but could involve an increase in tumor necrosis factor alpha responsible for actin cytoskeleton reorganization and secondary proteinuria.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma in which the bone marrow is infiltrated by immunoglobulin (Ig)M-producing clonal lymphoplasmacytic cells. Renal complications of malignant IgM-secreting monoclonal proliferations are rare (Table 8), with only few case series published. The first description of WM-related glomerulonephritis include characteristic intracapillary deposits of monoclonal IgM occluding capillary lumens and AL-amyloidosis (Fig. 9; Morel-Maroger et al. 1970). These intracapillary deposits occur in the setting of an advanced disease with high serum IgM levels and secondary hyperviscosity syndrome with or without detectable cryoglobulinemia. Recent data have shown that glomerulonephritis with intracapillary thrombi of IgM originally described as *Waldenström macroglobulinemic glomerulonephritis* was not specific for WM and could be observed in B-cell NHL and monoclonal gammopathy of renal significance (MGRS), a term that is proposed for patients without bone marrow infiltration but who present renal symptoms that are attributable to a monoclonal IgM (see section on "Monoclonal Gammopathy of Renal Significance"). Therefore, the term *intracapillary monoclonal deposits disease (ICMDD)* may be more appropriate in this context (Audard et al. 2008). Furthermore, the pathophysiology of ICMDD seem to be more related to abnormal physicochemical properties of the monoclonal IgM with secondary activation of the classical complement pathway than to hyperviscosity.

The frequency of ICMDD has decreased over time mostly because of improved treatment of WM, whereas AL amyloidosis, cryoglobulinemic

Table 8 Clinical presentation of glomerulonephritis occurring in patients with immunoglobulin M-secreting monoclonal B-cell lymphoproliferative disorders. N = number of patients

	Audard et al. (2008) N = 10	Chauvet et al. (2015) N = 26
Type of glomerular diseases	2 Ig amyloidosis (1 AL, 1 AHL) 3 MPGN 5 ICMDD	11 AL amyloidosis 9 MPGN (including 5 Cryoglobulinemic GN) 4 Mesangial GN 1 ICMDD 1 LCDD
Sex ratio (male to female)	8/2	12/14
Age (years)	66 (mean)	71 (median, in AL amyloidosis) 66 (median, in nonamyloid GN)
Hypertension	40%	42%
Acute kidney injury	40%[a]	11,5%[b]
Nephrotic syndrome	70%	68%
Hematuria	60%	77%
Hypocomplementemia	30%	31%
Mortality rate	30%	19%

Abbreviations: AL amyloidosis, immunoglobulin light-chain amyloidosis; AHL, immunoglobulin light- and heavy-chain amyloidosis; GN, glomerulonephritis; ICMDD, intracapillary monoclonal deposition disease; LCDD, light-chain deposition disease; MPGN, membranoproliferative glomerulonephritis

[a]AKI defined according to RIFLE (risk, injury, failure, loss, ESRD) criteria

[b]AKI defined according to AKIN (acute kidney injury network). The lower rate of AKI is explained in part by the inclusion of 11 patients with AL amyloidosis (compared with only two patients in the study of Audard et al.), none of them presenting AKI. In the other patients with nonamyloid glomerular diseases, the prevalence of AKI is 21%

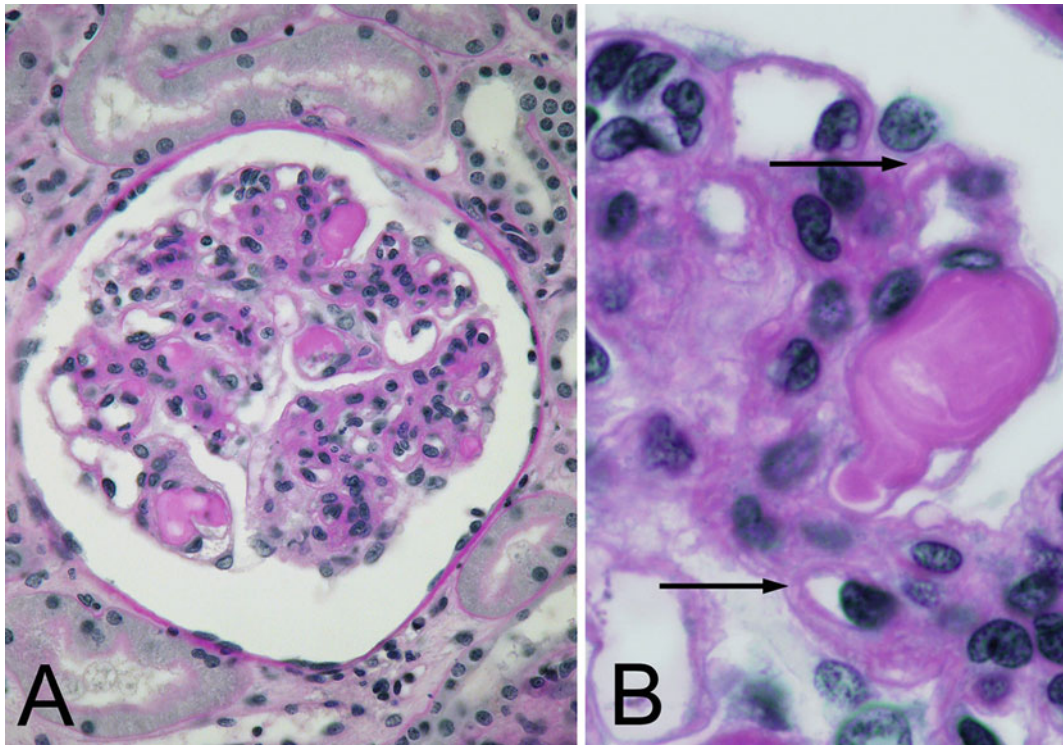

Fig. 9 (**a**) In this case, there is numerous intracapillary thrombi and a membranoproliferative pattern (PAS, ×100). (**b**) On this magnification, the double contour aspect is obvious (*arrow*), and the thrombus appears heterogeneous and lamellated (PAS, ×1000)

glomerulonephritis, and membranoproliferative glomerulonephritis (MPGN) are increasingly encountered (Chauvet et al. 2015). AL amyloidosis is the most common glomerular disorder in IgM monoclonal gammopathy, observed in up to 30% of the patients, whereas MPGN (with or without cryoglobulinemia) is found in about a quarter of the cases. Lymphomatous infiltration of the renal interstitium is frequently present, in half of the cases, and could explain the occurrence of acute tubular necrosis by increasing intrarenal pressure, in the absence of detectable glomerular IgM deposits or light-chain tubular casts. In glomerulonephritis associated with IgM monoclonal gammopathy, nephrotic syndrome is frequently encountered (Table 8). Treatment of these glomerulonephritis should target the IgM-secreting malignant clone and include rituximab in association with other chemotherapeutic agents such as cyclophosphamide, dexamethasone, or bortezomib (Dimopoulos et al. 2014).

Plasma Cell Dyscrasias

The definition of multiple myeloma (MM) has changed over time in order to identify more accurately patients who will require treatment. Currently, MM is defined by the presence of 10% or more clonal plasma cells in the bone marrow or histological evidence of extramedullary lesion (plasmacytoma) and at least one of the myeloma defining events: one of the CRAB criteria (hypercalcemia, renal impairment, anemia and bone lesions), or an involved-to-uninvolved free light-chain ratio >100, 60% or greater bone marrow plasma cells, or more than one bone lesion on magnetic resonance imaging (Rajkumar et al. 2014). Monoclonal gammopathy of undetermined significance (MGUS) is used for patients with a monoclonal-spike of less than 30 g/L and less than 10% bone marrow plasma cells in the absence of the CRAB criteria. Smoldering MM is an intermediate clinical stage between MGUS and MM

and is characterized by a monoclonal spike of 30 g/L or more (IgG or IgA) or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal bone marrow plasma cells between 10% and 60%, without myeloma defining events or amyloidosis. In patients presenting renal impairment, the most common histological lesions are myeloma cast nephropathy and acute tubular necrosis, but various glomerular diseases have also been reported. The spectrum of glomerulopathies occurring in patients with plasma cell dyscrasias has expanded dramatically and can be classified into two categories by electron microscopy according to ultrastructural characteristics of the deposits (Table 9). The most frequent glomerulopathy in plasma cell dyscrasias is immunoglobulin light-chain (AL) amyloidosis, followed by monoclonal immunoglobulin deposition disease (MIDD).

Immunoglobulin-Derived Amyloidosis

The amyloidoses are protein conformational diseases that result from tissues deposition of amyloid, a fibrillary material caused by misfolding and aggregation of various precursor proteins. All amyloid deposits are composed of highly ordered protein fibrils in a cross β-sheet conformation accounting for their birefringence under polarized light after Congo red staining (Fig. 10; Wechalekar et al. 2016). Amyloid deposits contain also several minor non-fibrillary constituents including glycosaminoglycans and serum amyloid P component. More than 30 different proteins have been identified to form amyloid (Sipe et al. 2014).

Immunoglobulin-related amyloidosis (Ig-related amyloidosis) is the most common type of systemic amyloidosis in the developed countries, accounting for 85.9% of the renal amyloidosis cases (Said et al. 2013). Its incidence remains stable over time with approximately one case per 100,000 person-years in the USA from 1958 to 1989 (Kyle et al. 1992) and in England from 2000 to 2008 (Pinney et al. 2013). In the vast majority of cases, the amyloid deposits are composed of fragments of monoclonal light chains and hence the name AL amyloidosis but rarely are derived from fragments of heavy chains and light chains (AHL amyloidosis) or fragments of heavy chains only (AH amyloidosis).

AL amyloidosis is the most frequent glomerulopathy in plasma cell dyscrasias, found in about 5–11% of patients with myeloma at autopsy (Ivanyi 1990) (Herrera et al. 2004). Conversely, in a large study of patients with AL amyloidosis, 40% were found to have more than 10% plasma cells in the bone marrow, but only 9.5% will meet the other criteria for MM (Kyle and Gertz 1995). AL amyloidosis can also occur in the setting of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or Waldenström's macroglobulinemia.

In AL amyloidosis, deposits are mainly composed of λ light chains (LCs), particularly the $V_{\lambda VI}$ variability subtype (Solomon et al. 1982), whereas IgG is the most frequent component in AH and AHL, followed by IgA and IgM. The pathogenesis of amyloidosis begins with the interaction of LCs with receptors on mesangial cells followed by their endocytosis and their transfer into mature lysosomes where they are processes and fibrils are formed (Teng et al. 2014). Tissue injury is mostly the consequence of the extensive extracellular deposition of amyloid.

The clinical presentation of AL amyloidosis depends on the pattern and severity of organ involvement, and almost any organ system may be affected by amyloid deposits. Except for the combination of macroglossia and periorbital purpura which is pathognomonic of AL amyloidosis and occurs in less than

Table 9 Pathologic classification of diseases with tissue deposition or precipitation of monoclonal Ig-related material

Organized			Nonorganized (granular)	
Crystals	Fibrillar	Microtubular	MIDD (Randall-type)	Other
Myeloma cast nephropathy	AL amyloidosis	Cryoglobulinemia kidney	LCDD (light-chain deposition disease)	Non-Randall-type proliferative GN
Fanconi syndrome	(Fibrillary GN)	Immunotactoid GN	LHCDD (light- and heavy-chain deposition disease)	Non-Randall-type nonproliferative GN
Crystal storage histiocytosis			HCDD (heavy-chain deposition disease)	IgM capillary thrombi

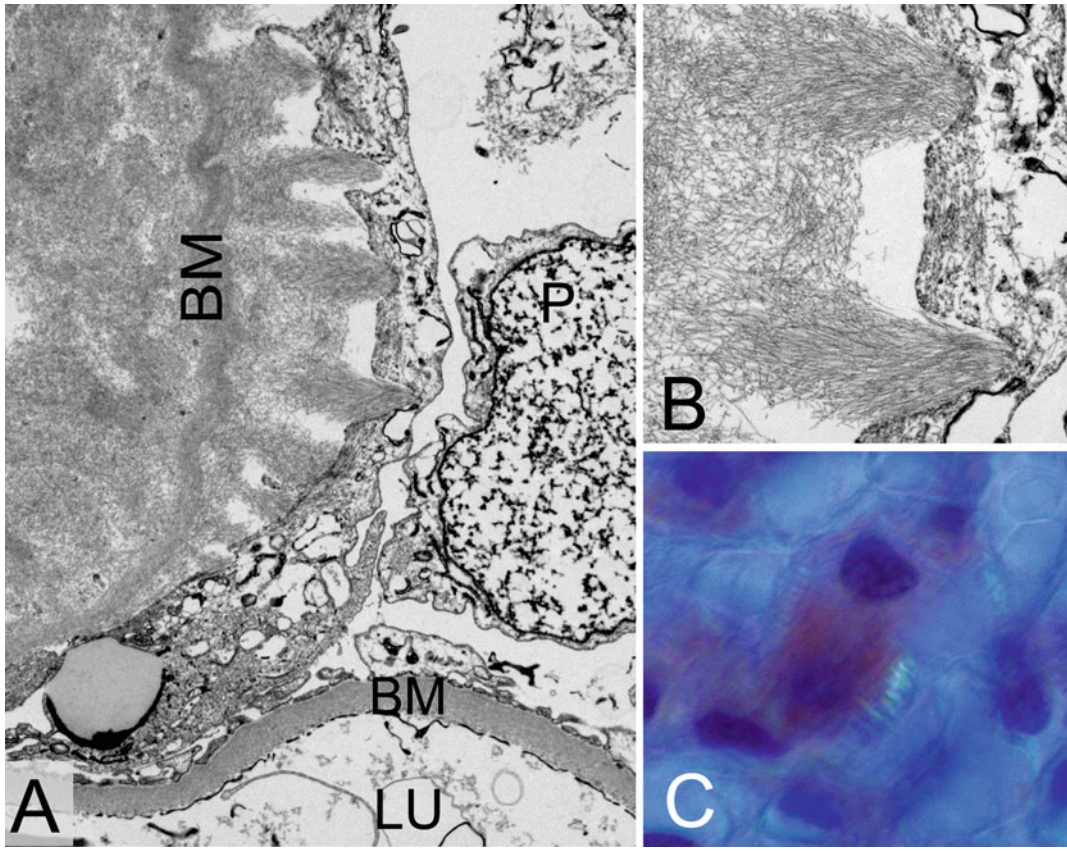

Fig. 10 Amyloidosis. (**a**) Amyloid fibrils occupy subepithelial and mesangial area (uranyl acetate and lead citrate, ×8900). (**b**) Typical ultrastructural appearance of amyloid fibrils extending into the subepithelial space (uranyl acetate and lead citrate, ×30000). (**c**) Appel *green* birefringence is elicited on polarization with Congo *red* (×900). *P*, podocyte; *Lu*, lumen; *BM*, basement membrane

a third of all cases, clinical features are rarely specific and mimic other more common conditions of the elderly. Kidneys are the organs most commonly involved in AL amyloidosis, with a high risk for progression to end-stage renal disease. Indeed, in a study of 145 patients with AL amyloidosis, 41.6% of patients who presented with renal manifestations required renal replacement therapy versus 4.9% of those who did not (Gertz et al. 2009). In a series of 407 patients with biopsy-proved renal Ig-related amyloidosis, the median age of patients was 64 years and 60% were male (Said et al. 2013). Renal insufficiency (serum creatinine > 1.2 mg/dl) was found in nearly half of the patients, with a median 24-h urine protein of 6.2 g and a full nephrotic syndrome in 68% of the patients. The urinary protein is mainly (70%) made up of albumin (Leung et al. 2012b), indicating that glomerular involvement is a common feature of AL amyloidosis, although rare forms of vascular limited AL amyloidosis present with renal insufficiency but little (<1 g/day) or no proteinuria (Eirin et al. 2012). There is a poor correlation between the extent of amyloid deposits seen on a kidney biopsy specimen and the extent of proteinuria. Renal manifestations may also include renal tubular acidosis and nephrogenic diabetes insipidus when amyloid deposits occur around proximal tubules and Henle's loops or collecting ducts, respectively. Microscopic hematuria is an exception and hypertension is rarely present.

Renal AH and AHL amyloidosis account for 7.3% of cases of renal Ig-related amyloidosis, affect older patients (with a median age at biopsy

of 63 years), and have a male predominance similar to AL amyloidosis (Nasr et al. 2013). Compared with patients with renal AL amyloidosis, those with renal AH and AHL amyloidosis present with less cardiac involvement (Table 10), probably explaining their better survival. Renal biopsy is needed to diagnose renal AH/AHL in most patients because other sites, such as fat pad and bone marrow, are usually not affected. Most of the patients with renal AH/AHL amyloidosis have a circulating intact monoclonal Ig found in more than 80% on serum and urine electrophoresis with immunofixation. The higher incidence of hematuria could be explained by local activation of complement secondary to the binding of Ig monoclonal protein.

Table 10 Significant differences between renal AH/AHL amyloidosis and renal AL amyloidosis

	AH/AHL (16 patients) (%)	AL (202 patients) (%)
Cardiac involvement	19	50
Presence of whole monoclonal protein on SPEP/UPEP	81/67	54/32
Positive bone marrow for amyloid	40	74
Positive fat pad biopsy for amyloid	15	72
Microscopic hematuria	60	26
Renal response to therapy (chemotherapy with or without SCT)	92	55

Abbreviations: AH/AHL, heavy-chain amyloidosis/heavy- and light-chain amyloidosis; SPEP, serum protein electrophoresis; UPEP, urinary protein electrophoresis (Adapted from Nasr et al. 2013)

The diagnostic procedures in AL amyloidosis include a stepwise approach (Table 11) to confirm the presence of amyloid deposition and identify the type of fibril and then assess the underlying plasma cell/B-cell clone and evaluate the extent and severity of amyloidotic organ involvement. The first step is to suspect this diagnosis, for instance, when heart failure is associated with nephrotic syndrome, or in patients at risk with monoclonal gammopathy of undetermined significance and abnormal free light-chain (FLC) ratio when urinary dipstick is positive for protein. The disease is diagnosed in more than 1 year after the onset of symptoms in almost 40% of cases (Loussada et al. 2015). The diagnosis of

Table 11 Stepwise approach for the diagnosis of AL amyloidosis

Clinical features suggestive of AL amyloidosis (not exhaustive)	Combination of macroglossia and periorbital purpura Combination of heart failure and nephrotic syndrome Thick-walled heart failure with normal or low electrocardiogram Positive biomarkers (NT-proBNP and albuminuria) in patients at risk (MGUS and abnormal FLC ratio) Peripheral and autonomic neuropathy
Confirmation of diagnosis	Salivary gland biopsy or abdominal fat aspirate for Congo red staining If negative, involved organ biopsy after careful assessment of hemostasis Amyloid typing with IHC, IEM or LMD/MS
Identification of the underlying B-cell clone	Serum and urine immunofixation electrophoresis and FLC ratio measurement Bone marrow studies including IHC, iFISH Lymph node biopsy (especially in IgM-related AL amyloidosis)
Assessment of organ involvement and staging	Heart: echocardiography, NT-proBNP, troponins, ECG, holterECG, MRI Kidney: 24-h urinary protein loss, eGFR Liver: liver function tests and liver imaging (CT, US, MRI) Nerve: electromyography

Abbreviations: CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FLC, free light chain; IHC, immunohistochemistry; IEM, immunoelectron microscopy; iFISH, immunofluorescent in situ hybridization; LMD/MS, laser microdissection/mass spectrometry; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; US, ultrasonography

amyloidosis requires the demonstration of characteristic green birefringence under polarized light after Congo red staining of biopsied tissue. With a 81% and 86% diagnostic sensitivity, abdominal fat and salivary gland biopsies remain, respectively, the most easily accessible biopsy sites (Hachulla et al. 1993). If necessary, the organ involved can be biopsied after careful assessment of hemostasis. The identification of the monoclonal protein requires the combination of immunofixation of both urine and serum and measurement of FLCs, but its presence doesn't ensure a diagnosis of AL amyloidosis and may lead to misdiagnosis in as many as 10% of cases (Lachmann et al. 2002). The characterization of amyloid deposits is therefore essential and may require several techniques. The use of antibodies on light microscopy immunohistochemistry (or immunoelectron microscopy, which is not a routine procedure) can correctly classify up to 94% of patients with systemic amyloidosis when performed at highly specialized centers (Schönland et al. 2012). However, in the real life, typing of AL/AH/AHL by immunofluorescence only may be challenging in some patients, and immunofluorescence staining for κ and λ can be negative in 7.3–35% of renal AL cases (Said et al. 2013; Novak et al. 2004). Therefore, one should be reluctant to accept a diagnosis of AL amyloidosis in those patients without urinary light chain. Mass spectrometry after laser capture microdissection of Congo red-stained deposits from a fixed tissue section is likely to become the gold standard for determining the amyloid type in difficult cases. Characterization of the underlying plasma cell/B-cell clone requires sampling of the bone marrow, peripheral blood or a pathologically involved lymph node, for a morphologic examination with additional techniques which may involve immunohistochemistry, and fluorescent in situ hybridization (FISH) with a standard myeloma panel looking for trisomies, translocation t(11;14), and chromosome 1 duplications and deletions.

Several criteria have been established to define organ involvement (Table 12). Particularly, elevation of NT-proBNP and cardiac troponins (cTn) are markers of myocardial dysfunction in AL amyloidosis that strongly correlate with prognosis and are therefore used for the risk assessment staging according to the Mayo risk stratification systems (Table 13). However, a limitation of NT-proBNP-based staging system is the influence of renal failure on the concentration of this biomarker that can be partly overcome by using BNP in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m^2 (Palladini et al. 2012). Patients presenting with a standard Mayo clinic stage III and very high concentrations of NT-proBNP (> 8500 ng/L) or systolic hypotension (< 100 mm Hg) have a poor prognosis, most of them are dying within a few weeks from diagnosis (Wechalekar et al. 2013). At variance with cardiac involvement, the effect of kidney involvement on survival is not major but limits the access to effective treatments. A recent staging system for renal involvement is used to predict the risk for dialysis and relies on the measurement of eGFR and proteinuria (Palladini et al. 2014b). Proteinuria > 5 g/24 h and eGFR < 50 mL/min per 1.73 m^2 are predictive of a high risk for progression to dialysis, respectively, 60% and 85% at 3 years.

Treatment of systemic AL amyloidosis relies mainly on chemotherapy to suppress the underlying clonal plasma cell, with the aim of rapidly decreasing production of amyloidogenic light chains to limit progressive damage to amyloidotic organs. Consensus criteria to define hematological (Table 14) and organ (Table 12) responses to treatment have been validated to identify early refractory patients. These criteria should be assessed at least every 2 cycles or 3 months. Patients usually die from organ failure rather than bone marrow failure, explaining why organ response is the ultimate goal of treatment. Because organ response is highly correlated with the hematologic response and is predictive of overall survival, the treatment aim is to achieve at least a very good partial response (Palladini et al. 2012). Patients with AL amyloidosis can be classified as at low, intermediate, or high risk. Only low-risk patients are potential candidates for high-dose melphalan followed by autologous stem cell transplantation (ASCT). These patients represent about 15–20% of all cases and are characterized by an age younger than 65 years; an excellent performance status; levels of NT-proBNP and cTnT lower than 5000 ng/mL and 0.06 ng/mL, respectively; a preserved renal function; and the absence of autonomic neuropathy or amyloid-

Table 12 Criteria for organ involvement, organ response, and organ disease progression in patients with AL amyloidosis

	Organ involvement	Organ response (validated for use as early as 3 months after treatment initiation)	Organ disease progression
Kidney	24-h urine protein ≥0.5 g, predominantly albumin	≥ 30% decrease in proteinuria or drop below 0.5 g/24 h, in the absence of renal progression defined as a > 25% decrease in eGFR[a]	> 25% decrease in eGFR
Heart	NT-proBNP >332 ng/L (in the absence of renal failure or atrial fibrillation) or mean wall thickness in diastole by echography >12 mm, no other cardiac cause	Decrease in NT-proBNP by >30% and 300 ng/L (if baseline NT-proBNP >650 ng/L) or a ≥ 2-point decrease in NYHA class (if baseline NYHA class III or IV)	NT-proBNP progression (> 30% and >300 ng/L increase)[b] or cTn progression (≥ 33% increase) or Ejection fraction progression (≥ 10% decrease)
Liver	Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times upper limit of normal	50% decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by ≥2 cm	50% increase of alkaline phosphatase above the lowest value
Nerve	P (clinical): symmetric lower extremity sensorimotor peripheral neuropathy	Improvement in electromyogram nerve conduction velocity (rare)	Progressive neuropathy by electromyography or nerve conduction velocity
	A: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration		

Abbreviations: A, autonomic; cTn, cardiac troponin; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; P, peripheral
[a]New criteria suggesting replacement of the 50% reduction of proteinuria used in the 2005 criteria (Palladini et al. 2014b)
[b]Treatment with immune modulatory drugs and progressively worsening renal function increase the concentration of NT-proBNP, preventing the assessment of cardiac response with this biomarker (Adapted from Comenzo et al. 2012)

Table 13 Validated staging systems for AL amyloidosis

Staging systems	Markers and thresholds	Stages
Standard Mayo Clinic (Dispenzieri et al. 2004)	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI >0.01 ng/mL)	I. No markers above the cutoff II. One marker above the cutoff III. Both markers above the cutoff
European staging of advanced cardiac involvement (Palladini et al. 2012)	Standard Mayo Clinic Stage III plus systolic blood <100 mm Hg NT-proBNP >8500 ng/L	a. No high-risk factors b. One high-risk factor c. Two high-risk factors
Revised Mayo Clinic (Kumar et al. 2012)	NT-proBNP >1800 ng/L cTnT >0.025 ng/ml dFLC >180 mg/L (measured with the Freelite immunonephelometric assay)	I. No markers above the cutoff II. One marker above the cutoff III. Two markers above the cutoff IV. Three markers above the cutoff
Renal (Palladini et al. 2014b)	eGFR <50 ml/min per 1.73 m^2 Proteinuria >5 g/24 h	I. Both eGFR above and proteinuria below the cutoffs II. Either eGFR below or proteinuria above the cutoffs III. Both eGFR below and proteinuria above the cutoffs

Abbreviations: cTn, cardiac troponin; dFLC, difference between involved and uninvolved serum immunoglobulin light-chain levels; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 14 Criteria for early hematologic response assessment in AL amyloidosis

Response criteria	Definition
Complete response (CR)	Negative serum and urine immunofixation and normal FLC ratio
Very good partial response (VGPR)	dFLC <40 mg/L
Partial response (PR)	FLC decrease ≥50% compared with baseline
No response	Less than a partial response

Abbreviations: dFLC, difference between involved and uninvolved serum immunoglobulin light-chain levels; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide (Comenzo et al. 2012)

related gastrointestinal bleeding. The other patients, and more particularly those with cardiac troponin T levels higher than 0.06 ng/mL or NT-proBNP levels higher than 5000 ng/L, should not be considered candidates for ASCT because of unacceptable transplant-related mortality (Gertz et al. 2013). Most patients are at intermediate risk (ineligible for ASCT, stages I-IIIa) and are treated with combination chemotherapy regimens, such as melphalan-dexamethasone (MDex), cyclophosphamide-bortezomib-dexamethasone (CyBorD), bortezomib-melphalan-dexamethasone (BMDex), or cyclophosphamide-thalidomide-dexamethasone (CTD) (Palladini and Merlini 2016). Most of the studies evaluating these regimens are retrospective and not randomized, limiting the comparison of their efficacy and making selection of the best treatment difficult. Immunomodulatory drugs (IMiDs) such as thalidomide, lenalidomide, and pomalidomide are used as rescue treatment for patients refractory to upfront regimens or those who relapse but cannot repeat frontline therapy. High-risk patients (stage IIIb) should be treated with low-dose chemotherapy under very close monitoring because of the risk to destabilize organ function with high doses of dexamethasone and bortezomib. Bortezomib can be preferred because of its rapidity of action. Supportive therapy is aimed at sustaining organ function with specific modalities such as salt restriction and diuretics for edema, adequate nutritional support, octreotide to control diarrhea, pacemaker implantation in patients with recurrent arrhythmic syncope, fitted elastic leotards and midodrine for hypotension, or gabapentin or pregabalin for neuropathic pain. The use of angiotensin-converting enzyme inhibitors is generally poorly tolerated because of hypotension.

Except for those with advanced cardiac disease who may benefit from emergency heart transplantation (Mignot et al. 2008), the long-term survival of patients with AL amyloidosis has improved in the last decade, with a 4-year overall survival ranging from 40% to 60% (Kumar et al. 2011). In patients eligible for ASCT, the hematologic response rate exceeds 70% (with 35% of complete response), and the overall median survival is 7.6 years (Sanchorawala et al. 2015). About half of these patients in complete response are projected to be alive at 14 years, raising the hope that they might be cured. Intermediate-risk patients treated with MDex have comparable results to that observed with ASCT, with hematologic response rate of 76% (31% of patients obtaining complete response) and a median overall survival of 7.3 years (Palladini et al. 2014c). The use of bortezomib is associated with higher hematologic response rate but fails to demonstrate an overall survival advantage (Palladini et al. 2014a).

IgM-related amyloidosis is a relatively uncommon variant of Ig-related amyloidosis, accounting for 6% of AL amyloidosis patients (Kyle and Gertz 1995). It is characterized by less cardiac involvement but more frequent lymph nodes and neuropathic involvement (Sachchithanantham et al. 2016). The lower frequency of cardiac involvement may be due to the relatively lower proportion of lambda light-chain isotype and lower light-chain clonal burden. On the other hand, the higher rate of peripheral neuropathy may limit the use of proteasome inhibitor bortezomib because of its neurotoxicity, probably explaining in part the poorer overall survival for patients with early-stage disease compared with non-IgM AL amyloidosis. Non-Hodgkin's lymphoma is the predominant underlying clonal disorder found in 54% of the patients, but plasma cell infiltration is still reported in 6% of the cases. Up to 74% of patients have an abnormal FLC ratio. Independent factors that have an impact on survival are Mayo

stage (or abnormal NT-proBNP and troponin), age older than 67 years, neuropathy (peripheral and autonomic nervous-s system), and liver involvement, leading to a new staging system for IgM AL amyloidosis (Table 15).

Monoclonal Immunoglobulin Deposition Disease

It has been known since the late 1950s that non-amyloidotic forms of glomerular disease could occur in multiple myeloma (Kobernick and Whiteside 1957). These glomerulopathies "resembling the lesion of diabetic glomerulosclerosis" differ from amyloidosis in that the granular deposits lack affinity for Congo red and do not have a fibrillary organization (Fig. 11). The

Table 15 New prognostic model for patients with IgM-related AL amyloidosis

Factors	Score
NT-proBNP >332 ng/L	1
cTnT >0.035 μg/L or cTnI >0.1 μg/L	1
Liver involvement	1
Involvement of PNS/ANS	1
Stage	
1	No abnormal factor
2	One abnormal factor
3	Two or more abnormal factors

Abbreviations: AL, light chain; ANS, autonomic nervous system; cTnI, cardiac troponin I; cTnT, cardiac troponin T; IgM, immunoglobulin M; NT-proBNP, N-terminal pro-brain natriuretic peptide; PNS, peripheral nervous system (Sachchithanantham et al. 2016)

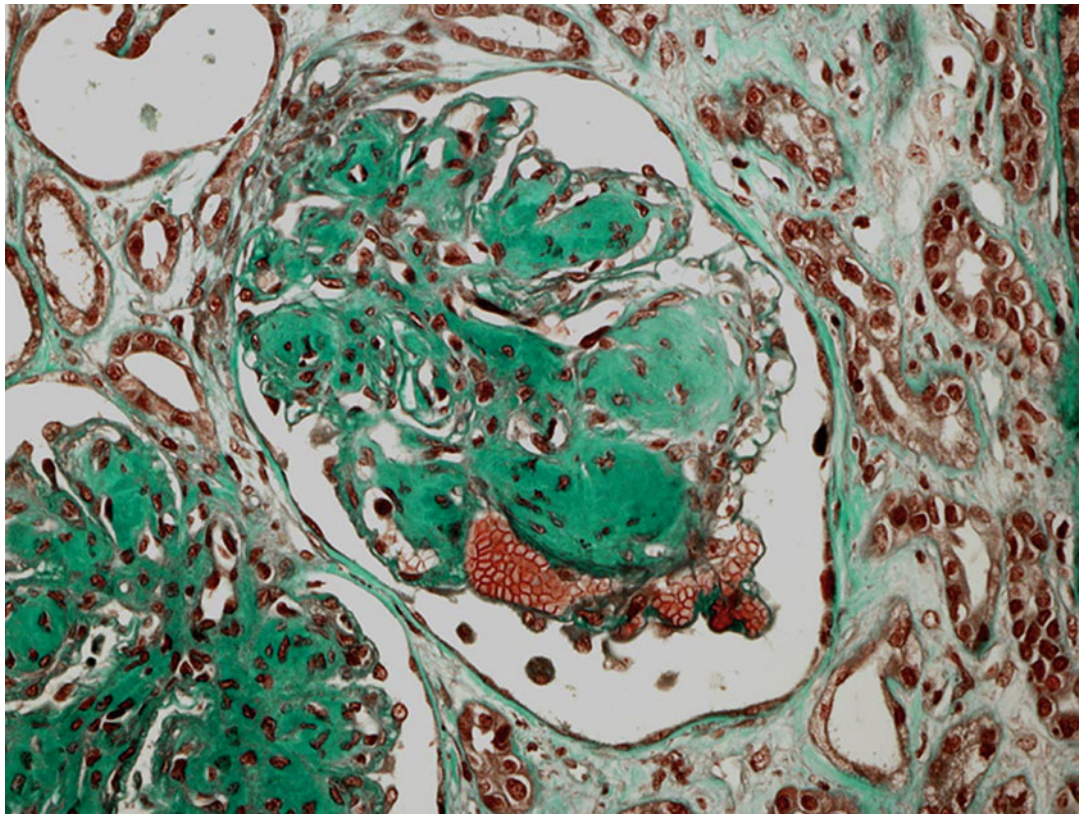

Fig. 11 Light-chain deposition disease. Nodular glomerulosclerosis with hypercellularity. The mesangial nodules are more evenly distributed than in diabetic nephropathy (trichrome stain; ×200)

presence of monoclonal light chains (LC) in these lesions was confirmed 26 years later by Randall et al. (1976), who introduced the term light-chain deposition disease (LCDD) to describe that new entity. Light- and heavy-chain deposition disease (LHCDD) was proposed later to describe monoclonal heavy chains (HC) that were found together with LC in the tissue deposits from certain patients (Buxbaum et al. 1990). Later, patients featuring typical Randall's disease and presenting deposits containing monoclonal HC in the absence of detectable LC led to the description of the heavy-chain deposition disease (HCDD) (Aucouturier et al. 1993). In clinical and pathological terms, LCDD, LHCDD, and HCDD are essentially similar and are now gathered under the generic term of monoclonal immunoglobulin deposition disease (MIDD).

MIDD remains a rare disease, with a prevalence that ranges from 0.1% (Li et al. 2016) to 0.7% (Nasr et al. 2012b). MIDD is the second most frequent glomerulopathy in plasma cell dyscrasias, found in about 5% of patients with multiple myeloma (MM) at autopsy, approximately half the incidence of AL amyloidosis (Ivanyi 1990). Conversely, the reported prevalence of multiple myeloma in MIDD ranged from 11% (Sayed et al. 2015) to 65% (Pozzi et al. 2003; Table 16) and depends on the definition used for the diagnosis of MM and more particularly on the presence or not of a symptomatic MM defined by the CRAB criteria (hypercalcemia, renal impairment, anemia, and bone lesions). Multiple myeloma is found in approximately 50% of patients with LCDD or LHCDD and in approximately 25% of those with HCDD, but MIDD occasionally may complicate WM, CLL, and NHL (Ronco et al. 2001). A significant proportion of patients with MIDD present a monoclonal gammopathy of undetermined significance (MGUS), but this term is now replaced by monoclonal gammopathy of renal significance (MGRS) to emphasize the significance of renal diseases associated with monoclonal immunoglobulin in patients who do not meet the criteria for multiple myeloma or symptomatic lymphoma (Leung et al. 2012a).

The pathogenesis of MIDD involves the kidney deposition of monoclonal Ig subunits inducing a dramatic accumulation of extracellular matrix that is responsible for glomerular and tubular basement membrane thickening, nodular glomerulosclerosis, and interstitial fibrosis. However, LC deposition does not mean pathogenicity, and singular properties of LC or HC are most likely required for completion of the pathogenetic process that leads to kidney fibrosis (Table 17). In HCDD, deletion of the first constant domain C_H1 is required for secretion of free HCs, which are rapidly cleared from the circulation by organ deposition (Bonaud et al. 2015). LCs are supposed to bind an as-yet unidentified common caveolae-associated receptor on mesangial cells and to induce their phenotypic transformation into myofibroblasts with an abundant endoplasmic reticular system leading to an increased in protein synthesis and a reduction in matrix metalloproteinase production, therefore explaining the dramatic accumulation of extracellular matrix (Teng et al. 2004). A role for transforming growth factor-β (TGF-β) is supported by its strong expression in glomeruli of MIDD patients and by in vitro experiments using cultured mesangial cells (Zhu et al. 1995). TGF-β is also found in nodular diabetic glomerulosclerosis, which may explain the similarities between MIDD and diabetes-induced nodular glomerulosclerosis, including the strong reactivity of lesions with periodic acid-Schiff (PAS) reagent.

MIDD is a systemic disease with Ig-chain deposition in a variety of organs leading to various clinical manifestations although visceral Ig-chain deposits may be totally asymptomatic and found only at autopsy. MIDD typically presents in the sixth decade. Renal involvement is a constant feature of MIDD and manifests itself by renal failure and proteinuria (Table 18). A nephrotic syndrome is found in 8–40% of the cases, but LCDD may also exhibit a tubulointerstitial syndrome with proteinuria being less than 1 g per day in about 20% of the cases (Gu and Herrera 2006). In these cases, the use of sFLC assay is essential to show abnormal serum FLC concentrations

Table 16 Hematologic features of patients with monoclonal immunoglobulin deposition disease

Series	Monoclonal component in blood or urine	Abnormal FLC ratio	Kappa isotype on kidney biopsy[a]	Clinical diagnosis
Lin et al. (2001) **n = 23** 12 LCDD 5 LHCDD 6 HCDD	20/23 (87%)	NA	14/17 (82%)	MM[c], 9 (39%) MGRS, 9 (39%) Isolated HCDD, 1 (4%) Insufficient data, 4 (17%)
Pozzi et al. (2003) **n = 63** 63 LCDD	59/63 (94%)	NA	43/63 (68%)	MM, 41 (65%) MGRS, 20 (32%) LPD, 2 (3%)
Nasr et al. (2012b) **n = 64** 51 LCDD 6 LHCDD 7 HCDD	55/64 (86%)	51/51 (100%)	48/57 (84%)	MM, 38 (59%) MGRS, 25 (39%) Lymphoplasmacytic lymphoma, 1 (2%)
Cohen et al. (2015) **n = 49** 35 LCDD 2 LHCDD 12 HCDD	49/49 (100%)	47/47 (100%)	24/37 (65%)	Symptomatic MM, 10 (20%) MGRS, 38 (78%), including 23 smoldering MM (47%) WM, 1 (2%)
Sayed et al. (2015) **n = 53** 53 LCDD	34 (64%)	53 (100%)	43/53 (81%)	MM, 6 (11%) MGRS, 46 (87%) CLL, 1 (2%)
Li et al. (2016) **n = 48** 48 LCDD	12/45 (26.7%)	41 (85.4%)[b] (ratio 0.26–1.65)	45/48 (94%)	Symptomatic MM, 12 (25%) MGRS, 32, including 1 smoldering MM NA, 4
Total n = 300	229/297 (77%)	192/199 (96.5%)	217/275 (79%)	MM, 116 (38.6%) MGRS, 170 (56.6%) WM, 1 (0.4%) Lymphoma, 3 (1%) CLL, 1 (0.4%) Other, 9 (3%)

Abbreviations: CLL, chronic lymphocytic leukemia; FLC, free light chains; HCDD, heavy-chain deposition disease; LCDD, light-chain deposition disease; LHCDD, light-and heavy-chain deposition disease; LPD, lymphoproliferative disorder; MGRS, monoclonal gammopathy of renal significance; MIDD, monoclonal immunoglobulin deposition disease; MM, multiple myeloma; NA, not available; SPEP, serum protein electrophoresis; UPEP, urinary protein electrophoresis; WM, Waldenström macroglobulinemia

[a]By definition, the presence of kappa light chains involves only cases of LCDD or LHCDD

[b]The ratio used was 0.26–1.65 and was not adapted for renal insufficiency

[c]The definition of MM varies according to the series:

– Lin et al.: renal MIDD plus at least one of the following criteria: positive bone marrow biopsy, presence of osteolytic lesions, hypercalcemia with positive UPEP or SPEP, or ≥10% bone marrow plasmocytosis with low quantitative serum immunoglobulins.

– Pozzi et al.: according to Durie BGM criteria (1986).

– Nasr et al.: renal MIDD plus ≥10% monoclonal plasma cells in the bone marrow and monoclonal protein identified in the serum and/or urine.

– Cohen et al. and Li et al.: according to IMWG criteria (2003).

– Sayed et al.: not available, but 46 patients present <10% clonal plasma cells in the bone marrow and 6 patients ≥10%

Table 17 Light-chain peculiarities associated with amyloidosis and LCDD

	AL Amyloidosis	LCDD
Predominant isotype	λ	κ
Variability subgroup	$V_{\lambda VI}$[a]	$V_{\kappa IV}$[a]
Size abnormalities	Fragments in urine	Short or large light chains (glysosylation)[b]
Amino acid residues exposed to solvent	Acidic	Hydrophobic
Interaction with	Extracellular matrix components[c]	–

[a]All $V_{\lambda VI}$ light chains are amyloidogenic. Not all $V_{\kappa IV}$ light chains induce LCDD
[b]Glycosylation correlates with the lack of circulating and urinary light chains by sensitive detection techniques as observed in about 20% of LCDD patients
[c]Reactivity with extracellular matrix components may be explained by high dimerization constant and antibody-like behavior of the V-domain (From Ronco (1999), with permission)

Table 18 Renal manifestations at presentation in patients with monoclonal immunoglobulin deposition disease (MIDD)

Series	Age (yrs)	Male-Female Ratio	Proteinuria	Nephrotic syndrome	Hematuria	Renal insufficiency (creatinine > 1.2 mg/dl)	HTA
Lin et al. (2001)[a] n = 23	57 mean (NS)	12/11	Mean proteinuria 4.2 g/d	6 (26%)	12 (52%)	22 (96%)	18 (78%)
Pozzi et al. (2003)[b] n = 63	58 median (28–94)	40/23	Median proteinuria 2.7 g/d	25 (40%)	NS	60 (96%)	NS
Nasr et al. (2012b) n = 64	56 mean (22–83)	42/22	Mean proteinuria 4.1 g/d	14/60 (23%)	38/61 (62%)	60/62 (97%)	53 (83%)
Cohen et al. (2015) n = 49	64 median (55–71)	27/22	Median proteinuria 1.5 g/d[c] (1.0–4.3)	3 (8%)	36 (73.4%)	CKD[d] 1–3: 24 (49%) CKD 4–5: 25 (51%)	36 (73.5%)
Sayed et al. (2015) n = 53	59 median (29–78)	37/16	Mean proteinuria 4.1 g/d (0.1–15.5)	10/45 (22%)	45/50 (90%)	CKD 2–3: 23 (43%) CKD 4–5: 30 (57%)	50 (94%)
Li et al. (2016) n = 48	53.5 median (NS)	29/19	Median proteinuria 2.8 g/d (1.3–5.1)	NS	36 (75%)	46 (95.8%)	38 (79%)

Abbrevations: CKD, chronic kidney disease; NS, not specified
[a]Cases of LCDD with myeloma cast nephropathy (MCN) (n = 11) are not included
[b]Including 10 cases with MCN that could not be distinguished from those without MCN
[c]Relatively low level of 24-h proteinuria because of the inclusion of 10 patients without glomerular involvement. When these patients are excluded, median proteinuria is 2.5 g/d
[d]CKD stages according to the KDIGO definition

because dysproteinemia is more difficult to detect on serum/urine protein electrophoresis or immunofixation (Sicard et al. 2014). The high prevalence, early appearance, and severity of renal failure are other salient features of LCDD. In most cases, renal function declines rapidly, which is a main reason for referral. The prevalence of hypertension is variable, but it must be

interpreted according to associated medical history. Extrarenal manifestations are frequent, with liver and cardiac involvement occurring in approximately 25% of patients with LCDD and LHCDD, thereby increasing the risk of death (Ganeval et al. 1982). Deposits also may occur along the nerve fibers and in the choroid plexus, as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, gastrointestinal tract, abdominal vessels, lungs, and skin (Ronco et al. 2001). Patients with HCDD appear to have a higher prevalence of hypertension, nephrotic syndrome and hematuria, and a lower rate of extrarenal deposits (Ronco et al. 2006). The prevalence of nephrotic-range proteinuria is higher in HCDD, reaching 70% at diagnosis, and is associated with constant deposition of mesangial monoclonal immunoglobulin deposits and nodular glomerulosclerosis (Bridoux et al. 2017).

The association of MIDD and myeloma cast nephropathy (MCN) is not so rare, found in 32% of patients with MIDD (Lin et al. 2001). Multiple myeloma is more frequently diagnosed in patients presenting MIDD with MCN, with a prevalence of up to 91%. Clinical features and outcomes of MIDD and MCN more closely resemble those in MCN than pure MIDD. It is characterized by higher creatinine, greater dialysis dependence, and subnephrotic proteinuria. The pathologic findings in these cases are dominated by severe tubular damages induced by cast nephropathy, with less extensive nodular glomerulopathy. Renal and patients survival is significantly worse in patients with MIDD and MCD compared with patients with pure MIDD.

The diagnosis of MIDD must be suspected in any patient with monoclonal gammopathy who presents glomerular proteinuria in association with hematuria, hypertension, and renal insufficiency. Diagnosis of disease still remains delayed by more than 1 year after the onset of symptoms (albuminuria or elevation in creatinine) (Kourelis et al. 2016). Since sensitive techniques including immunofixation fail to identify a monoclonal immunoglobulin component in 15–30% (Table 16), kidney biopsy plays an essential role in the diagnosis. Recent series show that all patients with MIDD tested for serum FLC have abnormal results, emphasizing the importance of considering serum FLC in the diagnostic workup of adults over 50 years presenting with renal disease. MIDD should not be considered a pure glomerular disease. In fact, tubular lesions may be more conspicuous than the glomerular damage and are characterized by the deposition of a refractile, eosinophilic, PAS-positive, ribbon-like material along the outer part of the tubular basement membrane (Fig. 12). The most characteristic glomerular lesion is nodular glomerulosclerosis, found in 30–100% of patients with LCDD and nearly all patients with HCDD (Lin et al. 2001). The definitive diagnosis of MIDD is made by immunofluorescence examination of tissue from an affected organ, using a panel of immunoglobulin chain-specific antibodies to stain the deposits. It requires the evidence of monotypic LC and/or HC fixation along tubular basement membranes on renal biopsies. If immunofluorescence fails to detect light chains or γ-, α-, or μHC while the findings on the kidney biopsy are suggestive of MIDD, IgD HCDD should be suspected and may require the use of laser microdissection and mass spectrometry because IgD is not detected on routine immunofixation studies (Royal et al. 2015). On electron microscopy, the most characteristic ultrastructural feature is the presence of granular electron-dense deposits that delineate the outer aspect of the glomerular and tubular basement membranes.

Treatment of MIDD should be aimed at reducing Ig production (Fermand et al. 2013). As illustrated in Table 19, the outcome of patients with MIDD has improved with a reduction in the rate of end-stage renal disease and mortality, respectively, at 20% and 10% in the latest study performed (Cohen et al. 2015). Such improvement is explained by earlier diagnosis, thanks to sFLC assay and more potent chemotherapeutic regimens, including stem cell transplantation. Stem cell transplants are now challenged by highly effective new drugs, such as bortezomib. Predictors of renal survival include a lower initial serum creatinine level and post-treatment difference between involved and uninvolved serum-

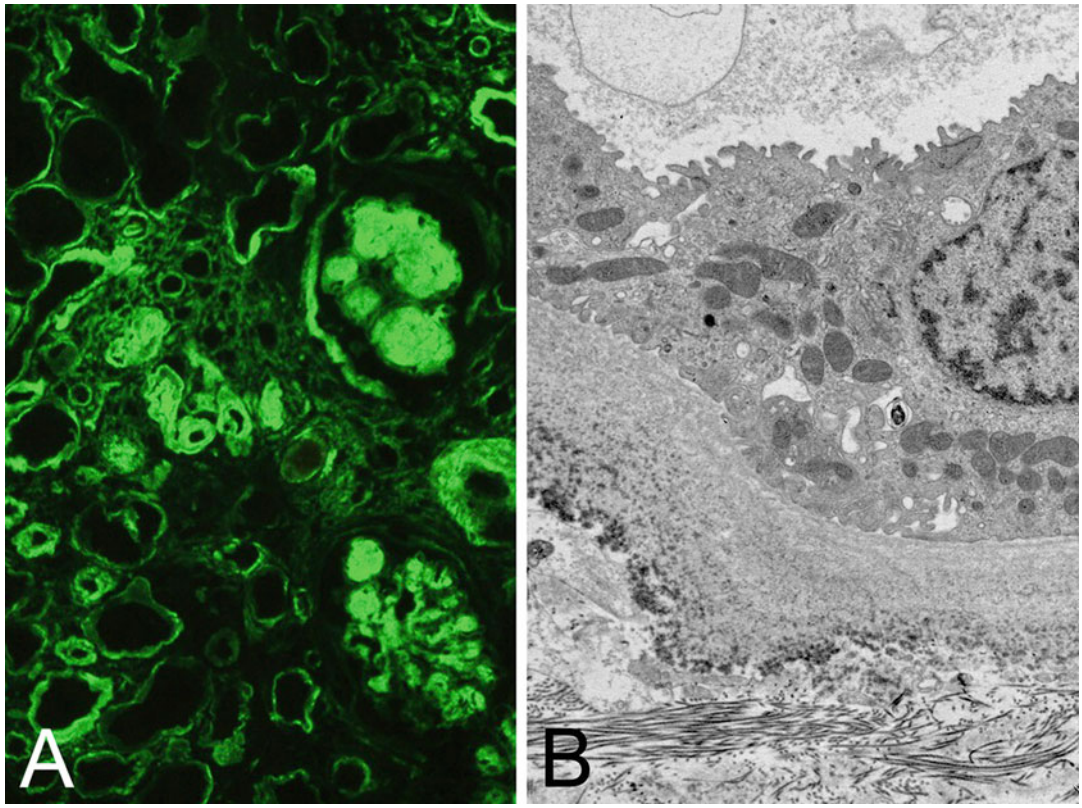

Fig. 12 Light-chain deposition disease IF and EM. (**a**) Linear staining along tubular membrane and mesangial nodules staining for kappa light chain (fluorescein, ×80). (**b**) The tubular basement membrane contains granular deposits, especially on the external side (uranyl acetate and lead citrate, ×12000)

Table 19 Outcome and prognostic indicators in monoclonal immunoglobulin deposition disease

	Pozzi et al. (2003)	Lin et al. (2001)	Nasr et al. (2012b)	Sayed et al. (2015)	Cohen et al. (2015)
Study period	1972–2002	1982–2002	1992–2011	2002–2015	NA
Number of patients	63	23	64	53	49
MIDD subtype	62 LCDD, 1 LHCDD	12 LCDD, 6 HCDD, 5 LHCDD	51 LCDD, 7 HCDD, 6 LHCDD	53 LCDD	35 LCDD, 12 HCDD, 2 LHCDD
Duration of follow-up (months)	Median 28	Mean 22	Mean 34	Median 74	Median 54
ESRD rate (%)	57	48	39	62	20
Mortality rate (%)	59	43	32	36	10

Abbrevations: ESRD, end-stage renal disease; HCDD, heavy-chain deposition disease; LCDD, light-chain deposition disease; LHCDD, light-and heavy-chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; NA, not available

free light chains under 40 mg/l (defining a very good partial hematologic response, similar to the hematologic response defined in AL amyloidosis). Several variables have been independently associated with a worse patient survival: older age, associated multiple myeloma, extrarenal LC deposition, and lytic bone lesions (Nasr et al. 2012b).

Other Dysproteinemia-Associated Glomerulopathies

As many complications of dysproteinemias such as AL amyloidosis and MIDD, the two entities described below may occur in patients with a malignant or more often a benign plasma cell or B-lymphocyte proliferation belonging to the MGRS entity.

Glomerulonephritis with non-organized Monoclonal Immunoglobulin Deposits

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is defined by the presence of nonorganized monoclonal immunoglobulin deposits that are confined to the mesangium and the glomerular basement membrane (Nasr et al. 2004). The first extensive description of PGNMID included 37 patients (Nasr et al. 2009), the majority being white (81%) and female (62%) with a mean age of 55 years. All patients had proteinuria and 49% of the patients developed full nephrotic syndrome. Microhematuria was documented in 77% of patients and renal insufficiency in two-thirds of patients. None of the patients had significant extrarenal symptoms. In most of the cases (70%), no monoclonal component could be detected in serum or urine. Four histologic patterns were described, the most common (57% of the cases) being membranoproliferative glomerulonephritis (MPGN) followed by endocapillary proliferative glomerulonephritis (35% of the patients). The third pattern, seen in 5% of the patients, was predominantly membranous nephropathy (MN) but with focal endocapillary and segmental membranoproliferative features. The fourth and rarest pattern was pure mesangial proliferative glomerulonephritis. Immunofluorescence demonstrated glomerular deposits that stained for a single light-chain isotype and a single heavy-chain subtype, most commonly IgG3κ (53%). Only one patient had multiple myeloma at presentation, and none developed hematological malignancy over the course of follow-up.

More recently, 26 patients with noncryoglobulinemic glomerulonephritis and monoclonal Ig deposits were reported (Guiard et al. 2011). A monoclonal component was detected in only 30% of the patients. Nine of the patients (35%) featured an overt hematologic malignancy: chronic lymphocytic leukemia (CLL) in four patients, multiple myeloma (MM) in two cases, and non-Hodgkin lymphoma (NHL) in three others. Histologic studies showed a striking correspondence between the localization of IgG deposits, defining either MPGN or MN histological patterns, and the subclass of the monoclonal IgG found in the deposits, with a predominance of IgG3 in MPGN and IgG1 in MN.

Although IgG3 subtype may be the more frequent monoclonal immunoglobulin deposit In PGNMID with MPGN pattern, a monoclonal IgM can also be found (Sethi et al. 2010). Among the 28 patients with monoclonal gammopathy and MPGN reported in this series, two patients showed CLL, one showed lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, three showed low-grade B-cell lymphoma, and six patients showed myeloma, while the remaining 16 cases featured the characteristics of a monoclonal gammopathy of undetermined significance (MGUS) which, in this context, should rather be called monoclonal gammopathy with related MPGN or monoclonal gammopathy of renal significance (MGRS) (Leung et al. 2012a).

Because this glomerulonephritis is a newly described entity, there are no studies to determine the optimal approach to therapy. In patients with an underlying malignancy such as MM, CLL, or NHL, the treatment of the primary disease is the first step. In patients with no overt hematological malignancy, every effort should be made to identify the type of clonal proliferation either plasmacytic or lymphocytic, which has an impact on the choice of therapy and the response to it (Hogan and Weiss 2016). Cyclophosphamide and bortezomib in association with dexamethasone seem to be the drugs of choice (Fermand et al. 2013) although rituximab alone may be efficient (Guiard et al. 2011).

Glomerulonephritis with Nonamyloid Organized Monotypic Deposits

These entities are characterized by fibrillary or microtubular deposits in mesangium and glomerular capillary loops that are not stained by Congo red (Fig. 13). They were termed fibrillary glomerulonephritis (FGN) (Alpers et al. 1987) and

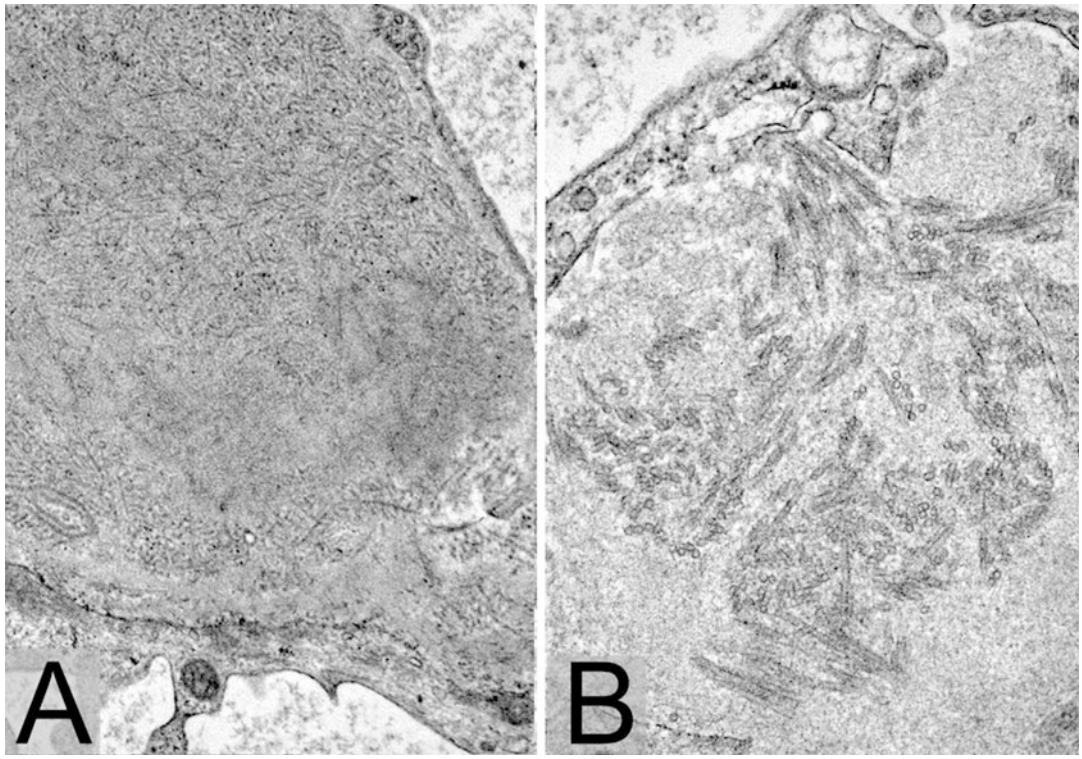

Fig. 13 Comparative aspects between fibrillary GN (**a**) and immunotactoid GN (**b**) (uranyl acetate and lead citrate, ×20000). (**a**) Subepithelial and mesangial deposits composed of fibrils; (**b**) Subepithelial and mesangial deposits composed of macrotubules with hollow centers (uranyl acetate and lead citrate, ×40000). P, podocyte; Lu, lumen

immunotactoid glomerulopathy (IT) (Korbet et al. 1985), respectively. Patients with IT and FGN have a mean age of 53–60 years and usually present with the nephrotic syndrome, microscopic hematuria, hypertension, and mild-to-severe renal insufficiency. Only IT has a significant association with underlying dysproteinemia, whereas FGN has a wide spectrum of etiologies (Nasr et al. 2011). At variance with IT in which immunoglobulin (Ig) deposits are usually monoclonal (IgGκ or IgGλ), those described in FGN are usually polyclonal (mostly IgG4) (Bridoux et al. 2002). Hematologic malignancy can be present in up to 38% of the patients with IT, including chronic lymphocytic leukemia in 19%, lymphoplasmacytic lymphoma in 13%, and multiple myeloma in 13% (Nasr et al. 2012a). Whereas renal parameters improve after immunosuppressive therapy or chemotherapy in most patients with IT, FGN is associated with poor renal outcome due to the progression to end-stage renal disease over a few years in half of the patients (Javaugue et al. 2013).

Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPN) are defined by a clonal expansion of one or more of the myeloid lineages. According to the 2008 World Health Organization system, the classification of MPN includes eight separate entities: chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis, chronic eosinophilic leukemia, and unclassifiable MPN. A transformation into acute myeloid leukemia and thrombotic or hemorrhagic events can complicate MPN.

Glomerulopathies have occasionally been reported in patients with myeloproliferative neoplasm (MPN). A first small series of five patients in 1999 showed FSGS and mesangial sclerosis (Au et al. 1999). The most recent study reported 11 patients with MPN who developed nephrotic-range proteinuria and chronic renal insufficiency after a mean time from the diagnosis of MPN of 7.2 years (Said et al. 2011). These glomerulopathies appear to be a late complication of MPN. Kidney biopsy revealed a peculiar form of glomerulopathy referred to as "MPN-related glomerulopathy," characterized by a combination of mesangial sclerosis and hypercellularity (Fig. 14), segmental sclerosis, features of chronic thrombotic microangiopathy, and intracapillary hematopoietic cell infiltration. The majority of the patients (73%) had PMF, a disease which is less common than PV, ET, and CML, suggesting that PMF patients are more at risk of developing MPN-related glomerulopathy. This entity is, however, not considered as a pure paraneoplastic disease because of the presence of hematopoietic cell infiltration.

Acute Leukemia

Acute lymphoblastic leukemia (ALL) is mostly a disease of childhood, whereas acute myeloid leukemia (AML) is more frequently seen in adults. Some patients with AML may exhibit a nephrotic-range proteinuria usually explained by the presence of large amounts of lysozyme in the urine leading to a pseudonephrotic syndrome (Patel et al. 2009). Lysozyme is a bactericidal protein produced by monocytes and macrophages, freely filtered by the glomerulus and then reabsorbed by

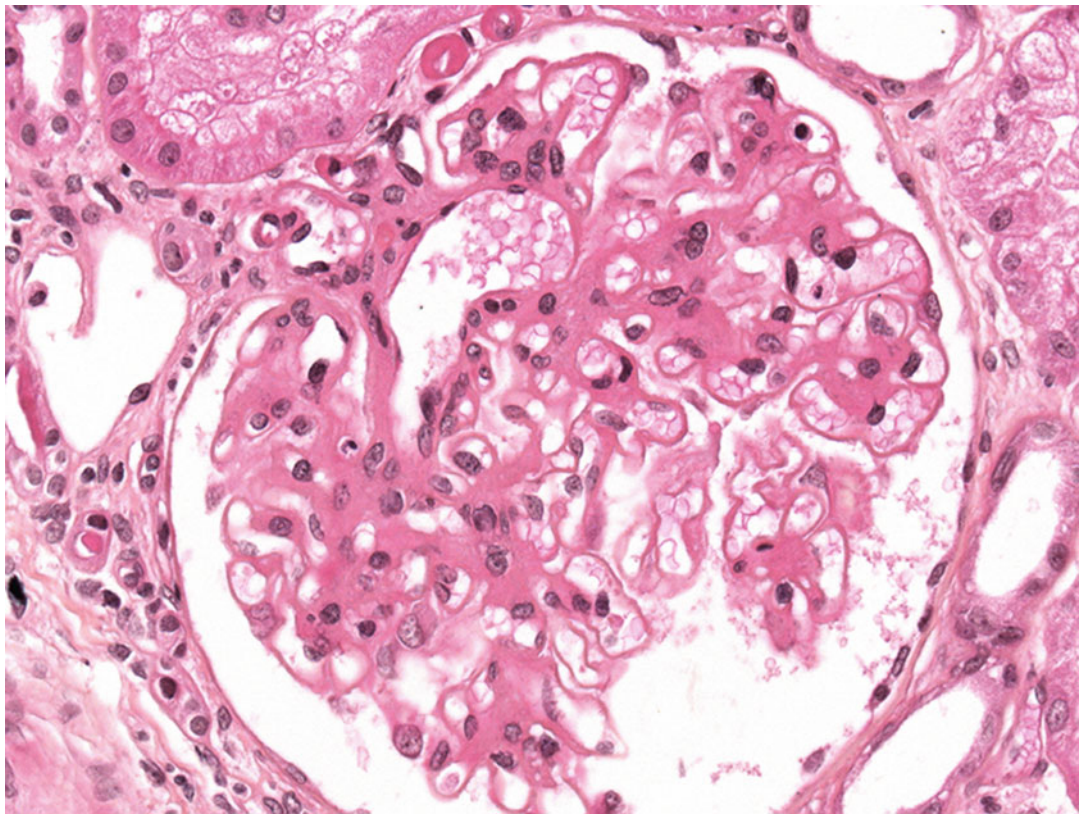

Fig. 14 MPN-related glomerulopathy. The flocculus shows mesangial expansion with slight hypercellularity (hematein eosin, ×170)

the proximal tubule cells. In AML, high levels of lysozyme produced by the leukemic cells can induce tubular necrosis. Profound hypokalemia resulting from renal wasting is a striking feature of lysozymuria-induced acute kidney injury. The diagnosis can be confirmed by the presence of lysozyme in the blood and the urines by protein electrophoresis with immunofixation (Levinson et al. 2002).

Hematopoietic Stem Cell Transplantation-Related Glomerulopathies

Hematopoietic stem cell transplantation (HSCT) is used to treat a wide range of hematologic malignancies. Recipient patients may develop nephrotic syndrome with an estimated incidence ranging from 0.4% to 6% (Hingorani 2016). The nephrotic syndrome usually occurs 6–12 months after the diagnosis of chronic graft-versus-host disease (GVHD) following cessation of immunosuppressive medication (Brukamp et al. 2006). Most of the patients (61%) present with membranous nephropathy, whereas minimal-change disease is found in 22% of the cases. The other patients may develop focal and segmental glomerulosclerosis, IgA nephropathy, and mesangial proliferative glomerulonephritis. Few cases may also occur in the absence of GVHD. Treatment of the nephrotic syndrome relies on high-dose prednisone, reinstitution of calcineurin inhibitors, or rituximab.

Thrombotic microangiopathy (TMA) following HSCT is also called bone marrow transplant or radiation nephropathy in some cases. Several risk factors for HSCT-related TMA have been identified, including treatment with total-body irradiation, the use of calcineurin inhibitors, the combined use and elevated levels of sirolimus and tacrolimus, acute GHVD grades 2–4, infections (including BK viremia), and transplantation of peripheral blood stem cells (Hingorani 2016). GVHD may induce endothelial damage leading to TMA upon activation of the coagulation system responsible for the formation of thrombin and the deposition of fibrin. Treatment of HSCT-related TMA is usually supportive including the control of blood pressure and proteinuria in association with the discontinuation of calcineurin inhibitors in most of the cases. Plasma exchange is frequently used despite the lack of definitive trials showing its effectiveness.

Monoclonal Gammopathy of Renal Significance

In 2012, the term monoclonal gammopathy of renal significance (MGRS) was introduced to describe kidney diseases due to monoclonal immunoglobulin (MIg) deposition which do not meet the criteria for symptomatic multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, or non-indolent lymphoma (Leung et al. 2012a). These patients escape the framework of monoclonal gammopathy of undetermined significance (MGUS) since the significance of the monoclonal gammopathy is now defined by the presence of an associated organ injury. These MIg are produced by small plasma cell or B-cell clone with low malignant potential (Merlini and Stone 2006).

The spectrum of renal diseases due to MIg deposition has expended dramatically and can be classified on the basis of the location of the injury (glomeruli, tubules, or vascular involvement) (Bridoux et al. 2015). However, such a classification remains difficult because the overlap is common, with multiple sites involved such as in immunoglobulin-derived amyloidosis that can deposit in the glomeruli, the tubules, and also the vessels. Another method of classifying these conditions is by the ultrastructural characteristics of the deposits.

The diagnostic approach in MGRS aims to identify the underlying plasma cell or the B-cell clones and their associated MIgs (Hogan and Weiss 2016) (Table 20). Detection and characterization of the MIg rely on serum protein electrophoresis with immunofixation, 24-h urine protein electrophoresis with immunofixation, and serum-free light-chain assays. The underlying clone may be characterized on a sample of the bone marrow, peripheral blood or a pathologically involved

lymph node, with additional techniques to confirm the clonal expansion and define its cell origin (plasma cell, B cell, or lymphoplasmacytic). These techniques include immunohistochemical staining, κ and λ *in situ* hybridization staining, and flow cytometry screening assays. Because MGRS is associated with high rates of progression to end-stage renal disease and recurrence after kidney transplant, the aim of the treatment of MGRS-associated nephropathies is preservation of the kidney, the associated hematologic condition remaining in the majority of cases

Table 20 Proposed workup for patients with glomerulopathy suspected to be associated with hematologic malignancy[a]

Clinical evaluation (signs associated with CLL/lymphoma, multiple myeloma, monoclonal immunoglobulin deposition disease, immunoglobulin-derived amyloidosis)	Lymphadenopathies and/or hepatosplenomegaly? Presence of B symptoms (fever, night sweats, and weight loss) Bone pain Signs of heart failure Autonomic neuropathy: postural hypotension, erectile/bladder/bowel dysfunction Peripheral neuropathy: areflexia, hypoesthesia, pain, weakness Macroglossia, signs of malabsorption (diarrhea, weight loss. . .) Periorbital purpura, xanthomas Nail dystrophy Signs of carpal tunnel syndrome
Laboratory investigations	**Serum protein electrophoresis and immunofixation** **Serum-free light-chain assay (sFLC)** to detect and quantify the excess of free light chains. Normal kappa/lambda ratio is 0.26–1.65 in healthy individuals and 0.37–3.1 in patients with renal impairment **Urine protein electrophoresis and immunofixation** to distinguish patients with glomerular involvement (predominant albuminuria) from those with tubulointerstitial lesions and identify Bence Jones proteinuria **Complete blood count and hemostasis** **Phenotypic characterization of peripheral blood lymphocytes and study of rearrangement of Ig genes** may be indicated in some cases **Serum cardiac biomarkers** (NT-proBNP and Troponin levels) **Liver tests** (alkaline phosphatase and bilirubin) **Search for hypocomplementemia C3/C4** **Search for ANF or ANCA**
Renal evaluation	**Kidney biopsy** in all patients, except for immunoglobulin-derived amyloidosis where the diagnosis can be obtained by extrarenal tissues (such as minor salivary glands or abdominal fat) **Congo red staining** to search for amyloidosis **Immunofluorescence study** using antibodies specific for the different light chains (LC) and immunoglobulin (Ig) isotypes to evidence Ig or LC restriction. Antibodies against IgG subclasses are useful in glomerular diseases related to deposition of an entire monoclonal IgG or of a truncated monoclonal heavy chain **Electron microscopy (EM)** to distinct organized from granular deposits and specify their localization **ImmunoEM and laser microdissection/mass spectrometry analyses** in difficult cases, to confirm the composition of renal deposits and their localization

(*continued*)

Table 20 (continued)

Hematologic evaluation	In *patients with IgG-, IgA- or LC only-related glomerulopathy*: **bone marrow aspirate and biopsy** are usually sufficient to identify the clone. Flow cytometry, κ and λ in situ hybridization staining, and/or immunohistological studies of bone marrow cells are sometimes useful. **Complete skeletal radiographs +/− magnetic resonance imaging** should be performed to exclude a solitary plasmacytoma when bone marrow fails to identify the clone In *patients with IgM-related glomerulopathy*: **lymph node biopsy** may be indicated. **Pet-CT or CT scan of the chest, abdomen, and pelvis** can help to identify lymph nodes

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibodies; ANF, antinuclear factor; CTs, computed tomography
[a]The workup is to be adapted to the clinical setting and the results of the kidney biopsy

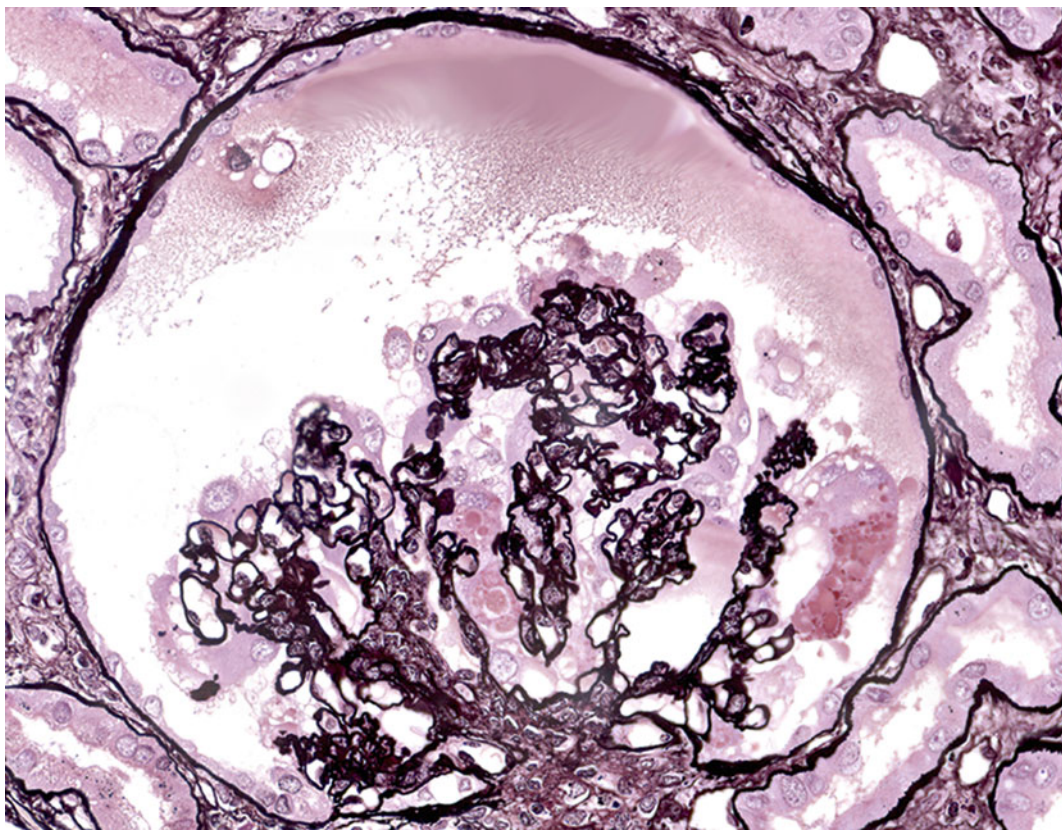

Fig. 15 Collapsing FSGS: The glomerulus shows diffuse capillary collapse and hypertrophied podocytes with vacuoles (Jones ×170)

low-grade plasma cell dyscrasia or lymphoproliferative disorders that do not immediately endanger the patient's life. The treatment takes into account the nature of the underlying clone, the renal function, and the presence, or not, of extra-renal involvement (Fermand et al. 2013). In general, rituximab can be used against the CD20-expressing clones but would have little effect

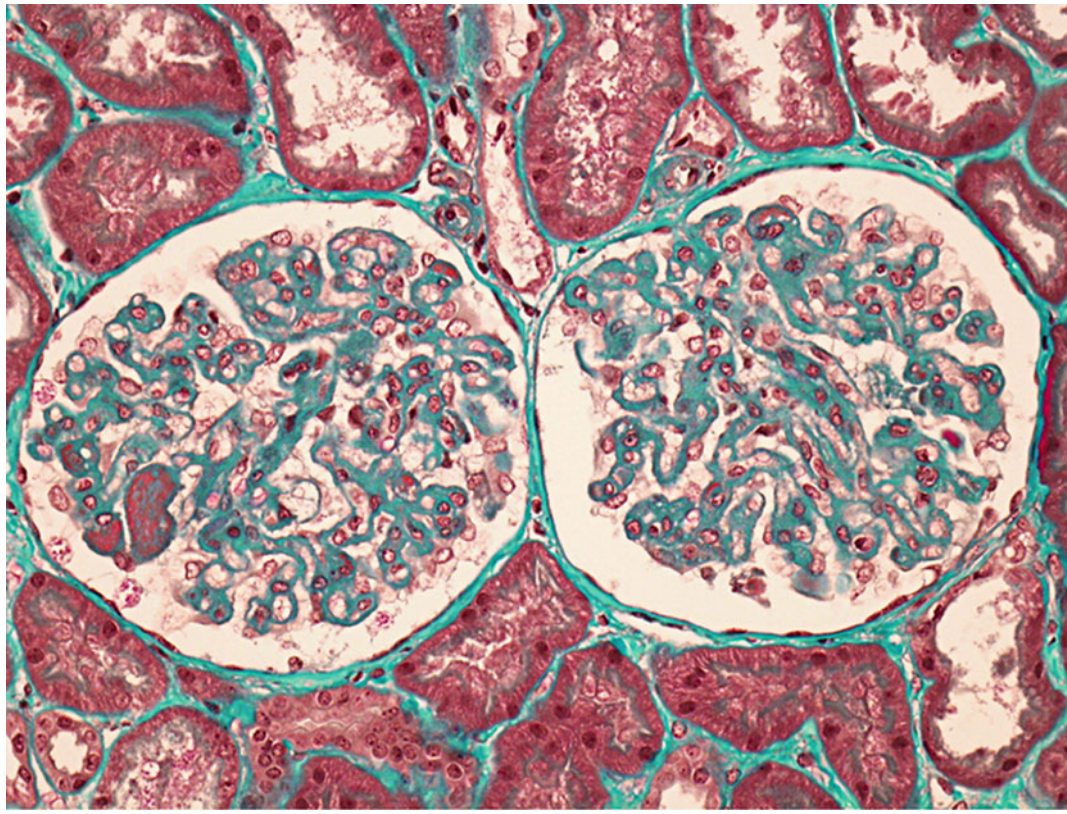

Fig. 16 Thrombotic microangiopathy associated with bevacizumab administration. In the glomerulus on the *left*, some dilated capillary lumina are occluded by fibrin thrombi. The glomerulus on the *right* is slightly flattened (trichrome stain, ×170)

against plasma cells for which the addition of alkylating agent, proteasome inhibitors, immunomodulatory drugs, or monoclonal antibody may be necessary. Autologous stem cell transplantation can be proposed in some patients, especially when renal transplantation is planned. When the kidney damages are irreversible, cytotoxic therapies should be avoided except in cases of kidney transplantation where the goal is to achieve a complete response to minimize the risk of recurrence.

Drug-Induced Glomerular Disease

In the past few decades, the number of anticancer therapies has dramatically increased. Drug-induced glomerular disease can be classified into two specific categories (Radhakrishnan and Perazella 2015). The first one results from a direct cellular toxicity involving the mesangial, endothelial, and epithelial cells and may present as minimal-change disease (MCD), focal and segmental glomerulosclerosis (FSGS), or thrombotic microangiopathy (TMA). The second one is characterized by glomerulopathies induced by immune-mediated causes such as lupus-like renal lesions, ANCA-related vasculitis, and secondary membranous nephropathy (MN). To date, glomerulopathies induced by anticancer therapies results only from a direct cellular toxicity. These complications are described in detail in another chapter.

The interferons are cytokines that have been used for the treatment of multiple malignancies such as renal cell carcinoma or melanoma. They may be responsible for the development of podocytopathies (MCD and FSGS) (Fig. 15) and also TMA. TMA and FSGS have also been described in patients treated with mTOR inhibitors for renal cell carcinoma (Markowitz et al. 2015).

Antiangiogenic drugs include monoclonal anti-vascular endothelial growth factor (anti-VEGF) antibodies, circulating VEGF decoy-receptor molecule, and VEGF receptor tyrosine-kinase inhibitors. They are used to treat a number of cancers and may induce nephrotoxicity (Fig. 16). The most common renal manifestations are proteinuria and hypertension, but acute kidney injury has been reported in severe cases because of TMA. Despite the findings of acute or chronic TMA on kidney biopsies, microangiopathic hemolytic anemia and thrombocytopenia are only observed in approximately 50% of patients (Izzedine et al. 2014). Proteinuria is a constant feature, whereas hypertension occurs in more than 80% of patients. Of interest, adverse renal effects often correlate with effective antitumor activity. Kidney function may recover with blood pressure control and drug withdrawal.

Mitomycin C and gemcitabine are associated with the occurrence of TMA probably explained by drug-induced endothelial injury. Although TMA can develop during drug exposure, it more often develops weeks to months after initiating therapy. Patients commonly present with microangiopathic hemolytic anemia and thrombocytopenia, while acute kidney injury is virtually present in all cases. Plasma exchanges are usually ineffective (Humphreys et al. 2004).

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Medication-Associated Glomerular Disease

45

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Abstract

Medication induced kidney injury can take on many forms including tubule-interstitial disease, acute hemodynamic mediated injury, nephrolithiasis or crystalline nephropathy, or glomerulonephritis. Glomerular disease caused by medication will present similarly with proteinuria, hematuria, and decreased clearance. Glomerular histologic patterns that encompass medication induced glomerular disease include minimal change disease, membranous nephropathy, focal segmental glomerulosclerosis, vasculitis, drug induced lupus, and thrombotic microangiopathy. Once identified as medication-related, treatment usually involves discontinuation of the medication, and additional interventions may be used for specific drugs or disease severity.

Keywords

Glomerulonephritis · Medication-induced kidney injury · Acute kidney injury · Nephrotic syndrome · Nephritic syndrome · Proteinuria · Hematuria

Introduction

Medications can have deleterious effects on kidney function; acute kidney injury (AKI) attributed to medications makes up approximately 20% of all AKI (Uchino et al. 2005). Medication induced AKI can affect any part of the nephron through a variety of histological presentations. The most common manifestations are acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) (Markowitz et al. 2015). Other presentations of medication-induced nephrotoxicity include hemodynamic mediated kidney injury, papillary necrosis, obstructive nephropathy, crystalline induced nephropathy and glomerular injury (Table 1) (Taber and Pasko 2008). Medication-induced glomerular disease has a wide array of presentations with various outcomes and treatment options. Since AKI is associated with increased morbidity and mortality, it is important for medical professionals to recognize medications that will lead to glomerular injury (Chertow et al. 2005).

Table 1 Medication induced nephrotoxicity

Kidney Injury	Examples
ATN	Aminoglycosides, amphotericin B, vancomycin, platin-based chemotherapy agents (cisplatin > carboplatin), cephaloporins, osmotically active agents (radiocontrast, mannitol, hydroxyethyl starch), nucleotide analogues (tenofovir, cidofivir, adefovir)
AIN	Antibiotics (beta-lactams, flurooguinolones, rifampin, sulfa based drugs, vancomycin), antivirals (acyclovir, atazanavir), proton pump inhibitors, NSAIDs, captopril, tyrosine kinase inhibitors, loop diuretics, thiazide diuretics, phenytoin
Hemodynamic AKI	NSAIDs, CNI, radiocontrast, amphotericin B
Papillary necrosis	Analgesics, NSAIDs
Obstructive nephropathy	Anticholinergic agents, opiates, antihistamines
Crystalline nephropathy	Sulfadiazine, acyclovir, indinavir, atazanavir, triamterene, methotrexate, orlistat, ciprofloxacin
Glomerular disease	Anti-platelet agents, anti-neoplastic agnets, immunosuppressive agents, antimicrobial agents, NSAIDs, anti-thyroid medications, biologics, anti-arrhythmics, bisphosphonates, hormones, interferon

Abbreviations: *ATN* acute tubular necrosis, *AIN* acute interstitial nephritis, *AKI* acute kidney injury, *NSAIDs* non-steroidal anti-inflammatory drugs, *CNI* calcineurin inhibitor

Minimal Change Disease

Minimal change disease (MCD) is a podocytopathy, characterized by defects in the podocytes, resulting in an abnormal glomerular basement membrane (GBM) and slit diaphragm. These abnormalities result in the clearance of otherwise impermeable molecules, such as albumin. Many etiologies of minimal change exist, including many medications (Table 2).

Pathogenesis of medication-induced MCD has not been completely elucidated but several hypotheses have been presented. Podocytes have numerous immunological receptors, and therefore the potential to respond to various chemokines produced by the immune system (Mathieson 2007). The main immune cell involved seems to be the T cell. After an immunological challenge by a new medication, T cells produce circulating factors (particularly IL-8 or IL-13) that impair the glomerular filtration barrier, through disruption of the GBM (Grimbert et al. 2003; Ishimoto et al. 2011). CD80, a transmembrane protein, present on antigen presenting cells (APC), has been demonstrated to be expressed in podocytes after exposure to lipopolysaccharide (LPS). CD80 provides a co-stimulatory signal for T cells. CD80 function is normally regulated by CTLA-4. In MCD, it is though that there is an inadequate CTLA-4 response, leading to impaired podocyte function (Ishimoto et al. 2011). Abnormal expression of vascular endothelial growth factor A (VEGF-A), produced in visceral glomerular epithelial cells and B cells, has also been postulated to contribute to the pathogenesis of MCD by leading to abnormal glomerular and capillary wall structure and function (Bertuccio 2011).

Table 2 Medications associated with minimal change disease

Drug Class	Examples
NSAIDs	COX-1 and COX-2 medications
Antibiotics	Ampicillin, rifampicin, cefixime
Interferon	Interferon-a, interferon-b
Miscellaneous	Lithium, pamidronate, tamoxifen, penacillamine, bucillamine, etanercept, gold, methimazole, enalapril, mercury

Abbreviations: *NSAIDs* non-steroidal anti-inflammatory drugs, *COX* cyclooxygenase

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a large class of drugs that act by inhibiting the cyclooxygenase (COX) enzyme, thereby preventing conversion of archadonic acid to prostaglandins. Since prostaglandins are

chemokines associated with inflammation, NSAIDs are potent anti-inflammatory medications. However, prostaglandins have other effects and functions in different tissues including the kidney. NSAIDs are associated with many nephrotoxic insults including glomerular disease, acute or chronic interstitial nephritis, acute tubular necrosis and papillary necrosis (Sekhon et al. 2005). All NSAID classes, both oral and topical, have been linked to nephrotoxicity. Selective COX-2 inhibitors were initially thought to have decreased nephrotoxicity due to the fact that COX-2 is not constitutively expressed in the kidney. Unfortunately, these medications have the same nephrotoxic risk as the non-selective COX inhibitors (Gambaro and Perazella 2003). Approximately 12% of all NSAID induced kidney injury is MCD.

NSAID-induced MCD is most commonly seen in older patients (average age of 63) with proteinuria at presentation usually above 3 g/day. It is commonly associated with interstitial nephritis and AKI as well. Around half of the cases improve with discontinuation of the drug and the other half requires treatment with steroids. Remission usually occurs within 5 weeks; renal replacement therapy is rarely required.

Pathophysiology is likely due to the inhibition of COX enzymes by NSAIDs. COX catalyze the conversion of arachidonic acid to prostaglandin G_2 (PGG_2). PGG_2 is further metabolized to a number of active prostaglandins (PGE_2, PGI_2, PGD_2, $PGF_{1\alpha}$ and thromboxane A_2) (Kim 2008). NSAID-induced COX inhibition may shunt the arachidonic conversion via lipoxygenase to leukotriene production. Leukotrienes function as pro-inflammatory and vasoactive chemokines leading to increased vascular permeability of the glomerular capillaries resulting in proteinuria. In addition, there is extensive leukocyte infiltration resulting in AIN, a histological finding commonly seen in association with the glomerular findings. Additionally, inhibiting PG production can increase ischemic renal damage by depleting intra-renal vasodilatory PG's which are increasingly necessary to maintain an adequate GFR in patients with nephrotic syndrome (Weir 2002).

Lithium

Lithium is a medication used to treat refractory depression and bipolar disease. Although highly effective as a psychiatric medication, lithium can be nephrotoxic and this may limit its use. Lithium induced nephrotoxicity includes nephrogenic diabetes insipidus, chronic interstitial nephritis, renal tubular acidosis, and glomerular disease (Boton et al. 1987). The most common cause of lithium-induced nephrotic-range proteinuria is MCD which is seen in 80% of cases (Bosquet et al. 1997). MCD usually presents within 1 year of lithium use, but rarely there is a small group of patients presenting after more than 10 years of lithium use (Bosquet et al. 1997). Proteinuria ranges can vary from 3 to 69 g/day. Renal prognosis is excellent if caught early, with resolution of proteinuria occurring within 2–6 weeks discontinuation of lithium. If lithium is restarted, MCD may recur in more than 50% of patients.

Pathophysiology is unclear but is thought to be secondary to lithium induced epithelial cell toxicity. Indirectly, lithium may modulate the phosphoinositol pathway leading to increased T-cell activation. T-cell activation will lead to increased cytokine production resulting in increased glomerular permeability and proteinuria.

Interferon

Named after its viral interference properties, interferon (IFN) was the first modern cytokine to be discovered. The major interferons, alpha (α), beta (β), and gamma (γ) are produced by non-lymphocyte white blood cells, fibroblasts, and T-cells/natural killer cells, respectively. Their role in our innate immune system is critical during a viral infection. Through recombinant DNA technology, cloned IFN is now used to treat a variety of diseases. IFNα has two subtypes, IFNα-1a and IFNα-2b, and both are used to treat chronic hepatitis B and C, whereas IFNα-2b is also used in hairy cell leukemia, malignant melanoma, follicular non-hodgkins lymphoma, genital warts, and AIDS-related Kaposi sarcoma. IFNβ,

sub-classified as IFNβ-1a and IFNβ-1b, is used to treat relapsing forms of multiple sclerosis. And lastly, IFNγ-1b is indicated for serious infections associated with chronic granulomatous disease and severe malignant osteoporosis.

IFNα and IFNβ have both been associated with nephrotic syndrome and MCD. Around 15–25% of patients taking IFN develop proteinuria, typically around 1 gram/day, while less than 0.001% develop nephrotic syndrome (Jones and Itri 1986). The incidence is greater in transplant patients with approximately 37% having AKI or proteinuria (Rostaing et al. 1996). IFN-induced MCD is rare and therefore most of the data on this association is found in case reports. IFN-induced MCD can occur anytime and with any dose during treatment (Weiss 1992). Proteinuria has been reported between 3 and 42 g/day (Aravindan et al. 2010). Renal prognosis is excellent upon discontinuation of therapy, with resolution of proteinuria within 1 month to 2 years. Refractory cases of IFN-associated MCD have been treated with prednisone/prednisolone therapy (Aravindan et al. 2010). Usually when IFN is re-introduced, nephrotic syndrome returns.

The pathophysiology is currently unknown, although many hypotheses have been proposed. Interferon is primarily metabolized in the kidney where levels can be 7–10 fold higher than levels in the spleen, liver, heart, lungs and brain, thereby suggesting that the increased concentration of IFN may contribute to its nephrotoxic potential. IFNα enhances tyrosine phosphorylation in the proximal tubule epithelial cells, consequently increasing the expression of abnormal junctional proteins (occludin and E-cadherin) thereby creating a "leaky" cell. Apart from the junctional protein expression, IFNα can cause apoptosis in healthy renal epithelial cells through an external cell receptor pathway (Lechner et al. 2008). Another hypothesis is that the formation of IFN-neutralizing antibodies directly leads to podocyte effacement. These antibodies can form between 4 and 20 months after initiation of therapy and decrease over months upon IFN withdrawal (von Wussow et al. 1989). It has also been suggested that IFN, being positively charged, can impair the charge barrier created by a negatively charged GBM. Lastly, IFN may active cellular immunity allowing T-cell infiltration leading to glomerular epithelial hypertrophy and hyperplasia, thereby causing proteinuria (Nishimura et al. 2002).

Membranous Nephropathy

Membranous nephropathy is a major cause of non-diabetic nephrotic syndrome in adults. It results from immune complex deposition in the epithelial portion of the GBM resulting in complement activation (Ronco and Debiec 2015a). One of the antigens implicated in membranous nephropathy is the podocyte M-type phospholipase A_2 receptor (PLA_2R) (Beck et al. 2009, Hogan et al. 2015). Disease associated with PLA_2R is now considered primary membranous nephropathy in the majority of cases. In addition, certain diseases or medications can lead to membranous nephropathy; these are referred to as secondary membranous nephropathy (Table 3). Approximately 29–45% of all cases of secondary membranous nephropathy are thought to be due to medications (Glassock 1992). However, this should be interpreted cautiously in light of recent classifications of primary and secondary membranous glomerulopathies based on PLA2R positivity.

Secondary membranous pathogenesis may be related to an immune response to the therapeutic agent. During a drug's metabolism, cationic drug-derived antigens may get trapped at the sub-epithelial portion of the basement membrane, leading to an alteration of GBM structure and function, resulting in proteinuria (Hogan et al. 2015). Patients present with proteinuria, which is

Table 3 Medications associated with membranous nephropathy

Drug Class	Examples
NSAIDs	COX-1 and COX-2 medications
Anti-rheumatic	Gold, penicillamine, bucillamine
Interferon	Interferon-a, interferon-b
Miscellaneous	Fluconazole, lithium, probenecid, captopril, mercury, clarithromycin

Abbreviations: *NSAIDs* non-steroidal anti-inflammatory drugs, *COX* cyclooxygenase

usually more in drug-induced membranous than non-drug induced membranous nephropathy (average 7 g/24 h vs. 3 g/24 h, respectively).

Non-steroidal Anti-Inflammatory Drugs

NSAID-induced membranous nephropathy has been seen in 19% of all NSAID induced nephrotoxicity. Average NSAID use prior to diagnosis is between 1 and 24 weeks. Patients present with approximately 10 g of protein/day. Once the offending NSAID was stopped, renal recovery may take up to 1–2 years. A minority of patients require glucocorticoids for recovery. (Radford et al. 1996). If the medication is reintroduced, symptoms typically return, yet using an NSAID from a different pharmaceutical class might be safe with reduced rates of recurrence.

Captopril

Captopril is an angiotensin converting enzyme inhibitor (ACE-I) used to treat hypertension. Nephrotic syndrome occurs in 3.7% of patients taking captopril (Textor et al. 1983). In a prospective cohort, 13 patients who took captopril were biopsied after 3–14 months of therapy and all patients had abnormal glomerular changes consistent with early membranous nephropathy (Hoorntje et al. 1980). One group of physicians obtained biopsies before and after captopril use, clearly showing captopril as the causative agent. Interestingly, captopril is the only ACE-I that causes membranous nephropathy. Unlike the other ACE-I's, captopril has an active sulfydryl group which is has been implicated in its association with membranous nephropathy.

Bucillamine/Penicillamine

Penicillamine (PCL) is a beta dimethyl analog of cysteine that is used for Wilson disease, cystinuria, and severe active rheumatoid arthritis. Around 9% of patients taking penicillamine develop proteinuria (Stein et al. 1986). Average duration of treatment to the development of any proteinuria is 7.6 months and to nephrotic syndrome is 11.9–18.8 months (Habib et al. 2006). Membranous nephropathy is the most common glomerular lesion seen with PCL and makes up 55% of PCL-induced nephrotic range proteinuria. The second most common lesion is minimal MCD (27%). Risk factors include HLA-B8 and DR3 alleles, prior gold-induced proteinuria, and poor sulfoxidizers (Stein et al. 1986).

Bucillamine (BCL; N-[2-mercapto-2-methylpropionyl]-l-cystine) is a disease-modifying anti-rheumatic therapy primarily used in Japan with patients who are unable to tolerate methotrexate (Hoshino et al. 2006). Starting in 2014, the US FDA has approved clinical trials for its use in gout. Patients typically develop proteinuria after 3–9 months of use with about half of the patients also presenting with reduced creatinine clearance (Yoshida et al. 1991). Renal prognosis is excellent when the drug is discontinued with the average time to recovery from proteinuria being 5–14 months (Obayashi et al. 2003; Hoshino et al. 2006).

Bucillamine and pencillamine have been shown to directly damage the podocyte and proximal tubule (Fujiwara et al. 2011). BCL and PCL both contain sulfhydrl groups with BCL having an extra group. BCL-induced membranous nephropathy demonstrates other IgG subclasses (IgG2, IgG3, IgG4) segmentally dispersed along the basement membrane as compared to primary membranous nephropathy that is associated with IgG4 and a diffuse distribution.

Interferon

IFN therapy has also been associated with membranous nephropathy. Nephrotic syndrome can be severe with proteinuria of well over 10 g/day. Treatment usually consists of discontinuation of the medication. Resistant or refractory patients have been successfully treated with mycophenolate mofetil or cyclosporine A (Auty and Saleh 2005).

Mercury

Mercury is used in thermometers, batteries, florescent light bulbs, certain topical agents, and

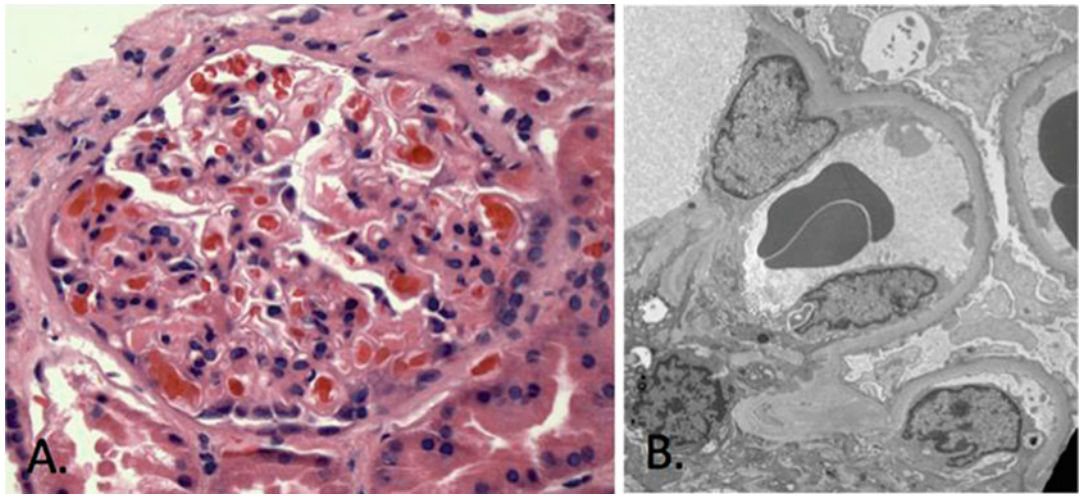

Fig. 1 (**a**) Light microscopy of glomerulus of patient with focal segmental glomerulosclerosis. Glomerulus shows segmental sclerosis. (**b**) Electrom micropgraph showing foot process effacement

dyes. Mercury-induced membranous nephropathy has been associated with mercury-containing drugs, skin-lightening cream, certain traditional Chinese herbal medications, mercury-containing hair dye, mercury-based diuretics, paint additives, fresh water fish and mercury vapor. Duration of use prior to diagnosis was 6–60 months before proteinuria and edema presented. Patients present with proteinuria (average 1–3 g/day) with a normal creatinine. Mercury-induced membranous nephropathy predominately stains for the IgG1 subclass. When mercury is stopped over 80% of patients have a complete recovery (Li et al. 2010). Pathophysiology is unknown but thought to involve a Th1 and Th2 response with the appropriate genetic susceptibility (Hu et al. 1999). Mercury has also been reported to cause MCD and focal segmental glomerulosclerosis.

Focal Segmental Glomerular Sclerosis

Focal segmental glomerular sclerosis (FSGS) refers to a histological and morphological pattern on kidney biopsy, rather than a specific disease. The main lesion seen is a segmental obliteration of the glomerular capillaries by the extracellular matrix (Fig. 1a). EM will show foot process effacement (Fig. 1b). The Columbia classification separates FSGS into five different variants based on morphology (D'Agati et al. 2004). The variants include, the tip variant, collapsing variant, cellular variant, perihilar variant and NOS (not otherwise specified) variant. Along with morphological differences, clinical presentations and outcomes are correlated with different variants (Stokes and D'Agati 2014). These variants will be discussed further as they pertain to drug-induced FSGS (Table 4).

Table 4 Medications associated with focal segmental glomerulosclerosis

Drug Class	Examples
Bisphosphanates	Pamidronate, zoledronate
Interferon	Interferon-a, interferon-c
mTOR inhibitors	Sirolimus, everolimus
Miscellaneous	Anabolic steroids, lithium, heroin

Abbreviations: *mTOR* mammalian target of rapamycin

Bisphosphonates

Bisphosphonates are derivatives of inorganic pyrophosphate that have a high affinity for hydroxyapatite crystals found in bone mineral. They can be grouped into two classes based on their molecular side chains. All bisphosphonates have a central carbon backbone with two

phosphate groups attached (P-C-P) and a hydroxyl group attached to the R1 carbon side chain. The difference lies in the R2 side chain, which can be either a nitrogen or non-nitrogen moiety. The nitrogen-based bisphosphonates (pamidronate, alendronate, zolendronate, ibandronate) have a more potent anti-resorptive effect than the non-nitrogen based bisphosphonates (etidronate, clodronate, tiludronate). Bisphosphanates are used to treat heritable skeletal disorders in children, osteoporosis, bone metastasis due to malignancy, Paget's disease of the bone, and calcific uremic arteriolopathy.

The association of high dose, intravenous pamidronate with collapsing FSGS was first recognized in a case series of older Caucasian patients, which was markedly different than the typical collapsing FSGS cohort (young African-Americans) (Markowitz et al. 2001). Of the bisphosphonates, pamidronate has most been reported to cause collapsing FSGS, but zoledronate and ibandronate have rarely been associated with collapsing FSGS. Apart from collapsing FSGS, less frequently seen glomerular lesions include non-collapsing FSGS and minimal change disease (Perazella and Markowitz 2008).

When given IV, approximately 50% of the bisphosphonate is taken up by bone, a negligible amount by other tissues and the rest filtered by the kidney (Miller 2011). The drug is not metabolized and therefore, excreted unchanged in the urine. Apart from passive glomerular filtration, the drug is actively secreted in the proximal tubular cells. Due to a paucity of data, the pathophysiology of bisphosphonate-induced nephrotoxicity is not entirely clear. With impaired renal function, bisphosphonates may accumulate and cause toxicity (Perazella and Markowitz 2008). Nitrogen based bisphosphonates inhibit osteoclast farnesyl diphosphate (FFP) synthase, and via the loss of prenylation of GTPase signaling proteins, the cell is unable to survive. FFP synthase inhibition resulting in cytotoxicity has also been shown to occur in the kidney (Luhe et al. 2008). In comparison, non-nitrogen based bisphosphonates can be metabolized to nonhydrolyzable nucleotide analogs, thereby competing with ATP for enzymatic reactions.

Interferon

As previously mentioned, interferons are associated with FSGS. IFN-induced FSGS can be split into two subtypes: IFN-induced collapsing FSGS (cFSGS) and non-collapsing FSGS. The non-collapsing variant is associated with IFNα and IFNγ (Markowitz et al. 2015). IFNγ-induced proteinuria is typically dose-dependent and resolves upon discontinuing IFN (Sriskandan et al. 1985). In CML patients treated with IFNα, early nephrotoxicity (within 1 month) is more likely to be FSGS and late nephrotoxicity (>6 months) is more commonly thrombotic microangiopathy (TMA). The presentation typically includes nephrotic range proteinuria. Apart from stopping the drug, IFN-induced non-collapsing FSGS lesions have variable responses to steroids, cyclosporine, cyclophosphamide and angiotensin converting enzyme inhibitors. Pathogenesis is unclear and many hypotheses are present. IFNγ can increase major histocompatibility complex (MHC) class I and II genes, thereby possibly having implications for an auto-immune mechanism. Other evidence demonstrates a possible allergic reaction to IFN with coombs positive hemolysis in setting of new onset non-collapsing FSGS.

IFN-induced collapsing FSGS is associated with all interferons (α, β, γ). Over 90% of reported cases are in patients of African ancestry. They usually present with AKI and nephrotic range proteinuria (up to 27 g/24 h with average of 9.7 g/24 h). IFNα-induced cFSGS presents at an average duration of therapy of 4–12.6 months (Markowitz et al. 2010). Biopsy often shows endothelial tubuloreticular inclusions on EM. These are 23-25 nm anastomosing tubular structures located in the cytoplasm and cisternae of the endoplasmic reticulum. There is a positive correlation between interferon and tubuloreticular inclusion, and therefore they are often referred to as "interferon footprints"(Markowitz et al. 2010). Most patients recover over 2 years following discontinuation of the drug and less than half require immunosuppression with uncertain success (Berdichevski et al. 2010; Markowitz et al. 2010). Pathogenesis is largely unknown. Current

hypotheses include IFN induced up-regulation of anti-viral machinery and the consequent alteration of cellular metabolism. Due to overlapping pathways, macrophages/natural killer cells become activated in addition to a th1response (Markowitz et al. 2010). Apol1 has been shown as a risk alleles risk of developing cFGSGS in African American patients (Genovese et al. 2010).

Heroin

Heroin is an opiate processed from morphine and occurs naturally in various poppy plant species. Adulterates are commonly found in heroin that include quinine, mannitol, lactose, procaine, caffeine, inositol, lidocaine, starches, sucrose, methapyrilene, acetylprocaine, and dextrose. Less than 1% of heroin users develop FSGS and nephrotic syndrome (Kilcoyne et al. 1972). The terminology heroin-associated nephropathy was coined when fourteen African-American heroin addicts developed FSGS with focal sclerotic changes. Patients who develop heroin nephropathy or heroin-induced FSGS tend to be young African-American males with the HLA-BW53 allele (Haskell et al. 1988). Renal prognosis is poor with progression to ESRD in 65% of patients (Cunningham et al. 1980). In the mid 1980s the spectrum of heroin nephropathy changed to more cases of heroin-induced AA amyloidosis due to longer duration of heroin use and increased chronic suppurative skin ulceration resulting in chronic inflammation (Dubrow et al. 1985). A decade later, a significant decrease in the incidence of heroin nephropathy occurred, thought to be due to the increased purity of heroin available.

Pathophysiology is currently unknown but thought to be related to heroin's active metabolite, morphine, that is capable of inducing mesangial expansion, attenuating phagocytosis of macromolecules by white blood cells and enhancing immune complex deposition in the mesangium (Dettmeyer et al. 2005; Jaffe and Kimmel 2006). Other forms of heroin induced kidney injury include MCD, interstitial nephritis, AKI from rhabdomyolysis, and heroin crystal nephropathy.

Anabolic Steroids

Anabolic-androgenic steroid (AAS) use has been steadily increasing since the 1990s and is a worldwide public health problem with a prevalence of 3.3% (Sagoe et al. 2014). AAS is a synthetic derivative of testosterone, primarily used in body builders and athletes, that can increase muscle mass and strength. Among male weightlifters, prevalence is 44%. In total, approximately 30% of AAS users develop dependence.

Anabolic steroids are associated with FSGS-NOS, but the collapsing variant and perihilar lesions can also be seen. Patients with AAS-induced FSGS present with nephrotic syndrome, glomerulosclerosis, interstitial scarring and an elevated serum creatinine (Herlitz et al. 2010). AAS-induced FSGS carries a good renal prognosis when the steroids are stopped. Renin-angiotensin system blockade might be beneficial in reducing proteinuria (Herlitz et al. 2010).

Pre-clinical models indicate that the pathogenesis of anabolic steroid-induced FSGS may be an adaptive response to increased glomerular pressure which results in glomerular tuft hypertrophy without an increase in podocyte cell numbers (D'Agati 2008). As the glomerulus expands, the podocyte hypertrophies and develops mechanical stress, resulting in detachment from the GBM. The podocyte is lost in Bowmans space, leaving behind a "bare" GBM. The increased glomerular pressure continues and pushes the tuft towards the parietal cells of Bowmans space, triggering attachment, and subsequently tuft adhesion. A similar pathogenesis is seen in obesity-related glomerulopathy. Mechanisms for why AAS demonstrates more severe kidney disease than obesity-related FSGS include increased protein intake which contributes to increased renal blood flow and glomerular filtration (Woods 1993), endothelial damage from extreme systolic blood pressure elevations during weightlifiting (as high as 400 mmHg) (MacDougall et al. 1985), and direct glomerular injury from testosterone, more pronounced in males than females which can amplify compensatory growth (Zeier et al. 1998).

Sirolimus

Originally developed to treat fungal infections, sirolimus was found to have remarkable antitumor and immunosuppressive effects due to its mechanism of mammalian target of rapamycin (mTOR) inhibition. Through mTOR inhibition, sirolimus blocks cell-cycle progression between G1 and the S phase. Everolimus, a newer mTOR inhibitor, contains the same effects of sirolimus (immunosuppression and antitumor activity) with better oral bioavailability and less nephrotoxicity.

Prevalence of proteinuria with sirolimus is varies from 23% to 94% and of those 3.6–56% develop nephrotic syndrome (Franco et al. 2007; Sayin et al. 2009) The prevalence of FSGS is 14.3–33%. Sirolimus-induced FSGS usually presents with sub-nephrotic range proteinuria between weeks to months of use. Proteinuria risk factors include elevated sirolimus levels (>12 ng/L) and a de novo sirolimus-based regimen (Letavernier et al. 2007). Risk factors, especially in African-American patients, include elevated arterial blood pressure at the time of conversion to sirolimus and native proteinuric kidney disease. It is most commonly seen in kidney transplant recipients, likely due to the majority of sirolimus use, but when used in other cohorts (for example, islet cell transplant recipients) reversible proteinuria is seen in native kidneys. Most cases do not require a kidney biopsy as proteinuric increase is usually mild (1.7 g/24 h) with stable serum creatinine. Sirolimus withdrawal can reverse proteinuria and therefore renal prognosis is excellent (Franco et al. 2007; Letavernier et al. 2007). Sub-nephrotic proteinuria can be controlled with ACE-I or angiotensin II receptor blocker (ARB) medications (Sayin et al. 2009).

Pathophysiology of sirolimus-induced FSGS is multifactorial. Sirolimus can decrease VEGF synthesis leading to disruption of podocyte integrity resulting in apoptosis (Letavernier et al. 2009; Muller-Krebs et al. 2013). Sirolimus also increases intra-glomerular pressure with a decrease in effective renal plasma flow (Saurina et al. 2006). This specific pathogenesis correlates with improvement of creatinine and proteinuria with ACE-I or ARB.

Lithium

FSGS makes up around 16% of lithium-induced nephrotic syndrome (Tandon et al. 2015). However, if a patient also has increased creatinine then the prevalence of lithium-induced FSGS increases to 50% in this population (Markowitz et al. 2000). Proteinuria on presentation averages 4–9 g/24 h. Outcomes vary with some patients recovering when lithium is discontinued, while others obtain partial recovery, and some fail to recover. Pathophysiology is similar to that seen with MCD and explained in the previous section.

ANCA Vasculitis

Antineutrophil cytoplasmic antibodies (ANCA) are largely IgG autoantibodies, directed against lysosomal granules of neutrophils and monocytes. They are classified by their immunofluorescence staining patterns: a perinuclear pattern (p-ANCA) and a cytoplasmic pattern (c-ANCA). The pathogenic ANCA antibodies are anti-myeloperoxidase (anti-MPO) anti-serine proteinase 3 (anti-PR3) (Bosch et al. 2006). Drug-induced ANCA vasculitis accounts for approximately 12% of new anti-MPO + ANCA vasculitis (Choi et al. 2000). Numerous drugs have been reported to cause ANCA associated vasculitis (Table 5). Whereas idiopathic vasculitis usually presents with a single positive immunoglobulin against MPO or PR3, drug-induced ANCA

Table 5 Medications associated with ANCA-associated vasculitis

Drug Class	Examples
Anti-thyroid	Propylthiouracil, benzylthiouracil, methimazole
Anti-rheumatic	Penicillamine, sulfasalazine, TNF-a inhibitors
Antibiotics	Minocycline, cephotaxime
Miscellaneous	Pantoprazole, phenytoin, allopurinol, clozapine, montelukast, statins, thioridazine, levamisole (cocaine adulterant)

Abbreviations: *ANCA* anti-neutrophil cytoplasmic antibody, *TNF* tumor necrosis factor

vasculitis patients may present with very high anti-MPO antibody titers, dual antibody (anti-MPO and anti-PR3) positivity, and a variety of other auto-antibodies including lactoferrin, anti-histone, anti-elastase, or antiphospholipid.

Renal histology is similar to idopathic ANCA vasculitis and can show necrotizing or crescentic inflammation with some interstitial nephritis and tubular damage (Fig. 2, a–d). However, in general, the severity of renal lesions was significantly less in patients with drug induced ANCA vasculitis as compared with idopathic ANCA vasculitis.

There seems to be a common pathogenesis in the development of drug induced ANCA, particularly with MPO antibodies. The specific drug directly activates the immune system or interacts with the MPO enzyme, damages the cell, and this releases antigenic compounds. These cytotoxic products are effectively immunogenic metabolites of the given drug, and through T cell presentation to B cells, ANCA is produced. Pathophysiology for each drug is discussed in detail in their respective sections.

Often times, the only intervention needed is discontinuation the drug. If severe enough, usually with pulmonary-renal syndrome, immunosuppressive regimens, which are typically

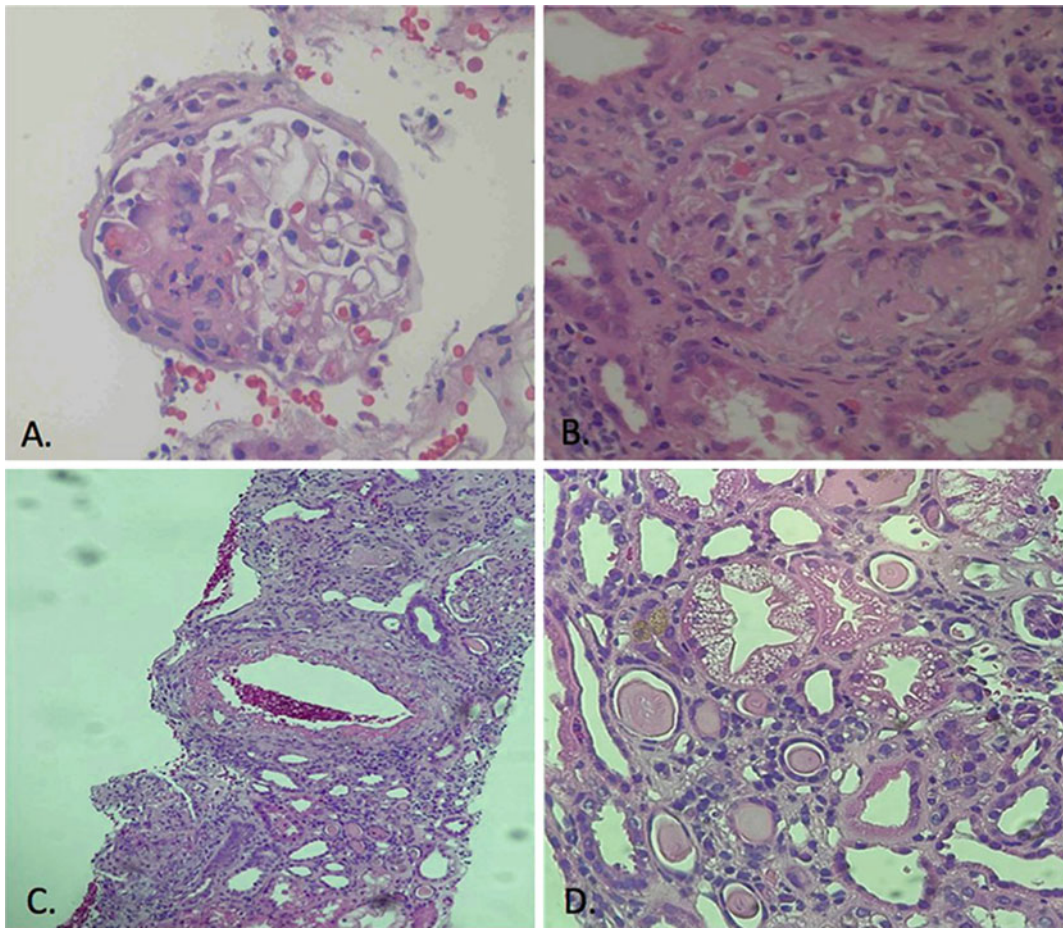

Fig. 2 Light microscopy of kidney biopsy from a patient with medication associated ANCA vasculitis. (**a**) Glomerulus showing focal necrosis. (**b**) Glomerulus showing necrosis with fibrocellular crescent formation. (**c**) Interstitial showing a dense cellular infiltrate. (**d**) Tubules showing vacuolization and dilation

similar to those used to treat primary vasculitis, can be used (Hogan et al. 2015).

Levamisole/Cocaine

Cocaine is an alkaloidal agent derived from the plant *Arythroxylon coca*. It was originally discovered in the year 1884 by an opthamologist, Dr. Carl Koller, as an analgesic agent for eye surgery. It is currently a drug of abuse with euphoric effects. Cocaine can cause AKI through rhabdomyolysis, malignant hypertension, interstitial nephritis, kidney infarction, vasculitis, and TMA (van der Woude 2000; Goel et al. 2014). Apart from the drug itself, cocaine is often mixed with an adulterant, levamisole. For the past decade in the United States there has been an increase in the use of levamisole, and currently it is found in approximately 70–80% of cocaine (Lee et al. 2012). Levamisole is synthetic imidazothiazole that was originally used to treat helminthic infections in cattle and sheep. It was used in humans during the 1970s for inflammatory conditions, primarily rheumatoid arthritis, but due to agranulocytosis it was withdrawn from the market in 1999. The reason for the use of levamisole as an adulterant in cocaine is not entirely clear, but it may potentiate the euphoric effect, serve as a marker to trace distribution, or increase drug volume.

Levamisole-contaminated cocaine is associated with ANCA-vasculitis and can present with acute or chronic use. Presenting symptoms include arthralgia (83%), skin lesions (61%) and renal involvement (44%) (McGrath et al. 2011). Patients are positive for anti-MPO antibody and half of them are also positive for anti-PR3 antibody. On immunofluorescence patients are predominantly p-ANCA positive and if patients also have anti-PR3 then they are c-ANCA positive. The anti-MPO titer in cocaine-associated vasculitis is significantly higher as compared to primary ANCA vasculitis (median 1702 vs. 112). As compared to primary ANCA vasculitis, other antibodies are frequently elevated as well including ANA, lupus anticoagulant, anti-dsDNA, or anticardiolipin (McGrath et al. 2011). Other laboratory abnormalities include decreased complements and leukopenia. In patients with cocaine-induced local destructive changes to the nasal septum and upper respiratory tract, also referred to as, cocaine-induced midline destructive lesions, a positive anti-elastase antibody can discriminate between cocaine-induced ANCA vasculitis and primary ANCA vasculitis. The plasma half-life if levamisole is approximately 5.5 h, therefore at 2 days after use, blood and urine levamisole levels can be negative.

The most effective treatment is stopping cocaine use. Intravenous steroids have been used for skin lesions with variable response rates. In patients with resolution of levamisole-contaminated cocaine ANCA-vasculitis, 27% had vasculitis recurrence with continued cocaine use.

The pathogenesis is currently unknown but it has been hypothesized that, since levamisole is a thioazole it behaves as a hapten and triggers an immune response (Raymon and Isenschmid 2009). There is evidence of levamisole-induced dendritic cell activation, specifically, increasing cell membrane CD80, CD86, CD83 and human leucocyte antigen D-related (HLA-DR) molecules with increased production of IL-12 and IL-10. Through dendritic cell activation, a Th1 cell response ensues resulting in IFN- γ secretion and significant inflammation (Szeto et al. 2000).

Anti-Thyroid Drugs

Thiouracil derivatives, (propylthiouracil (PTU), methimazole (MMI), carbimazole and benzylthiouracil) inhibit the synthesis of thyroid hormone and are therefore used for the treatment of hyperthyroidism. Anti-thyroid drugs are typically associated with MPO+ ANCA vasculitis although other subtypes (PR3, lactoferrin) have been described (Balavoine et al. 2015).

The prevalence of ANCA positivity in PTU users is 4.1–64%, with most studies demonstrating a prevalence of >26%; the prevalence with MMI use is approximately 6%. Despite this high prevalence, only 15–40% of ANCA-positive patients present with clinical symptoms. Despite a positive correlation between thyroid disease and

ANCA vasculitis, anti-thyroid drugs significantly increase the risk of developing a drug-induced ANCA vasculitis (Balavoine et al. 2015).

The mean duration of PTU treatment before symptoms is 4 months to 4 years. Renal involvement commonly presents with hematuria and proteinuria (protein/creatinine on average of 1.1 g/g) with half of patients developing AKI (Chen et al. 2007; Yu et al. 2007). When compared to an idiopathic ANCA vasculitis, antithyroid-induced ANCA vasculitis has more skin involvement, and a less severe renal disease with better prognosis (Bonaci-Nikolic et al. 2005). Common symptoms include fever (in 43% of patients), arthralgia (36%), pulmonary symptoms (26%), skin lesions (23%), myalgia (18%), eye involvement (11%) and central nervous system involvement (2%). Pulmonary-renal syndrome, the most severe presentation, occurs in about 15% of patients with PTU-induced ANCA vasculitis, and 80% of the patients in this group have a good prognosis when the drug is stopped.

Serology and autoimmune markers also differ between idiopathic and antithyroid-induced ANCA vasculitis. In idiopathic vasculitis there is usually one autoantibody, whereas antithyroid-induced vasculitis presents with many autoantibodies, with the most common being against MPO (Bonaci-Nikolic et al. 2005). Other autoantibodies commonly seen in conjunction with anti-MPO include anti-lactoferrin, azurocidin, elastase, cathepsin G, PR3, bactericidal/permeability-increasing protein, IgM anticardiolipin, and histone antibodies (Gao et al. 2007). Anti-MPO antibody subclass elevation of IgG3 is associated with renal involvement. One of the antibodies produced, anti-endothelial cell antibody, is only found in active PTU-induced ANCA vasculitis and not-detected when the vasculitis is quiescent. Compared with patients on PTU who develop anti-MPO antibodies in the absence of clinically evident vasculitis, patients who develop ANCA vasculitis have higher MPO antibody titer, increased IgG avidity and anti-endothelial cell antibodies.

Treatment involves discontinuation of the medication, with improvement in renal function and a negligible rate of relapse (Balavoine et al. 2015). ANCA can still be seen up to 2 years after cessation of PTU but over these years the avidity decreases which correlates with decreased disease activity.

PTU and MMI accumulate in neutrophils but only PTU has the ability to cause a dose-dependent inhibition of MPO oxidation by inducing a structural change (Zhang et al. 2007). This leads to a reactive intermediate that covalently binds to self-proteins making it immunogenic to T-cells. During this process, neutrophils disintegrate their nuclear envelope and granular membranes, allowing the cytoplasmic, granular and nuclear components to mix. As a result, chromatin interacts with granular proteins, creating a matrix that is secreted from the cell forming a net-like structure with high anti-microbial activity, referred to as a neutrophil extracellular trap (NETs). PTU can cause abnormal NET formation, leading to the former intra-cytoplasmic proteins being targeted as neo-epitopes (. The activated T-cells can then induce a polyclonal B cell response where multiple ANCA target antigens can be recognized. The antibodies produced have a higher avidity, reactivity and quantitatively bind to more epitopes on the MPO molecule than those produced in a primary ANCA vasculitis (Gao et al. 2005, Wang et al. 2013). A genetic predisposition has also been implicated in the pathophysiology; HLA haplotypes DR4 and DR9 have been associated with PTU-induced ANCA vasculitis.

Hydralazine

Hydralazine is a direct arterial vasodilator used to treat hypertension. Hydralazine-induced ANCA vasculitis is rare (Pendergraft and Niles 2014). The average age of onset is 64 years old, with average duration of exposure 4.7 years, and average hydralazine dose of 142 mg/day. The most commonly affected organs by hydralazine-induced ANCA vasculitis are the kidney (81%), skin (25%) and joints (24%) (Yokogawa and Vivino 2009). The most severe presentation is pulmonary-renal syndrome, occurring in approximately 25% of hydralazine-induced ANCA vasculitis.

The renal manifestations are a nephritic presentation with dysmorphic red blood cells, and proteinuria with protein-to-creatinine ratio of 1–2 g/mg. The hallmark feature is AKI with pauci-immune glomerulonephritis. In the setting of active glomerulonephritis, there may also be elevated c-reactive protein, erythrocyte sedimentation rate, anticardiolipin IgM and IgG antibodies, and β2 glycoprotein IgM antibodies. Serology can be positive for the following: anti-MPO-ANCA, ANA in a homogenous pattern, anti-dsDNA, human neutrophil elastase-ANCA, lactoferrin-ANCA and hypocomplementemia (Yokogawa and Vivino 2009; Pendergraft and Niles 2014). The findings of anti-MPO antibody and anti-elastase antibody were found to be elevated in hydralazine-induced ANCA vasculitis but negative in hydralazine users without vasculitis.

Since hydralazine-induced ANCA vasculitis tends to be more severe than other drug induced vasculitides, in addition to stopping the drug, treatment usually involves immunosuppression (Yokogawa and Vivino 2009). In the case of pulmonary-renal syndrome, even with treatment, the mortality rate is quite high at approximately 40%.

One hypothesis for the pathogenesis of hydralazine-induced ANCA vasculitis is that hydralazine can accumulate in neutrophils and inhibit DNA methylation by binding to DNA methyltransferase (DNMT) (Bonaci-Nikolic et al. 2005; Pendergraft and Niles 2014). Inhibition of DNMT reverses the epigenetic silencing of MPO and PR3. This induces cytotoxic products that lead to neutrophil apoptosis. These cytotoxic products are effectively immunogenic metabolites of the given drug, and through loss of tolerance, T cells become activated, present to B cells, and ANCA is produced (Jennette and Falk 2014). Hydralazine is metabolized through acetylation, and patients who are slow acetylators have an increased risk of vasculitis (Timbrell et al. 1980).

Minocycline

Minocycline is a tetracycline antibiotic that binds to the bacterial ribosomal subunit 30S to inhibit protein synthesis. It is commonly used for acne vulgaris, and due to its anti-inflammatory properties it is also a disease-modifying anti-rheumatic drug.

In the setting of minocycline use, a polyarteritis nodosa (PAD)-like vasculitis can develop. PAD is a systemic necrotizing vasculitis that affects medium-sized vessels. Minocycline-induced vasculitis presenting symptoms include fatigue, weight loss, arthralgia and rash. Anti-MPO/p-ANCA positivity has been found in approximately 7% of people using minocycline, and ANCA seroconversion usually takes more than a year to develop (Marzo-Ortega et al. 2007). Patients usually have positive p-ANCA, but only 20% are positive for anti-MPO antibody. Other autoantibodies that have been elevated include anti- bactericidal/permeability-increasing protein, anti-elastase, anti-cathepsin G, anti-cardiolipin and anti-histone. ANA is positive in approximately 30% of cases (Kermani et al. 2012).

Renal involvement occurs in less than 25% of cases although in many cases this may be underreported due to the normal creatinine (Kermani et al. 2012; Lenert et al. 2013). Renal manifestations consist of renal hypertension, artery microaneurysms and vasculitis in the interlobular arteries consistent with a medium-vessel vasculitis usually in the absence of glomerular necrosis and inflammation. Renal biopsy demonstrates ischemic vasculitis-type changes in the glomerulus and interstitium.

Treatment of the vasculitis requires discontinuation of minocycline. Approximately half of patients with vasculitis will also require immunosuppression (Kermani et al. 2012). Treatment outcomes are generally favorable.

The pathogenesis is unknown, but many hypotheses exist. As with other drug-induced ANCA vasculitides, MPO-mediated metabolism of minocycline, leads to oxidation and the generation of toxic intermediates. Anti-elastase autoantibodies activate surface-bound elastase on neutrophils, resulting in increased endothelial damage and extra-cellular matrix protein degradation in the kidney. Genetic factors may play a role in ANCA development. Patients with minocycline-induced ANCA positivity had an

association with the MHC class II alleles, HLA-DR4, HLA-DR2 and HLA-DQB1 (Dunphy et al. 2000). These alleles are associated with other autoimmune conditions such as mixed connective tissue disease and scleroderma.

Drug-Induced Lupus

Drug-induced lupus (DIL) has an estimated incidence of 15,000–30,000 per year in the United States with over 80 drugs identified as potential causes (Table 6) (Borchers et al. 2007). The presentation differs between DIL and primary systemic lupus erythematosus (SLE); DIL is associated with fever, weight loss, arthralgia however, the malar and discoid rash are uncommon (Hogan et al. 2015). Serologies also differ, in that with DIL, ANA, anti-chromatin (anti-histone) antibody, rheumatoid factor, and anticardiolipin, are positive, whereas anti-dsDNA and anti-smith antibodies are usually negative (Borchers et al. 2007). Anti-MPO antibodies are often positive in the setting of DIL, and therefore could be overlapping diseases or part of the drug metabolism byproduct.

DIL is currently defined as having a temporal relationship with continuous drug exposure (within 1 month to a decade) that resolves after discontinuing the drug in a patient without a prior history of SLE (Vedove et al. 2009). In cases of DIL, kidney involvement is approximately 10%, yet highly dependent on the causative drug (Chang and Gershwin 2011). The histology of DIL is similar to primary SLE and organized into six classes. The mechanism of nephritis in DIL is different for each drug and will be discussed below. The following sections will not include drugs (such as NSAIDs, penicillin, mesantoin, sulfonamides, para-aimnosalacyclic acid, hydrochlorothiazide and cimetidine) that can exacerbate symptoms of pre-existing primary SLE (Hogan et al. 2015).

Table 6 Medications associated with drug-induced lupus

Drug Class	Examples
Anti-arrhythmics	Procainamide, quinidine, amiodarone
Anti-hypertensives	Hydralazine, methyldopa, captopril, beta-blockers, minoxidil, clonidine
Anti-psychotics	Chlorpromazine, lithium
Antibiotics	Isoniazid, minocycline, sulfamethoxazole, tetracycline, cefuroxime, streptomycin
Anticonvulsants	Carbamezapine, phenytoin, valproic acid
Anti-thyroid	Propylthiouracil, methimazole
Diuretics	Chlorthalidone, hydrochlorothiazide, spironolactone
Biologics	TNF-a inhibitors, interferon-a
Miscellaneous	Statins, levodopa, estrogens, progesterones, sulfasalazine,

Abbreviations: *TNF* tumor necrosis factor

Procainamide

Procainamide is a class Ia antiarrhythmic and has high-risk drug for causing DIL (Chang and Gershwin 2011). Around 83% of patients develop ANA antibodies when taking procainamide. Sixty-four percent of these patients also develop anti-histone antibodies that correlate with procainamide dose. Around 20% of these patients develop symptoms consistent with SLE (Araujo-Fernandez et al. 2014). ANA antibody formation appears to be associated with procainamide metabolism. Procainamide undergoes acetylation in the liver and people who are slower acetylators have an increased risk of ANA sero-conversion. The duration of therapy required for 50% seroconversion in slow versus fast acetylators is 2.9 and 7.9 months respectively. The duration of procainamide use resulting in a clinical lupus-like syndrome for slow versus fast acetylators is aopproximately 12 months and 48 months, respectively (Woosley et al. 1978). Renal involvement is rare and is present in less than 1% of procainamide-induced SLE.

The pathogenesis of procainamide DIL might be from the drug effect on autoantibody production. The procainamide metabolite, procainamide hydroxylamine, has an immunomodulating effect and results in an increase of autoantibodies. It is possible that this is achieved through the metabolites ability to influence structural features in the chromosomal DNA, thus exposing structural epitopes in the DNA.

Anti-thyroid Drugs

Anti-thyroid drug-induced lupus is associated with renal involvement in approximately 26% of cases. The average PTU treatment time until the development of DIL is 36 months. Withdrawal of PTU will usually resolve the syndrome in approximately 58% of patients, and the remaining patients may need glucocorticoid therapy. There is substantial overlap between anti-thyroid-induced ANCA vasculitis and DIL; between 30–100% of patients diagnosed with anti-thyroid DIL also have positive MPO-ANCA (Yamada et al. 2002; Wu and Li 2012). Pathophysiology is similar to antithyroid drug-induced ANCA vasculitis in that the dysregulation of NETs contribute to the production of abnormal autoantibodies. NET degradation is regulated by deoxyribonuclease I (DNase I) and therefore decreased DNase I activity has been demonstrated in patients with PTU DIL. When PTU is stopped, a reduction in G-actin-mediated inhibition of DNase I occurs allowing DNase I to clean up the NETs.

Hydralazine

Hydralazine is also implicated in DIL. Around 50% of patients develop a positive ANA and the incidence of clinical hydralazine-induced lupus at 1-year is 5–8% and 3-years is 6.7% (Cameron and Ramsay 1984; Araujo-Fernandez et al. 2014). Incidence also increase with higher dosages. Hydralazine DIL has a predominance in females (11.6%) as compared to males (2.8%) (Cameron and Ramsay 1984). Renal involvement has been reported between 4.5% and 54% of patients with DIL (Alarcon-Segovia et al. 1967). Other than duration and dose, HLA-DR4 antigen, a slow acetylation phenotype, and the C4 null allele increase the risk of developing DIL (Shapiro et al. 1984).

Hydralazine DIL presents with positive anti-histone antibodies and anti-single stranded or denatured DNA antibodies (Shapiro et al. 1984). Patients with renal involvement can have microscopic hematuria and proteinuria and elevated ESR and ANA.

Renal prognosis is excellent upon discontinuation of hydralazine, with upwards of 80% of patients improving after discontinuation and approximately 20% of patients requiring immunosuppression. If hydralazine is unrecognized or continued in the setting of DIL, progression to ESRD can occur in 4 weeks to 4 months (Bjorck et al. 1985).

Pathogenesis involves hydralazine's ability to bind DNA and structurally change it to the immunogenic Z-DNA conformation. In hypertensive patients taking hydralazine Z-DNA levels were found to be two standard deviations higher than age-matched controls not on hydralazine (Thomas et al. 1993). Hydralazine also inhibits DNA methyltransferase 1 (DNMT) enzyme expression. This enzyme performs DNA methylation after mitosis and is therefore important in cell division and differentiation. DNMT is involved in the extracellular signal-regulated kinase (ERK) pathway. By inhibiting this pathway, DNA is hypomethylated leading to lymphocyte function-associated antigen 1 (LFA-1) overexpression resulting in T-cell autoimmunity and a lupus-like syndrome. Hydralazine has also been demonstrated to interact with B-cell self-tolerance. Auto-reactive B-cell, undergo receptor editing, whereby the genes for the heavy or light chains are rearranged, producing a new B-cell receptor that is not autoreactive. This is accomplished through recombination activating gene (RAG) upregulation; hydralazine inhibits upregulation of RAG-2 gene expression leading to pathogenic autoreactivity.

Anti-tumor Necrosis Factor- α

Anti-tumor necrosis factor-α (anti-TNF-α) agents, which include infliximab (44–64% of cases), etanercept (30–40% of cases) and adalimumab (6–16% of cases) have been implicated in DIL (Ramos-Casals et al. 2007; Costa et al. 2008). Incidence rates vary between 0.13% and 1.3% depending on the particular agent. The clinical features and laboratory abnormalities in anti-TNF-α DIL, are rash (67%), dsDNA antibodies (72%), extractable nuclear antigens (ENAs) (53%), and low complements (59%) (Ramos-Casals

et al. 2007; Costa et al. 2008). Anti-histone antibodies present in only 57% of patients with anti-TNF-α-DIL, as compared to in >95% of patients with other forms of DIL (Costa et al. 2008). It is common for patients to become seropositive without actually developing a lupus-like syndrome. For example, in rheumatoid arthritis patients treated with infliximab 11% became positive for ANA, and 15% for dsDNA yet only 0.6% developed a lupus-like syndrome.

Renal involvement is seen in 7–9% of anti-TNF-α-DIL. Renal involvement does vary by underlying rheumatologic condition. Rheumatoid arthritis (RA) is the most common underlying disease making up 76% of cases, followed by ankylosing spondylitis (17.2%) and then psoriatic arthritis (6.8%) (Costa et al. 2008). Etanercept is the most common drug implicated in anti-TNF-α-DIL with renal dysfunction, making up 51.7% of cases. Adalimumab was the second most common with 31% of cases and infliximab, the least common implicated in renal disease in 10.3% of cases (Piga et al. 2014).

Duration of TNF-α therapy prior to renal-related dysfunction is usually within 18 months of treatment (Stokes et al. 2005; Piga et al. 2014). TNF-α-induced lupus nephritis commonly presented with cutaneous lesions (41.6%), AKI (75%), hematuria (100%), nephrotic range proteinuria (75%), elevated ANA titer ≥1:640 (100%), anti-dsDNA (100%), class IV lupus nephritis (75%).

Treatment of TNF-α-DIL involves stopping therapy, however in 40% of cases glucocorticoids are required, and in 12%, other immunosuppressive agents (methotrexate, cyclophosphamide, leflunomide, mycophenolate, azathioprine) (Ramos-Casals et al. 2007). In TNF-α-induced lupus-related renal dysfunction treatment has been more aggressive, including removal of offending agent with almost 100% of patient receiving steroids and/or immunosuppression Piga et al. 2014). Renal prognosis is poor with only 25% of patients having complete recovery. Re-challenging patients with different anti-TNF-α-drugs results in a low level of recurrence.

In order to understand the pathophysiology, it's important to briefly discuss the normal role of TNF, and its association with lupus. TNF, typically known for its pro-inflammatory actions, also has an immune- or disease-suppressive role. In the setting of a viral infection, plasmacytoid dendritic cells (pDC) secrete type I IFN (IFNα + IFNβ), that in turn, activate immature myeloid dendritic cells that further activates autoreactive T-cells, specifically $CD4^+$ and $CD8^+$ T-cells (. In the presence of type I IFN-stimulated dendritic cells and T-cells, autoreactive B-cells develop and differentiate into plasma cells. IFN production is inhibited by TNF secretion, acting as a negative feedback mechanism (Banchereau and Pascual 2006).

TNF-α inhibitors lead to a sustained release of IFN (Palucka et al. 2005). This alone will not induce a lupus-like syndrome, but in the presence of TLR-7 activation with the appropriate genetic predisposition, lupus ensues (Pascual et al. 2006). In the setting of cell death auto-antibodies are formed inciting the autoimmune cascade.

Minocycline

Minocycline can cause DIL with an 8.5-fold increased risk as compared to those not using minocycline. Major risk factors include cumulative dose and female gender. Patients typically present with polyarthritis, fever, fatigue, and weight loss (Schlienger et al. 2000; Schaffer et al. 2001). ANA is usually present in over 80% of patients in a homogeneous pattern. Other commonly seen labs include abnormal liver enzymes and elevated ESR and CRP. Less than half the patients have positive, anti-smith, anti-DNA, anti-histone or anticardiolipin antibodies (Elkayam et al. 1999; Schaffer et al. 2001). Overlapping serologies are frequently encountered with 71% of minocycline DIL patients also having positive ANCA. Average time of use is before acquiring DIL is 19–28 months (Schaffer et al. 2001). Renal involvement is rare, occurring at and incidence rate of approximately 2%. Restarting the drug results in rapid recurrence of symptoms and elevation of CRP within 24 h. Pathogenesis of minocycline DIL is thought to occur through the enzymatic hydroxylation of minocycline by MPO in neutrophils. This leads to the formation of

immune complexes that act as haptens and induce an immunologic response.

IgA Vasculitis

IgA vasculitis (IgAV) is a systemic and more acute form of IgA nephropathy. The underlying pathogenesis of IgAV involves the abnormal production of IgA1 without galactose molecules in the O-linked glycan hinge region. These systemic, aberrantly glycosylated, galactose-deficient IgA1 antibodies are antigenic, binding with IgG, IgM and other aberrantly glycosylated IgA1antibodies forming circulating immune complexes. The immune complexes are too large to be cleared by the liver and deposit in the renal mesangium resulting in mesangial proliferation and variable infiltration of macrophages, monocytes and T-cells (Lai et al. 2016). Immune complexes affect other organs, and most commonly they are deposited in the skin resulting in leukocytoclastic vasculitis (Pohl 2015).

Light microscopy can vary from normal-appearing glomeruli, to pronounced mesangial expansion, to crescentic and necrotizing lesions, or sclerotic glomeruli. Immunofluorescence shows pronounced IgA deposits in the mesangium (Lai et al. 2016). IgAV renal biopsy is nearly identical to IgAN, but can show more endocapillary proliferation, epithelial crescents, perivascular glomerular IgA, subepithelial or subendothelial dense deposits and increased fibrin deposition (Fig. 3).

IgAV is more common in children and more likely to present with a combined nephritic/nephrotic syndrome. As compared with children, adult IgAV is less common, but with more nephritis (incidence children 20–40% vs. adults 72%) and worse renal prognosis (Fervenza 2003). Progressing to CKD occurs in 30% of adults compared to 5–15% in children and end-stage renal disease (ESRD) progression occurs in 15.8% in adults and 7% in children (Pillebout et al. 2002).

Many TNFα inhibitors have been implicated in contributing to the development of IgAV which include, from most to least common, etanercept, infliximab and adalimumab. The average duration of treatment is 9.6–34.5 months. Common presenting features include palpable purpura (80%), peripheral nervous system involvement (50%) and kidney injury (13–18%). Over 75% of TNFα inhibitors-induced IgAV occurs in women (Sokumbi et al. 2012). There is overlap with drug-induced lupus and ANCA vasculitis, with a little more than 50% of patients also having a positive ANA and approximately 12% with positive ANCA.

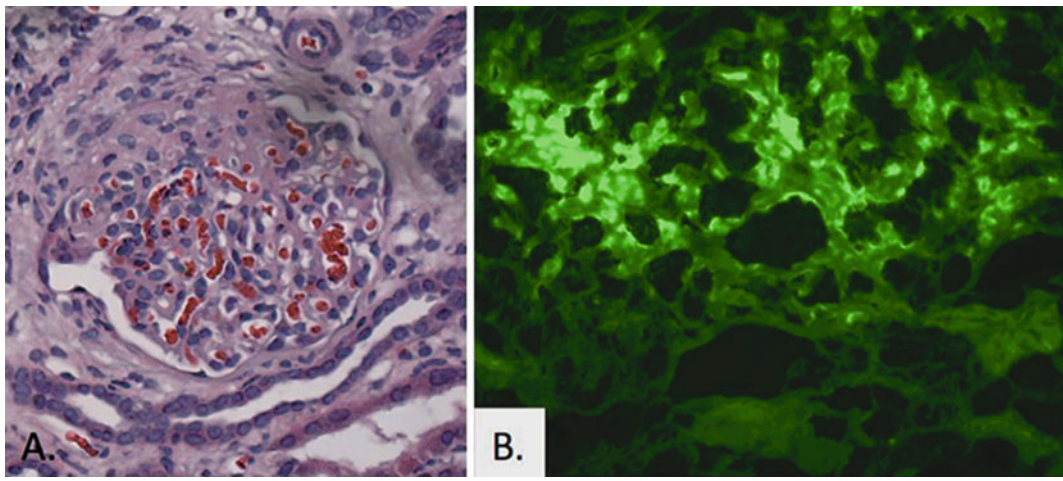

Fig. 3 (**a**) Light microscopy from a kidney biopsy of a patient with IgA vasculitis. Glomerulus shows mesnagial expansion. Also noted is cellular crescent formation. (**b**) IgA mesnagial staining of a glomerulus from a patient with IgA vasculitis

Treatment involves discontinuation of the TNFα inhibitor and treatment with glucocorticoids in resistant cases. In one series, around 54% of patients only required stopping the drug for resolution of vasculitis and approximately 42% of patients will required immunosuppression. Average time to resolution was 6.9 months (Sokumbi et al. 2012). Re-challenging with TNFα inhibitors led to disease recurrence in between 20–67% of patient.

Crystalline Glomerulonephritis

Crystal-induced renal failure or crystalline nephropathy is described as pathological crystal deposition in the kidney and mostly refers to intratubular crystal deposition, however, a subgroup, can present with the majority crystal deposition in the glomerulus (Herlitz et al. 2012). Only foscarnet has been shown to develop a predominantly intra-glomerular crystal deposition pattern that has been linked to kidney injury (Perazella 1999).

Foscarnet is an antiviral agent that is currently approved to treat cytomegalovirus (CMV) retinitis and mucocutaneous acyclovir-resistant herpes simplex virus (HSV) infections. It is a pyrophosphate analogue that inhibits herpesvirus DNA polymerases and HIV reverse transcriptase. Foscarnet can cause ATN, electrolyte abnormalities, tubulointerstitial nephritis, distal renal tubular acidosis, diabetes insipidus and glomerular disease (Deray et al. 1989, 1990).

Foscarnet-associated glomerular diseaes present with a combination of AKI, nephrotic syndrome, and microscopic hematuria. Kidney biopsy shows crystal deposition in the glomerular capillaries and proximal tubules with many cases presenting with fibrocellular crescents and irreversible glomerular sclerosis (Justrabo et al. 1999; Zanetta et al. 1999). Crescents are seen in 5–50% of glomeruli specimens. If biopsy occurs months after the initial exposure glomerular sclerosis is prominent (Justrabo et al. 1999). EM demonstrates crystals in the glomerular capillary lumens with perforation of the basement membranes into capsular space. The crystals are short polarized sticks with angular edges composed of trisodium foscarnet with mixed sodium-calcium salts. This is due the result of the higher affinity of ionized calcium for foscarnet, resulting in a less soluble salt that leads to increased glomerular deposition (Maurice-Estepa et al. 1998). Foscarnet-induced crystalline nephropathy occurs in less than 15% of biopsied foscarnet-induced AKI (Beaufils et al. 1990). Once the drug is stopped the kidneys can partially recover within several months, with resultant chronic kidney disease.

Thrombotic Microangiopathy

Primary thrombotic microangiopathy (TMA) syndromes, which include thrombotic thrombocytopenia purpura (TTP), Shiga toxin-mediated hemolytic-uremic syndrome (HUS) and complement mediated or drug induced TMAs cause micoangiopathic hemolytic anemia and thrombocytopenia. Apart from these primary syndromes, there exist secondary disease processes that can present with a MAHA and thrombocytopenia, including pregnancy associated syndromes of preeclampsia and HELLP syndrome, severe hypertension, autoimmune disorders, and malignancies or infections. It is important to distinguish between primary and secondary forms of MAHA with thrombocytopenia as pathophysiology and therapies differ.

TMA is characterized by endothelial damage with microvascular thrombi, microvascular hemolytic anemia, and thrombocytopenia. These events lead to end-organ ischemia and contribute to the variety of symptoms seen including AKI, cerebral dysfunction, myocardial ischemia, and gastrointestinal pain (Barbour et al. 2012). The kidneys are affected in 62% of patients with TMA (Dierkes et al. 2012). Apart from systemic involvement, organ limited TMA exists, yet the pathophysiology is poorly understood..Many causative factors for TMA have been identified with drugs making up less than 15% of cases (Table 7).

Renal biopsy features of TMA on light microscopy include arteriolar and glomerular intracapillary thrombosis with fragmented erythrocytes and focal ischemia of the glomerular tufts

Table 7 Medications associated with thrombotic microangiopathy

Drug Class	Examples
Anti-platelet	Ticlopidine, clopidogrel, prasugrel, dipyradamole, defibrotide
Anti-neoplastic	Anti-angiogenesis drugs, mitomycin-c, gemcitabine, cisplatin/carboplatin, estramustine, cytarabine, tmoxifen, bleomycin, daunorubicin, hydroxyurea
Interferon	Interferon-a, interferon-b
Immunosupprressive	CNIs, mTOR inhibitors, anti-cd33
Antibiotics	Valcyclovir, penicillins, rifampin, metronidazole, tetracycline, albendazole
NSAIDs	Diclofenac, piroxicam, keterolac
Hormones	Conjugated estrogens +/− progestins
Miscellaneous	Quinine, simvastatin, iodine, cocaine

Abbreviations: *CNI* calcineurin inhibitor, *mTOR* mammalian target of rapamycin, *NSAIDs* non-steroidal anti-inflammatory drugs

(Fig. 4) (Barbour et al. 2012). Widening of the subendothelial space is present as well. In glomerular capillaries and pre-glomerular arterioles, endothelial cells can become detached from the basement membrane or become swollen which can obstruct glomerular capillary flow (Noris and Remuzzi 2015). Chronic TMA may show a membranoproliferative pattern and the glomerular membrane demonstrates a 'double contour' (Barbour et al. 2012). Non-glomerular pathology may show intimal edema, proliferation, and necrosis of the arterial wall with luminal narrowing and thrombosis. Cortical necrosis due to ischemia from microcirculatory obstruction is correlated with CKD. IF shows fibrin, fibrinogen and IgM deposits along the glomerular capillaries, arteriolar lumen wall, and within the intersitium. EM demonstrates fibrin tactoids, endothelial swelling, and expansion of the lamina rara interna. Mesangial and GBM deposits are absent. In chronic TMA new basement membrane can form with early interposition with expansion of lamina rara interna (Fogo 1999).

Thienopyridine-Derivatives

Thienopyridine-derivatives (ticlopidine, clopidogrel and prasugrel) antagonize the ADP receptor on platelets to decrease aggregation. Ticlopidine, the first thienopyridine approved by the FDA, causes TTP within 2–12 weeks from drug initiation with incidence of 1 per 1600–5000 (Zakarija et al. 2009). Ticlopidine-induced TTP is associated with severe thrombocytopenia, normal kidney function, and disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13) activity levels less than 5%, due to the formation of autoantibodies that inhibit ADAMTS13 (Bennett et al. 2007). Treatment is drug withdrawal and therapeutic plasma exchange (TPE). Patients who receive TPE have 86% survival as compared those who did not receive TPE (46% survival) (Bennett et al. 2007; Markowitz et al. 2015).

Between 1998 and 2011, clopidogrel was the most common drug associated with TTP, with 197 cases in the FDA safety database, representing 1.1–27.8 new cases per million. Clopidogrel-induced TTP has an incidence rate 4 fold higher than that of idiopathic TTP (Jacob et al. 2012). TTP presents within 2 weeks of clopidogrel initiation, with mild thrombocytopenia, AKI and ADAMTS13 levels greater than 15% (Bennett et al. 2007; Jacob et al. 2012). Similar to ticlopidine, clopidogrel-induced TMA presents with auto-antibodies to ADAMTS13 as well (Bennett et al. 2000). Survival rate for clopidogrel-induced TTP is 71.2% but highly influenced on TPE timing. TPE within 3 days of TTP onset, results in significantly increased survival rates as compared to treatment delayed by >3 days (100% vs. 27.3%, respectively) (Zakarija et al. 2004; Markowitz et al. 2015). In patients who do not respond to TPE or have relapsing disease, rituximab has been used with excellent success and complete renal recovery. The major limitation is that long term data with rituximab use is not available.

The data on prasugrel is limited due to the paucity of cases, although the pattern of TTP is similar to clopidogrel (Jacob et al. 2012). A case study demonstrates prasugrel-induced TTP occurring approximately 40 days after initiation. The

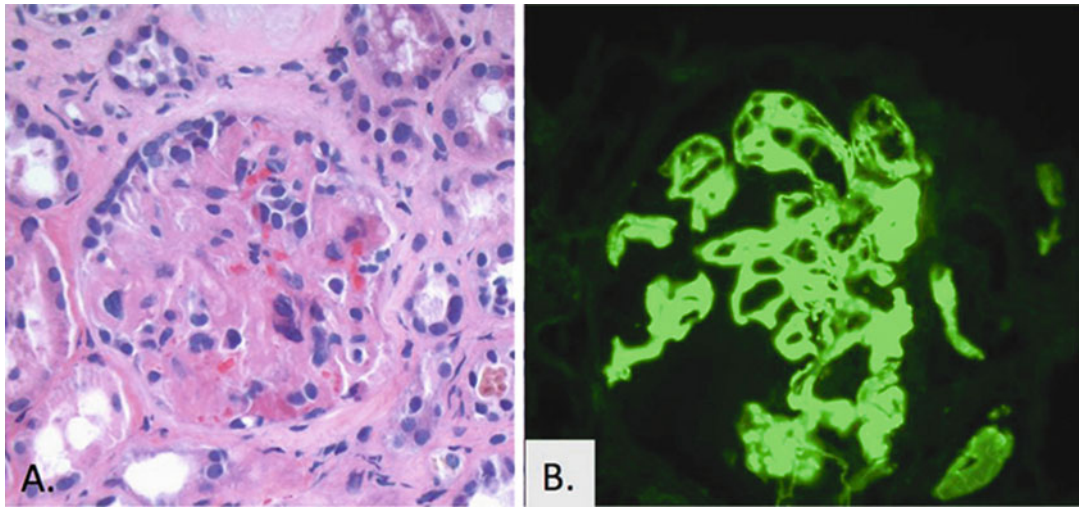

Fig. 4 (**a**) Light microscopy from a patient with tacrolimus induced thrombotic microangiopathy. Necrosis of glomerulus with red cell fragments. (**b**) Fibrinogen staining of glomerulus

ADAMTS13 level was 0.3% and inhibitory antibodies were present. Despite TPE and improving creatinine, the patient expired approximately 10 days after diagnosis, clearly displaying the severity of disease (Lopez et al. 2016). However caution must be used when interpreting treatment efficacy with prasugrel as this only represents one published case.

TTP is characterized as a deficiency in ADAMTS13. The normal function of ADAMTS13 is to degrade large von Willebrand factor (vWF) multimers released by the endothelial cells. The main pathogenesis of ticlopidine is due to IgG ADAMTS13 autoantibody production, resulting in direct inhibition of ADAMTS13. This results in an accumulation of large vWF in the plasma, which can bind platelets and promote thrombosis (Tsai et al. 2000). Ticlopidine has also been demonstrated to directly cause endothelial apoptosis through the mitogen-activated protein kinase (MAPK) signaling cascade (Mauro et al. 2004). Another possible contributor is a mutation in the soluble complement factor H that is seen in patients with ticlopidine-induced TMA and aHUS. Factor H usually cleaves vWF and therefore its mutation may further promote large vWF pathological accumulation. Normally, cleaved vWF can inhibit complement activation whereas the large vWF multimer is unable to do so.

The mechanism of action of clopidogrel induced TTP is still unclear. Due to clopidogrel-induced TTP's short duration of therapy, elevated ADAMTS13 activity and variable response to TPE it was hypothesized that a non-immunological mechanism was at play (Bennett et al. 2007). Thienopyridines have been shown to increase nitric oxide release from endothelium in a dose-dependent fashion, independent of their anti-platelet effects. This is accomplished when thienpyridine bind with nitrite forming thienopyridine-derived nitrosothiols, directly from both, the parent compound and active metabolites (ticlopidine-SNO, clopidogrel-SNO, prasugrel-SNO). Clopidogrel-chloride-SNO, as compared to clopidogrel-sulfate and –besylate, demonstrated significant vascular relaxation and all clopidogrel salts exhibit greater relaxation than prasugrel. This demonstrates that the drug salt, or it associated anion, may somehow contribute to its effects.

Interferon (α and β)

The first paper to introduce a correlation between IFNα and TTP/HUS was in 1993 describing a patient with hairy cell leukemia, treated with IFNα, who developed HUS resulting in AKI

(Cr 2.3 mg/dl), hypertension (SBP 190), headache, and thrombocytopenia (127 × 10^9/L). IFNα was stopped and TPE was performed for 30 days, but the patient ended up requiring lifelong hemodialysis. IFN induced TMA occurs from 5 to 50 months after initiating therapy (Jadoul et al. 1995; Zuber et al. 2002). IFNα-induced TMA presents with nephrotic syndrome (average 4.2 g/day) and AKI (mean creatinine 3.0 mg/dL). Most cases of IFN- α-induced TMA are seen in patients with chronic myelogenous leukemia, likely due to the high doses indicated to treat this condition, although in many cases, hepatitis C is present as well. Vascular pathology is prevalent (87%), presenting as hypertension or distal ischemic lesions. Renal prognosis is poor with around 30% of patients requiring short or long term hemodialysis, and 30% ending up with advanced CKD. A major risk factor for TMA is the cumulative dose of IFN.

Pathophysiology has not been entirely elucidated but current hypothesis include IFN- α induced-antiphospholipid (APL) antibodies damaging endothelial cells, lytic anti-endothelial cell antibodies, and anti-von willebrand factor proteinase antibodies (Zuber et al. 2002). IFN-α has been shown to increase leukocyte adherence to the vascular endothelium via promoting β_{1-2}-integrin function, which in turn can damage the endothelium releasing vWF, in a dose dependent manner (Zuber et al. 2002; Galesic et al. 2006). Leukocytes and chemokines (TNF, IFN, IL-1) may play a large role in the pathogenesis as animal models with leukocyte-depletion do not develop HUS. In typical HUS, interferons are increased (as compared to controls) and can be elevated for months following an episode, therefore similar mechanisms are present with a non-drug-induced form.

Interferon-β can also induce a renal limited TMA which has been demonstrated mostly in patients with multiple sclerosis and those undergoing hepatitis C treatment (Ubara et al. 1998). Duration of treatment with IFNβ can be between 2 weeks and greater then 10 years, and has been broken down to early- and late-onset. Early-onset IFNβ-induced TMA is associated with rash and fever, whereas late-onset is characterized by headache, hypertension, and thrombocytopenia, and both presentations include renal failure. Because half the cases present late, sometimes years after starting IFN, an association between the IFN and TMA/TTP/HUS can be difficult. There is a prodrome of symptoms including newly diagnosed HTN, new headache, hematological abnormalities and renal impairment that occur months before the diagnosis thereby allowing early diagnosis before the development of HUS/TTP. Renal prognosis is poor with many patients ending up dialysis permanently, despite TPE and rituximab. IFN- β pathogenesis is thought to be similar to IFN-α with the major cause being ADAMTS13 antibodies.

Calcineurin Inhibitors

Cyclosporine (CsA) is one of the most common causes of TMA in the kidney transplant population, but can be seen in native kidneys in the setting of other solid organ transplants (Shulman et al. 1981; Jumani et al. 2004). Incidence is between 2.9% and 12%, with the wide variability attributed to the heterogeneity of the studies and differing definitions of TMA/HUS (Ho et al. 2005). It can present early or late in regards to transplant status. Early is usually within 3 months, yet more typically approximately 6 weeks after transplant and late is more than 1 year after transplant (Singh et al. 1996). In a solid organ transplant cohort, 96% of patients presented with TMA within 1-year of the transplant. Risk factors include older age, hepatic veno-occlusive disease, high CsA trough, cadaveric kidney, and grade II-IV acute graft versus host disease (GVHD) in the setting of a bone marrow transplant (Wiener et al. 1997; Navarro-Antolin et al. 2007).

Patients commonly present with increased creatinine (mean serum creatinine 6.1 mg/dl) as the first sign of disease followed by thrombocytopenia (41–64% of cases) and coombs negative hemolytic anemia (53–86% of cases) with an increased LDH (70%). However, systemic signs are not required, as some studies show that biopsies of transplant kidneys reveal TMA despite neither signs nor symptoms.

CNI-induced TMA in other transplant cohorts is similar to that in the renal allograft. In lung

transplant cohorts, the main difference is the duration of CNI use is around 6 months, as compared to renal allograft population of 3 months (Verbiest et al. 2014). TMA in lung transplant recipients can rarely present with alveolar hemorrhage and a little over half of patients have concurrent disease process, such as infection or rejection. One cohort demonstrated that 100% of TMA patients had a "clinically relevant" infection shortly prior to the diagnosis of TMA. Risks for TMA include CNI and sirolimus combinations, female gender, and history of TMA (Hachem et al. 2006).

In regards to liver transplant, TMA usually presents within 2-weeks of surgery (Verbiest et al. 2014). Thoughts as to why TMA develops in liver transplant patient are focused on hepatic size and function. Small-for-size syndrome, refers to transplanting an organ that is significantly less than a standard liver weight for the patient. This more often occurs with living transplantation. CNI's are metabolized in the liver, and therefore a small-for-size syndrome can create variable clearances and therefore contribute to higher CNI levels in the blood (Fukatsu et al. 2001). Higher CNI levels may put liver transplant recipients at risk for developing TMA. Another contributing factor to TMA is an elevated vWF/ADAMTS13 ratio. After liver transplant ADAMTS13 is low, likely from decreased hepatic production, and an elevated vWF is also seen, possibly from ischemia-reperfusion injury. This will lead to an abundance of vWF and can increase risk of TMA.

The development of TMA in cardiac transplant recipients is extremely rare as there are currently less than ten cases reported in the literature. It presents late, with a median time of 2-years after transplantation and is associated with poor outcomes. Out of five patients, three died and the remaining two required long-term hemodialysis. Two patients have been re-challenged with CNI, resulting in recurrence of TMA (Verbiest et al. 2014). TMA in intestinal transplantation is also very rare, as of 2014, only eight cases have been published. Time to development is approximately 8 weeks post-transplant and seven of eight patients had concurrent acute rejection (Verbiest et al. 2014). In bone marrow transplant recipients, the TMA incidence is 8.2% with average onset 7 weeks post-transplant.

Many treatments have been used to treat CNI induced TMA, including fresh frozen plasma, steroids, streptokinase, aspirin, dipyridamole, isradipine, pentoxifylline, plasma exchange, cyclophsphamide, IVIG, azathioprine, and antithymocyte globulin (Ho et al. 2005). Patients that only had glomerular TMA, as compared to those with glomerulus and small arteries and/or arterioles invovlement, required less dialysis. The main treatment is discontinuing the medication, which has been demonstrated to have a response rate of 81–85% (Bren et al. 1998). Plasma exchange has not been shown to be consistently effective with a total response rate of only 45%, and therefore should not be used as standard of care given this poor response rate. Restarting CsA is risky. Some studies have demonstrated success with lower trough goals, however recurrence is possible. Therefore alternative immunosuppressive regimens should be used. CsA is substituted most often with an alternate calcineurin inhibitor, tacrolimus. In one study, after transitioning to tacrolimus the majority of patients had resolution of TMA within 1 week (Morris-Stiff et al. 1998).

Tacrolimus (FK506) is a macrocyclic antibiotic isolated from *Streptomyces tsukubaensis* that has excellent immunosuppressive effects. Its mechanism is through a tacrolimus/FK506-binding protein complex that inhibits the phosphorylation of calcineurin thereby preventing activation of T-cells. The incidence of tacrolimus-induced TMA is between 1% and 4.7% (Trotter et al. 2002). Average duration of tacrolimus use is 7.1–9.3 months and approximately 80% of cases occur in kidney allograft patients (Hershko et al. 2012). Patients also have thrombocytopenia (average platelets 49,000/mm2), elevated LDH (average 1516 IU/L), and anemia (average hemoglobin 8.4 g/dL). Many patients (approximately 56%) also have concurrent infections, most commonly CMV and HCV which may contribute to the oxidative stress on the endothelium.

Treatment of tacrolimus induced TMA is similar to that of CsA induced TMA with the mainstay being discontinuation of tacrolimus. Switching from tacrolimus to CsA has resulted in successful

resolution of TMA, however as previously mentioned this should be done cautiously.

Pathophysiology for calcineurin induced TMA is similar between CsA and tacrolimus. CNIs can exert a direct cytotoxic effect on endothelial cells in a time and dose-dependent manner which is often the first step in thrombi formation and TMA cascade (Zoja et al. 1986). Endothelial cell death is a non-apoptotic event and described as having the morphological characteristics of necrosis but under molecular regulation by oxidative stress and cathepsin D, a lysosomal protease. The generation of reactive oxygen and nitrogen species leading to the intracellular production of peroxynitrite, resulting in nitration of proteins and cell death (Kidokoro et al. 2012). CsA can inhibit endothelial cell proliferation, through an IL-6-dependent mechanism and disrupt capillary cell-to-cell junctions, via elevated endothelin-1. Endothelial damage causes significantly increased urinary thromboxane metabolite and increased circulating vWF. The increased thrombotic risk is, in part, due to an increased in plasminogen activator inhibitor (PAI). which inhibits plasminogen, thereby preventing fibrinolysis.

CsA can also bind directly to cyclophilin B (CypB), a peptidyl-prolyl cis-trans isomerase involved with protein folding, and critical to the proper functioning of ADAMTS13. CsA-induced inhibition of CypB results in decreased extracellular ADAMTS13 levels thereby contributing to the thrombotic mechanism (Hershko et al. 2012). Thrombomodulin activity is reduced by CsA consequently downregulating protein C anticoagulation pathway which then promotes thrombosis. Lastly, if CsA is delivered with cremaphor, its drug vehicle, vWF release is stimulated, again exacerbating the thrombogenic response.

Another mechanism CsA can induce nephrotoxicity is through increased sympathetic tone and renin-aldosterone-angiotensin access resulting in HTN, tachycardia mesenteric and renal vasoconstriction. These affects, which contribute to decreased renal blood flow, are caused by CsA-induced inhibition of prostacyclin (PGI_2) and the increased thromboxane A2 release (Verbiest et al. 2014). CsA also activates the renin-angiotensin-aldosterone system (Burdmann et al. 2003). CsA has also been demonstrated to increase TGF-β, increased tubular epithelial cell apoptosis, decrease eNOS, increased tissue hypoxia, and increased nitrotyrosine in the kidney. A TGF-β neutralizing antibody ameliorated all these changes. There is also an increase in plasminogen activator inhibitor type-1 and fibronectin. Tacrolimus shows similar patterns as CsA, yet not at severe.

Because it is not uncommon for a CsA-induced TMA to present without any systemic signs, a direct effect of CsA on the kidney also occurs. Apart from the vascular/TMA effects, CsA can induce renal cell apoptosis. Four pathways have been implicated and they include, the Fas/Fas-L pathway demonstrating an upregulation of Fas/Fas-Ligand expression with down-regulation of Bcl-2 which is an immune regulatory and oxidative stress pathway. Second is the mitochondrial pathway in which oxidative stress causes mitochondrial damage, third is the endoplasmic reticulum pathway that includes increased expression of HERP, GRP8 and CHOP. Lastly, the nitric oxide pathway, increased iNOS via p53 pathway that in turn increased nitric oxide. All these pathways end in a similar fashion with caspase activation and cell apoptosis.

Antiangiogenesis Drugs

Vascular endothelial growth factor (VEGF) is a potent stimulus for angiogenesis and has been shown to be constitutively expressed in a variety of organs and tissues, including the kidney. More specifically, kidney expression of VEGF is mostly in the podocytes, with a lesser degree of expression in the proximal convoluted tubule. There are three main receptors, VEGFR1 (also referred to as fms-like tyrosine kinase, FLT1), VEGFR2 (also referred to as fetal liver kinase 1/kinase insert domain receptor, FLK1/KDR) and VEGFR3 (Flt-4) (Izzedine 2014). Two major splice variants of FLT1 exist, a transmembrane form and a truncated, secreted, soluble receptor (sFlt1) (Shibuya 2001). VEGF is primarily upregulated in the setting of hypoxia which can be seen in certain

tumors that rely on angiogenesis for survival and progression. Other cancers acquire mutations in the VEGF singling cascade; for example an activating mutation of platelet-derived growth factor receptor (PDGFR) can be seen in ~35% of gastrointestinal stromal tumors.

Due to VEGF's critical role in endothelial cell function, vascular permeability modulation and interstitial matrix remodeling, anti-VEGF agents were developed to treat cancer with the goal of stopping tumor growth by inhibiting unregulated angiogenesis. Current FDA approved VEGF inhibitors include bevacizumab, ramucirumab and aflibercept (Cosmai et al. 2016). Certain VEGF receptor tyrosine kinase inhibitors (VEGFR-TKI) that preferentially inhibit VEGF-R through interference with intracellular signaling cascades are sunitinib, pazopanib, axitinib, cabozantinib, cediranib, lenvatinib, and vandetanib (van den Meiracker and Danser 2016).

Of the anti-VEGF renal complications, hypertension and proteinuria are the most common, and of biopsied AKI cases, TMA followed by MCD/FSGS are most common (Izzedine et al. 2014b). Renal limited TMA can be seen in all VEGF-inhibitors as a class effect of inhibiting the action of VEGF, either by binding to the VEGF ligand, VEGF receptor or VEGF intracellular signaling cascade (Eremina and Quaggin 2010). TMA is more common with VEGF-ligands and podocytopathies are more common with VEGFR-TKI (Izzedine et al. 2014b).

The first VEGF inhibitor approved by the FDA was bevacizumab (BEV), a recombinant humanized monoclonal IgG1 antibody against VEGF,. The incidence of proteinuria is dose-dependent, with low-dose incidence between 21% and 41% as compared to high-dose of 22–63%. High-grade proteinuria (+4 protein on dipstick or protein >3.5 g/24 h) has an incidence of 2.2%, which is a relative risk of 4.79 compared with chemotherapy regimens without BEV. Furthermore, nephrotic syndrome has a relative risk of 7.78 (Wu et al. 2010). The major risk factor for proteinuria was having the diagnosis of renal cell carcinoma. BEV-induced TMA can present with AKI and sub-nephrotic proteinuria with an average duration of BEV use of 3–9 months (Eremina et al. 2008). Incident proteinuria during aflibercept use is 62.2% for all grades of proteinuria, but for high-grade proteinuria incidence is only 7.8%. Similar risks of high-grade proteinuria are seen with ramucirumab (Ranpura et al. 2010).

VEGFR-TKIs are a class of medications that inhibit the tyrosine kinase inhibitor associated with the VEGF. By doing this, there is also inhibition of other growth factors, including platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (c-kit), FMS-like tyrosine kinase-3 (Flt-3), colony-stimulating factor type 1 (CSF-1R), glial cell-line-derived neutrophic factor receptor (RET), b-raf and Bcl-Abl (Jhaveri et al. 2011, Izzedine 2014). VEGFR-TKIs have incident proteinuria of 18.7% and incident high-grade proteinuria of 2.4% (Zhang et al. 2014). Other clinical aspects of VEGFR-TKIs-induced TMA include an elevated creatinine (>1.4 mg/dL), more likely to demonstrate ATN on biopsy and moderate, but sub-nephrotic range proteinuria (1.5–2.5 g/24 h) (Vigneau et al. 2014). Proteinuria is a direct effect of the anti-VEGF mechanism and therefore a direct assessment of the patient's response to the drug. Patients treated with pazopanib or sunitinib for renal cell carcinoma that developed high-grade proteinuria (HR 0.53, 95% CI 0.30–0.92) had significantly improved survival at 30 months (Sorich et al. 2016). In addition, hypertension incidence is 23.4% and similarly correlates with the VEGFR-TKI activity (Wu et al. 2008).

Anti-VEGF-induced TMA occurs mostly in females (71.2% vs. 18.5% in non-TMA glomerulopathies), presents with <1 g of protein a day, and approximately 4–7 months after treatment initiation (Izzedine et al. 2014b). In approximately 50% of patients with anti-VEGF or VEGFR-TKI-induced TMA, a typical HUS/TTP syndrome was not seen, but rather a renal-limited TMA, exclusively seen in the glomerulus. Anti-VEGF-induced TMA is not the typical drug-induced TMA, as ADAMTS13 activity persisted and there is no anti-ADAMTS13 antibodies presents, nor are there mutations in factor H, factor I, or membrane cofactor protein. Non-TMA findings in patients receiving anti-VEGF and VEGFR-TKI therapy include chronic endothelial

cell injury with varying degrees of vascular sclerosis, AIN, ATN with or without focal necrosis. ATN usually has a rapid increase in creatine and in this setting it is recommended to stop the offending agent (Vigneau et al. 2014). Other glomerular lesions include non-collapsing and collapsing FSGS, MPGN, MCD, cryoglobulinemic glomerulonephritis, immune complex glomerulonephritis, and glomerular endotheliosis (Izzedine et al. 2014b).

The mainstay of treatment involves discontinuation of therapy and improvement in renal function, typically within 1–6 months (Izzedine et al. 2013). The data for restarting therapy and symptom recurrence is not profound. Switching between agents has lead to a reduction in proteinuria and stable renal function, but recurrence is a risk. There is currently not enough data to predict which patients will have recurrence. Treatment of anti-VEGF has not been studied, but if proteinuria is minimal, treatment with ACE-I or ARB is recommended. However, if this drug is demonstrating a response, experts recommend temporary holding therapy, initiating treatment with an ACE-I or ARB, and then re-starting therapy with a 50% dose reduction (Izzedine 2014).

Mechanism of anti-VEGF induced TMA has been well studied. VEGF is produced in the podocyte and is critical for proper mesangial cell survival and differentiation. VEGF is upregulated in response to HTN or an increase in renin-angiotensin system, thereby demonstrating a protective role (Advani et al. 2007). VEGF seems to traverse the GBM where it can bind to VEGF receptors on endothelial cells promoting their survival and triggering fenestrae to enhance glomerular epithelial permeability. In VEGF knockdown mice, death occurs within 3 weeks due to kidney failure. Anti-VEGF agents have been demonstrated to cause the same presentation of proteinuria, HTN and TMA seen in VEGF knockout mice (Eremina et al. 2008).

Nephrin is an adhesion molecule in podocytes, primarily localized to the slit diaphragm and involved with proximal signal transduction through its oligomerized form with signaling microdomains, referred to as, lipid raft clustering. The role of nephrin is multifactorial, which includes a structural role in the slit diaphragm maintaining its integrity, actin cytoskeleton reorganization, podocyte calcium metabolism, and intracellular signaling critical for podocyte function and viability. C-maf inducing protein (c-mip), found in podocytes, is normally suppressed by a constitutively expressed protein, RelA (a subunit of NF-kb) transcription factor, through binding to c-mip's promoter region resulting in c-mip transcription inhibition (Izzedine et al. 2014b). RelA is phosphorylated by VEGFR, allowing it to inhibit the transcriptional activity of c-mip. Glomerular endothelial cells and podocytes have VEGFR2, that when activated by VEGF, gets phosphorylated and in turn recruits Fyn, resulting in a phosphorylation cascade with Nck, PAK-2, N-WASP that activates the Akt pathway allowing cell survival, actin polymerization and actin stress-fiber formation (Lamalice et al. 2006). There is also a direct interaction between VEGFR2 and nephrin forming a complex involving Nck and actin (Bertuccio et al. 2011). Angiotensin II can induce podocyte apoptosis through a Csk-dependent pathway resulting in nephrin dephosphorylation.

VEGFR-TKI drugs inhibit the VEGFR, which is a tyrosine kinase inhibitor thereby preventing phosphorylation and activation. This causes inhibition of NF-kB, leading to decreased phosphorylation of nephrin leading to cytoskeletal disorganization, endothelial swelling, and podocyte effacement (Zhang et al. 2014). Most patients being treated for RCC have a nephrectomy causing the other kidney to hyperfiltrate. This normally leads to the upregulation of the Akt cell survival pathway is upregulated. However, when VEGFR-TKI therapy is initiated, the Akt pathway is blocked resulting in podocyte instability and proteinuria (Ollero and Sahali 2015). VEGF inhibition also leads to impaired endothelium-mediated vasodilation, and elevated surface adhesion molecules that results in leukocyte adhesion. Endothelium integrity is also dependent on nitric oxide release, and nitric oxide itself can inhibit exocytosis of cell vacuoles (also called Weibel Palade bodies) which contain vWF. When VEGF is inhibited, nitric oxide production decreases causing endothelial dysfunction

and increases Weibel Palade bodies (and vWF) exocytosis resulting in accumulation in vWF.

Gemcitabine

Gemcitabine, a nucleoside analogue structurally related to cytarabine, is approved for the treatment of ovarian cancer, breast cancer, and non-small cell lung cancer. The incidence of gemcitabine-induced TMA is 0.19–1.13% (Izzedine et al. 2006). The average duration of gemcitabine use before TMA is between 7.56 months and many patients present with a subacute course of new or worsening HTN and AKI (Izzedine et al. 2006; Glezerman et al. 2009). The typical findings that are seen include, microangiopathic hemolytic anemia (100%), thrombocytopenia (100%), schistocytes (87%), decreased haptoglobin (84%), and elevated LDH (100%) (Glezerman et al. 2009). Other presenting signs and symptoms are worsening or new-onset hypertension (86%), shortness of breath (51%), overt congestive heart failure (24%), edema (72%), hematuria (93%), and proteinuria (93%) and red blood cell casts (27%) (Glezerman et al. 2009). Hypertension occurrs 0.5–10 weeks before the clinical diagnosis of TMA in the majority of patients (Dasanu 2008).

Renal prognosis is poor. Even with discontinuation of gemcitabine, antihypertensive therapy, and plasma exchange approximately 25% of patients will require long term hemodialysis and a full renal recovery can be seen in only 24–33% of patients, with the remaining developing CKD (Glezerman et al. 2009). Patients that develop gemcitabine-induced TMA/HUS usually have an advanced stage malignancy and approximately 59% of patients die from tumor progression in less than 1.5 years (Izzedine et al. 2006).

There are limited treatment options other than the discontinuation of gemcitabine. Plasma exchange can improve some of the hematological parameters but renal function is not improved. Other treatments that have been used with variable degrees of success include protein A immunoadsorption, doxycycline, aspirin, dipyridamole, eculizimab, and corticosteroids (Izzedine et al. 2006; Glezerman et al. 2009). Rituximab has been used with success in a small case series with 3 of 4 patients in one case series and 3 of 3 patients in another series showing improvement (Gourley et al. 2010; Murugapandian et al. 2015; Ritchie et al. 2016).

Pathogenesis of gemcitabine induced TMA is still unknown although some hypotheses present in the literature include a direct effect on the endothelium through complement activation, increased thrombotic risk and ADAMTS13 deficiency (Izzedine et al. 2006; Zupancic et al. 2007; Saif et al. 2009). The effect of gemcitabine on the endothelium is still not known, but some studies demonstrate that it can induce apoptosis. Models show that gemcitabine induces expression of thrombospondin-1 (TSP1), a natural inhibitor of VEGF and resulting in endothelial cell apopotosis. TSP1 can also cause platelet aggregation through a TSP-fibrinogen interaction (Leung 1984). ADAMTS13 normally binds to CD36 on endothelial cells, where it can perform enhanced cleavage of vWF. TSP1 competitively competes with ADAMTS13 for CD36, resulting in large multimers of vWF that promote thrombosis (Davis et al. 2009). TSP1 also increases TGF β, expression, a cytokine that has been implicated in TMA.

Mitomycin C

Mitomycin C (MMC) is an antibiotic isolated from *Streptomyces caepitosus* that selectively inhibits DNA synthesis. Its current indication includes adenocarcinoma of the stomach or pancreas in combination therapy but also has been used in breast cancer, non-small-cell lung cancer, bladder cancer and head and neck cancer. General renal toxicity occurs in 8.5–9.7% of patients and the incidence of MMC-induced TMA/HUS is 4.2% (Fogo et al. 1999).

Patients with MMC-induced TMA typically presented with hypertension (SBP 180-200), MAHA, AKI and significant proteinuria. Non-cardiogenic pulmonary edema can be seen in 65% of patients. A major risk factor for development of TMA is higher MMC > than 50–60 mg (Lusco et al. 2015). Prognosis is poor with 50%

dying within 4–8 weeks of onset, and influenced by remission. The treatment with the most benefit is staphylococcal protein A (SPA) immunoadsorption yet only 45% patients respond to the treatment with a 1-year survival rate is 61%, which is significantly higher than the non-responders with 22% survival at 1 year. Other treatments that have been studied with minimal benefit include plasma exchange, dialysis, aspirin, dipyridamole and heparin.

Pathogenesis is directly from MMC-induced glomerular endothelial damage resulting in platelet accumulation and TMA/HUS. Endothelial cells exposed to MMC demonstrate a decrease in prostacyclin PGI_2 synthesis (Duperray et al. 1988). Endothelial cells normally produce small quantities of PGI_2 that can prevent or reverse platelet aggregation and cause vasodilation; therefore with inhibition of PGI_2, the risk of thrombosis increases (Ramot et al. 2013). MMC can also cause a dose-dependent reduction of endothelial cell proliferation and extracellular matrix production.

There is also an immune-complex mechanism that most likely contributes to MMC induced TMA. Through protein A immunoadsorption, two immune complexes have been identified. A 15S non-platelet aggregating immune complex that contains IgG with an antigen from the malignancy and an 11S platelet aggregating complex that contains IgG with platelet glycoprotein capable of activating.

Phospholipidosis

Lysosomal storage diseases are infrequent with a prevalence of 1 out of every 7700 births. Apart from the genetic lysosomal storage diseases such as Gaucher disease and Fabry disease, an acquired form, phospholipidosis, exists. Drug-induced phospholipidosis (DIP) is due to loss or inhibition of lysosomal enzyme function resulting in abnormal phospholipid metabolism. The current diagnosis is based on four features: (1) excessive phospholipid accumulation in cells; (2) membranous lamellar inclusions; (3) accumulation of inciting drug in association with increased phospholipids; (4) and reversibility after drug withdrawal. Many drugs are associated with DIP (Table 8), with gentamicin, chloroquine, hydroxychloroquine and amiodarone representing the most common. These are all cationic amphiphilic drugs containing a hydrophobic aromatic ring structure and a hydrophilic side chain with charged cationic amine group. In order for a drug to cause phospholipidosis, it needs to meet three requirements: (1) the drug needs to be able to enter cells; (2) it needs to be enriched in lysosomes; (3) it needs to inhibit lysosomal phospholipases (Alakoskela et al. 2009).

Table 8 Medications associated with phospholipidosis

Drug Class	Examples
Antibiotics	Azithromycin, erythromycin, gentamicin, amikacin, chloroquine
Antihistamines	Meclizine, hydroxyzine, chorcyclizine
Appetite suppressants	Fenfluramine, chlorphentermine
Cardiac	Perhexiline, amiodarone, ranolazine
Psychiatric	Imipramine, clomipramine, citalopram, fluoxetine, sertraline, clozapine
Miscellaneous	Tamoxifen, ambroxol

DIP patients may present with painful neuropathy, premature vascular disease, angiokeratomas, cardiomyopathy or hyperhidrosis (Woywodt et al. 2007; Zhao 2016). Approximately 50% of the drugs causing phospholiposis affect three or more organs, with the most common being lung (90%), lymph nodes (50%), spleen (48%), liver (35%), reproductive organs (15), kidney (15%), adrenal gland (13%), thymus (10%) and bone marrow (5%) (Barone et al. 2012). Kidney presentation of DIP typically includes nephrotic proteinuria and AKI.

In all available cases, patients have ranged in age from 15 to 66 years old. Duration of therapy attributed to phospholiposis has been reported as 11 days to 5 years. In addition patients can also demonstrate findings of phospholiposis years after discontinuation of a culprit medication (Ferluga 2010).

Renal biopsy demonstrates diffusely enlarged podocytes with an abundance of finely vacuolated

cytoplasm. Podocytes are the major cell affected, but abnormal phospholipid accumulation can occur in all renal cells. EM podocytes show enlarged lysosomes with electron-dense lamellated membrane structures (also called zebra bodies, myelin figures, or myelin bodies) (Fig. 5). IF is typically negative. In a case series of six patients, all biopsies showed cytoplasmic, lysosomal inclusions with smaller dense bodies, larger concentrically lamellated myeloid bodies and straight parallel arranged lamellated zebra-like bodies (Ferluga 2010). Proteinuria is correlated with podocyte foot process effacement. Biopsy findings have been compared and similar to a female heterozygote mild form of Fabry nephropathy. Family history and genetic testing are imperative because pathology for DIP is nearly identical to Fabry disease.

Subtle differences do exist that can distinguish inherited from acquired phospholiposis. DIP may have curvilinear bodies on EM whereas Fabry disease does not. These curvilinear bodies, usually found in cardiac myocytes and neurons in patients with neuronal-ceroid lipofuscinosis, are inclusion bodies surrounded by a single membrane and a lamellated/twisted microtubular substructure. Another difference to suggest DIP are small, round, homogeneously dense granular inclusions

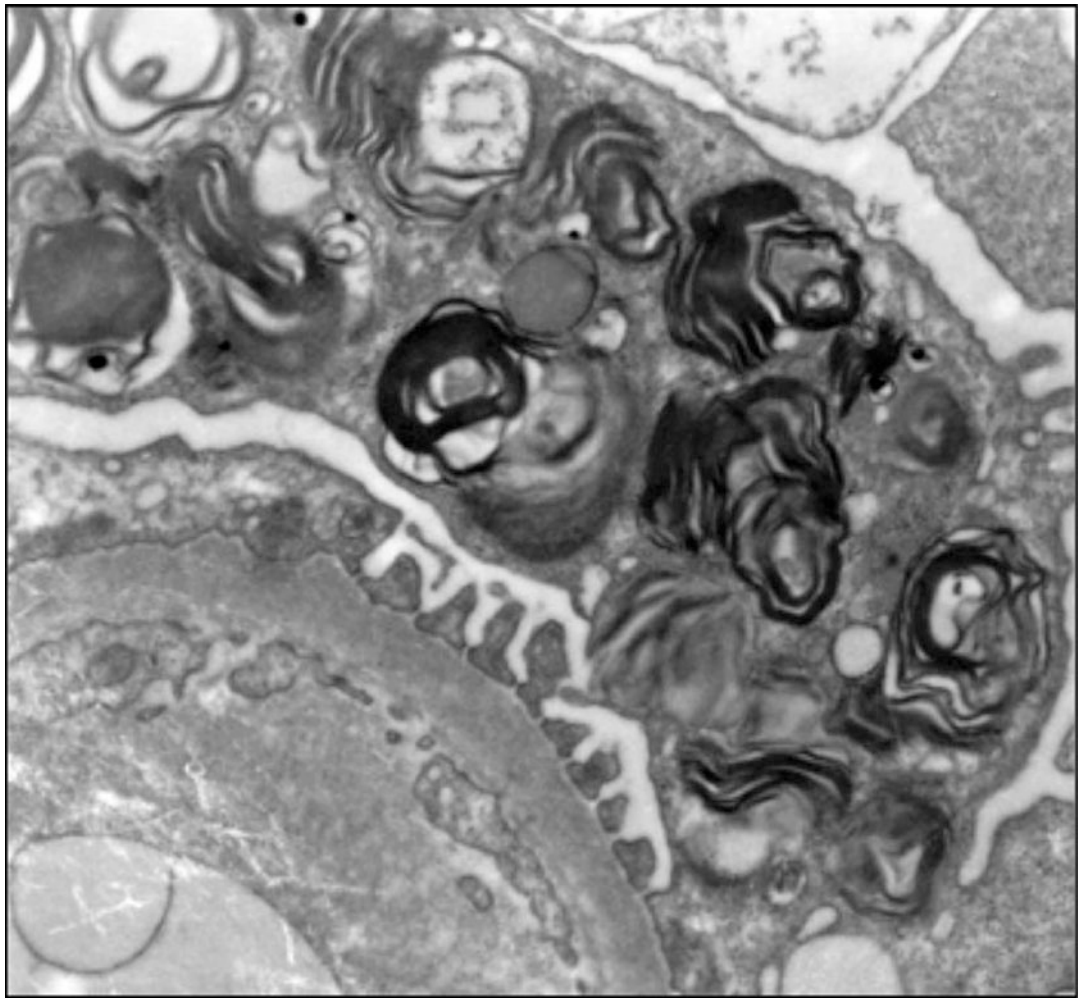

Fig. 5 Electron micrograph of a patient with phospholipidosis. Lysosomal inclusions with a myelin body appearance in the podocyte

within mesangial, endothelial or tubular cell mitochondria (Loh and Cohen 2009). A third possible difference is inclusions in infiltrating monocytes and macrophages in DIP. And the last, subjective, difference is a greater number of classic lamellated podocyte inclusions in Fabry disease.

The treatment is discontinuation of the offending agent with resolution in months to years. Enzyme replacement therapy has not been used in DIP as with inherited lysosomal storage disease. If renal involvement is significant, renal replacement therapy may be required (Scheurle et al. 2014).

Pathogenesis involves lysosomal uptake of the drug or metabolite, drug trapping via protonation, and drug-induced impairment of phospholipid metabolism resulting in phospholipid accumulation. The most likely inhibited enzymes are sphingomyelin phosphodiesterase, phospholipase A2, and lysosomal phospholipase A1.

Glomerular Hemorrhage

More commonly referred to as warfarin-related nephropathy (WRN) or anticoagulant-related nephropathy, glomerular hemorrhage can be seen with patients who are on anticoagulation. The major histologic finding is the presence of numerous red blood cells in Bowman's space (Fig. 6). Light microscopy also shows RBC casts in the tubules and ATN. Immunofluorescence can show mild mesangial IgG and electron microscopy can show scattered mesangial immune-type deposits (Brodsky 2014). Glomerular hemorrhage causes downstream tubular obstruction via red blood cell

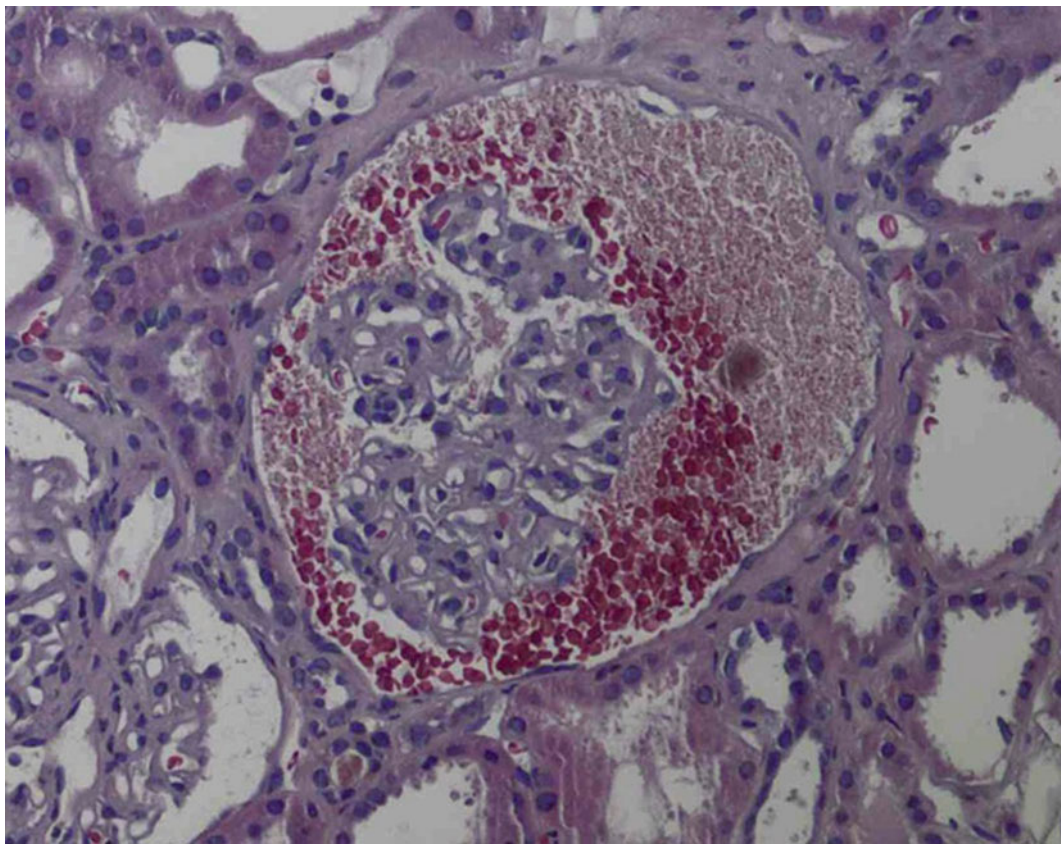

Fig. 6 Light microscopy from a patient with dabigatran induced glomerular hemorrhage. Numerous blood cells within Bowman's space

casts. Another important mechanism is oxidative stress damage to the tubules from RBC, even without RBC obstruction. Free hemoglobin released from RBC incorporates into tubular epithelial cells via cell surface receptors, where intracellular hemoglobin activates caspases to induce apoptosis and dissociates into globin and heme. Heme is a potent oxidant, activating pro-inflammatory pathways (Brodsky 2014). Decreased antioxidant enzyme activities in patients with baseline kidney disease might limit the ability of the kidney to manage the oxidative stress. WRN is almost completely seen in patients with pre-existing glomerular disease, suggesting that it may be a requirement, even if previously undiagnosed (Brodsky 2014). Atheroemboli, interstitial nephritis and glomerular endothelial cell apoptosis might also contribute to the pathophysiology (Yang et al. 2014). Warfarin can also inhibit growth specific gene 6 (GAS-6), a vitamin K-dependent matrix Gla protein. GAS-6 inhibition results in inhibition of mesangial cell proliferation and interference of vascular smooth muscle migration (Narasimha Krishna et al. 2015). Dabigatran, a direct thrombin inhibitor, has also been demonstrated to cause WRN with the similar histological findings (Moeckel et al. 2013).

WRN occurs in patients who are over-anticoagulated with an international normalized ration (INR) above three, average INR in the low 4s. An incidence of 25% was seen in a general cohort and 33% seen in a CKD cohort (Brodsky et al. 2011). Risk factors include older age, diabetes mellitus, diabetic nephropathy, hypertension, heart failure, low basal serum albumin, gene polymorphism affecting warfarin metabolism (CYP2C9*3 polymorphism) and simultaneous use of aspirin, angiotensin converting enzyme inhibitors, and calcium channel blockers (Narasimha Krishna et al. 2015).

Patients typically present with AKI (average creatine 4.3 mg/dl) and microscopic hematuria (Brodsky et al. 2009). Renal prognosis is poor with a large percentage of patients becoming dialysis-dependent (Brodsky et al. 2009). One-year mortality averages 31.1% in WRN. Patients who recover, tend to do so within 3 months (Brodsky et al. 2011). Besides discontinuing or holding the anticoagulant few other treatments have served a clinical role. In animal models, N-acetylcysteine can ameliorate AKI, but not hemorrhage. Prednisone has been used to improve AKI in case studies, but is not used as a primary therapy (Di Maso et al. 2014).

Glomerular Sclerosis

Carmustine (also referred to as BCNU), lomustine (CCNU), semustine (methyl CCNU), and streptozocin are alkylating chemotherapy agent used in the treatment of brain tumors and for bone marrow transplantation. Semustine and streptozocin AKI incidence is 75–99% and carmustine and lomustine AKI incidence is 10% (Sahni et al. 2009). Risk factors include higher doses (more than 1.5 g/m^2) and longer treatment time (Harmon et al. 1979; Schacht et al. 1981).

Nephrotoxicity presents with insidious creatinine rise, occurring 1–6 years after the start of chemotherapy, with mild proteinuria typically less than 100 mg/day (Ellis et al. 1985). Tubular dysfunction can be seen as well, manifesting as proteinuria, glycosuria, phosphaturia and hypophosphatemia (Schacht et al. 1981). In fact, hypophosphatemia may be the first sign of renal dysfunction in some patients (Kintzel 2001). The most common finding on biopsy is glomerular sclerosis affecting 5–35% of total glomeruli and focal thickening and reduplication of the GBM (Fig. 7). Interstitial inflammation and tubular atrophy are common findings as well.

Treatment involves discontinuation of the medication, but given that proteinuria is mild and creatinine rise is slow, patients are often recognized late. Renal prognosis is quite poor; between 20% and 30% of reported cases lead to ESRD.

It is thought that these medications are metabolized to release an N-nitroso group which is secreted in the tubule, and can release an active methyl group which acts as a toxic radical producing nephrotoxic effects. However, it is probable that other mechanisms exist since not all of these agents can generate similar N-nitroso groups, yet still lead to similar patterns of renal injury (Schacht et al. 1981).

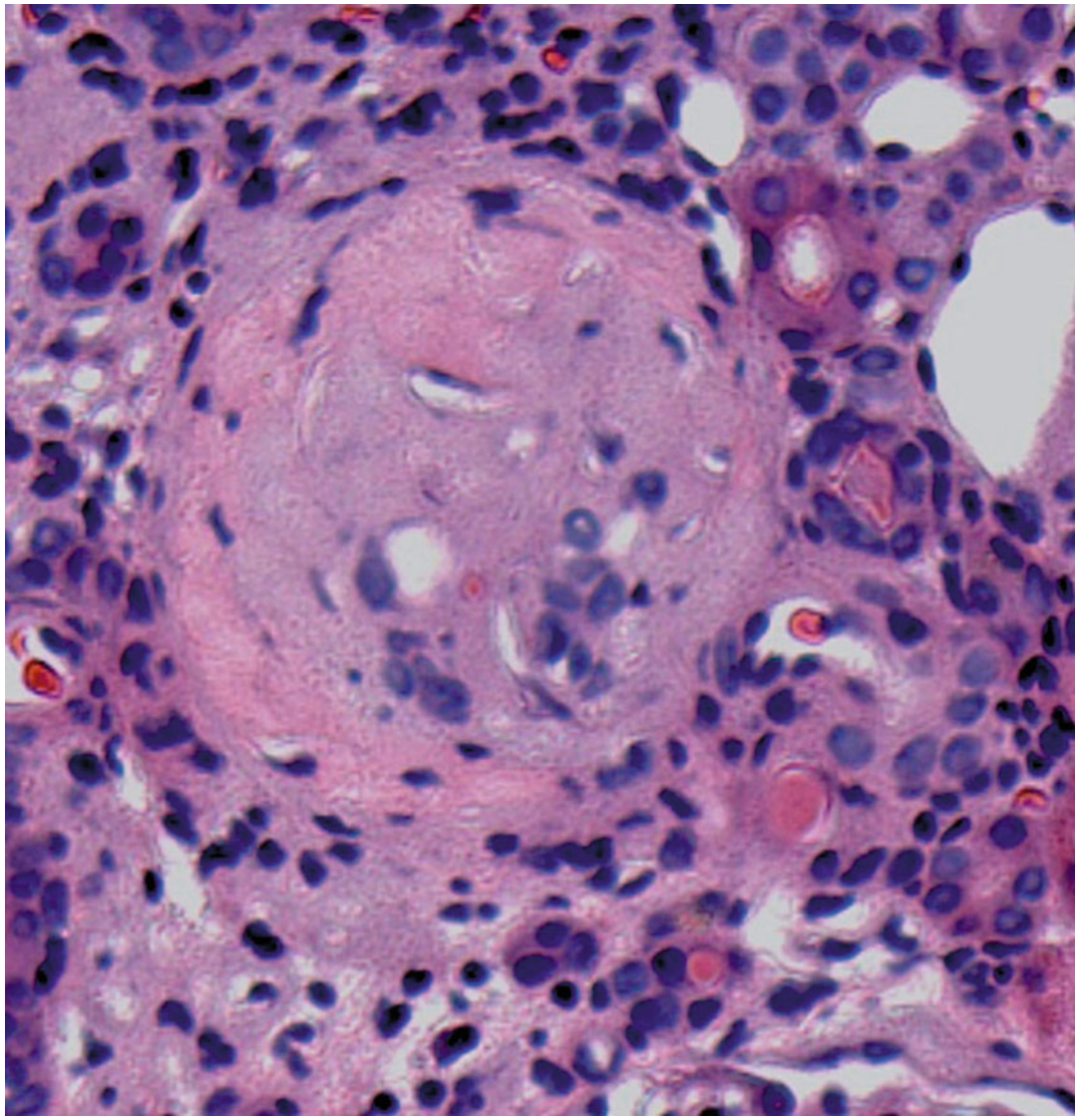

Fig. 7 Light microscopy from a patient with medication induced glomerulosclerosis. Glomerulus is shrunken with loss of architecture

Conclusions

Medications can cause many forms of kidney injury. Glomerular involvement can present with an array of glomerular lesions. With close overlap to non-medication induced glomerular injury, it is important for the clinician to recognize medications that have been associated with glomerular disease. Often quick recognition and subsequent withdrawal of the offending medication will lead to improvement in kidney function and prevent ongoing kidney damage.

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Glomerular Disease Associated with Rheumatic Diseases Other than SLE

46

Julia M. Hofstra and Jack F. M. Wetzels

Contents

Abstract

Nephrologists will frequently be consulted to evaluate kidney injury in patients with rheumatic diseases. In the majority of patients, kidney injury will be a side effect of the antirheumatic drugs. Also, it is now well recognized that chronic kidney disease (CKD) is more frequently observed in patients with rheumatic diseases.

Glomerular diseases are rare, with the exception of glomerular thrombosis in patients with scleroderma (scleroderma renal crisis). In most patients with rheumatic diseases and evidence of glomerular injury, a kidney biopsy is needed to establish a diagnosis and guide therapy.

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Introduction

In clinical practice, nephrologists will regularly be confronted with patients with rheumatic diseases. Sometimes, the rheumatic disease is the consequence of an underlying kidney disorder (e.g., gouty arthritis in a patient with high urate levels due to kidney insufficiency). Conversely, the kidney disease may be associated with the rheumatic disease. Best characterized are the situations where the kidney disease and the rheumatic disease are different manifestations of a single underlying pathogenetic process (e.g., arthritis and glomerulonephritis in patients with SLE or systemic vasculitis). The kidney disease may also be a complication of drugs used for the treatment of the rheumatic disease (e.g., acute kidney injury after NSAID use, membranous nephropathy during D-penicillamine or NSAID use, glomerulonephritis during anti-TNF alpha therapy). Importantly, it is now well recognized that the prevalence of chronic kidney damage is increased in patients with rheumatic diseases.

In this chapter, we discuss kidney diseases that are associated with rheumatic diseases and specifically focus on the glomerular disorders that are observed in patients with scleroderma, Sjögren's syndrome, rheumatoid arthritis, and mixed connective tissue disease (MCTD). Glomerular damage in patients with rheumatic diseases can be the consequence of immune complex deposition, glomerular capillary thrombosis, drug-induced injury, or secondary glomerular sclerosis. An overview of the glomerular diseases associated with rheumatic diseases is given in Table 1. Although the focus is on glomerular disorders, we also discuss other kidney disorders associated with rheumatic diseases since this will be helpful in the differential diagnosis.

Kidney Disease in Scleroderma

Scleroderma is an autoimmune disease characterized by thickening of the skin, with increased collagen deposition, and a generalized vasculopathy that can affect many organ systems. Two types of scleroderma are discerned: limited cutaneous scleroderma, characterized by involvement of the skin of the face, hands and feet, and diffuse scleroderma, characterized by additional involvement of the trunk. The pathogenesis is poorly understood. Important elements are environmental and genetic factors causing endothelial cell damage and inflammatory and autoimmune responses, with subsequent activation of fibroblasts resulting in progressive fibrosis.

Kidney involvement in scleroderma is not infrequent. By far the most frequent renal manifestation is the "scleroderma renal crisis," although other kidney disease manifestations do occur (see Table 1).

Table 1 Kidney disorders in patients with rheumatic diseases

Rheumatic disease	Kidney disorders
Scleroderma	Thrombotic microangiopathy (scleroderma renal crisis) ANCA-positive extracapillary (crescentic) glomerulonephritis Renal artery stenosis Oxalate nephropathy

Sjögren's syndrome	Renal tubular acidosis
	Nephrogenic diabetes insipidus
	Glomerulonephritis
	  Membranoproliferative glomerulonephritis
	  Mesangial proliferative glomerulonephritis
	  Membranous nephropathy
	  Focal segmental sclerosis
	  Minimal change disease
	  IgA nephropathy
	Tubulointerstitial nephritis

Rheumatoid arthritis	Mesangial proliferative glomerulonephritis Membranous nephropathy Amyloidosis Extracapillary (crescentic) glomerulonephritis
MCTD	Membranous nephropathy

Abbreviations: *MCTD* mixed connective tissue disease, *ANCA* antineutrophil cytoplasmic antibody

Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) is a severe, life-threatening complication of scleroderma. Scleroderma renal crisis was first described more than 50 years ago. In its typical form, SRC is characterized by the development of acute kidney injury and accelerated hypertension. In most patients, retinal exudates, retinal hemorrhages, and papilledema are seen with fundoscopy. Histologically, the defining lesions in the kidney are hyperplasia of the vessel wall of the interlobular arteries (onion skin appearance), fibrinoid necrosis of the arterioles, ischemia of the glomeruli, and arteriolar and glomerular capillary thrombosis.

Before 1970, in the absence of treatment, the development of SRC predicted death. Traub et al. summarized the experience in Pittsburgh (Traub et al. 1983). All 29 patients diagnosed with SRC before 1971 died within days to months after SRC onset. In the next decade, prognosis improved, some patients surviving due to the introduction of dialysis and transplantation, and the use of antihypertensive therapy, either surgical (bilateral nephrectomy) or medical (with antihypertensive agents such as propanolol, reserpine, guanethidine, methyldopa). Still, from 1970 to 1980 mortality was high, exceeding 50% within the first year after onset of SRC.

The development and introduction of more effective antihypertensive drugs such as minoxidil further improved outcome. A major breakthrough came with the introduction of the first angiotensin converting enzyme inhibitor, captopril. Lopez-Ovejero et al. (Lopez-Ovejero et al. 1979) is credited for describing the first case of a patient with SRC treated with captopril (see Box 1).

The current view is that the routine use of ACE inhibitors in patients with SRC has "dramatically improved outcome" (Guillevin et al. 2012). This view is primarily based on the publication of Virginia Steen and colleagues (Steen et al. 1990). These authors retrospectively described the outcome of 108 patients with SRC admitted to the University of Pittsburgh Medical Center in the period 1972–1987. In the second half of this period, captopril (and later enalapril) became available for routine treatment of patients with SRC. One year survival was 76% in patients treated with the angiotensin converting enzyme inhibitor as compared to 15% in the historical control group. Obviously, these findings received wide and enthusiastic attention, creating hope of improved outcomes in all patients with SRC, and even fostering the idea that prophylactic therapy with captopril might eliminate SRC as a clinical problem. Unfortunately, current literature data indicate otherwise: SRC is still a common complication of scleroderma, and outcomes are still mediocre.

The Epidemiology of SRC

There is a wide belief that the incidence of SRC has decreased, from 12–25% in 1970 to 5% more recently (Mouthon et al. 2014; Teixeira et al. 2008). However, these comparisons are invalid. The older studies mainly included patients with diffuse scleroderma (who are more likely to develop SRC), whereas recent registry data included both patients with diffuse and limited scleroderma. In fact, diffuse scleroderma constituted only 20–43% of the total (Walker et al. 2003; Walker et al. 2007; Penn et al. 2007; Guillevin et al. 2012).

Moreover, the reported 5% incidence of SRC in recent years is based on the study of Walker et al. (2007). However, this study analyzed cross-sectional data of patients who had been followed for more than 7 years. Since SRC usually develops within 3 years after disease onset, and overall survival is worse in patients with SRC, this was likely an underestimate.

The incidence of SRC in patients with diffuse scleroderma in the period 1955–1987 in the USA was approximately 10% (Traub et al. 1983; Helfrich et al. 1989; Steen et al. 1990). In more recent studies, the average incidence of SRC in comparable patients was 13% (DeMarco et al. 2002; Walker et al. 2003; Penn et al. 2007). Thus, SRC is not an extinct disease.

The Outcome of SRC

Steen et al. should be credited for pointing to the efficacy of captopril in the treatment of patients with SRC (1990). However, 24% of patients had died within 1 year after disease onset. Moreover, good outcome, defined as survival without dialysis, occurred in only 56% of patients after 1 year.

Nowadays, SRC remains associated with high morbidity (the persistent need for renal replacement therapy) and mortality. Mortality ranged from 20% to 50% (DeMarco et al. 2002; Walker et al. 2003; Penn et al. 2007; Guillevin et al. 2012). Morbidity is also high, approximately 30–50% of patients need renal replacement therapy, which is temporary in only half. Thus, 25–40% of survivors need lifelong renal replacement therapy. Guillevin et al. reported an actuarial 5-year survival without dialysis of 33.7% (2012). Thus, SRC still carries a bad prognosis.

The Clinical Picture of SRC

Criteria used to define SRC are given in Table 2.

In routine clinical practice, a diagnosis of SRC can easily be made in patients who present with accelerated hypertension, accompanied by hypertensive encephalopathy, abnormalities at fundoscopy, acute kidney injury, and signs of microangiopathic hemolytic anemia (hemolysis, schistocytes) and thrombocytopenia. Proteinuria and hematuria are also frequently observed.

Although hypertension is considered an important feature of SRC, acute kidney injury due to microangiopathy can develop in patients with scleroderma in the absence of overt hypertension. A diastolic blood pressure <90 mmHg is observed in 6–14% of scleroderma patients with SRC (Walker et al. 2003; Guillevin et al. 2012). Helfrich et al. described a cohort of 15 patients with normotensive SRC (1989). These patients differed from the hypertensive cohort in having a higher incidence of signs of microangiopathic hemolysis (90% vs 38%), a higher incidence of thrombocytopenia (83% vs 21%), and higher frequency of having used high-dose (>30 mg/day) prednisone in the preceding period (69% vs 16%). In the study by Traub, survival was worse in normotensive SRC (13%) than in the hypertensive cohort (35%). Of note, most of these patients were admitted in the era before the routine use of captopril. Normotensive SRC is not extinct. The prevalence was 7% in a very recent study (Hudson et al. 2014). Normotensive SRC was seen more frequently in patients who used an ACE inhibitor (13%) than in untreated patients (5%). Of note, normotensive SRC is defined by a diastolic blood pressure <90 mmHg at presentation. In most of the patients with "normotensive SRC" a clear increase in blood pressure was noted and many patients had stage III or IV retinopathy, indicating that not just absolute blood pressures but also relative changes in blood pressure must be considered when evaluating a patient with scleroderma.

Table 2 Scleroderma renal crisis – definition of hypertensive SRC[a]

Blood pressure >140/90 mmHg or increase in blood pressure >30/20 mmHg And one of the following:
a. Acute kidney injury
b. Proteinuria
c. Hematuria
d. Thrombocytopenia < 100 . 10^9/l
e. Hemolysis
f. Hypertensive encephalopathy

[a]Normotensive SRC is defined by AKI and one of the criteria b till f
Adapted from Hudson et al. 2014

Although SRC is the consequence of microangiopathic vascular damage, many patients do not fulfill the criteria for TMA. In various studies, the prevalence of microangiopathic hemolysis ranges from 30% to 81%, and the prevalence of thrombocytopenia ranges from 39% to 50% (Mouthon et al. 2014). Again, if we would include a change in thrombocytes as parameter, the number of patients with abnormalities would certainly be higher.

Of note, in 22% of patients, SRC is the first manifestation of scleroderma. In most patients, a diagnosis of scleroderma will be made after careful inspection of the skin, digits, and face. Still, some patients do not have skin abnormalities (scleroderma sine scleroderma).

Risk Factors of Scleroderma Renal Crisis

Scleroderma renal crisis is predominantly observed in patients with diffuse scleroderma (cumulative incidence 13% in diffuse vs 2% in limited scleroderma). As a rule SRC is observed within 3–4 years after disease onset (mean interval from disease onset till SRC 7–15 months; (DeMarco et al. 2002; Walker et al. 2007; Penn et al. 2007; Guillevin et al. 2012). The risk of SRC is higher in patients with more severe skin lesions

(higher skin score, more severe joint contractures, digital ulcers). Other risk factors include the use of high-dose prednisone, the presence of hypertension, and the presence of tendon friction rubs. Antibody patterns, which also associate with skin lesions, can also be of help. The presence of antibodies against RNA polymerase is associated with a three- to fivefold higher risk, whereas patients with anti-centromere antibodies seldom develop SRC.

The observations that captopril greatly improved survival in patients with SRC fostered the idea that the use of ACE inhibition could prevent the development of SRC. Thus far, this idea has not been tested in a randomized, controlled trial, and most authors now agree that ACE inhibitors are not effective in preventing SRC. Indeed, in a case control study, comparing patients with SRC (cases) and patients without SRC (controls), Steen and Medsger observed no differences in the use of ACE inhibitors between cases and controls (1998). Of note, in this study only 7% of patients had ever used an ACE inhibitor, and the analysis could easily have been biased by confounding by indication. Still, the data show that ACE inhibitors do not provide complete protection against development of SRC.

In later studies, it was even suggested that early use of ACE inhibitors, by masking hypertension, could negatively affect the outcome of patients with SRC. This was evaluated by Hudson et al. (2014), who sent a questionnaire to 589 physicians in the period 2008–2009, asking to report any case of SRC admitted in the previous 2 weeks. Of the 75 patients with SRC who were reported, five were normotensive at presentation, and three patients had no skin scleroderma. ACE inhibitors were used in 16 patients. In multivariable analysis, the risk of death was higher in patients who were using ACE inhibitors at presentation. However, significance was lost after adjustment for blood pressure. Therefore, the study does not provide sufficient evidence that ACE inhibitor use is associated with worse outcome in SRC. Despite treatment, blood pressure was still higher in the patients that received ACE inhibition ($139 \pm 26/85 \pm 19$ vs $124 \pm 16/75 \pm 11$ mmHg), suggesting that undertreatment of blood pressure may be the most relevant problem.

Despite the lack of data supporting the prophylactic use of ACE inhibitors in scleroderma, their use has grown. In a German registry, the use of an ACE inhibitor or ARB increased from 26% in 2005 to 36% in 2009. Of note, almost 50% of patients used a calcium channel blocker (Moinzadeh et al. 2016).

Treatment of SRC

Immediate blood pressure lowering is the main stay of treatment of SRC. Angiotensin converting enzyme inhibitors are the preferred drugs, and we and others prefer captopril as initial therapy because of its short half-life. Renal failure is reversible in approximately half of the patients, and this is best achieved with more rapid blood pressure control (Steen et al. 1990). Thus, failure of captopril to lower blood pressure in the first 24 h should lead to the added use of other antihypertensive agents, such as calcium channel blockers, angiotensin receptor blockers, minoxidil, or diuretics (the latter particularly in patients with fluid overload). Beta-blockers might be less preferable because of their negative effects on skin perfusion. Other risk factors that predict reversibility are lower age, lower serum creatinine at baseline, and, counterintuitively, more severe hemolytic anemia and thrombocytopenia. Clearly, since also recent studies (all reporting patients treated with ACE inhibitor) report mediocre outcomes, more effective treatment is needed. One way to improve outcome is to detect SRC in an early stage (see guidelines below).

One of the characteristic features in scleroderma is Raynaud's phenomenon. In its most severe form, the periodic ischemia of the fingers leads to digital ulcers. Some consider SRC as a manifestation of Raynaud's phenomenon (with vasoconstriction) in the kidney. Calcium channel blockers can alleviate complaints in patients with Raynaud's syndrome. Thus, the prophylactic use of calcium channel blockers to prevent SRC has been advocated. One study indeed suggested that CCB might be effective, although these findings have not been validated (Montanelli et al. 2013).

Secondly, alternative treatments should be considered. Recent studies have suggested benefits from add-on treatment with endothelin receptor antagonists such as bosentan. Its potential role in SRC is supported by the finding of an increased expression of endothelin, and the endothelin A

and B receptors in the kidney of patients with SRC. Incidental case studies indeed have suggested additional benefits of bosentan, although more data are certainly needed (Izzedine et al. 2013, Penn et al. 2013). In view of the similarities between the clinical presentation of atypical hemolytic uremic syndrome and SRC and the possibility that scleroderma renal crisis may develop in patients with underlying complement disorders, some authors advocate the use of eculizumab (Thomas et al. 2015). Clearly, given that the costs of this drug are extreme, clinical trials are urgently needed.

Clinical Practice Guidelines (Denton et al. 2016)

Patients with scleroderma should be carefully monitored for the development of SRC. Since hypertension is one of the earliest (and treatable) signs of SRC, it is advised that patients with scleroderma should perform home blood pressure measurements at least weekly. Development of hypertension (diastolic blood pressure >90 mmHg) should be reported and followed by laboratory studies and treatment. Not only the absolute level of blood pressure should be considered, an increase of blood pressure of more than 20 mmHg should cause concern and actions taken. In patients who are not able or willing to perform home blood pressure measurement, we suggest measuring blood pressure in the outpatient clinic at 3-month intervals. Serum creatinine should also be measured regularly, and a 3-month interval is advised in patients at the highest risk of SRC (patients with diffuse scleroderma, within 4 years after disease onset, with high skin score, digital ulcers, using high-dose prednisone, or positive ARA antibodies). Laboratory analysis of hemoglobin, platelets, LDH, and evaluation of a blood smear for schistocytes is needed in patients with suspected SRC. To be able to compare data, these measures should be available at baseline. Fundoscopy is helpful in patients with suspected SRC and may be particularly useful in normotensive patients with renal function deterioration.

In every patient with scleroderma and acute kidney injury, a diagnosis of SRC must be considered. The differential diagnosis includes various other causes of acute kidney injury (Table 3). The disease history and clinical and laboratory characteristics may be helpful (Table 3). In patients with typical features of SRC, a diagnosis can be made on clinical grounds. Otherwise, a kidney biopsy is needed to exclude an alternative diagnosis.

There is no hard evidence to support the use of prophylactic antihypertensive therapy in patients with scleroderma. However, we advise early start of therapy in patients at high risk for SRC and even mildly elevated blood pressure. Target blood pressures are ≤130/80 mmHg and even lower in patients with a lower baseline blood pressure. For example, in patients with a blood pressure of 100/65 mmHg, a consistent increase to levels of 130/80 mmHg warrants antihypertensive therapy. Calcium channel blockers should be considered in patients with severe Raynaud's phenomenon or digital ulcers, independent of blood pressure. In patients with hypertension, angiotensin converting enzyme inhibitors are preferred, with angiotensin receptor blockers as alternative.

Treatment-naïve patients who present with SRC should receive captopril, with rapid uptitration to reduce blood pressures within 24 h and to values

Table 3 Differential diagnosis of kidney damage in scleroderma (and possible/useful clinical clues)

Diagnosis	Clinical clues
Malignant hypertension	Preexisting hypertension, LVH
Atypical HUS	Family history of aHUS, complement disorder
Antiphospholipid syndrome	Miscarriages, thrombotic events
Renal parenchymatous disease:	
Glomerulonephritis	Hematuria, severe proteinuria, ANCA
Tubulointerstitial nephritis	Bland sediment, eosinophilia
Paraprotein-associated glomerulonephritis	Paraprotein in serum/urine
Infectious glomerulonephritis	History, complement
Rhabdomyolysis[a]	Creatinine kinase, myoglobin

Abbreviations: *HUS* hemolytic uremic syndrome, *LVH* left ventricular hypertrophy, *ANCA* antineutrophil cytoplasmic antibodies

[a]In patients with myositis

<140/90 mmHg within 72 h. In normotensive SRC, we aim to reduce blood pressures to pre-SRC values. If captopril is not effective, additional antihypertensive drugs must be added, the choice being dependent on physician and patient preference. We favor adding an ARB and/or a calcium channel blocker. In patients with hypervolemia, diuretics should be used, and minoxidil is useful in treatment resistant cases.

In patients with persistently elevated blood pressures, persistent TMA, and no improvement of kidney function, additional treatment must be considered. Based on the limited evidence, we would favor a trial of bosentan.

ANCA-Vasculitis in Scleroderma

Approximately 1 in 200 patients with scleroderma will develop vasculitis. In most patients an atypical antineutrophil cytoplasmic antibody (ANCA) pattern is observed on indirect immunofluorescence. The vasculitis typically involves the skin, sometimes the lungs. In one third of the patients, the kidneys are involved. Most patients with renal vasculitis are anti-MPO ANCA positive. The renal vasculitis develops later in SSC (mean disease duration 8 years), and patients have less often hypertension (32%), TMA (14%), or thrombocytopenia (13%). Typical presentation includes rapidly progressive glomerulonephritis (83%), alveolar hemorrhage (28%), limb ischemia (13%), and skin vasculitis (10%). When compared to patients with SRC, patients with ANCA-associated vasculitis are more often positive for anti-Scl70 antibodies (76% vs 21%) and anticentromere antibodies (24% vs 1.2%) (Arad et al. 2011; Derrett-Smith et al. 2013; Quemeneur et al. 2013). Treatment should follow the guidelines for ANCA-associated vasculitis.

Chronic Kidney Damage in Scleroderma

Patients with scleroderma may develop gastrointestinal disturbances, sometimes leading to bile acid diarrhea. These patients are at increased risk for developing oxalate nephropathy (Ligon et al. 2015). In recent years, much attention in rheumatology has been on cardiovascular risk management. Indeed CKD has been frequently observed, 26% of patients with scleroderma being reported with either proteinuria or renal insufficiency. However, in most patients this abnormality was related to an underlying defect (low kidney perfusion in patients with heart failure, pulmonary artery hypertension) or the use of drugs (diuretics, NSAIDs).

Sjögren's Syndrome

Primary Sjögren's syndrome (pSS or Sjögren's disease) is a progressive autoimmune disease of the exocrine glands that was first described in 1933 by the Swedish ophthalmologist Henrik Sjögren. In this disease, lymphoplasmacytic infiltration of the exocrine glands leads to the typical "sicca syndrome" of dry eyes and dry mouth. The incidence of the disease is higher than that of most autoimmune diseases, with estimates of 1–10/1000 (Qin et al. 2015). It occurs predominantly in females over 50 years. The autoantibodies anti-Ro and anti-La (also known as anti-SSA an anti-SSB) are present in up to 70% of patients. Diagnosis can be confirmed by a positive lip biopsy or a positive Schirmer's test. Extraglandular manifestations occur in about 25% of patients, often including interstitial lung disease, peripheral neuropathy, vasculitis of the skin, and hematological and renal complications.

Kidney involvement in Sjögren's syndrome has been estimated at approximately 10% of patients. In most patients, kidney involvement is mild including asymptomatic tubulopathy or chronic kidney disease. Severe kidney injury is less frequent, and few patients develop glomerular disease. Kidney biopsy studies then mainly include a selected group of patients with overt kidney disease.

Glomerular Disease in Sjögren's Syndrome

Epidemiology

Kaufman et al. (2008) summarized the data of 180 reported cases of renal involvement in pSS.

Of these patients, 53% had overt proteinuria, with only 9% having nephrotic syndrome. Glomerulonephritis was present in a minority of patients (n = 33; 18%). Other diagnoses included distal RTA in 108 (60%), Interstitial nephritis in 49 (27%), proximal RTA (2%), and hypokalemic periodic paralysis (11%). In this cohort, the clinical findings in patients with glomerulonephritis were hypertension, mild proteinuria, and microscopic hematuria. Glomerulonephritis typically occurred late in the course of the disease and was always preceded by manifestations of the sicca complex. Furthermore, development of glomerulonephritis was strongly predicted by cryoglobulinemia and low C4 levels. These latter factors are also predictors of lymphoma, which has an increased incidence in patients with pSS. It has been suggested that the development of cryoglobulinemia denotes the oligoclonal or monoclonal B-cell activation that can lead to both immune complex glomerulonephritis and the development of lymphoma.

In a study by Goules et al. (2013), 35 of 715 patients with pSS (4.5%) had biopsy-proven kidney disease. Of these patients, 37% had interstitial disease, 49% had glomerular disease, and 14% had both entities. When patients with interstitial disease were compared with patients with glomerular disease, glomerular disease occurred later in the disease course (3 ± 3 vs 7 ± 5 years, respectively). As expected, patients with glomerulonephritis more often presented with proteinuria and an active urine sediment. Neither the autoantibody profile nor the proportion of patients with extraglandular manifestations were different between the groups. Although the presence of mixed cryoglobulinemia was associated with glomerulonephritis, C4 levels were similar between groups, but C3 levels were more frequently low in patients with glomerulonephritis. Of note, cryoglobulinemia was present in 14/22 patients (63%) with glomerulonephritis. As reported before, lymphoma occurred more frequently in patients with glomerulonephritis (respectively, 8/22 vs 1/13). Of note, other immune complex-related manifestations (such as purpura or peripheral neuropathy) did not differ between groups.

Histopathological Findings

Glomerular disease is attributed to deposition of immune complexes, and in some cases, cryoglobulins may drive this process. Table 4 summarizes three recent studies that included 38 patients with biopsy-proven glomerular disease (Goules et al. 2013; Kidder et al. 2015; Maripuri et al. 2009). The most common histological patterns were membranoproliferative glomerulonephritis (MPGN; 45%), mesangial proliferative glomerulonephritis (MSGN; 26%), membranous nephropathy (MN; 8%), FSGS (5%), and minimal change disease (5%). Other entities such as ANCA-associated extracapillary glomerulonephritis have been reported. Immunofluorescence studies show immune complex deposition of various origin (mainly IgG and IgM) and complement (mainly C3 but also C1q). Cryoglobulins can be observed in the biopsy, but they can be absent despite presence in the blood.

Treatment and Outcome

Due to the rarity of the diseases, there are no clinical trials that evaluated treatment of glomerular disease in patients with pSS. As the disease is immune mediated, it seems rational to treat with immunosuppressive drugs. In the literature review of Kaufman et al. (2008), treatment data were reported in 32 cases of biopsy-proven renal

Table 4 Glomerular diseases in patients with Sjögren's syndrome: biopsy studies

	Maripuri et al. (2009)	Goules et al. (2013)	Kidder et al. (2015)
	N = 7	N = 22	N = 9
Membranoproliferative glomerulonephritis	2	10	5
Mesangial proliferative glomerulonephritis	–	7	–
Membranous nephropathy	1	1	1
Focal segmental glomerulosclerosis	2	2	–
Minimal change disease	1	–	1
IgA nephropathy	–	–	1
Other	–	2	1

Adapted from Maripuri et al. (2009), Goules et al. (2013), and Kidder et al. (2015)

disease (14 interstitial, 16 glomerular, 2 combined diseases). About half of patients (n = 17) were treated with steroids and cyclophosphamide, whereas the other half (n = 15) were treated with steroids only. Outcome data were available for 19 patients, with improvement reported in 16 of them. In the Goules cohort (Goules et al. 2013), 20/22 patients with glomerulonephritis were treated with different induction therapies (steroids combined with cyclophosphamide, azathioprine, or rituximab), 7 of whom also received long-term immunosuppression. Two patients did not receive any immunosuppression. The authors report that clinical response was good in the majority of patients, with some patients reaching complete remission of the disease. However, two patients progressed to end-stage renal disease despite immunosuppressive treatment and required hemodialysis.

Patients at the Mayo Clinic (Maripuri et al. 2009) were mainly treated with steroids (5/7 patients with glomerular disease), with rituximab added in one of them over the years. Two patients were not treated with steroids, one was not treated at all, and the other received azathioprine and later mycophenolate mofetil. The authors show a statistically significant trend toward improvement in estimated GFR and degree of proteinuria in all patients treated with immunosuppressives.

Outcome was worse in the Scottish patients described by Kidder et al. (2015). Seventeen out of 25 patients in the study received treatment with immunosuppressives, with the nine patients with glomerular disease received significantly more agents than the patients with interstitial disease (mean 2.5 vs 1.1 agent, p = 0.007). Although renal outcome was favorable in most cases, some patients died from treatment-related complications.

Tubulointerstitial Disease in Sjögren's Syndrome

Tubulopathies in Sjögren's Syndrome

Tubular dysfunction is observed in many patients with Sjögren's syndrome. In fact, the reported incidence of kidney involvement in Sjögren's syndrome is largely explained by the presence of such "tubulopathies." In the absence of renal insufficiency or proteinuria, a kidney biopsy is usually not performed. The tubulopathy can be the consequence of mild tubulointerstitial nephritis. Alternatively, tubular ion channel function may be disturbed by specific antibodies. Various tubulopathies have been described including distal renal tubular acidosis, proximal renal tubular acidosis, and nephrogenic diabetes insipidus (Ren et al. 2007). The clinical presentation is variable and includes no symptoms, hypokalemic paralysis, polyuria, tiredness, or kidney stone disease. In patients with mild disturbances, no specific therapy is advised. In patients with severe electrolyte disturbances, a kidney biopsy should be done to document the presence of tubulointerstitial infiltrates. Treatment should follow the guidelines for the management of tubulointerstitial nephritis.

Tubulointerstitial Nephritis in Sjögren's Syndrome

Tubulointerstitial nephritis (TIN) in Sjögren's syndrome is characterized by the same lymphocyte infiltration that is seen in the exocrine glands. This infiltrate is mainly a T-cell infiltrate with CD4/CD8 subsets, located in the interstitium around the tubules. Patients with TIN may present with the symptoms of the associated tubulopathy (see above), or with systemic complaints (low-grade fever, tiredness, malaise). There is usually mild proteinuria (<1 g/day), in the absence of hematuria. Kidney function is variable.

Kidney biopsies are usually only performed in the most severe cases, which explains the relatively low incidence of biopsy-proven TIN. Treatment with steroids is indicated in patients with renal insufficiency. There is no evidence that steroids improve outcome in patients with normal renal function, so its use in such patients is debated. We favor a trial of steroids in patients with moderate-severe tubular dysfunction and a documented cellular infiltrate, guided by the urinary excretion of low molecular weight proteins.

Clinical Practice Guidelines

We recommend performing yearly screening for renal disease in all patients with Sjögren's syndrome: serum creatinine and electrolytes, urine screen for pH, osmolarity, erythrocyturia and proteinuria. Screening for kidney involvement should be performed in patients who present with evidence of vasculitis. A kidney biopsy should be considered if renal function is impaired or decreasing, in combination with proteinuria >1 g/day, and in patients with rapidly progressive acute kidney injury, an active sediment or nephrotic syndrome.

When a glomerular disease is diagnosed, additional studies must be performed to exclude cryoglobulinemia (plasma cryoglobulins, complement C4) and lymphoma. Patients with a lymphoma should be referred to the hematologist for evaluation. If a lymphoma is ruled out, immunosuppressive therapy should be considered. In case of cryoglobulinemia, the therapy of choice is rituximab (alternatively treat with steroids and cyclophosphamide). If the glomerulonephritis is not related to cryoglobulinemia, we suggest treating according to the current guidelines of the underlying disease (e.g., use treatment schedules for either MPGN, FSGS, MN, etc.). Optimal conservative treatment, including strict blood pressure control (target <130/80 mmHg) and sodium restriction, remains important as well.

Overall, renal prognosis in Sjögren's syndrome is good, although this is based on case series data with limitations (Maripuri et al. 2009).

Rheumatoid Arthritis

Glomerular Diseases in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most prevalent rheumatic disease, characterized by the presence of antibodies (anti-CCP antibodies, rheumatoid factor). The natural history of RA has changed dramatically over the past decades, particularly after the introduction of anti-TNFα therapy. These changes in the efficacy of therapy and the type of drugs used have also changed the epidemiology of RA-associated kidney disease. In the past, proteinuria and glomerular hematuria were common findings in patients with RA (Anders and Vielhauer 2011). Proteinuria was often related to drug toxicity, whereas hematuria was associated with RA disease activity.

Epidemiology

In kidney biopsy studies, the most common findings were mesangial proliferative glomerulonephritis characterized by the deposition of IgM immune complexes, secondary (AA) amyloidosis, and membranous nephropathy. Very rarely, patients have developed a necrotizing, extracapillary glomerulonephritis characterized by immune complex deposition, which may be associated with rheumatic vasculitis. Whereas amyloidosis and mesangial proliferative glomerulonephritis are related to the disease activity of RA, membranous nephropathy was mainly related to treatment with D-penicillamine and gold. More recently, an association between membranous nephropathy and NSAIDs was suggested. With the introduction of more effective, anti-TNFα therapy, the incidence of these glomerular diseases has decreased.

In a recent study, it was demonstrated that the incidence of glomerulonephritis, as defined by the number of kidney biopsies, had decreased by more than 40% in the period 1979–1989 to 2003–2015 (Vinicki et al. 2015). The relative rarity of glomerular kidney involvement is reflected by the low number of biopsies, approximately one per year. When considering the various glomerular patterns of injury, there was a clear decrease in the number of patients with a diagnosis of AA-amyloidosis, membranous nephropathy, and extracapillary glomerulonephritis. In contrast, a diagnosis of mesangial proliferative glomerulonephritis was made relatively more often in the recent study period (Table 5).

Clinical Presentation

Not unexpectedly, in the study by Vinicki et al. (2015), there was a clear association between clinical presentation and glomerular morphology: 26/31 patients with amyloidosis and membranous

Table 5 Glomerular diseases in patients with Rheumatoid Arthritis

	1976–1989	1990–2002	2003–2015
Amyloidosis	10	6	4
Membranous nephropathy	7	3	1
Extracapillary glomerulonephritis	6	3	1
Mesangial proliferative glomerulonephritis	3	5	4

Adapted from Vinicki et al. (2015)

nephropathy presented with nephrotic syndrome, and only 9/31 had hematuria. All patients with mesangial proliferative glomerulonephritis had hematuria, most of whom mild proteinuria. Patients with extracapillary glomerulonephritis presented with acute renal failure. Of note, the IF microscopy findings in patients with extracapillary glomerulonephritis were remarkable: in 50% there were immune complexes, and in the other 50%, there were no immune complexes (pauci-immune).

Glomerular Disease Associated with Anti-TNFα Therapy

The introduction of anti-TNFα therapy has dramatically improved the prospects of patients with RA. In parallel, renal diseases associated with the older antirheumatic drugs or associated with RA disease activity have almost become extinct. However, the new agents have also been associated with the development of glomerular diseases.

In the literature, case reports and small case series have described the development of glomerular pathology during anti-TNFα therapy (Dumitrescu et al. 2015; Kaneko et al. 2010; Koya et al. 2012; Stokes et al. 2005). Anti-TNFα therapy is known to induce autoimmune diseases and a lupus-like pattern has been described with the development of antinuclear antibodies, anti-cardiolipin antibodies, and ANCAs. In parallel, patients with lupus nephritis and ANCA-associated extracapillary glomerulonephritis have been reported. Additional glomerular injury patterns have been noted such as ANCA-negative extracapillary GN, membranous nephropathy, minimal change disease, and FSGS. The association between anti-TNFα therapy and glomerular disease has been supported by the close temporal relationship between disease onset after initiating anti-TNFα therapy, disease resolution after withdrawal of therapy, and disease recurrence after drug rechallenge.

Diagnosis and Treatment

Glomerular involvement in patients with RA can be detected by the presence of urine abnormalities (hematuria and proteinuria) with or without renal dysfunction, with a kidney biopsy needed to establish a firm diagnosis. Treatment is not based on evidence from randomized trials. However, in general the following rules apply. If a drug therapy is the cause, the offending drug should be stopped. Although remissions have been described after drug withdrawal, many patients need additional immunosuppressive therapy with corticosteroids. In patients with glomerulonephritis attributed to anti-TNFα therapy additional treatment with alkylating agents or rituximab has been used. In most case reports, outcome has been good.

If the glomerular disease is associated with RA disease activity (AA-amyloidosis, RA vasculitis, mesangial proliferative glomerulonephritis), more intensified RA therapy is needed. Additional immunosuppressive therapy must be considered; the timing of which depends on the underlying pathology and clinical picture. Thus, in patients with acute kidney injury due to extracapillary glomerulonephritis, immediate or early start of methylprednisolone and cyclophosphamide is indicated, whereas in patients with membranous nephropathy, nephrotic syndrome, and normal renal function, initiation of such additional therapy can be delayed.

CKD in Rheumatoid Arthritis

Patients with RA are more likely to develop reduced kidney function. This is associated with a higher prevalence of cardiovascular disease risk factors such as age, hypertension, and other Framingham risk factors. It has been shown that persistent inflammation contributes to the higher risk of CKD in RA (Kochi et al. 2016; Hickson et al. 2014).

Clinical Practice Guidelines

In view of the increased cardiovascular risk of RA patients, we suggest that patients with RA should be evaluated for the presence of CVD risk factors, including blood pressure, eGFR, and proteinuria. In the absence of firm evidence, we suggest that these parameters should be evaluated yearly, and more frequently in patients with active disease. Of note, secondary (AA) amyloidosis may develop insidiously in patients with longstanding moderately active disease and low but measurable CRP levels. In patients with signs or symptoms of kidney disease, a kidney biopsy is often needed to document the underlying pathology and guide therapy.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) was first described in 1972 by Sharp and colleagues (Sharp et al. 1972). Although debated, most authors consider it a separate disease entity, although patients have clinical manifestations that overlap with those seen in patients with systemic lupus erythematosus (SLE), scleroderma, and polymyositis (Ortega-Hernandez and Shoenfeld 2012). Characteristic for MCTD is the presence of high serum titers of anti-U1-Ribonucleopeptide (RNP) autoantibodies. Classical features are Raynaud's syndrome, serositis, arthritis, swollen hands, and muscle weakness. MCTD is a rare disease, with an incidence of two per million/year in Caucasian populations (Gunnarson et al. 2016).

Glomerular Disease in MCTD

Although originally assumed to be rare in patients with MCTD, kidney disease has been reported in 20–30% of patients, most often with a mild presentation. Although severe renal involvement has been described as a major complication of MCTD, literature reports are limited to mainly case reports or small series. The most notable case series was a study of 30 patients with MCTD from 1986 (Kitridou et al. 1986), in which the authors identified 17 patients (56%) with renal involvement based on proteinuria. Kidney biopsy was performed in ten, leading to a diagnosis of glomerular disease in all. The authors also reviewed the literature and identified 76 additional published patients with MCTD and renal pathology. Glomerular diseases accounted for renal involvement in the majority of cases (86%). In some patients cryoglobulins were present. Membranous nephropathy (about 50% of GN cases) and mesangial proliferative glomerulonephritis were most frequently observed. Case reports of patients with MCTD and anti-MPO ANCA-positive glomerulonephritis have been described. Some patients also present with a scleroderma-like TMA (Kitaura et al. 2006). Treatment usually involves steroids, and overall response is good with 70% of patients responding. In steroid-resistant cases, additional immunosuppressive therapy may be offered, in particular in patients with severe proliferative lesions. Treatment for patients with anti-MPO antibodies or TMA should follow the guidelines for these entities.

Clinical Practice Guidelines

Since kidney involvement is frequent and even subtle CKD increases cardiovascular (and possibly renal) risk, we suggest monitoring kidney function, blood pressure, and proteinuria at yearly intervals. Hematuria should be evaluated in patients with documented abnormalities. Similar kidney biopsy recommendations apply as in patients with rheumatoid arthritis.

Box 1 Reversibility of Scleroderma Renal Crisis with Captopril

Two years after she was diagnosed with scleroderma, this 35-year old female patient presented with headaches and vomiting. Blood pressure was 240/140 mmHg. Fundi showed bilateral exudates. There were

(*continued*)

Box 1 (continued)
digital ulcers. Despite treatment with propranolol, hydralazine, methyldopa, and furosemide blood pressure remained elevated a 180/110 mmHg.

She had renal insufficiency, serum creatinine rising to approximately 180 μmol/l. Platelet count was 140×10^9/ml; the blood smear showed fragmentocytes.

10 mg of captopril lowered blood pressure to a nadir of 125/55 mmHg. The patient noted immediately warming of the fingers. Blood pressure was maintained at 140/70 mmHg with captopril at 150 mg/6 h. After 3 days fragmentocytes had disappeared, platelet count increased to 265×10^9/ml, and serum creatinine had dropped to 105 μmol/l. Blood pressure remained well controlled during follow-up with captopril as single drug.

Adapted from Lopez-Orejevo et al. (1979).

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Glomerular Disease After Kidney Transplantation

47

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Contents

Abstract

Both primary and secondary glomerular diseases that cause end-stage kidney disease in native kidneys can recur in allografts of kidney transplant recipients. Several of these recurrent glomerular diseases can lead to significant allograft failure and loss. De novo glomerular diseases can also develop in the kidney allograft. In this chapter, we review the incidence, risk factors, pathogenesis, clinical features, diagnosis, and prognosis of several of these primary

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and secondary recurrent and de novo glomerular diseases that affect the allograft. Management of these allograft diseases is also briefly reviewed.

Keywords
Recurrent glomerular diseases · De novo glomerular diseases · Posttransplantation · Kidney transplantation · Primary glomerular diseases after kidney transplantation · Secondary glomerular diseases after kidney transplantation

Introduction

Primary and secondary glomerular diseases that cause end-stage kidney disease in native kidneys can also recur in allografts of kidney transplant recipients. While minimal change disease has rarely been reported to recur in the allograft, several other primary glomerular diseases like membranous nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and IgA nephropathy tend to recur more commonly. Secondary glomerular diseases like lupus nephritis, diabetic nephropathy, and ANCA-associated vasculitis can also recur in the transplanted kidney. Several of these primary and secondary recurrent diseases can lead to significant allograft failure and loss.

De novo glomerular diseases can also develop in allograft. Several primary and secondary glomerular pathologies that are well known to cause diseases of the native kidneys can also occur for the first time in the allograft. Several of these glomerular processes can lead to poor allograft outcomes.

In this chapter, we will review the incidence, risk factors, pathogenesis, clinical features, diagnosis, and prognosis of several of these primary and secondary recurrent and de novo glomerular diseases that affect the allograft. Management of these allograft diseases will also be briefly reviewed.

Primary Glomerular Diseases Following Kidney Transplantation

Membranous Nephropathy (MN)

Recurrent MN

MN can recur in the transplanted kidney; however, the true incidence of this disease recurrence is unknown. The reported incidence ranges from as low as 10% to as high as 42%. Higher incidences are usually reported by centers that routinely perform protocol kidney transplant biopsies in absence of clinical symptoms. For example, in a study of kidney transplant patients who underwent protocol biopsies, 8 (42%) out of 19 patients were found to have recurrent MN (Dabade et al. 2008). It is unclear if deceased donor allograft recipients have a lower risk of recurrence as compared to living related transplant recipients. While some studies have made this suggestion, larger case series of patients with recurrent MN have failed to confirm this risk (Moroni et al. 2010).

Since the association between circulating anti-phospholipase A2 receptor (PLA2R) antibodies and primary MN was revealed in 2009, several reports have found the presence of these antibodies in patients in recurrent MN following kidney transplantation (Stahl et al. 2010; Blosser et al. 2012). The recurrence of MN soon following kidney transplantation suggests that circulating anti-PLA2R antibodies may have been present at the time of transplantation. In fact, several studies have suggested that the presence of circulating anti-PLA2R antibodies at or following kidney transplantation to be important risk factor for the recurrence of MN in the allograft. Patients with high anti-PLA2R antibody titers have also been associated with higher risk of MN recurrence as compared to patients with lower antibody titers (Kattah et al. 2015; Quintana et al. 2015). While the reappearance or persistence of circulating anti-PLA2R antibodies following kidney transplantation may predict a poor allograft outcome, the loss of these circulating antibodies, on the other hand, with either transplant or other immunosuppressive

medications for recurrent MN has shown to result in improved clinical outcomes (Kattah et al. 2015; Seitz-Polski et al. 2014). Hence, in patients with known history of primary MN, serial testing for circulating anti-PLA2R antibodies prior, at and following kidney transplantation may help to identify high risk individuals who may benefit from increased or additional immunosuppressive medications. Although, circulating antibodies to other glomerular antigens like thrombospondin type-1 domain-containing 7A (THSD7A) have been identified in individuals with primary MN, they have not been reported in recurrent MN.

Kidney transplant recipients who develop recurrent MN present commonly with varying degree of proteinuria. This clinical manifestation while can be seen earlier, it is more commonly seen a year to 15 months following kidney transplantation (Ponticelli and Glassock 2010). Transplant centers that perform protocol biopsies routinely tend to see patients with recurrent MN with none or lower degree of proteinuria. Proteinuria tends to increase over time, especially in patients who do not receive additional immunosuppressive therapy for recurrent MN (Dabade et al. 2008). While allograft function may not be impaired on initial presentation, it does declines with progression of underlying disease.

The diagnosis of recurrent MN can be confirmed with the performance of transplanted kidney biopsy in patients with known history of primary MN. While the indications for biopsy may vary among kidney transplant programs, it should be considered in individuals with increasing proteinuria and or declining renal function. The kidney biopsy findings are similar to those seen in patients with primary MN. Enhanced glomerular staining for PLA2R antigen has also been seen in patients with recurrent MN. As seen in patients with primary MN, the predominant IgG subclass found on transplant kidney biopsies of patients with recurrent MN is IgG4.

Management of recurrent MN depends upon the degree of proteinuria and renal failure at the time of diagnosis. Kidney transplant recipients who are diagnosed with recurrent MN but have proteinuria <1 g/day, normal or stable renal function should be primarily treated with angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) therapy (Ponticelli and Glassock 2010). BP should also be optimally controlled in this group. On the other hand, for transplant recipients with proteinuria >2 g/day and/or declining renal function, additional immunosuppressive therapy should be considered as this group is more likely to have progressive disease. Recent case series suggest the beneficial role of rituximab therapy (Sprangers et al. 2010; El-Zoghby et al. 2009). Immunosuppressive therapies other than rituximab have either not shown to be effective or not been well studied (Ponticelli and Glassock 2010). However, cytotoxic agents like cyclophosphamide may need to be considered in patients with rituximab resistance. Of note, the above approach to recurrent MN is based on studies done prior to the known association between circulating anti-PLA2R antibodies and primary MN. Therefore, management of recurrent MN should also depend upon the presence of circulating anti-PLA2R antibodies or the presence of enhanced glomerular staining for PLA2R antigen on kidney biopsy. Increased or additional immunosuppressive therapy should be considered for patients who are found to have persistent or high circulating anti-PLA2 antibodies on serial testing.

De Novo MN

De novo MN can occur in the transplanted kidney. The reported incidence ranges from as low as 1.5% to as high as 9% (Truong et al. 1989; Heidet et al. 1994). Higher incidence of de novo MN has been reported in children following kidney transplantation.

De novo MN seems to be associated with chronic and/or antibody-mediated rejection. Although the exact mechanisms for this association are unknown, patients with de novo MN also commonly have kidney biopsy findings of chronic rejection. Circulating donor-specific antibodies, a lab finding characteristic of antibody-mediated rejection have been reported to be present in patients with de novo MN (Honda et al. 2011).

In kidney transplant recipients, de novo MN has also been associated with new-onset hepatitis C virus infection, ureteral obstruction, Alport syndrome, and recurrent IgA nephropathy.

As compared to recurrent MN, de novo MN tend to occur many years after kidney transplantation. The mean times from kidney transplantation to the diagnosis of de novo MN on kidney biopsy, in two large retrospective studies were 63 and 102 months (Honda et al. 2011; Schwarz et al. 1994). Many patients are asymptomatic and present with varying degrees of proteinuria. Subnephrotic range proteinuria is seen up to one-third of the cases with de novo MN.

In addition to presence or absence of clinical history of primary MN on native kidney biopsy (if available), several laboratory and transplant biopsy findings may help to differentiate de novo MN from recurrent MN. Kidney transplant recipients with de novo MN do not usually have either circulating anti-PLAR antibodies or enhanced glomerular staining of PLA2R on kidney biopsy (Debiec et al. 2011). Also, in de novo MN, IgG1 is the predominate IgG subclass seen in immune deposits as compared to recurrent MN in which IgG4 subclass predominates on kidney biopsy. Patient with de novo MN may also have kidney biopsy features of transplant glomerulopathy (duplication of glomerular basement membrane) and chronic antibody-mediated rejection (C4d staining in peritubular capillaries). Circulating donor-specific antibodies have been reported in up to two-thirds of transplant recipients with de novo MN (Debiec et al. 2011; Honda et al. 2011). Work-up for underlying cancer and infection should be also be considered in this group of patients as MN has also been associated with malignancy and infection.

The optimal management of de novo MN in kidney transplanted recipients is unknown. Studies have suggested poor outcomes; however, it remains unclear if this is a result of de novo MN occurrence or the presence of concurrent chronic rejection (Truong et al. 1989). It also remains unclear if increasing the maintenance transplant immunosuppressive therapy or additional immunosuppressive therapy (with rituximab or cyclophosphamide) would have beneficial renal outcomes in patients with de novo MN. Such patients may be better managed in a transplant center and their treatment should be based on the current available best and safe practices.

Focal Segmental Glomerulosclerosis (FSGS)

Recurrent FSGS

FSGS can recur in the transplanted kidney. While the true rate of recurrence of primary FSGS is not well known, reports suggest an incidence of approximately 30%. However, the incidence of recurrent FSGS may be higher in the younger group of patients with primary FSGS (in the native kidney) that rapidly progress (<3 years) to end-stage kidney disease. The incidence of allograft loss from recurrent FSGS however was low at 2.6% in a large United States Renal Data System analysis of adult patients with primary FSGS (Abbott et al. 2001). The mean follow-up in this study was 3 years. The incidence of allograft loss at 10 years was relatively higher at 12.7% in an Australian and New Zealand Transplant Registry study (Briganti et al. 2002).

Several important risk factors for recurrent FSGS have been identified including younger age of onset and rapid progression of primary FSGS in native kidney, white race, and history of recurrent FSGS in previous allograft. Response to initial steroid therapy may also predict recurrence in the allograft. Interestingly, in a study of pediatric kidney transplant recipients with history of primary FSGS, patients who initially remitted with steroid therapy had a much higher risk of recurrence than patients who are steroid resistant from the onset (Ding et al. 2014). History of familial FSGS or a specific histological pattern of primary FSGS does not seem to increase the risk for recurrence of FSGS in the allograft.

The exact pathogenesis of recurrent primary FSGS is currently not known. Several studies over the years have speculated that recurrent primary FSGS results from the presence a circulating factor in the plasma. This circulating factor could be playing an important role especially in patient with recurrent FSGS that is seen soon after kidney

transplantation. This factor may potentially cause recurrent FSGS by injuring the glomerular podocyte leading to diffuse effacement of their foot processes and proteinuria. Recently there was a suggestion of an association between circulating soluble urokinase plasminogen activator receptors (suPARs) and FSGS; however, subsequent studies have not been able to confirm this relationship.

Factors that are associated with FSGS in the native kidney such as infections and drugs are unlikely to recur especially if patients are treated or the offending agent is discontinued prior to kidney transplantation. Various genetic mutations involving podocyte proteins such as podocin and TRPC6 have also been associated with recurrent FSGS in the transplanted kidney (Schachter et al. 2010).

Kidney transplant recipients who develop recurrent primary FSGS present with varying degree of proteinuria. This clinical manifestation can be seen as early as 1–2 weeks following transplantation, especially in children. Acute onset nephrotic range proteinuria is also a common manifestation of this recurrent disease. Patient may present with other clinical (edema, fluid overload) and laboratory (hypoalbuminemia, hyperlipidemia) findings of nephrotic syndrome. Acute kidney injury (AKI) from acute rejection has also been commonly found in patients who develop recurrent FSGS soon after transplantation. Allograft loss is also a common occurrence in patients who develop recurrent FSGS. In one case series, over half (56%) of patients with recurrent FSGS developed end-stage allograft failure at an average of 2 years from the time of diagnosis (Artero et al. 1992).

Kidney transplant recipients with known history of primary FSGS should undergo screening for proteinuria soon following kidney transplantation. Serial spot urine examination for protein-to-creatinine ratio should be instituted beginning the first posttransplantation day and continued to the first year after transplantation. While concentration of urinary apolipoprotein A1 has been found to be increased in patients with recurrent primary FSGS, its utility as useful biomarker in clinical practice needs to be further studied (Lopez-Hellin et al. 2013).

The diagnosis of recurrent FSGS should be confirmed with the performance of transplanted kidney biopsy. While the indications for biopsy may vary among kidney transplant programs, it should be considered in recipients with significant proteinuria (>1 g/day) and or worsening renal function. Of note, patients who present with recurrent FSGS soon after kidney transplantation, epithelial foot process effacement may be the earliest and only abnormality seen on kidney biopsy. However, it is important to see the characteristic light microscopy findings of FSGS on kidney biopsy before a definite diagnosis of recurrent FSGS is made. Once an allograft biopsy diagnosis of FSGS is confirmed, it is important to rule out other potential causes of FSGS, namely medication (sirolimus) or viral infections. Testing for viral infections including hepatitis C, BK polyomavirus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, and HIV should be considered.

Patients with history of primary FSGS who rapidly progress to ESRD (in their native kidneys) are considered as high risk for recurrence of the disease following transplantation. While several prophylactic therapies including plasmapheresis, rituximab, and other induction immunosuppressive agents have been studied, none of these approaches have definitely shown to prevent recurrence of primary FSGS in the allograft.

Optimal therapy for recurrent primary FSGS in the allograft is currently unknown. However, plasmapheresis and treatment with immunosuppressive medications need to be considered in patients who develop recurrent primary FSGS in the allograft especially those who present with rapid onset significant proteinuria and within a year of kidney transplantation. Plasmapheresis is usually performed in this selected group of recurrent FSGS patients for a total of 2 weeks. Plasmapheresis is thought to decrease the amount of circulating factor (as discussed previously) leading to reduction in proteinuria and with complete remission in some cases. Patients receiving plasmapheresis soon (within a week) after the onset of proteinuria are more likely to remit as compared to patients who have irreversible pathological changes (like hyalinosis) on kidney biopsy (Cheong et al. 2000). Prolonged benefits of plasmapheresis in combination with immunosuppressive agents such

as cyclophosphamide, rituximab, high dose corticosteroids with intravenous (followed by oral) cyclosporine have been reported in cases with recurrent primary FSGS. Agents that block B7-1 (CD80) pathway like abatacept and belatacept have also been studied in patients with recurrent FSGS who had failed to respond to plasmapheresis and/or rituximab. While an initial small study suggested the benefit of B7-1 blocker in recurrent FSGS, a subsequent larger case series failed to show any response to this novel approach (Delville et al. 2016). Treatment with ACE-I or ARB should also be considered in all patients with recurrent FSGS as these antiproteinuric and antifibrotic agents have been well known to slow the progression of proteinuric native kidney diseases.

The approach to patients who present with recurrent FSGS after a year of kidney transplantation depends upon the degree of proteinuria. For patients who present with nephrotic range proteinuria or nephrotic syndrome, additional immunosuppressive therapy should be considered. Increasing doses of cyclosporine and prolonged daily high dose corticosteroid therapy have also been tried in patients with recurrent FSGS. For patients who fail to respond to these approaches, a trial of plasmapheresis should be strongly considered. Patients who present with nonnephrotic range proteinuria should be closely monitored on standard transplant immunosuppressive medications. Limited reports of improved proteinuria and stabilization of renal function with galactose use in cases of recurrent FSGS have also been described.

Patients with known history of allograft loss from recurrent FSGS have a very high risk of recurrence in subsequent kidney transplants. Optimal approach to lower the risk of recurrent FSGS in this group is unknown; however, limited case studies suggest the potential role of prophylactic plasmapheresis and rituximab therapy.

De Novo FSGS

De novo (noncollapsing or collapsing) FSGS can occur in the transplanted kidney of patients who did not have FSGS in their native kidneys. De novo FSGS could be primary (in absence of a known cause) or could be secondary to a known infection, medication, or condition that is associated with FSGS in native kidneys. Several viral infections are more commonly seen in immunocompromised individuals including kidney transplant recipients. BK polyomavirus, cytomegalovirus, Epstein-Barr virus, and parvovirus B19 have been associated with de novo (noncollapsing or collapsing) FSGS in the allograft. Infection with HIV can also cause FSGS in the transplanted kidney. While certain medications (like pamidronate, interferons, anabolic steroids) have been associated with (noncollapsing or collapsing) FSGS in the native kidneys, they can also cause de novo (noncollapsing or collapsing) FSGS when used in kidney transplant recipients. Of interest in kidney transplant recipients, mammalian target of rapamycin (mTOR) inhibitors (sirolimus) have been associated with (noncollapsing or collapsing) FSGS. FSGS can also be seen with chronic calcineurin inhibitor (CNI) use, chronic allograft rejection, or from compensatory glomerular hyperfiltration related injury.

As compared to recurrent primary FSGS, patients with de novo FSGS present with varying degree of proteinuria (including nephrotic syndrome), hypertension, and progressive loss of kidney allograft function usually several months or years following kidney transplantation. Patients with collapsing FSGS however can present with rapid onset nephrotic syndrome and worsening allograft failure. Prognosis of de novo primary (noncollapsing) FSGS is poor, and patients who are untreated often progress to end-stage kidney disease. Similarly, renal prognosis of kidney transplant recipients with de novo collapsing FSGS remains very poor (Swaminathan et al. 2006). The diagnosis of de novo (noncollapsing or collapsing) FSGS should be confirmed with the performance of transplanted kidney biopsy. Patients with CNI nephrotoxicity also have additional dominant chronic lesions on kidney biopsy including interstitial nephritis, striped interstitial fibrosis, tubular atrophy, and focal or global glomerulosclerosis. Subsequently, it would be important to rule out other potential causes of (noncollapsing or collapsing) FSGS, namely medication (as mentioned earlier) or viral infections. Testing for viral infections including hepatitis C, BK,

cytomegalovirus, Epstein-Barr virus, parvovirus B19 and HIV should be considered.

Medications that have been associated with FSGS should be discontinued and viral infection (as mentioned above) if detected should be treated. However, the optimal management of de novo primary FSGS in kidney transplanted recipients is unknown. The approach should be similar to patients who present with recurrent FSGS.

IgA Nephropathy (IgAN)

Recurrent IgAN

IgAN causing end-stage renal disease in native kidneys can also recur in the allograft. The rate of recurrence of IgAN has been reported to be between 12% and 61% (mean 33%); however, not all histologic recurrences on kidney biopsy are clinically relevant (Ponticelli et al. 2004). This incidence increases with time following kidney transplantation (Andresdottir et al. 2005; Choy et al. 2006).

Several risk factors for this recurrence have been identified. Recurrent IgAN occurs more frequently in younger transplant recipients and in those who had rapidly progressive IgAN in their native kidneys (Ponticelli et al. 2001; Chailimpamontree et al. 2009). Whether the risk for recurrent IgAN is higher in recipients with living related kidney transplant as compared to those with living unrelated transplant remains unclear. While some studies have found an increased risk of recurrence in patients with living related kidney transplants (Han et al. 2010; McDonald and Russ 2006), several other retrospective studies have not seen this association (Ponticelli et al. 2004; Ortiz et al. 2012). Recipients with zero-HLA mismatched living related kidney transplants or those with HLA-B35, HLA-DR4, HLA-B8, and HLA-D3 alleles (Andresdottir et al. 2009) or interleukin-10 polymorphisms (Bantis et al. 2008; Coppo et al. 2007) have increased risk of IgAN recurrence. Pretransplant IgA concentration may also play a role in recurrence, as high serum IgA levels in recipients and presence of latent IgA deposits in the donor kidney have been associated with recurrent disease (Berger 1988; Wang et al. 2001). Higher risk of recurrence has also been associated with steroid free immunosuppressive therapy following transplantation (Sutherland et al. 2009; Von Visger et al. 2014).

The exact mechanism of recurrent IgAN is not well understood. The major components that may play a role in development of recurrent disease include presence of circulating galactose-deficient IgA1 and IgA-IgG immune complexes and lack of circulating complexes of IgA-soluble CD-89 (Berthelot et al. 2015). Recipients of donor kidneys with latent IgA deposits have a greater chance of recurrent IgAN. It has been suggested that the circulating autoantibody to exposed *N*-acetylgalactosamine residues on galactose-deficient IgA1 in recipients can react with the implanted IgA deposits from the donor kidney, causing exposure of neo-*N*-acetylgalactosamine epitopes (as they are also deficient in galactose residues), further leading to recurrence of IgAN (Glassock 2009).

Patients with recurrent IgAN usually present with isolated microscopic hematuria, new onset proteinuria, increasing degree of proteinuria, or worsening of renal function (Moroni et al. 2013). Patients may also present with combination of these above lab findings. Transplant recipients can also present with rapidly progressive disease especially when associated with crescentic IgAN in native kidneys (Kowalewska et al. 2005; Soler et al. 2005). Immunopathologic recurrence of IgAN is more common and occurs earlier after transplantation, as compared to clinical recurrence of IgAN that manifests rarely within the first 5 years (Ortiz et al. 2012). However, patients who had rapid progression to end-stage disease in their native kidneys tend to have early onset of recurrence. The overall graft survival for transplant recipients with IgAN in native kidneys is better as compared to allograft recipients with end-stage kidney disease from other causes (Soler et al. 2005; Samuel et al. 2011). However, recurrent IgAN can lead to allograft loss, especially in those who develop crescentic GN in the allograft.

Biopsy of the transplant kidney is required to confirm diagnosis of recurrent IgAN. Patients who present with a rise in serum creatinine, or persistent proteinuria >0.5 g/day despite ACE-I/

ARB therapy, or persistent hematuria despite negative urologic work-up should undergo kidney biopsy. The histological pattern on kidney biopsy is similar to IgAN in native kidneys.

Currently, there is no specific therapy for the treatment of recurrent IgAN. All patients with recurrent IgAN should be treated with ACE-I or ARB therapy for their anti-proteinuric and anti-hypertensive effects (Oka et al. 2000). Patients with crescentic IgAN should undergo trial of pulse dose glucocorticoids, cyclophosphamide, and plasmapheresis (Ponticelli and Glassock 2010). High dose glucocorticoid therapy should be first initiated. Cyclophosphamide can be used for patients who continue to have rapid increase in serum creatinine despite high dose glucocorticoid therapy. The antimetabolite agents (mycophenolate or azathioprine) should be held during treatment with cyclophosphamide. Besides medical therapy, some data also suggests that patients with recurrent IgAN may have favorable outcomes with use of fish oil and by undergoing tonsillectomy (Hotta et al. 2013; Ushigome et al. 2009).

De Novo IgAN

Latent mesangial IgA deposition (IgAD) (defined as deposition of IgA in the renal mesangium without any evidence of clinical symptoms or urinary findings) has been seen in both recipients and donors of kidney transplants. De novo IgAD is observed frequently in the allograft of recipients whose native kidney disease was not IgAN. While many cases of de novo IgAN have been reported, no studies till date have estimated the incidence of occurrence of de novo IgAN.

The definite mechanism for development of de novo IgAD or IgAN following transplantation is currently not well established. However, donor kidneys with latent IgAD or IgAN have thought to be the major risk factor for development of this de novo disease in the allograft. This suggests transmission of disease from donor to recipient as opposed to occurrence of de novo disease. The reduced ability of the recipient to clear mesangial IgA deposits (received from the donor kidney) has also been thought to play a role in pathogenesis of de novo IgAN (Ji et al. 2004).

De novo IgAD has been mostly observed at 1 year following transplantation (Sofue et al. 2015). The clinical course of de novo IgAN is variable and can range from asymptomatic IgAD to rapidly progressive crescentic GN (Kowalewska et al. 2005; Tang et al. 2008). De novo IgAN can be detected on protocol allograft biopsies, even when clinical manifestations of the disease are not yet apparent. Patients can present with microscopic hematuria, proteinuria, hypertension, or decline in renal function. Patients with crescentic GN have a more aggressive rapidly progressive disease course.

Posttransplant asymptomatic IgAD has not been associated with reduced allograft function or graft loss (Sofue et al. 2013). In contrast, patients who develop decline in allograft function due to de novo disease can progress to allograft loss. The outcomes of the disease also depend on its severity. The course of de novo IgAN may be relatively favorable in patients with mild mesangial cell proliferation. However, patients with crescentic GN have poor prognosis.

Allograft biopsy is required for diagnosing de novo IgAN. Histological findings are similar to IgAN seen in native kidneys. In addition, crescents may also be seen in patients with rapidly progressive disease. Protocol allograft biopsies may be helpful in detection of de novo IgAN before onset of clinical symptoms, however are not recommended as a routine procedure in patients who undergo kidney transplantation.

Treatment for patients with mild to moderate de novo IgAN is nonspecific and is targeted at lowering proteinuria and BP with use of ACE-I and ARB agents. Patients with rapidly progressive course should undergo trial of pulse steroids with cyclophosphamide and plasmapheresis.

Membranoproliferative Glomerulonephritis (MPGN)

Recurrent MPGN

MPGN is classified into two subtypes based on type of deposits seen on immunofluorescence (IF). In immune complex–mediated MPGN both immunoglobulins (Ig) and complement factors are

deposited in the kidney, while in C3 glomerulopathy only complement deposits are seen. Immune complex–mediated MPGN can be associated with either polyclonal or monoclonal deposits. C3 glomerulopathy is further divided into two subtypes that include dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), based on type of deposits seen on electron microscopy (EM). Both immune complex–mediated MPGN and complement-mediated MPGN can recur. Recurrence of MPGN generally occurs due to secondary causes including chronic infections, autoimmune diseases, monoclonal gammopathies, and thrombotic microangiopathy (TMA). When a secondary cause of MPGN is not identified, it is defined as idiopathic MPGN.

Recent data suggests that 30–90% of kidney transplant recipients can develop recurrence of MPGN following transplantation. However, this reported rate of recurrence may be an overestimation of true rate of recurrence as both immune complex–mediated idiopathic MPGN and chronic transplant rejection have similar histologic findings on kidney biopsy (Cheigh et al. 1980). The rate of recurrence is variable for different subtypes of MPGN. The recurrence rate varies between 30% and 35% in transplant recipients with polyclonal immune complex–mediated MPGN and is around 66% in those with monoclonal immune complex–mediated MPGN. C3GN recurs at higher rates, with 70% recurrence rate seen in patients with C3GN and 80–90% recurrence rate in those with DDD (Cosio and Cattran 2017).

Recipients of living related renal transplant (LRRT) have shown to have higher risk of recurrence of MPGN. Recurrent MPGN is also common in transplant recipients who lost their initial allograft due to recurrent disease (Andresdottir et al. 1997). There has also been evidence suggesting the increased rate of recurrence in recipients with persistent or recurrent low complement levels after kidney transplantation (Lorenz et al. 2010).

MPGN with polyclonal Ig deposits involves activation of classic complement pathway, as suggested by presence of glomerular C4d deposits on kidney biopsy (Sethi et al. 2015). Monoclonal Ig deposits associated MPGN usually has glomerular deposits composed on IgG3-k, however can also have presence of other paraproteins. C3GN and DDD are caused due to abnormalities in regulation of alternate complement pathway, leading to overproduction of activated C3 and activation of terminal pathway (C5–C9). There can be various causes of this dysregulation, including presence of autoantibodies against C3 convertases (C3 and C4 nephritic factors) or against factor H. Gene polymorphisms and genetic mutations related to complement regulatory proteins, mainly factor H have also been identified (Sethi et al. 2012).

Patients with recurrent MPGN usually present with variable degree of proteinuria and/or hematuria. Hypertension and worsening of renal function may also be other presenting signs of recurrent disease. Proteinuria is usually >1 g per day (Andresdottir et al. 1997). Low levels of complement factors may be observed prior to development of clinical signs and symptoms of recurrent disease in the kidney. The time of onset of recurrent disease varies with the type of MPGN. MPGN with polyclonal Ig deposits and DDD usually present late and progress slowly (Appel et al. 2005; Lorenz et al. 2010), as compared to MPGN with monoclonal Ig deposits and C3GN that generally present within 1–2 years after transplantation, and have more aggressive course with higher risk of graft failure (Lorenz et al. 2010; Nasr et al. 2011; Zand et al. 2014).

The prognosis depends on degree of proteinuria, renal function, presence or absence of hypertension, and crescents or tubulointerstitial disease on biopsy. The risk of progression increases with the increase in severity of tubulointerstitial disease. Graft loss with recurrent MPGN is common in kidney transplant recipients. The rate of allograft loss differs with type of recurrent MPGN. Patients with recurrent MPGN with polyclonal Ig deposits have a 10% rate of graft failure. The rate of graft failure is higher (~50%) in patients with recurrent MPGN associated with monoclonal Ig deposits. Recurrence of C3GN leads to graft failure in 50% transplant recipients, while the reported rate of graft failure is 25% in patients with recurrent DDD (Cosio and Cattran 2017).

The diagnosis of recurrent MPGN should be confirmed with the performance of transplanted

kidney biopsy. The biopsy should be analyzed by light microscopy, IF, and EM, to differentiate various types of MPGN. Secondary causes of MPGN including chronic infections, autoimmune diseases like lupus, and monoclonal gammopathies should be excluded in all patients who present with recurrent MPGN. Anti-donor specific antibodies (DSAs) should be measured to exclude transplant glomerulopathy. Patients with C3GN should undergo evaluation of alternative complement pathway to detect any abnormalities in its regulation.

Recurrent idiopathic MPGN may have similar findings as chronic transplant rejection on LM. IF shows both complement and Ig deposits in immune complex–mediated MPGN. Ig deposits are absent in C3GN. Glomerular C4d deposits may be seen in patients with polyclonal Ig associated MPGN. Monoclonal Ig deposits associated MPGN usually has glomerular deposits composed on IgG3-k, however can also have presence of other light chains. EM is required to diagnose DDD. Presence of abnormal intramembranous electron-dense material is pathognomonic for DDD. EM also helps in distinguishing immune-mediated MPGN from chronic allograft rejection as electron dense deposits are absent in patients with allograft rejection (Andresdottir et al. 1998).

The treatment of recurrent MPGN depends on the type and severity of MPGN. For secondary MPGN, the treatment should be directed at the underlying cause. Recurrent MPGN can be classified as mild, moderate, and severe based on degree of proteinuria and renal function. Mild disease would refer to the disease with proteinuria less than 3.5 g/day and stable renal function. The disease is considered to be of moderate severity if proteinuria is greater than 3.5 g per day with stable or slowly worsening renal function. The disease is severe when there is a rapid decline in renal function or when kidney biopsy shows crescentic glomerulonephritis. The aim for therapy is to decrease proteinuria to less than 1 g/day. Patients with mild recurrent disease do not require immunosuppressive therapy and should be treated with ACE-I or ARB therapy for their anti-proteinuric effect. Treatment of moderate immune complex–mediated MPGN is directed at suppression of antibody production. This requires enhancement of immunosuppressive therapy in addition to treatment with ACE inhibitor or ARB therapy. Dose of oral corticosteroid therapy should be increased. If no response is seen by 4 months, the dose of antimetabolite (mycophenolate or azathioprine) therapy (if the patient is taking for prevention of allograft rejection) should be increased. Patients that fail to respond to the increased dose of antimetabolite therapy could be initiated on cyclophosphamide that can be used up to a period of 4 months (Lien and Scott 2000). Rituximab, an anti-CD20 antibody has been reported to be effective for treatment of MPGN with monoclonal Ig deposits (Lorenz et al. 2010; Guiard et al. 2011). Treatment for recurrent moderate C3GN is targeted at the underlying abnormality of complement pathway. Rare case reports suggest that eculizumab may be an effective treatment for patients with recurrent C3GN (Bomback et al. 2012; Le Quintrec et al. 2015). Severe recurrent disease either immune complex–mediated MPGN or C3GN requires combination therapy with immunosuppressive agents and plasmapheresis. Patients with moderate or severe disease, who have known serum factor deficiency, can receive periodic fresh frozen plasma (FFP) infusions (Smith et al. 2007). The antirejection immunosuppressive regimen can be continued among patients receiving rituximab, eculizumab, plasmapheresis, or FFP infusions. However, among patients receiving cyclophosphamide, the antimetabolite agent that the patient was already taking for prevention of rejection should be held. The antimetabolite agent can be resumed after therapy with cyclophosphamide is completed.

De Novo MPGN

De novo MPGN can develop in the transplanted kidney. Usually, de novo immune complex–mediated MPGN occurs secondary to development of systemic diseases including infections, autoimmune diseases, monoclonal gammopathies, and TMA (Sethi and Fervenza 2012). De novo C3GN develops less frequently in the kidney allograft.

The occurrence of de novo immune-mediated MPGN and C3GN is not as frequent as recurrence of the disease in the allograft. The true incidence

of de novo MPGN is unknown. However, immune complex–mediated de novo MPGN occurs more commonly as compared to C3GN (Boyer et al. 2008). Most of the de novo immune complex–mediated MPGN cases have been associated with HCV infection.

The exact pathogenesis for development of de novo MPGN remains unknown. However, it is thought that glomerular deposits of HCV and anti-HCV antibodies may be responsible for development of de novo immune complex–mediated disease in HCV positive patients. Circulating cryoglobulins have also been suggested to play a role in pathogenesis; however, their role remains controversial as the detected concentration of cryoglobulins is low in patients with transplanted kidneys in contrast to those who develop HCV-related cryoglobulinemic MPGN in native kidneys. De novo cryoglobuminemic MPGN has also been seen in kidney transplant recipients with Hepatitis E viral infection (Del Bello et al. 2015). A case of de novo MPGN in association with Hepatitis G virus infection has also been described (Berthoux et al. 1999). Persistent viral replication inside the kidney with local production of immune complexes and/or activation of the different cytokine cascades leading to inflammation may also be responsible for development of de novo immune complex–mediated MPGN. Development of de novo C3GN may be attributed to abnormalities of regulatory factors of alternate complement pathway.

Most patients present with proteinuria of >1 g/day. Patients can also present with nephrotic syndrome. Clinical features of HUS can also be seen in patients who present with de novo immune complex–mediated MPGN in association with TMA. Patients who have non-nephrotic range proteinuria and normal renal function at the time of presentation have a slower rate of progression, as compared to those who present with nephrotic range proteinuria and abnormal renal function.

Biopsy of the allograft is required to make the definitive diagnosis. The biopsy findings in de novo disease are similar to those of recurrent MPGN. All patients should undergo lab testing for evaluation of a secondary cause of MPGN, including testing for viral, fungal, and parasitic infections. Blood cultures, echocardiography, and CT scan of abdomen and pelvis should be obtained to look for foci of infection including endocarditis. Screening for autoimmune diseases and monoclonal gammopathies should also be performed.

The treatment of de novo MPGN is same as that for recurrent MPGN. Therapy for secondary MPGN should be directed at the underlying cause. Steroid therapy and enhancement of immunosuppression is recommended for treatment of de novo idiopathic MPGN.

Minimal Change Disease (MCD)

Recurrent MCD

Recurrent MCD is an extremely rare entity. A case of recurrent MCD seen within 2 weeks of living related kidney transplant has been reported. The diagnosis was confirmed by histological evidence of MCD in allograft nephrectomy sample. There was no evidence of FSGS (Jan et al. 2003). This patient clinically presented with nephrotic syndrome, and renal failure. Optimal treatment of this rare recurrent disease is unknown. The authors in the above case report propose treatment with corticosteroid, high dose cyclosporine, and early plasma exchange.

De Novo MCD

De novo MCD is an uncommon glomerular disease seen after kidney transplantation. The true incidence and prevalence of de novo MCD is unknown. Most of the knowledge about this entity is from case reports or series. Living related donation has been suggested as a risk factor for this disease (Zafarmand et al. 2002). In a case series, most developed nephrotic range proteinuria shortly (within 4 months) after kidney transplantation (Zafarmand et al. 2002). Clinically, patients present with nephrotic syndrome and varying degree of renal impairment, although most cases reported in the literature had normal renal function (Madhan and Temple-Camp 2009; Markowitz et al. 1998; Mochizuki et al. 2012; Zafarmand et al. 2002). It has been suggested that the diagnosis of de novo MCD

should be made with great caution especially in the immediate posttransplant period as there could be many other common causes of nephrotic range proteinuria that spare the glomeruli. Also, FSGS, which has a high recurrence rate, should be high on the differential. Transplant biopsy specimens in such cases should be evaluated by light microscopy, immunofluorescence, and electron microscopy (Markowitz et al. 1998). Clinical course should be also characterized by spontaneous remission or response to increased dose of steroids or other immunosuppressive medications (Markowitz et al. 1998).

Secondary Glomerular Diseases Following Kidney Transplantation

Diabetic Nephropathy (DN)

Recurrent or de novo DN can occur in the transplanted kidney. The occurrence of de novo DN seems to be similar to that of recurrent DN. A retrospective study analyzing allograft biopsies showed histologic recurrence of DN in nearly 40% of patients with pretransplantation diabetes mellitus. The mean time of development of recurrent DN in the allograft was 6.7 years (Bhalla et al. 2003). Similarly, the mean time to development of de novo DN in the patients with new-onset diabetes mellitus after transplantation (NODAT) in the same study was 5.9 years. Recurrent DN has also been reported in type 1 diabetic patients who received both kidney and pancreas transplantation simultaneously.

The occurrence of NODAT increases the risk for development of de novo DN. In addition to traditional risk factors for the development of diabetes mellitus, several immunosuppressive medications used to prevent rejection in kidney transplant recipients are diabetogenic. Glucocorticoids, calcineurin inhibitors (cyclosporine and tacrolimus), and mTOR inhibitors (like sirolimus) are well-known diabetogenic medications that are commonly used in various combinations in kidney transplant recipients.

Clinically, presence of microalbuminuria may suggest the development of histological DN in the allograft. Later in the course, overt nephropathy, nephrotic syndrome, and progressive renal failure are seen. Diagnosis of recurrent and de novo DN can be confirmed by performance of kidney biopsy.

As compared to nondiabetic kidney transplant recipients, studies suggest similar kidney allograft survival rates in recipients who have pretransplantation diabetes (Boucek et al. 2002; Rømming Sørensen et al. 2006). Patient survival rates up to 5 years after kidney transplantation have also shown to be similar between diabetic and nondiabetic recipients. However, longer term (10 years) patient survival rates have shown to be poorer in recipients with pretransplantation diabetes (Rømming Sørensen et al. 2006). The development of NODAT may worsen allograft and patient prognosis. In a single center prospective study, patients who developed NODAT had significantly worse serum creatinine and 12-year allograft survival than nondiabetic controls that had concurrently received kidney transplants (Miles et al. 1998).

Preventing the possible development of NODAT should be considered in all transplant recipients. In addition to dietary restrictions, physical activity and weight loss in the overweight and obese kidney transplant recipients, reduction in doses of immunosuppressive agents that are diabetogenic should be considered. In patients who develop recurrent and de novo DN, treatment approaches are similar to patients who develop DN in their native kidneys. Addition of ACE-I or ARB should also be considered in patients who develop microalbuminuria or overt proteinuria.

Lupus Nephritis (LN)

Recurrent LN

Recurrence of lupus nephritis (LN) remains a concern in kidney transplant recipients with known history of ESRD from LN. However, the reported rate of recurrence of LN has been variable, ranging from 0–54%. It is thought that the studies that have reported a lower recurrence rate may have actually underestimated the true

incidence due to high rate of subclinical recurrence of the disease (Goral et al. 2003). Transplant centers that routinely perform protocol allograft biopsies report a higher recurrence rates (Nyberg et al. 1992; Norby et al. 2010). Other factors that may account for this wide variation in the reported rate of recurrence include the differences in patient characteristics and length of follow-up. The time of onset for recurrent disease after kidney transplant is also variable, and can range from days to years after transplantation, with the median time to recurrence being reported as 4.3 years post transplantation. While recurrence of LN has been reported as early as 6 days following kidney transplantation, very late recurrence, up to 16 years has also been observed (Goral et al. 2003; Contreras et al. 2010).

A number of factors increase the risk of development of recurrent LN including young, female kidney transplant recipients with African-American and non-Hispanic ancestry (Contreas et al. 2010). Recipients with antiphospholipid (aPL) autoantibodies and lupus anticoagulant have also a higher risk of recurrence (Moroni et al. 2005). Living donor kidneys are also associated with higher recurrence rate (Norby et al. 2010). Whether the presence of low complement levels plays a role in increasing the risk of recurrent LN remains unclear.

The pathogenesis of recurrent LN is generally similar to that of the original disease; however, transplant recipients may have either milder or more severe histologic lesions as compared to the original disease.

Patients may have subclinical recurrence of the disease or can present with clinical features including new onset or worsening proteinuria, glomerular hematuria and/or decline in allograft function. Patients may also have extrarenal manifestations of lupus like skin rash or arthralgia at the time of presentation.

While some earlier studies reported greater risk of allograft failure in patients who developed recurrent disease, several recent studies suggest otherwise (Burgos et al. 2009; Contreras et al. 2010). Only 7% of patients with recurrent LN developed graft failure on an analysis of the United Network for Organ Sharing (UNOS) data (Contreras et al. 2010). Rejection or chronic allograft nephropathy were the main causes of graft failure in transplant patients with LN rather than recurrent disease (Moroni et al. 2005; Meehan et al. 2008; Norby et al. 2010). African-American inheritance is an independent factor associated with poor outcomes (Burgos et al. 2009). Patients with aPL antibodies have higher risk of thrombotic complications (Vaidya et al. 2004).

Diagnosis of recurrent LN is made by biopsy of the transplant kidney. Measurement of serologic markers including complement levels and anti-double stranded DNA antibody titers are not helpful in establishing the diagnosis. Most of the reported data suggests that recipients who underwent elective protocol biopsy of the allograft had mesangial lesions or atypical pauci-immune proliferative GN (Norby et al. 2010). In contrast, recipients who presented with clinical features of recurrent LN mostly had diffuse proliferative GN on biopsy (Burgos et al. 2009). Patients should also undergo evaluation for other causes of decline in renal function that includes acute rejection, chronic allograft nephropathy, and calcineurin inhibitor toxicity.

Most kidney transplant recipients with recurrent LN do not require an enhancement in their immunosuppressive regimen. Patients with significant proteinuria should be treated with ACE-I or ARB therapy. Immunosuppressive therapy should be enhanced for patients who present with severe lupus flare with life-threatening extrarenal complications or rapid decline in renal function associated with pathologic presence of crescentic GN or Class III/IV LN (Weening et al. 2004; Ponticelli et al. 2011). This includes use of pulse steroid therapy, along with either increase in dose of mycophenolate or initiation of cyclophosphamide. Rituximab is an additional treatment option for patients whose disease is resistant to treatment with mycophenolate and cyclophosphamide. Presence of aPL antibodies increases the risk of thrombosis and early graft failure (Wagenknecht et al. 2000). Kidney transplant candidates with LN should be screened for aPL antibodies prior to transplant as this can help to determine the need for anticoagulant agents in these patients.

ANCA-Associated Vasculitis (AAV)

Recurrent AAV

Recurrence of AAV may develop within few to several years following kidney transplantation. In an older study of 127 kidney transplant recipients, 17% developed recurrent ANCA-associated vasculitis (AAV) with an average time of 31 months after transplantation (Nachman et al. 1999). Renal involvement occurred in 12 of 22 (55%) patients with the recurrent AAV. Four of the 12 patients with renal vasculitis had graft loss. In a more recent single center case series of 35 patients, recurrence of AAV occurred rarely (9%). The three patients who developed recurrent AAV presented more than 1.5 years after transplantation and did not have renal involvement (Gera et al. 2007). Several factors including ANCA pattern or titers at the time of transplant, duration of original disease, duration of dialysis, treatment with cyclosporine, and source of donor do not seem to influence the risk of recurrence (Nachman et al. 1999; Gera et al. 2007; Elmedhem et al. 2003; Moroni et al. 2007). In addition, these clinical parameters are not useful in predicting the risk of recurrence (Gera et al. 2007; Moroni et al. 2007). Nachman et al. reported no difference in the rate of recurrence between patients with Wegener's granulomatosis, microscopic polyangitis, or necrotizing crescentic GN alone (Nachman et al. 1999). Little et al. reported that presence of circulating ANCA at the time of transplantation was significantly associated with vascular lesions, but not with graft loss (Little et al. 2009). These authors also suggest waiting for one full year after complete remission of vasculitis before proceeding with kidney transplantation.

Most of these recurrences present with microscopic hematuria, proteinuria, and deteriorating graft function. Histologically, there is presence of focal or diffuse pauci-immune necrotizing GN.

Most studies have reported similar patient and graft survival in recipients with AAV and general transplant population (Moroni et al. 2007; Geetha et al. 2011). Briganti et al. reported that graft loss directly related to relapse of AAV occurred in 7.7% of patients at 10 years (Briganti et al. 2002).

Management of recurrence AAV is quite similar to treatment of AAV involving native kidneys. Therapeutic options include cyclophosphamide with corticosteroids. Plasma exchange therapy is an option in selected patients based on the severity of relapse. Rituximab has been reported for treatment of recurrence with favorable outcome (Geetha et al. 2007; Murakami et al. 2013).

De Novo AAV

De novo AAV can rarely occur in the transplanted kidney. Rare case reports of de novo AAV have been reported in the literature. Patients usually present after many (>10) years following kidney transplantation (Asif et al. 2000; Tabata et al. 2009). Clinical features include hematuria, proteinuria, and rapid deterioration in allograft function. Treatment should be similar to AAV involving the native kidneys.

Anti-GBM Antibody Disease

De Novo Anti-GBM Antibody Disease in Alport Syndrome

Alport syndrome, a rare inherited kidney disease, is caused by mutations in the type IV collagen genes leading to structural defects in the GBM and consequent proteinuria and progressive renal failure. Patients with Alport syndrome who undergo kidney transplantation can develop de novo anti-GBM antibody disease. These antibodies are produced by the presence of antigenic epitopes in the GBM of the allograft that are lacking in the native kidneys. While kidney transplant recipients with Alport syndrome can develop transient linear IgG deposits along their GBM without the presence of circulating anti-GBM antibodies, a small number (3–12%) of patients develop anti-GBM antibody disease (Byrne et al. 2002; Rutgers et al. 2000). Patients mainly with X-lined (juvenile type) Alport syndrome and mutation of COL4A5 genes develop the disease.

Patients with this disease may present either soon after kidney transplantation or within a year of kidney transplantation. Kidney transplant recipients who develop de novo anti-GBM disease present clinically with rapidly progressive

glomerulonephritis. Diagnosis is confirmed by the presence of circulating anti-GBM antibodies and the characteristic kidney biopsy findings (crescentic GN on light microscopy and strongly positive linear IgG staining of GBM on immunofluorescence) of anti-GBM antibody disease. Of note, anti-GBM antibodies in kidney transplant recipients with Alport syndrome are directed against different epitopes on the GBM than that seen with anti-GBM antibody disease in native kidneys; hence, the routine assays for anti-GBM antibodies may be negative.

The prognosis of Alport patients who develop de novo anti-GBM antibody disease is poor. While the optimal therapy for de novo anti-GBM antibody disease is unknown, the approach should be similar to patients who present with this condition in their native kidneys. Hence, both plasmapheresis and immunosuppressive therapy should be considered in patients who develop this disease in their allografts.

Thrombotic Microangiopathy (TMA)

De Novo TMA

The reported incidence of de novo TMA in allograft kidney is variable. According to the US Renal Data System (USRDS), only 0.8% of patients develop de novo TMA after kidney transplantation (Reynolds et al. 2003). However, this may be an underestimated incidence rate, as few other single center studies have reported a greater incidence rate ranging between 4% and 14% (Karthikeyan et al. 2003; Zarifian et al. 1999). De novo TMA is generally seen within the first year after transplantation (Caires et al. 2012). Although rare, de novo TMA is a severe condition that may have poor allograft outcomes.

Several factors may increase risk of development of de novo TMA in kidney allografts. These include marginal kidneys (Pelle et al. 2005), antibody-mediated rejection, ischemia-reperfusion injury, use of anti-rejections agents such as calcineurin inhibitors (CNIs) (Zarifian et al. 1999; Lin et al. 2003) and mTOR inhibitors (Sartelet et al. 2005), viral infections, malignancies (Gohh et al. 1997), and presence of anticardiolipin and aPL antibodies (Baid et al. 1999; Jumani et al. 2004). Other therapeutics including valacyclovir and clopidogrel can also lead to de novo TMA (Balfour 1999; Evens et al. 2002). Viral infections associated with occurrence of de novo TMA include cytomegalovirus, parvovirus B19, and polyoma BK virus (Waiser et al. 1999; Murer et al. 2000). The risk of occurrence increases with combined use of CNIs and mTOR inhibitors (Robson et al. 2003). Patients who have undergone ABO-incompatible kidney transplantation are also at increased risk of development of de novo TMA (Miura et al. 2011).

The exact mechanism for pathogenesis of de novo TMA remains unclear; however, multiple theories for development of this disease in the allograft have been suggested. It is thought that factors including ischemia-reperfusion injury, viral infections, graft rejection, and use of antirejection agents promote endothelial injury. CNIs also lead to activation of renin-angiotensin system, augment synthesis of vasoconstrictor agents like endothelin and thromboxane A2, and inhibit synthesis of vasodilators including nitric oxide and prostacyclin (Burdmann et al. 2003). This results in nodular hyalinosis or mucinoid thickening of the intimal layer of renal arterioles. All these abnormalities increase platelet aggregation, which in combination with CNI and mTOR inhibitor associated antifibrinolytic (due to release of plasminogen activator inhibitor) and pro-necrotic effects on endothelial cells eventually leads to TMA. In addition, mTOR inhibitors also cause downregulation of vascular endothelial growth factor, which is essential for repair of CNI induced nephrotoxicity. It has been also seen that endothelial cells affected by cyclosporine release microparticles that can activate alternate complement pathway, further enhancing development of TMA (Renner et al. 2013).

The clinical presentation of de novo TMA is variable. De novo TMA usually occurs in the allograft within first year of transplantation however has also been seen to occur later (2–6 years) after transplantation (Karthikeyan et al. 2003; Zarifian et al. 1999). Patients may present with clinical and lab findings consistent with hemolytic uremic syndrome (HUS); however, the disease is

usually less severe as compared to non-transplanted patients. Other patients may present with decline in allograft function and/or hypertension.

The prognosis depends on severity of clinical features and pathologic lesions. Patients with isolated TMA in the kidney have better prognosis. In contrast, patients who develop systemic signs and symptoms of HUS have poor outcomes with a greater chance of graft loss (Schwimmer et al. 2003; Bren et al. 2005). Recipients of allografts from living donors and those who develop de novo TMA later in posttransplant period have more favorable prognosis and rarely undergo graft loss (Wiener et al. 1997).

Patients may or may not have typical lab findings suggestive for microangiopathic hemolytic anemia, which include presence of anemia, thrombocytopenia, elevated LDH, low haptoglobin levels, and appearance of schistocytes. Allograft biopsy is required to make a definitive diagnosis. However, in patients who present only with a progressive decline in graft function, it is difficult to differentiate TMA from vascular rejection even with allograft biopsy, as glomerular thrombosis can be seen in both of these entities (Mor et al. 2000). Features that are exclusive to vascular rejection include positive C4d staining, and presence of irregular intimal proliferation with mononuclear cells and infiltration of the subendothelial layer with neutrophils. An overlap of these features may also be seen suggesting a role of vascular rejection in the development of TMA (Mauiyyedi et al. 2002).

While there are no specific treatment for this condition, therapy should be aimed at elimination of cause of TMA, when known. This includes either complete withdrawal or reduction in the dose of the offending agents such as CNIs. Patients may also be switched from cyclosporine to tacrolimus or from tacrolimus to sirolimus (Oyen et al. 2006; Yango et al. 2002). However, these switches should be made with great caution, as all CNIs and mTOR inhibitors can potentially lead to TMA. The offending CNI may be resumed cautiously in patients after resolution of TMA and recovery of graft function. Antiviral agents can be used in patients suspected to have viral infection induced TMA. Trial of plasmapheresis or plasma exchange with FFP infusions is also recommended (Zarifian et al. 1999; Mor et al. 2000; Caires et al. 2012). Intravenous immunoglobulin (IVIG) can be used for patients who do not respond to plasmapheresis (Gatti et al. 2003). Recent case reports also describe the successful use of eculizumab for treatment of posttransplant de novo TMA (Wilson et al. 2011; Stewart et al. 2012).

AA Amyloidosis

Recurrent AA Amyloidosis

End-stage kidney disease is a well-known complication of secondary (AA) amyloidosis, with kidney transplant being an established treatment option for such patients. Risk of recurrence of AA amyloidosis mostly depends on the type and activity of the original disease (Ponticelli et al. 2011). Recurrence is more commonly seen in patients with ongoing active inflammatory conditions like familial Mediterranean fever (FMF), rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis. This condition is rare when the underlying inflammation is controlled.

Data regarding patient and allograft outcomes for these patients is limited and conflicting. Sherif et al. compared the long-term outcomes of live donor kidney transplant recipients with renal amyloidosis to that of controls and found similar 5- and 10-year allograft and patient survival rates in both groups (Sherif et al. 2003). Of note, this study included patients with primary and secondary renal amyloidosis. A French multicenter retrospective study also studied the long-term outcomes of kidney transplantation in patients with AA amyloidosis. As compared to non-amyloidosis recipients, the 5- and 10-year patient survival rates was significantly lower for recipients with AA amyloidosis; however, there was no statistical difference in death-censored allograft survival rates between both groups (Kofman et al. 2011). The recurrence rate of renal AA amyloidosis in this study was 14% (8/59 patients). The mean time between the onset of recurrence and kidney transplantation was 118 months (ranging

from 9 to 233 months). Also, a multivariate analysis in this study, showed a significant association of risk of death with AA amyloidosis recurrence in the allograft and with older age of recipient (Kofman et al. 2011).

Clinically, recurrence is most often associated with varying degrees of proteinuria including nephrotic syndrome and decline in graft function. AA amyloid transplant patients also exhibit a higher incidence of infectious and cardiovascular complications (Kofman et al. 2011; Haq et al. 2007; Heering et al. 1998).

On the kidney biopsy, characteristic Congo red positivity with reddish brown material in glomeruli, interstitium, and vessels is seen. The material shows apple-green birefringence under polarized light. Immunoperoxidase stain for serum amyloid A is strongly positive. EM typically shows collection of amyloid fibrils in mesangium and along basement membrane (Sethi et al. 2011).

The treatment approach for recurrent renal amyloidosis in transplant recipients is similar to native kidney amyloidosis, primarily targeting the suppression of underlying inflammatory condition. Newer therapies like eprodisate, which directly targets the amyloid fibril, may be a promising future treatment option (Dember et al. 2007). Early administration of colchicine for indefinite period has been shown to prevent amyloid deposition in the transplanted kidney of recipients with FMF (Sever et al. 2001).

De Novo AA Amyloidosis

Development of de novo AA amyloidosis in allografts of kidney transplant recipients has been very rarely reported in the literature. These recipients developed de novo AA amyloid in the setting of chronic granulomatous disease, recurrent urinary tract infections or from no apparent cause (Yilmaz et al. 2014; Harrison et al. 1993; Peces et al. 2002).

Light Chain Deposition Disease (LCDD)

Recurrent LCDD

LCDD has a very high rate of recurrence in the allografts of kidney transplant recipients and is frequently associated with graft failure (Leung et al. 2004; Short et al. 2001).

In a retrospective study, five of seven kidney transplant recipients with history of LCDD in their native kidneys developed recurrent LCDD (Leung et al. 2004). Median time from transplantation to recurrence of the disease was 33.3 months (ranging from 2.9 to 45.9 months). The median time to reach end-stage kidney disease after recurrence was 10.9 months (Leung et al. 2004). The median allograft survival in the same study was 37.3 months. Another study reported a similar high rate of recurrence (Short et al. 2001). Graft failure was seen in cases in which LCCD was associated with proliferative glomerulonephritis (Short et al. 2001). Clinical features of recurrent LCCD include hypertension, varying degrees of proteinuria, and renal insufficiency (Leung et al. 2004). A circulating monoclonal protein is usually detected.

The most characteristic feature of LCDD on the kidney biopsy is nodular glomerulosclerosis. The mesangial nodules are made of extracellular matrix proteins mixed with monoclonal light chain deposits (Taneda et al. 2008). Deposition of kappa or lambda light chain is universally detected by IF. These deposits are characteristically Congo red negative. Glomerular basement membrane, tubular basement membrane, and vessel walls are variably thickened due to light chain deposition (Taneda et al. 2008).

In spite of this high risk of recurrence and death, kidney transplantation can be offered to patients with LCDD who respond satisfactorily to chemotherapy and achieve sustained remission (Ponticelli et al. 2011). Intensive chemotherapy followed by autologous stem cell transplantation can be offered to these patients before committing to kidney transplantation (Lorenz et al. 2008). Rituximab has been reported to offer benefit in preventing or delaying the recurrence of LCDD in allograft of kidney transplant recipients (Kuypers et al. 2007). Bortezomib has been shown to successfully reverse recurrence of LCDD in kidney allograft (Kaposztas et al. 2009; Moiz et al. 2014). While these are interesting cases, the management of recurrent LCDD should focus on identifying and targeting the underlying plasma cell disorder.

De Novo LCDD

De novo LCDD is a very rare occurrence in kidney transplant recipients. A case of de novo LCDD without any evidence of malignancy was seen 16 years after cadaveric kidney transplantation (Ecder et al. 1996).

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Glomerular Diseases in Pregnancy

48

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Contents

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Abstract

Although the primary glomerulonephritides (GN) often affect young patients, these are overall rare diseases within the general population. A major concern for generations of nephrologists has been and continues to be the impact that these rare renal diseases have on pregnancy outcomes. Little literature is available to guide counseling and treatment during pregnancy, and experience is often based on case reports and single-center studies. Disease-specific outcome data and treatment strategies are even more limited, hampering individualized counseling. In primary GN, disease activity must be under control or in remission before conception since risk factors for adverse outcomes include impaired renal function, uncontrolled hypertension, and significant or nephrotic-range proteinuria. As a general approach, experts in the field recommend multidisciplinary pre- and perinatal care to optimize treatment of hypertension and proteinuria as well as to facilitate early diagnosis of preeclampsia, flares of the underlying glomerulonephritis, or impaired development of the fetus, thereby assuring the best possible outcome for mother and her baby.

Keywords

Pregnancy · Glomerulonephritis · Preeclampsia · Prematurity

Introduction

Pregnancies in women with chronic kidney disease (CKD) are associated with an increased risk of adverse maternal and fetal outcomes. As the primary glomerulonephropathies encompass only a small percentage of renal diseases in the overall population with an incidence estimated between 0.2–2.5/100,000/year (McGrogan et al. 2011), data is scarce on the primary glomerulonephritides (GN) and pregnancy, making these pregnancies anxiety-provoking for most clinicians. The literature on primary GN during pregnancy is comprised of single-center experiences or case reports. Even in the nonpregnant population, treatment of primary GN presents with challenges, and the best-studied medications are often contraindicated in pregnancy due to teratogenicity.

In the past, the adverse pregnancy outcomes associated with renal disease led to recommendations either not to pursue pregnancy or to consider pregnancy termination when an unplanned pregnancy occurred (Pregnancy and renal disease 1975). However, in the last decade, patient-centered care has overtaken this more paternalistic approach to practicing medicine wherein these women may have been advised to forgo the notion of a family. As such, increased numbers of young women with chronic medical illnesses, including those with CKD due to glomerular diseases, are pursuing high-risk pregnancies that require specific counseling on potential adverse outcomes, thorough preparation preconception, strong support, and frequent assessments during pregnancy as well as close follow-up postpartum.

In this chapter, we highlight the considerations for preconception, pre- and perinatal care of women with underlying kidney disease (Fig. 1), what effect pregnancy could have on maternal health and kidney function, and what effect chronic kidney disease could have on the pregnancy outcome.

General Management Principles

Due to the paucity of data, following patients with GN during pregnancy is more an art than a science. The potential for acute disease flares, progressive renal function loss, and potential side effects of treatments to mother and fetus have to be explored thoroughly, and a dedicated

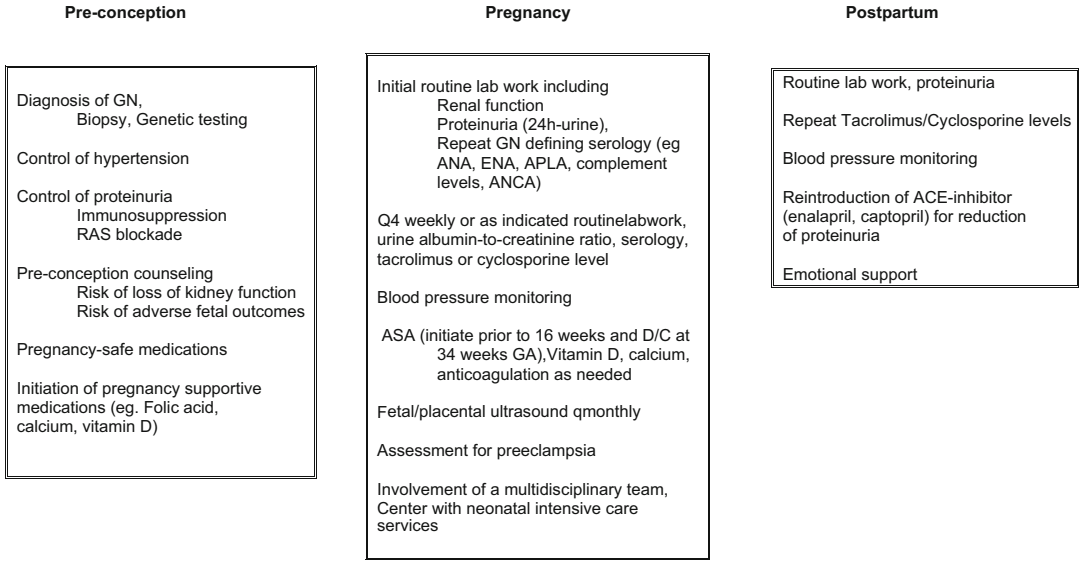

Fig. 1 Pregnancy counseling and management

multidisciplinary team should follow the majority of pregnancies in this patient population. Careful assessment of the health status of the mother, activity of underlying disease, treatment availability, and response to treatment as well as previous pregnancy outcomes should all be considered when counseling on pregnancy risk and potential outcomes. The time of observation should ideally start before conception and should continue postpartum for ongoing support. Pregnancies in patients with kidney disease also involve complex medical, ethical, and psychosocial considerations that if not considered can introduce feelings of worthlessness and disengagement (Tong et al. 2015). Opposing rather than supportive counseling may jeopardize trust and willingness to work with the health-care professional to achieve the best outcome for mother and baby.

It Takes a Health-Care Team

In addition to availability of a neonatal intensive care unit (NICU) care for the neonate if necessary, pre- and perinatal care should involve a multidisciplinary team. In addition to the obstetrician, nephrologist and neonatologist, nurses, dietitians, social workers, and pharmacists may make up the team caring for the pregnancy. Depending on preexisting and developing comorbidities, various other specialists may also need to be involved in care as the underlying disease dictates (e.g., rheumatology for systemic lupus). Hereditary diseases may benefit from preconception genetic counseling to ensure understanding of the inheritance pattern of their condition and the potential implications to their unborn child. Reproductive medicine specialists cannot only assist with fertility issues, but are expanding the field of preimplantation genetic diagnosis, which may prevent the birth of a child with a genetic disorder. Finally, these pregnancies are very emotionally taxing, and the need for psychological support cannot be understated. Having a newborn while managing a chronic medical condition has been shown to be associated with increased rates of postpartum depression (Katon et al. 2014), so regular screening for inadequate coping or bonding along with prompt mental health support is often necessary.

Fertility

While primary GN does not cause infertility in itself, various mechanisms related to disease activity may contribute to difficulties in

conception. For example, in patients with systemic lupus erythematous (SLE), autoimmune oophoritis and chronic inflammation causing dysfunction of the hypothalamic-pituitary axis both may contribute to infertility (Oktem et al. 2015). Further, changes to the hypothalamic-pituitary-ovarian axis in advanced CKD can result in impaired ovulation or anovulation through absence of preovulatory estradiol and LH peaks, increased prolactin levels, and dysfunctional uterine bleeding (Holley et al. 1997; Hou et al. 1985; Lim et al. 1980). Enhanced clearance for patients with ESRD by either intensive dialysis or renal transplantation can reverse the altered hormonal milieu, increasing the rates of successful conception (Barua et al. 2008; van Eps et al. 2012; Saha et al. 2002).

Another source for infertility can be the pharmacological treatment of the underlying disease. Irreversible primary ovarian failure after exposure to cyclophosphamide has been reported as cumulatively dose-dependent and increasing with age with rates as high as 12% reported in females <25 years of age, 27% in women 26–31 years of age, and 62% in women >30 years old (Boumpas et al. 1993). Also, the route of administration can impact fertility with oral cyclophosphamide inducing a more sustained amenorrhea than IV administration (Mok et al. 2006). To potentially limit ovarian damage from cyclophosphamide, leuprolide acetate, a synthetic GnRH analog, has been studied, but results are mixed. Of three recent meta-analyses conducted in women with malignancies and other rheumatological diseases, two found a significant benefit with regard to resumption of menses and ovulation with GnRH analog co-treatment (Bedaiwy et al. 2011; Del Mastro et al. 2014), while another found no benefit (Elgindy et al. 2015).

Control of Underlying Primary GN and Proteinuria

Most evidence for pursuing a remission of the underlying GN prior to embarking on a pregnancy derives from data in SLE, wherein lupus activity, particularly active nephritis, is linked to higher rates of preeclampsia, increased premature delivery, small for gestational age births, and accelerated loss of renal function (Koh et al. 2015; Smyth et al. 2010). From this, we deduce that other types of glomerulonephritis when poorly controlled will potentially contribute to adverse pregnancy outcomes, and control of the glomerular disease with pregnancy-safe immunosuppression is recommended where possible. Potentially teratogenic medications should be stopped in addition to those medications with limited long-term neonatal safety data (Table 1). Cyclophosphamide and mycophenolate mofetil should be discontinued at least 6 weeks prior to a pregnancy attempt, while current recommendations for rituximab is to wait at 6–12 months after exposure per the manufacturer's guidelines, but more clinical data is required. A reasonable approach includes treatment with pregnancy-safe immunosuppression to attain remission for at least 3–6 months prior to a pregnancy attempt (Cabiddu et al. 2016). A repeat kidney biopsy may prove necessary in select cases wherein it is difficult to clinically confirm absence of active nephritis on pregnancy-safe immunosuppression.

In patients without immunological treatment options, control of urine protein with agents that block the renin angiotensin system (RAS) is the mainstay of treatment (Table 1). Although clearly teratogenic in the second and third trimesters of pregnancy (*see Management of Hypertension*), data for teratogenicity with only early pregnancy exposure is no longer supported, and unintentional first trimester exposure does not require termination (Diav-Citrin et al. 2011). Again the potential use of these agents in pregnancy planning is not derived from data published in the management of GN, but comes from small, uncontrolled studies in patients with diabetic nephropathy wherein intensive treatment with angiotensin-converting enzyme inhibition in addition to optimization of glucose control prior to conception has been shown to stabilize proteinuria during pregnancy (Hod et al. 1995; Bar et al. 1999) and, compared to older preexisting literature, prolong gestation and improve birth weights (Nielsen et al. 2009). A pragmatic approach may be to intensify RAS blockade prior to pregnancy in women with renal diseases wherein there are no immunosuppressive treatment options,

Table 1 Commonly used drugs in glomerulonephritis, considering pregnancy

Medications	FDA class*	Maternal adverse effects, during pregnancy	Placental passage	Human teratogenicity	Fetal/neonatal effects	Excreted in breast milk	Breastfeeding
Corticosteroids	C	Gestational diabetes Hypertension Preeclampsia Perinatal adrenal suppression	Deactivated by 11beta-HSD2 (except betamethasone, dexamethasone)	Possible orofacial cleft lip and palate	Possible intrauterine growth restriction Premature rupture of membranes	Trace	Acceptable except at high doses
Azathioprine	D	Myelosuppression in TMPT deficient women	Yes, but not activated due to lack of IPPase	None	None	Low levels	Acceptable
Cyclosporine	C	Gestational diabetes Hypertension Decreased plasma drug levels due to increased distribution volume	Yes	None	Possible intrauterine growth restriction Hyperkalemia Reversible renal impairment	Low levels	Acceptable
Tacrolimus	C	Gestational diabetes Hypertension Decreased plasma drug levels due to increased distribution volume	Yes	None	Possible intrauterine growth restriction Hyperkalemia Reversible renal impairment	Low levels	Acceptable
Rituximab	C	None	Yes	None	Leukopenia, increased peri-/postpartum infectious risk	Unknown	Not recommended
Hydroxychloroquine	C	None	Yes	None	None	Trace	Acceptable

(*continued*)

Table 1 (continued)

Medications	FDA class*	Maternal adverse effects, during pregnancy	Placental passage	Human teratogenicity	Fetal/neonatal effects	Excreted in breast milk	Breastfeeding
Cyclophosphamide	D	None	Yes	Abnormalities of craniofacial structures, ears, limbs, and visceral organs	Impaired neurological development Decreased hematopoiesis Growth restriction	Yes	Not recommended
Mycophenolate mofetil	C	None	Yes	Cleft lip and palate, microtia with atresia of the external auditory canals, micrognathia, and hypertelorism	Neonatal anemia and hydrops fetalis	Unknown	Not recommended
Eculizumab	C	None	Yes	None reported	None reported	No	Use with caution
ACE inhibitors/ ARB	X	Oligohydramnios	Yes	Atrial/ventricular septal defects, microcephaly,and pulmonary hypoplasia	Peripartum renal failure	No, but only studied in a handful of ACE inhibitors	Enalapril, captopril, quinapril acceptable, otherwise contraindicated

FDA class: A = Generally acceptable, studies show no evidence of fetal risk; B = May be acceptable, animal studies showed not risk and human studies not available, or animal studies showed minor risks, human studies did not confirm risk; C = Use with caution if benefit outweighs risk, animal studies show risk, or no studies done; D = Use in life-threatening emergencies when no safer drugs available, evidence of human fetal risk; X = Risks outweigh benefits, and safer alternatives exist. 11beta-HSD2 = 11beta-hydroxysteroid dehydrogenase type 2, IPPase = Inosinatopyrophophorylase, TPMT = Thiopurine methyltransferase

stopping at the time of conception, which is our practice in women with significant proteinuria. This approach, however, requires careful counseling with respect to associated risks and aggressive surveillance for a potential pregnancy in order to minimize the risk of fetal exposure. Other practitioners may choose to discontinue these agents when attempts at conception begin. Significantly worsening proteinuria prior to conception though is also associated with worse pregnancy outcomes. As such, these decisions should be individualized, and this is an area that requires further study in women with GN.

Renal Dysfunction and Adverse Pregnancy Outcomes

The risk of loss in renal function and poor pregnancy outcome increases with severity of renal dysfunction; however, even stage 1 CKD seems to pose a higher risk for adverse pregnancy outcomes as compared to the general population, including preterm delivery, small for gestational age babies, requirements for admission to the neonatal intensive care, and increased rates of caesarian section (Piccoli et al. 2010, 2015). This was confirmed by a population-based study from Norway (HUNT II) when there is concurrent hypertension with CKD stage 1, but not microalbuminuria (Munkhaugen et al. 2009).

Moderate renal dysfunction is currently defined as a creatinine clearance between 40 and 70 ml/min or CKD stage 2–3, whereas severe renal insufficiency is defined as a creatinine clearance below 40 ml/min or CKD stages 3–4 (Piccoli et al. 2015). Progressive renal dysfunction is found in these pregnancies at a higher rate than women who have similar renal dysfunction, but do not become pregnant. A study with 82 pregnancies in 74 patients from 1996 reported overall renal function stability in 79% during pregnancy but a decrease of 25% in renal function in 20% of women (Jones and Hayslett 1996). In 23% (16 pregnancies) renal function declined directly after delivery and eight women progressed to end-stage renal disease by 6 months postpartum despite stability of renal function during pregnancy. A such, a significant loss of renal function during pregnancy or postpartum occurred in 43%, while recovery of pregnancy-related renal function decline was seen in only 8% of pregnancies by 6 months postpartum. The progression of renal dysfunction was not necessarily linear. Some women with severely reduced creatinine clearance did not progress, while others with less severe disease had a more significant renal function loss, suggesting that other factors contribute to the deterioration of renal function, namely, hypertension, proteinuria, or the underlying etiology of renal dysfunction.

Support for the impact of proteinuria on renal function decline comes from a prospective study that assessed 49 women with a calculated eGFR <60 ml/min stratified by the degree of proteinuria (Imbasciati et al. 2007). Only women with an eGFR <40 ml/min and >1 gram of proteinuria showed significantly hastened renal function decline postpartum (0.21 ± 0.20 increased to 1.17 ± 1.23 ml/min/month prior to and after pregnancy, respectively). The study was limited by a small sample size particularly in the group with a higher eGFR (>40 ml/min) and >1 gram of proteinuria ($n = 6$), which is unfortunate as this would represent the largest group of women with glomerular disease that require pregnancy counseling.

Perhaps as a consequence of this progressive loss of renal function during pregnancy, remarkably worse pregnancy outcomes are noted in women with advanced CKD with much higher rates of cesarean section (70%), preterm delivery <37 (89%) and <34 (44%) weeks, and small for gestational age babies [$<10\%$ (50%) and $<5\%$ (25%)] as well as an increased need for NICU care (70%) (Piccoli et al. 2015). The aforementioned prospective cohort noted a stepwise decline in gestational age and birth weight with successive worsening in eGFR and amount of proteinuria. Women with >40 ml/min and <1 gram of proteinuria delivered their babies at 36.7 ± 2.5 weeks of gestation, weighing 2519 ± 670 grams, while women with <40 ml/min of eGFR and >1 gram per day of proteinuria had shorter gestations and smaller babies, delivering their babies at 33.5 ± 3.5 weeks gestation, weighing 1864 ± 806 grams (Imbasciati et al. 2007).

Clinical Visits During Pregnancy

Follow-up visits should be scheduled regularly every 4–6 weeks after conception and then more frequently as the pregnancy progress or as the patient's condition dictates (Cabiddu et al. 2016). These visits include both an assessment of the mother and baby and are, therefore, likely best provided in multidisciplinary clinics attended by both nephrologists and high-risk obstetricians together. Nephrologists can carefully assess the mother's well-being including blood pressure, volume status, and signs or symptoms of a disease flare, while obstetrical staff can carefully assess fetal well-being and growth as well as placental integrity to assist with the diagnosis of superimposed preeclampsia.

Laboratory Evaluations

Blood work should include routine laboratory values including CBC, electrolytes creatinine, blood urea nitrogen, uric acid, iron stores, liver function tests, and serum albumin. A urine albumin or protein to creatinine ratio should be measured and, if abnormal, a 24 h urine collection for protein for quantification. Patients with SLE should have monthly anti-dsDNA and complement levels checked, especially if these markers have been concordant with past disease activity. Of note, pregnancy is a state of the acute phase response, so complement levels can be normal or even high. Falling complement levels, even within the normal range, may suggest that lupus is becoming more active in an individual patient. It is unknown whether monitoring changes to the ANCA titer during pregnancy helps to predict relapses of vasculitides. If on prednisone, random blood glucose should be checked regularly and before the routine oral glucose tolerance test in the second trimester. For patients on tacrolimus or cyclosporine, closer monitoring is needed as the increase in the volume of distribution can cause a decrease in drug levels.

Supportive Medications

Prenatal vitamins are commonly used prior to conception except for women with end-stage renal disease where supplementation with vitamin E and A is not recommended due to the concern of accumulation. Folic acid 5 mg daily has been advised for patients with renal dysfunction, as well as iron supplementation orally or intravenously (Khalafallah et al. 2012). For GFR less than 30 ml/min, erythropoietin-stimulating agents can be used and are safe in pregnancy to hopefully omit the requirement for red blood cell transfusions (Breymann et al. 2001). Vitamin D and calcium should be supplemented for bone health of the mother and fetus especially if on steroid therapy. Further, calcium supplementation has been shown to lower the risk of preeclampsia in high-risk women and those whose dietary intake is insufficient (Hofmeyr et al. 2006). Low-dose acetylsalicylic acid (75–100 mg/d) started after 8 but, before 16 weeks of gestation, is currently considered to help placentation and has been shown to reduce the risk of preeclampsia in high-risk patients (Roberge et al. 2013; Henderson et al. 2014). Initiation prior to conception is typical in women with thrombophilias, including a positive antiphospholipid antibody. To date, there appears to be no risk of congenital malformations (Slone et al. 1976), and low doses (below 100 mg/d) do not hamper closure of the ductus arteriosus (Di Sessa et al. 1994). In higher doses, aspirin may cause perinatal cerebral hemorrhage and clotting abnormalities when exposed up to 1 week prior to delivery (Stuart et al. 1982). It is our practice to stop aspirin after 34–36 weeks of gestation in most women wherein preeclampsia prevention is the only indication for its use.

Immunosuppression

Corticosteroids are a mainstay in induction therapy for many GNs and are considered acceptable for use during pregnancy, as the benefit tends to outweigh the risks of untreated underlying disease. The placenta poses a natural barrier to

maternal cortisol by degrading it to inactive cortisone through high 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2) activity on the syncytiotrophoblasts at the fetal-maternal interface (Hallman 2015), and low doses (5–10 mg/d) are thought to not induce thymic hyperplasia or adrenal suppression (Transplantation 2002). Betamethasone and dexamethasone bypass this enzymatic step, and fetal serum levels reach approximately 30% that of the maternal level and, as such, are used to accelerate fetal lung maturation (Hallman 2015). Orofacial clefts have been reported with corticosteroid use in the first trimester (Fraser and Sajoo 1995), but this finding was not confirmed by a larger, more recent population-based study from Denmark (Hviid and Molgaard-Nielsen 2011). However, there may be an increased risk of intrauterine growth restriction and premature rupture of the membranes associated with corticosteroids (Murphy et al. 2008; Guller et al. 1995). Maternal risks include dose-dependent gestational diabetes, pregnancy-induced hypertension, infections, cataracts, bone necrosis, and, if used chronically, osteoporosis (Ostensen et al. 2006). Adrenal suppression needs to be considered and treated during labor and delivery, if the woman has been taking more than 20 mg/d for more than 3 weeks within the 6 months prior to delivery (Lockwood et al. 1996).

Azathioprine, when taken at doses $\leq$2.0 mg/kg/day, is considered a pregnancy-safe medication, as it requires conversion to its active metabolite 6-mercaptopurine by inosinate pyrophosphorylase, an enzyme lacking in the fetal liver. This medication has mainly been used in renal transplantation and non-renal inflammatory conditions, and in these small matched cohort studies, the rate of fetal malformation has not been noted to be increased (Bar et al. 2003; Schramm et al. 2006) However, a cohort study from a population-based prescription registry in Denmark assessed the use of azathioprine or 6-mercapotpurinol in the first trimester and reported an increased risk in malformations, prematurity, and perinatal mortality (Norgard et al. 2003). Similarly, another larger retrospective cohort study documented an increased risk for premature birth and ventricular and atrial septum defects (Cleary and Kallen 2009), but these findings have not been confirmed by data from the National Transplantation Pregnancy Registry with the exception of a higher prematurity rate that may be related to the underlying medical condition or the calcineurin inhibitors that are typically used in conjunction with azathioprine (Armenti et al. 2002). Maternal side effects are more pronounced with low enzyme activity of thiopurine methyltransferase (TPMT), causing bone marrow suppression with possible anemia, hepatitis, and pancreatitis. Assessment of TPMT activity prior to initiation is recommended to guide dosing.

Most of the data on the *calcineurin inhibitors* (cyclosporine and tacrolimus) in pregnancy is derived from transplant patients (Armenti et al. 1994; Lamarque et al. 1997). Up to 50% of the cyclosporine dose crosses the placenta, and transient immune alterations in neonates have been noted without renal dysfunction (Shaheen et al. 1993). Congenital malformations have not been documented to exceed the general population as confirmed by a meta-analysis analyzing the risk for preterm delivery, congenital malformations, and low birth weight (Bar Oz et al. 2001). One retrospective and one prospective study reported pregnancy outcomes with tacrolimus use in renal, combined renal/pancreas, and liver transplantations (Jain et al. 2003, 2004). Prematurity and preterm delivery was seen in about 50% of women, and one neonate presented with congenital malformations. A retrospective analysis between 1992 and 1998 reported 100 pregnancies exposed to 12 mg/day of tacrolimus (Kainz et al. 2000). Outcomes were available for 95 pregnancies with 68 lives births (12 pregnancy terminations, 12 spontaneous abortions, 1 stillbirth, and 2 neonatal deaths), and the mean pregnancy duration was 35 weeks of gestation with a normal birth weight in 90% of live births.

As mentioned, serum levels of the calcineurin inhibitors should be regularly assessed and the dose adjusted as needed. Nephrotoxicity does occur, and these medications can exacerbate maternal hypertension. Even though there is more data available on cyclosporine in pregnancy due to its longer availability on the market,

tacrolimus may be preferred when treating lupus nephritis in pregnancy given its efficacy compared to cyclophosphamide and mycophenolate mofetil in inducing remission and its lower risk of infectious complications (Lee and Song 2015). Small amounts of cyclosporine are excreted into breast milk, and although the FDA advises not to breastfeed when on this medication, most studies have no documented neonatal side effects (Moretti et al. 2003). Even less tacrolimus is excreted into breast milk, approximately 0.06% of maternal weight adjusted dose (French et al. 2003). As such, the benefits of breastfeeding outweigh any documented risks.

Rituximab, a monoclonal antibody against CD20, crosses the placenta, and high concentrations have been found in the umbilical cord blood. One case report noted transient complete depletion of B-lymphocytes in a neonate after being exposed multiple times to rituximab in utero up to the 32nd week of gestation for maternal Burkitt's lymphoma (Friedrichs et al. 2006). At 26 months after delivery, the baby had no documented immunological complications and responded normally to vaccinations. Another case report of fetal exposure to rituximab early in the first trimester for membranous nephropathy noted normal B-lymphocyte counts at delivery and no short-term complications (Al-Rabadi et al. 2016). Beyond case reports, there is a growing experience from the rituximab global drug safety database including 90 live births from 153 exposed pregnancies (Chakravarty et al. 2011). Among the live births, there were only 2 birth defects, but hematological abnormalities were seen in 11 children. Long-term outcome data is not available. Expert opinion suggests to wait at least 6–12 months after exposure to rituximab to conceive, but if it is critically important to use this medication during pregnancy, it should be given as early on as possible to reduce the risk of neonatal infections due to B-lymphocyte depletion at delivery.

Cyclophosphamide and *mycophenolate mofetil* are both established teratogens that are contraindicated in pregnancy and while breastfeeding. Cyclophosphamide has an inconsistent and unpredictable teratogenic effect in the human fetus when given during the first trimester. Defects of the calvaria, ear and craniofacial structure, limb, and visceral organ abnormalities have been reported in case studies, as well as developmental delay during childhood has been documented (Greenberg and Tanaka 1964; Toledo et al. 1971; Murray et al. 1984; Kirshon et al. 1988; Zemlickis et al. 1992, 1993; Enns et al. 1999). When administered in the second or third trimester, structural abnormalities were not found, but growth restriction, suppression of hematopoiesis, and neurological impairments have been documented (Zemlickis et al. 1992; Durodola 1979). It is excreted into breast milk (Wiernik and Duncan 1971), and breastfeeding while on this medication is contraindicated for the concern of hematopoietic suppression. Mycophenolate mofetil is a purine biosynthesis inhibitor that is contraindicated in pregnancy and while breastfeeding. A systematic review reported on pregnancy outcomes in 65 women exposed to mycophenolate mofetil, noting miscarriages in 31% and congenital abnormalities in 15% (Ostensen et al. 2006). The characteristic phenotype of these abnormalities includes cleft lip and palate, microtia with atresia of the external auditory canals, micrognathia, and hypertelorism (Perez-Aytes et al. 2008).

Management of Hypertension

There are two types of hypertension during pregnancy: prepregnancy chronic hypertension, which is often diagnosed in pregnancy prior to 20 weeks of gestation, and transient gestational hypertension often developing as part of the preeclampsia syndrome after the 20th week of gestation. With the initial physiological changes of pregnancy that include systemic vasodilatation, blood pressure may decrease in women with chronic hypertension, necessitating temporary cessation or a reduction in dose of antihypertensive medications. However, toward the end of the second trimester, re-initiation of antihypertensive medication may be necessary. Significant hypertension in the first trimester is associated with poor pregnancy outcomes.

For decades, the target for blood pressure control has been debated. Recently the Control of Hypertension in Pregnancy Study (CHIPS) trial concluded that tighter control of maternal blood pressure is preferable (Magee et al. 2015). This large, international, multicenter, randomized, controlled trial enrolled 987 women between 14^{+0} and 33^{+6} weeks with chronic hypertension or gestational hypertension and randomized them to either "less tight" (target diastolic BP 100 mmHg) or "tight" blood pressure control (target diastolic BP 85 mmHg). No difference was noted in the primary composite perinatal outcome (pregnancy loss, high level neonatal care), which was 31.4% in the "less tight" versus 30.7% in the "tight" control group. Further, there was no significant difference in the size of the babies. The most significant finding, however, was that severe hypertension (>160/110 mmHg) was significantly more common in women receiving "less tight" (vs. "tight") control at 40.6 vs. 27.5%, respectively. Although women with renal disease were not represented in the CHIPS trial, intuitively controlling blood pressure in this population is likely to be even more critical, and the goal is to achieve blood pressure values consistently <140/90 mmHg. Blood pressure should be checked on a regular basis during follow-up visits and at home by the patient herself to assure early detection of potential preeclampsia. For this the patient's cuff should be assessed for accuracy early in the pregnancy.

Safe medications for blood pressure control during pregnancy include methyldopa, extended-release dihydropyridine calcium channel blockers, and hydralazine. Labetalol crosses the placenta and conflicting findings on perinatal effects on the neonate, including bradycardia and hypoglycemia, have been reported (Bateman et al. 2016; Thewissen et al. 2016) A subanalysis of the CHIPS trial also noted that women prescribed methyldopa at randomization instead of labetalol had was fewer babies with birthweight <10th percentile (adjusted odds ratio 0.48; 95% CI 0.20–0.87) (Magee et al. 2016). Finally, another study found higher rates of hospitalization for respiratory distress syndrome, sepsis, and seizures in the babies of mothers prescribed labetalol only compared to those prescribed only methyldopa (Xie et al. 2014). Although labetalol is still widely prescribed and considered a safe alternative for the management of hypertension in pregnancy, more definitive randomized controlled trials are likely required.

Blockade of the renin angiotensin system (RAS) is contraindicated in pregnancy, and women planning to conceive should be on alternative antihypertensive agents, unless the indication for use is to reduce proteinuria, in which case these medications should be discontinued as soon as the pregnancy is detected and preferably within 8 weeks of gestation. An earlier retrospective analysis of Medicaid data of 29,507 children born between 1985 and 2000 in Tennessee of which 209 were exposed to ACE inhibitors and 202 to other antihypertensive medications suggested the potential for teratogenicity with first trimester exposure that included major congenital malformations such as atrial/or ventricular septal defects and patent ductus arteriosus (2.9 versus 0.8% neonates) (Cooper et al. 2006). However, a larger subsequent study that was better able to control for potential confounders including maternal age, ethnicity, parity, and obesity did not find an increased risk of teratogenicity after first trimester exposure to drugs that block the RAS compared to other antihypertensive agents (Li et al. 2011). In addition to cardiac and renal malformations, exposure to ACE inhibitors in the second and third trimester can reduce fetal GFR through changes in fetal hemodynamics, which can lead to oligohydramnios through decreased fetal urine production, which in turn may lead to fetal pulmonary hypoplasia and potentially death (Shotan et al. 1994; Tabacova et al. 2003). Peripartum fetal renal failure can be seen, which may slowly improve over time (Schubiger et al. 1988). In the postpartum period, enalapril, captopril, and quinapril have not been noted to pass into breast milk in significant quantities, and breastfeeding while on these medications for reduction in proteinuria and blood pressure control is acceptable (Beardmore et al. 2002; Begg et al. 2001).

Assessment and Management of Nephrotic Syndrome

De novo presentation of idiopathic nephrotic syndrome during pregnancy is rare. A thorough work-up includes medical history, clinical symptoms, physical examination, urinalysis, and serological testing to assess for systemic and secondary causes. After excluding secondary causes and preeclampsia, the most important differential diagnosis (often associated with hypertension in the late second or third trimester), de novo idiopathic nephrotic syndrome can be diagnosed. Early in gestation, a renal biopsy is recommended to determine the underlying etiology. As gestation progresses, delivery should be considered, and renal biopsy considered postpartum, unless marked improvement of the nephrotic syndrome is seen. Treatment depends on presentation timing and severity of the nephrotic syndrome. If diagnosis is not possible, and treatment needs to be administered on speculation, either steroids or calcineurin inhibitor, alone or in combination, can be considered.

Due to the physiological changes that accompany pregnancy, including a lower serum albumin, a higher tendency to develop edema, and hypercoagulabity (Abbassi-Ghanavati et al. 2009; Kamel et al. 2014), the symptoms that accompany the nephrotic syndrome can be particularly severe in pregnancy, and supportive therapy is often needed while awaiting a response to treatment or when diagnosis and treatment are delayed due to the inability to perform a biopsy during pregnancy. Conservative treatment for edema includes elevation of the extremities and compression stockings, but often diuretics are required, and furosemide is appropriate for severe edema when conservative measures fail. Case reports also describe the use of albumin infusions in women with severe nephrosis (Sebestyen et al. 2008; Ope-Adenuga et al. 2015).

Nephrotic syndrome with severe hypoalbuminemia (albumin <25 g/L) is associated with an increased risk of venous thromboembolic disease (Barbour et al. 2012), and pregnancy itself is a prothrombotic state (Kamel et al. 2014). Presently, there is no data to guide the practice of prophylactic anticoagulation for severe hypoalbuminemia from nephrotic syndrome in pregnancy. In the nonpregnant population, nephrotic syndrome from membranous nephropathy with an albumin level < 28 g/L was found to be the most significant risk factor for venous thromboembolism (Lionaki et al. 2012), and expert opinion suggests consideration for prophylactic anticoagulation when serum albumin levels drop below 25 g/L after considering the risk of bleeding (Alfaadhel and Cattran 2015); a risk-benefit calculation tool is available online (gntools.com (Lee et al. 2014)), but the extrapolation to the pregnant state is unclear, and likely the indications for anticoagulation should be even more aggressive. In our practice, we recommend that any women with severe proteinuria and serum albumin <20 g/L should receive thromboprophylaxis throughout pregnancy, but anticoagulation should also be considered in those with less severe nephrotic syndrome with additional risk factors, e.g., obesity, immobility (including prescribed bed rest), membranous nephropathy, or vasculitis. Treatment with heparins (unfractionated and low-molecular-weight heparin) during pregnancy is considered safe (Singh et al. 2013). Warfarin crosses the placenta and is contraindicated due to associations with higher rates of fetal loss (Soma-Pillay et al. 2011) and teratogenicity, including skeletal and central nervous system defects (Basude et al. 2012). Thromboprophylaxis should be held prior to delivery, but resumed as soon as possible postpartum and continued for at least 6 weeks, as the postpartum period carries a particularly high risk of thrombosis (Kamel et al. 2014).

Safety of Kidney Biopsy

Renal disease can be found in approximately 3% of pregnancies, but in most cases the pathological diagnosis is known prior to conception or can be diagnosed without tissue (such as diabetic nephropathy, lupus nephritis, vasculitis, etc.), and only a small subset will prompt the discussion for requirement of a biopsy during pregnancy to obtain a tissue diagnosis. Indications for this intervention include a sudden and severe decline in renal function or to obtain the diagnosis in cases of de novo nephrotic syndrome.

Severe complications from renal biopsies in the nonpregnant population have been reported to be as low as 0.1%, but there is less safety data in pregnancy. A systematic review of 30 years of data (1980–2012) compared outcomes of 243 biopsies performed during pregnancy to 1236 performed postpartum, mostly within the first 2 months (Piccoli et al. 2013a). Overall, 2% of interventions developed adverse outcomes, including need for transfusion, embolization of the renal artery, early preterm delivery, and presumed related fetal death. Significantly more complications were observed in biopsies performed during pregnancy compared to the postpartum period (7 vs. 1%, respectively; $p = 0.001$). With respect to timing, only minor hemorrhage occurred between 0 and 20 weeks of gestation, whereas severe biopsy-related complications occurred between 23 and 26 weeks of gestation. However, it should be noted that the indication for biopsy in many of the older studies was to diagnose preeclampsia, which is particularly precarious. In fact, once preeclampsia enters the differential diagnosis, delivery should be considered as opposed to a kidney biopsy, which can be performed more safely in the postpartum period should there be no improvement in the renal parameters. As such, we agree with other authors with respect to the judicious use of renal biopsy in pregnancy (Chen et al. 2001; Lindheimer and Davison 1987). There is no absolute contraindication to perform a kidney biopsy; however, it should be considered only when maternal well-being is at risk and knowledge of the underlying pathology will change or help guide the most appropriate and safe treatment approach and when waiting until after delivery is not an option. Further, the earlier the better, as the growing uterus will further complicate correct positioning for the procedure.

Diagnosing Superimposed Preeclampsia

Proteinuria is a common finding in GN and distinguishing the etiology of proteinuria during pregnancy is of paramount importance to dictate follow-up and plan further treatment and time delivery. Preeclampsia rarely presents before 20 weeks of gestation and is, therefore, unlikely to be the reason for worsening proteinuria early in pregnancy. However, the onset or worsening of proteinuria after 20 weeks of gestation includes preeclampsia in the differential diagnosis in addition to de novo presentation or a flare of glomerulonephritis. At this point, the work-up should proceed as in the nonpregnant patient, including urinalysis and serological assessment. In patients with preexisting diseases like lupus nephritis and vasculitis, it is helpful to have baseline serology available for comparison. However, in some cases, superimposed preeclampsia occurs along with a flare of underlying renal disease, and the presentation may be severe (ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists 2002). As already mentioned, kidney biopsy has no role in the diagnosis of superimposed preeclampsia, but fortunately an enhanced understanding of its pathophysiology as a placentally mediated disease can assist with this difficult diagnostic dilemma, including the assessment of angiogenic and antiangiogenic markers, the assessment of placenta morphology and blood flow patterns through the uterine and umbilical arteries, and finally the assessment of fetal growth and well-being.

The pathophysiology of preeclampsia includes an ischemic placenta that releases antiangiogenic factors including soluble fms-like tyrosine kinase 1 (sFlt-1), which binds and removes from the maternal circulation vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), while soluble endoglin (sEng), a truncated tumor growth factor (TGF) beta co-receptor, antagonizes the action of TGF-beta and augments the effects of sFlt-1 on the endothelium. Cumulatively, this results in maternal endothelial dysfunction producing the usual signs and symptoms associated with preeclampsia, the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and eclampsia.

Although not as yet widely available, there is mounting evidence to suggest that the measurement of these angiogenic factors will prove useful diagnostically, especially in women with preexisting

renal disease. The prognosis study noted that a sFlt-1/PlGF ratio of 38 or less predicted short-term absence of preeclampsia in singleton pregnancies in women without other comorbidities (Zeisler et al. 2016). In the PROMISSE study, after adjusting for clinical risk factors, sFlt-1 was the strongest predictor of severe adverse outcomes in pregnancies in patients with systemic lupus at 12–15 weeks of gestation, while the combination of elevated sFlt-1 and depressed serum levels of PlGF were predictive of adverse pregnancy outcomes between 16 and 19 weeks (Kim et al. 2016). In a cohort of hypertensive pregnant women, sFlt-1, sEng, and the sFlt-1/PlGF ratio were found to be significantly higher, while PlGF was significantly lower in women with superimposed preeclampsia (Perni et al. 2012). Also, in women with chronic kidney disease, preeclamptic patients demonstrated higher sFlt-1, lower PlGF, and a higher sFlt-1/PlGF ratios (Rolfo et al. 2013; Masuyama et al. 2012) with a low PlGF having the highest diagnostic accuracy for superimposed preeclampsia requiring delivery within 14 days (Bramham et al. 2016).

Until these markers are better studied in women with different forms of GN at different levels of CKD, assessment of the placenta can be very helpful in diagnosing superimposed preeclampsia. High resistance patterns and low velocity waveforms in uterine and umbilical arteries can distinguish chronic kidney disease (normal flow waves) from preeclampsia (high resistance flows with a pulsatility index >1.4) (Piccoli et al. 2013b). If not available, poor fetal growth is also indicative of poor placentation, which can help diagnostically to make appropriate treatment decisions.

Disease-Specific Pregnancy Outcomes

Lupus Nephritis in Pregnancy

Unlike other rheumatologic diseases, systemic lupus erythematous (SLE) is well described and studied in pregnancy due to its predominant disease onset in young females (Pons-Estel et al. 2010). Overt renal disease develops in about 30% of lupus patients over 10 years with East and South Asians having the highest occurrence of lupus nephritis, followed by Afro-Caribbean and Europeans (Morais and Isenberg 2016). The de novo presentation of lupus during pregnancy has been reported (Ergin 2014; Patel et al. 2012), but pregnancy as a risk factor for a flare of systemic lupus has been debated for years (Bramham et al. 2012). A newer hypothesis is that pregnancy in itself is not the risk factor, but that a blunted increase in T-lymphocyte-2-helper cells induced cytokine levels along with lower levels of estrogen and progesterone leads to amplification of inflammatory effects (Iaccarino et al. 2012; Doria et al. 2004).

Overall outcomes of pregnancies affected by SLE have significantly improved in developed countries in recent years, but in developing countries ongoing poor outcomes is a concern (Chandran et al. 2005), reflecting that there is a need for medical resources to appropriately prepare these women for pregnancy. There are subsets of SLE patients who have higher risks of pregnancy-related complications. Women with active disease, especially nephritis, at the time of conception, have worse outcomes, and pregnancy should be delayed until their disease is controlled (Imbasciati et al. 2009; Saavedra et al. 2012). Endocapillary proliferative lupus nephritis (class III and IV) may present more frequently with preeclampsia and lower birth weight babies than mesangioproliferative (class II) or membranous (class V) lupus nephritis (Carmona et al. 2005), while women with antiphospholipid antibodies can develop pregnancy-related thrombosis, preeclampsia, and fetal loss (Ruiz-Irastorza and Khamashta 2005).

A comprehensive systematic review of the literature summarized results for 1842 patients and 2751 pregnancies from 37 smaller studies and noted the most common maternal risk was a disease flare, occurring in 26% with a flare of nephritis occurring in 16% of pregnancies (Smyth et al. 2010). Predictors for renal flares during pregnancy and the long-term outcome of these flares have been retrospectively studied in 183 patients with SLE and preexisting lupus nephritis (Koh et al. 2015). In this retrospective analysis, there

was a high rate of renal flares in patients with preexisting lupus nephritis (50.7%). Predictors of renal flare were preexisting lupus nephritis (OR 17.7; 95% CI, 5.77–54.48), active disease preconception (OR 2.74; 95% CI, 1.07–7.00), and a prepregnancy eGFR of less than 90 ml/min/1.73m^2 (OR 11.15; 95% CI, 3.29–37.77). Patients were followed for a median of 5.9 years postpartum, and 33% of those who flared during pregnancy had persistent renal disease activity 1 year after delivery with high rates of progression to chronic kidney disease when proteinuria could not be reduced ≥50% of the presenting proteinuria within 6 months postpartum. Other feared maternal complications include the development of gestational hypertension (16.3%), preeclampsia (7.5%), and eclampsia (0.8%), while fetal risks include spontaneous abortion (16%), intrauterine fetal death or stillbirth (3.6%), intrauterine growth restriction (12.5%), premature rupture of membranes and premature delivery (39.4%), and neonatal lupus and perinatal mortality (2.5%) (Smyth et al. 2010; Warren and Silver 2004; Clowse 2007).

There is new evidence though to support the fact that careful preconception counseling and close observation during pregnancy can minimize maternal risk and improve perinatal morbidity and mortality. The recently published PROMISSE study is a large prospective study of 385 women from multiple ethnic and racial backgrounds (Buyon et al. 2015). It included only women with largely quiescent disease at conception by excluding women with a urine protein to creatinine ratio >1000 mg/g, creatinine level greater than 1.2 mg/dL, and daily prednisolone use >20 mg/day. Overall, 81% of 236 women had uncomplicated pregnancies, and fetal and infant deaths were very rare. Severe maternal flares in the second and third trimesters occurred only in 2.5% and 3.0%, respectively. Risks for adverse pregnancy outcomes included being positive for lupus anticoagulant (OR 8.32 [CI, 3.59 to 19.26]), use of antihypertensive medications (OR, 7.05 [CI, 3.05 to 16.31]), a physician global activity score that exceeded 1 (OR, 4.02 [CI, 1.84 to 8.82]), and a low platelet count (OR, 1.33 [CI, 1.09 to 1.63] per decrease of 50 x 109 cells/L). Of note, the vast majority of these women received specialized care and oversight. As such, most patients with SLE, especially those with normal renal function and controlled proteinuria, will have minimal maternal or fetal complications and overall good pregnancy outcomes, if the pregnancy has been carefully planned, monitored, and managed.

As already mentioned, monitoring includes the regular assessment of anti-dsDNA titers, complement levels, CBC, liver enzymes and renal function including urinalysis for hematuria and quantification of proteinuria by microalbumin-to-creatinine ratio, and when increasing by 24 h urine collection. It is our practice to monitor these parameters once monthly or more frequently where indicated. As anti-dsDNA and decreased C3 and C4 complements have been associated with poor pregnancy outcome, knowledge of the baseline values and whether the patient presents with concordant or discordant serology during flares is helpful when trying to judge disease activity during pregnancy. The usual clinical presentation of a lupus flare should be also noted and used as reference for the clinical assessment during pregnancy. Other serology that should be evaluated at least once before or in the first trimester include antiphospholipid antibodies, which may inform anticoagulation, as well as Anti-SSA (anti-Rho) and Anti-SSB (anti-La) to assess the risk of neonatal lupus with congenital heart block (Jaeggi et al. 2010). Pregnancies with positive Anti-Rho and anti-La titers should be monitored with serial fetal echocardiography. Blood pressure monitoring in office and at home when elevated should be an ongoing part of assessment to pick up the first signs of gestational hypertension or preeclampsia. As mentioned, a low sFlt-1 and elevated PlGF were effective in predicting severe adverse pregnancy outcomes in patients with SLE as noted in the PROMISSE study and may very well become the standard of care in the not too distant future (Kim et al. 2016).

Treatment of SLE should ideally have led to disease quiescence for at least 6 months prior to conception, and the patient should be switched and stable on pregnancy-safe medications (Bertsias et al. 2012). Azathioprine should replace mycophenolate mofetil for at least

3 months before conception, while biologic agents such as rituximab should not be administered closer than 3–6 months prior to conception whenever possible (Bertsias et al. 2012). Generally safe medications for use during pregnancy include prednisone, which could be used as pulse and maintenance therapy, calcineurin inhibitors, and azathioprine. Hydroxychloroquine is a mainstay of therapy in this disease. Although this antimalarial medication crosses the placenta, there is no evidence of fetal toxicity in doses of 200–400 mg/d. Hydroxychloroquine has been demonstrated to maintain remission of extrarenal manifestations of lupus, and decrease neonatal lupus when anti-Rho and anti-La antibodies are present (Tsakonas et al. 1998; Abarientos et al. 2011; Clowse et al. 2006). Hydroxychloroquine discontinuation during pregnancy has also been reported to promote lupus flares, resulting in a higher exposure to prednisone (Clowse et al. 2006). Ideally, it should be started prior to pregnancy, but we will also start it at the first pregnancy visit before the end of the first trimester along with low-dose ASA for preeclampsia prevention. Anticoagulation with low-molecular-weight heparin may also be required in women with positive antiphospholipid antibodies or a significant flare accompanied by nephrotic-range proteinuria.

Systemic Vasculitis, Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is fortunately rare in pregnancy as, unlike SLE, these diseases lack a female preponderance, and the peak onset is after 65 years of age. As such, little data is available on these diseases in pregnancy with respect to renal function decline and the potential for a pregnancy-associated relapse as well as adverse maternal and fetal outcomes. As such, the principles of management are largely extrapolated from studies on lupus nephritis.

Active vasculitis at time of conception can result in spontaneous abortions, and disease deterioration has led clinicians to recommend therapeutic abortions in the attempt to maintain maternal health given the teratogenicity of first-line therapies. De novo disease during pregnancy is rarely reported, so it is difficult to determine if there is a predilection for any particular trimester. In a retrospective review of 65 pregnancies followed by specialists in 8 institutions between 1995 and 2014, only 2 presented for the first time during pregnancy (Fredi et al. 2015). In another review of published cases, 8 of 21 patients developed relapse during pregnancy (Koukoura et al. 2008), but other studies have documented fewer relapses with only 18% of patients reporting worsening of vasculitis symptoms during pregnancy (Clowse et al. 2013).

Pregnancy outcomes are worse than the general population, and these pregnancies are not without significant risk to both mother and baby. In the aforementioned review of 65 pregnancies, vasculitis-related complications occurred in 23 pregnancies (35.4%), including 3 cases of transient ischemic attack (TIA). Further, early preterm delivery (<34 weeks) was significantly more frequent than in the general population (11.3% vs 5.0%, $p = 0.049$). Postpartum flares also occurred in 21.4% of pregnancies (Fredi et al. 2015). A survey of participants in the Vasculitis Clinical Research Consortium Patient Contact Registry that compared pregnancy outcomes prior to and after diagnosis of vasculitis reported higher rates of pregnancy loss and preterm delivery in those who conceived after diagnosis, especially among those wherein vasculitis activity worsened during pregnancy (Clowse et al. 2013).

Given the low number of cases and the high potential for reporting bias, it is important to closely observe these pregnancies within a multidisciplinary team in a tertiary health center to adjust the treatment approach on an individual basis. There is limited data to suggest well-managed patients that enter pregnancy in a remission do better. A small case series from the United Kingdom reported on 15 pregnancies noting that all were successful given that all, but one, were planned following a minimum of 6 months of clinical remission (Croft et al. 2015). The single flare was successfully treated with increased dose of azathioprine and corticosteroids, intravenous

immunoglobulin, and plasma exchange therapy, all safe in pregnancy. IVIG crosses the placenta in significant amounts (Hockel and Kaufmann 1986), but no side effects have been reported in neonates (Bellisai et al. 2004). Transplacental transmission of anti-MPO antibodies does occur. One case described neonatal pulmonary renal syndrome, which was successfully treated with steroids and exchange transfusions (Bansal and Tobin 2004), but antibodies have been detected in fetal blood after delivery without causing vasculitis-related symptoms (Alfhaily et al. 2009).

Antiglomerular Basement Membrane Antibody Disease

The experience with antiglomerular basement membrane (anti-GBM) antibody disease in pregnancy is minimal with only a handful of case reports in the literature that were recently summarized (Thomson et al. 2014), and overall outcomes are very poor. Renal biopsies were obtained in seven of eight women, three of them during the early second trimester (14–18 weeks). Dialysis was required in seven of eight patients during and in most chronically after pregnancy. Only two recovered renal function after treatment, one of which underwent therapeutic abortion at gestational age of 15 weeks. Significant pregnancy-related maternal morbidity was reported (2/8 preeclampsia, 2/8 hyperemesis gravidarum, 3/8 gestational diabetes, and 1/8 severe infection due to immunosuppressive pharmacotherapy). Treatments varied significantly and were partially started during pregnancy, and more aggressively pursued after delivery, including plasmapheresis and steroids in all pregnancies, cyclophosphamide in two cases during pregnancy with three delayed until after delivery. In the absence of cyclophosphamide during pregnancy, azathioprine was used for induction treatment. Fetal demise was seen in two of eight pregnancies. Prematurity was universal in all live-born babies (6/6) of which one was severely premature (26.5 weeks). Growth restriction and small for gestation age babies were also frequent. Congenital abnormalities were found in two of six live births. Anti-GBM antibodies could be found in some of the newborn's blood (2/5), but none were symptomatic with renal or pulmonary disease.

IgA Nephropathy

IgA nephropathy is the commonest primary nephropathy in the developed world so it is common in pregnancy as well. There is a low risk of deterioration of renal function in women with IgA nephropathy during pregnancy so long as renal function is preserved (Abe 1994). A study that compared 62 women who had 69 pregnancies to 62 matched nonpregnant controls determined that pregnancy was not an independent risk factor for disease progression over 45.7 months, but progression was minimal in both groups (−2.5 vs −2.4 mL/min/1.73m^2 per year, respectively, P = 0.7) (Liu et al. 2014). A large Italian study of patients recruited patients with IgA nephropathy and an eGFR >60 ml/min from 1974 to 2003, followed patients for a median of 10 years postpartum and confirmed no difference in progression between pregnant and nonpregnant groups (Limardo et al. 2010). Pregnancy outcomes in this cohort included 3% perinatal death, 10% premature delivery, and 21% development of hypertension with 8.5% superimposed preeclampsia. Shimizu and colleagues followed 67 patients with IgA nephropathy during pregnancy, and similarly renal function remained stable, and comparable to a nonpregnant control group, in the observation interval of 5 years postpartum, when entering pregnancy with eGFR >45 ml/min (N = 16) (Shimizu et al. 2015). However, women with eGFR <45 ml/min showed worsening renal function, with 91% of the women entering pregnancy at CKD stage 4 (eGFR 27+/− 4.2 ml/min; N = 11) reaching end-stage renal disease within 5 years postpartum, with requirement of renal replacement therapy after 3.9+/−0.7 years. Regardless of the eGFR, women with proteinuria >1 g/d (N = 10) developed hypertension in 60% and had low birth weight neonates in 30% of pregnancies. In a single-center retrospective study, proteinuria at conception was independently associated with a faster decline in

postpartum maternal eGFR (Oh et al. 2011). Based on this data, proteinuria should be stabilized and decreased prior to conception.

Hereditary Nephritis/Alport Syndrome

Type IV collagen mutations in the alpha-3, alpha-4, and alpha-5 chains cause longitudinal splitting and irregular thinning and thickening of the lamina densa of the glomerular basement membrane in Alport syndrome. It is a familial nephritis, which is passed on, in the majority of cases, as a X-linked trait (gene COL4A5) in the alpha-5 chain, and penetrance is widely variable in women due to differing degrees of X-gene lyonization (Artuso et al. 2012). The autosomal-recessive or more rarely autosomal-dominant forms of Alport syndrome are introduced through mutations in the alpha-3 chain (gene COL4A3) or alpha-4 (gene COL4A4) type IV collagen. As such genetic assessment and counseling is required in addition to discussions about potential pregnancy-associated complications.

Unfortunately, the only data available to guide pregnancy counseling is in form of case reports. The baseline renal function and the extend of proteinuria at conception seemingly determines progression of renal disease during pregnancy. One report documented good maternal and fetal outcomes in two consecutive pregnancies in a woman with X-linked Alport syndrome with normal renal function, normal blood pressure, and mild proteinuria at conception (Matsubara and Muto 2012), while women with more advanced CKD or higher grades of proteinuria are at higher risk for adverse outcomes as one would expect. One woman with Alport and stage 3 CKD (creatinine 106 umol/l, eGFR 57.8), controlled blood pressure below <140/90 mmHg, and 0.9 g/24 h proteinuria at conception developed severe pre-eclampsia at 25 + 2 weeks of gestation with renal failure and severe early-onset fetal growth restriction (Matsuo et al. 2007). Two women, both with proven missense mutations in the alpha-5 chain of type IV collagen, entered pregnancy with normal renal function and blood pressure at conception (Alessi et al. 2014), but different levels of baseline proteinuria, <1 g/24 h and 3.26 g/24 h, which increased in both to overt nephrotic-range proteinuria during pregnancy. The woman with baseline nephrotic-range proteinuria developed hypertension and delivered at 33 weeks of gestation. Her renal function declined to 42 ml/min postpartum at 22 months of follow-up, and her proteinuria returned to 3.21 g/24 h, while the woman with non-nephrotic-range proteinuria preconception maintained her renal function with a GFR 85 ml/min and returned to preconception proteinuria levels of 0.9 g/24 h. One may deduct from these reports that both a compromised GFR and the severity of baseline proteinuria impacts negatively on renal outcome in pregnancy, and despite the lack of data, general principles of counselling, already reviewed, apply to this subset of young women.

Thin Basement Membrane Nephropathy

Persistent (isolated) hematuria, normal renal function, minimal proteinuria, a family member with hematuria, and an overall benign course clinically characterize thin basement membrane nephropathy. Tissue biopsies exhibit diffuse thinning of the lamina densa of the glomerular basement membrane. Women and men are equally affected, and the incidence is about 5–9% in the general population (Dische et al. 1990). Women seemingly come more frequently to medical attention due to their thinner glomerular basement membranes resulting in more prominent and, therefore, more easily noticed hematuria (Savige et al. 2003). Usually, the prognosis is excellent, and this is equally true for renal and fetal outcomes during pregnancy.

However, earlier studies noted that isolated hematuria, which may very well represent women with thin basement membrane disease or mild IgA nephropathy, increased the risk of adverse pregnancy outcomes in particular an impressively increased odds ratio for both pre-eclampsia (OR 9.5, 95% CI 3.1–28.2) and preterm delivery (OR = 3.8, 95% CI 1.5–9.7) (Stehman-Breen et al. 2000). A subsequent analysis by the

same author utilizing data from the trial of Calcium for Preeclampsia Prevention (CPEP) study found a similar association, but of less magnitude with an adjusted odds ratio of 1.89, 95% CI 1.12–3.18 (Stehman-Breen et al. 2002). This association though was not confirmed by a large Australian study that assessed 1000 women for dipstick-positive hematuria, noting first that dipstick-positive hematuria in pregnancy was common (20%) and that there was no difference the development of gestational hypertension, preeclampsia, or small for gestational age babies between women with and without microscopic hematuria (Brown et al. 2005). This suggests that not all hematuria is of glomerular origin and perhaps studies need to look more carefully at pregnancy outcomes in women with microscopic hematuria in association with low-grade proteinuria.

Other Primary Glomerular Diseases

There is limited data on the pregnancy outcomes in women with the other primary causes of nephrotic syndrome, including minimal change disease, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy. Further many of the larger studies are quite dated. The largest study, spanning 1965–1994, assessed disease progression in 360 women with glomerular disease and preserved renal function (creatinine $\leq$ 100 μmol/l) and reported that pregnancy was not associated with accelerated progression, regardless of disease etiology (Jungers et al. 1995). Similarly, another study noted no hastened progression relative to a nonpregnant population, but higher rates of prematurity and neonatal death was documented compared to the general population, most notably in women with acceleration of hypertension and proteinuria during pregnancy (Barcelo et al. 1986).

There are a few case reports on de novo minimal change disease in pregnancy treated with prednisone, the standard treatment outside pregnancy. Overall outcomes were quite good with the exception of mild prematurity in one fetus (35 weeks) (Nelson 2003; Hamilton et al. 2014). There is a similar paucity of data available for the treatment of FSGS in pregnancy, and treatment choices are prednisone and/or a calcineurin inhibitor.

There are also few reports on pregnancies in idiopathic membranous nephrology describing overall poor outcome associated with nephrotic-range proteinuria in the first trimester (Aoshima et al. 2013). In an older study of 33 pregnancies, there was a significant increase in proteinuria in 55% with nephrotic syndrome in 30%, gestational hypertension in 46%, and a decrease in renal function in 9% (Packham et al. 1987). Fetal loss occurred in 24%, and 43% of neonates were delivered prematurely (Packham et al. 1987). Idiopathic membranous nephropathy presents with circulating M-type phospholipase A2 receptor (PLA2R) antibodies in the nonpregnant population (Beck et al. 2009). Even though one report confirmed that this antibody can be found during pregnancy (Al-Rabadi et al. 2016), it is not clear if this biomarker can be used to reliably diagnose idiopathic membranous nephropathy. Calcineurin inhibitors and low-dose prednisone have been used for treatment; also a combination of prednisone and azathioprine was used with variable success (Aoshima et al. 2013; Sebestyen et al. 2008). As mentioned there is not as yet enough experience with rituximab in pregnancy available to determine the long-term fetal outcomes after exposure to this medication.

Atypical Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura (TTP)

Atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) both fall into the spectrum of thrombotic microangiopathies characterized by microvascular endothelial activation, cell injury, and thrombosis. Both these conditions pose a significant threat in pregnancy. As HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and preeclampsia share common features with aHUS and TTP, such as hypertension, proteinuria, microangiopathic hemolysis, and decreased

platelet count, distinction can be challenging, but is critical as treatment varies significantly. Although TTP can present in any trimester, it more commonly presents later in gestation as does the HELLP syndrome, while aHUS most commonly presents in late gestation and the early postpartum. The absence of improvement of the platelet count 3–5 days after delivery may be an indicator that indeed the underlying etiology is aHUS or TTP rather than preeclampsia or HELLP syndrome.

As pregnancy in some way incites the cascade of endothelial disruption resulting in microthrombi, it is a well-described precipitant (George et al. 2004), and a significant percentage of young women with TTP present for the first time during pregnancy (Wiznitzer et al. 1992; Meti et al. 2010). There are a number of theories why pregnancy might pose a heightened risk for the development of TTP, including the procoagulant state that accompanies pregnancy as well as the potential effect of estrogen on the level of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motifs 13), which progressively decreases throughout pregnancy to nadir in the early postpartum period. In the largest, most complete patient registry of TTP-HUS from Oklahoma City, pregnancy accounted for 26 of the 352 cases collected over approximately 15 years, and the vast majority presented in the third trimester and early postpartum period (George et al. 2004). Plasmapheresis, which is the mainstay of treatment, inhibits platelet aggregation, replenishes absent ADAMTS13, and/or removes pathogenic antibodies.

Atypical HUS, secondary to genetic mutations involving the activation or regulation of the alternative complement pathway, can be induced by pregnancy, presenting clinically with low serum complement levels and predominant renal involvement. Currently, data is limited, but overall maternal outcome appears to be quite poor. Documented cases most frequently present in the postpartum period with only 20% presenting during pregnancy, without preference for a specific trimester. Severe renal involvement is typical, necessitating dialysis during the acute phase of the disease in 81% with 62% reaching ESRD within a month despite therapy, a number that increased to 79% on further follow-up (Fakhouri et al. 2010). However, given the late onset of disease, fetal outcomes are reasonable with the vast majority proving uneventful (74.7%). Eculizumab, a humanized monoclonal antibody, blocks the terminal step in the formation of the membrane attack complex by inhibiting cleavage of C5a to C5b, and stops with it the uncontrolled alternative complement pathway activation. Eculizumab is likely to improve pregnancy outcomes, as successful pregnancies in women with known aHUS on maintenance treatment with eculizumab have been reported (Servais et al. 2016). However, most of the current experience with this drug comes from patients with paroxysmal nocturnal hemoglobinuria and the PNH registry (75 pregnancies from 61 women) (Kelly et al. 2015). Although eculizumab was documented in 7/20 cord blood samples, the antibody was not found in breast milk samples (0/10). Reported dosing of this medication in known aHUS is every other week; however, the authors suggest to individually dose treatment based on the complement level suppression, which may vary during pregnancy (Servais et al. 2016).

Summary Statements

The rarity of glomerular diseases in general results in a challenge in pregnancy due to the paucity of data beyond case reports and case series available to guide counseling and management. However, it must be remembered that overall live births are the rule and that careful prepregnancy counseling and optimization likely improves outcomes. Further, there is a renewed interest in these patients with large observational cohorts including Nephrotic Syndrome Study Network (NEPTUNE) (NCT01209000) and Cure GN (https://curegn.org), which will also assess pregnancy outcomes and can potentially guide future collaborative research.

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Lipoprotein Glomerulopathy, Non-AL Amyloidosis, LCAT, ING

49

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Abstract

Lecithin cholesterol acyl transferase (LCAT) deficiency is a disorder of cholesterol metabolism caused by reduced or absent activity of LCAT. The condition may arise from genetic inheritance of a defective or absent enzyme or may be acquired by development of an autoantibody that inhibits the enzyme's function (Vaziri et al. 2001). In either case, the result is accumulation of non-esterified cholesterol in various sites, particularly the glomerulus.

Keywords

LCAT deficiency · Lipoprotein glomerulopathy · Idiopathic nodular glomerulosclerosis · Smoking-associated glomerulopathy · Amyloidosis · ALECT2 · AA amyloidosis

LCAT Deficiency

Lecithin cholesterol acyl transferase (LCAT) deficiency is a disorder of cholesterol metabolism caused by reduced or absent activity of LCAT. The condition may arise from genetic inheritance of a defective or absent enzyme or may be acquired by development of an autoantibody that inhibits the enzyme's function (Vaziri et al. 2001). In either case, the result is accumulation of non-esterified cholesterol in various sites, particularly the glomerulus. Patients present with proteinuria and later renal insufficiency, and kidney biopsy demonstrates lipid deposits in the glomerular basement membrane and mesangium. Treatments for this rare disorder remain largely experimental (Hirashio et al. 2014).

Clinical Presentation

There are three clinical syndromes caused by deficiency of LCAT: Familial LCAT deficiency (inherited absence of LCAT activity), fish eye disease (inherited partial LCAT activity), and acquired LCAT deficiency. The diversity of mutations described in familial LCAT deficiency accounts for some variation in severity and onset of symptoms, and polymorphisms of apoE interact as a clinical modifier (Baass et al. 2009). The earliest manifestations, usually in the first two decades of life, are cloudy corneal opacities due to accumulation of free cholesterol in the cornea (Winder and Bron 1978). Kidney involvement presents with proteinuria, which may also develop early in life; however, the severity and age of onset are variable. Mild hematuria and hypertension are additional possible findings. The development of renal insufficiency usually takes place in adulthood. Patients may also have extra-renal organ involvement, including the liver and spleen. Anemia is common and is likely due to the combined effects of hemolysis from excess cholesterol integration into red blood cell membranes, and cholesterol deposition with macrophage reaction in the bone marrow. Laboratory findings reflect altered lipid metabolism, with markedly reduced serum HDL and increased serum free cholesterol, ApoE, and lipoprotein X levels.

Patients with the Fish-eye disease syndrome, in which there is genetically reduced but not absent LCAT activity, develop corneal opacities but tend not to have kidney involvement (Saeedi et al. 2015). Patients with the syndrome of acquired deficiency of LCAT harbor a circulating inhibitor of the enzyme, likely an autoantibody. Such patients accordingly present concurrently with or sometime after the development of the

autoantibody, and on average present later in life than in the familial syndrome. Acquired LCAT deficiency may also present with more rapidly evolving and severe proteinuria due to a simultaneous membranous nephropathy (see below).

Histopathologic Findings

The renal lesions in LCAT deficiency most prominently affect the glomerulus, where lipid deposits accumulate in the mesangium and glomerular capillary walls. Lipid may also deposit in the walls of arteries and arterioles. Microscopic examination of tissue sections reveals glomeruli with widened capillary walls of pale and vacuolated appearance. There may be basement membrane holes and spikes visible on silver stains, similar to those seen in membranous glomerulopathy. The mesangium is expanded with a bubbly or rarefied matrix and may contain cells with intracellular lipid giving the appearance of foam cells. Foam cells may also be present within capillary lumens (Fig. 1). Immunofluorescence is unremarkable. Electron micrographs demonstrate lipid deposits in the glomerular basement membrane and the mesangium. Such deposits may appear as clear holes with a dark electron-dense central area with granular or serpiginous quality (Hirashio et al. 2014) (Fig. 2). In acquired LCAT deficiency, the lesion may also be accompanied by membranous glomerulopathy with typical subepithelial or intramembranous immune complex deposits that stain for IgG on immunofluorescence (Takahashi et al. 2013). Interestingly, antibodies specific to LCAT show the presence of LCAT protein in the immune deposits, indicating that the autoantibody inhibiting the enzyme is also likely the same antibody forming immune complexes in the glomerular basement membrane (Takahashi et al. 2013).

Therapy and Prognosis

At the present time there is no established therapy for LCAT deficiency. Some authors report beneficial effects of restricting fats in the diet, with renal disease potentially abrogated by both dietary fat reduction and angiotensin II receptor blockers (Naito et al. 2013). Lipid lowering drugs have not been proven to be effective thus far. Investigative efforts are focused on developing enzyme replacement therapy as a means to correct the lipid metabolic abnormalities (Dimick et al. 2014). Kidney transplantation is eventually required in patients progressing to renal failure, and although recurrence of lipid deposits is expected and may be quite early, the allograft may survive many years as the deposits slowly accumulate. Sequential kidney-liver transplantation can be curative (Ahmad et al. 2016).

Pathophysiology

LCAT is an enzyme synthesized in the liver and circulates in association with HDL, and to a lesser extent LDL and VLDL, lipoprotein particles. LCAT catalyzes esterification of free cholesterol on the surface of lipoprotein particles, transferring a fatty acid from phosphatidyl choline to cholesterol. This activity allows for the net movement of cholesterol away from cells toward lipoprotein particles by establishing a concentration gradient. The biochemical assays refer to LCAT activity present on HDL as α-LCAT, while that associated with LDL and VLDL is called β-LCAT.

Genetic LCAT deficiency has an autosomal recessive inheritance pattern, with homozygous mutations in the LCAT gene causing loss of enzyme activity (so-called familial LCAT deficiency) or loss of the α-activity with retention of the β-activity ("Fish-eye disease"). There are nearly 90 different mutations reported describing families with LCAT deficiency, resulting in a spectrum of disease severities. Pathology involving the cornea, kidney, liver, spleen, red cells, and marrow is due to accumulation of cholesterol and lipoprotein X in these tissues (Hirashio et al. 2014).

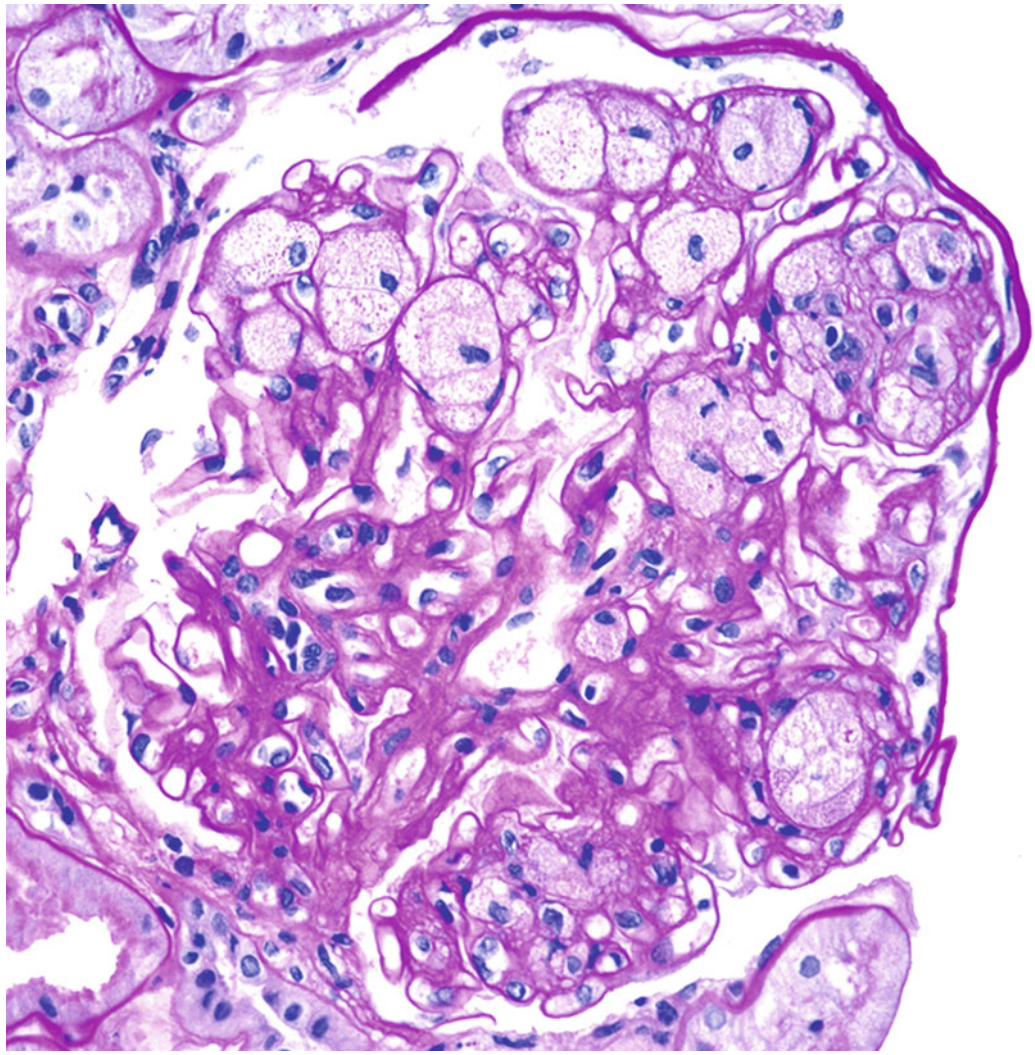

Fig. 1 Glomerulopathy of LCAT deficiency. There are cells distended with lipid (foam cells) in the mesangium and capillary lumens. Segmental capillary wall widening and palor are present (12 o'clock). PAS, 400× (Image courtesy of Dr. Patrick Walker, Little Rock, AR)

Lipoprotein Glomerulopathy

Lipoprotein glomerulopathy is a recently described, rare glomerular disease associated with genetic mutations in the Apolipoprotein E (apoE) gene. It presents with proteinuria or sometimes overt nephrotic syndrome in otherwise asymptomatic patients. The majority of cases described to date originate in Asian populations, although some more recent cases affect individuals with European ancestry. Thrombi composed of lipid are lodged in the glomerular capillaries, and occasional mesangial foam cells may be seen. There is variable progression to end stage renal disease. The treatments reported with some success have employed lipid-lowering agents such as fibrates (Saito et al. 2014).

Clinical Presentation

Patients with lipoprotein glomerulopathy typically present with isolated proteinuria of varying

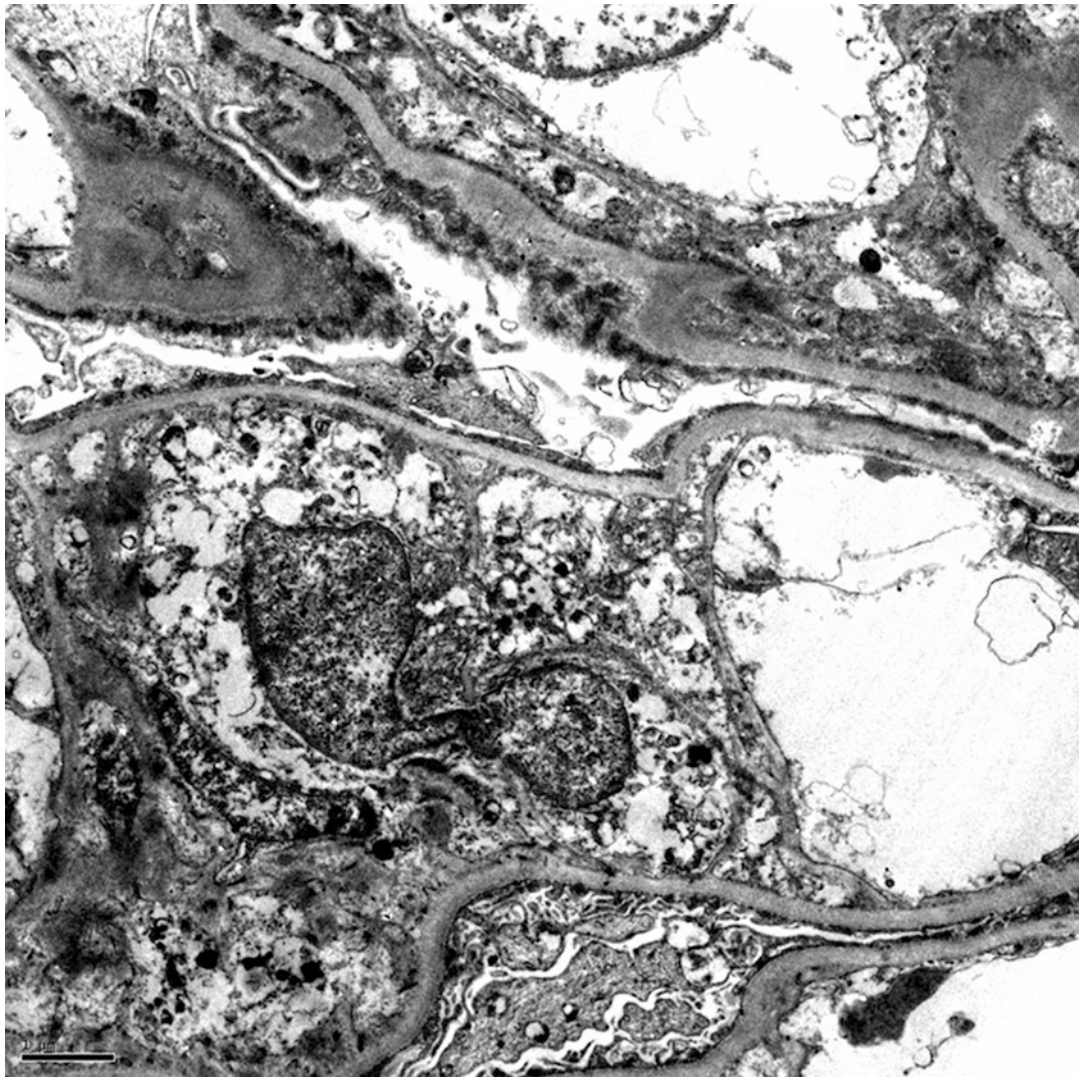

Fig. 2 Glomerulopathy of LCAT deficiency. On electron microscopy, lipid deposits within foam cells and mesangial matrix appear as clear spaces with dark granular or serpiginous cores. Electron micrograph, 8000× (Image courtesy of Dr. Patrick Walker, Little Rock, AR)

severity, but usually asymptomatic without extra-renal involvement. Some patients develop nephrotic syndrome during the course of the disease (Saito et al. 2006). An interesting feature of this disease is its nearly exclusive involvement of the glomerulus, with only rare extra-renal symptoms of lipidosis such as xanthomas. Plasma lipid abnormalities are present and resemble type III hyperlipidemia, characterized by elevated triglycerides and total cholesterol, with increased VLDL and IDL fractions, along with increased ApoE.

Histopathologic Findings

Glomerular capillaries are distended and contain luminal microthrombi of material that appears pale on sections stained with H&E or toluidine blue (Fig. 3). There may be foam cells present in the mesangium. Special stains such as Oil Red O or Sudan Black identify the composition of the capillary luminal material as lipid. Immunohistochemistry has been employed to demonstrate the presence of ApoE also within the microthrombi.

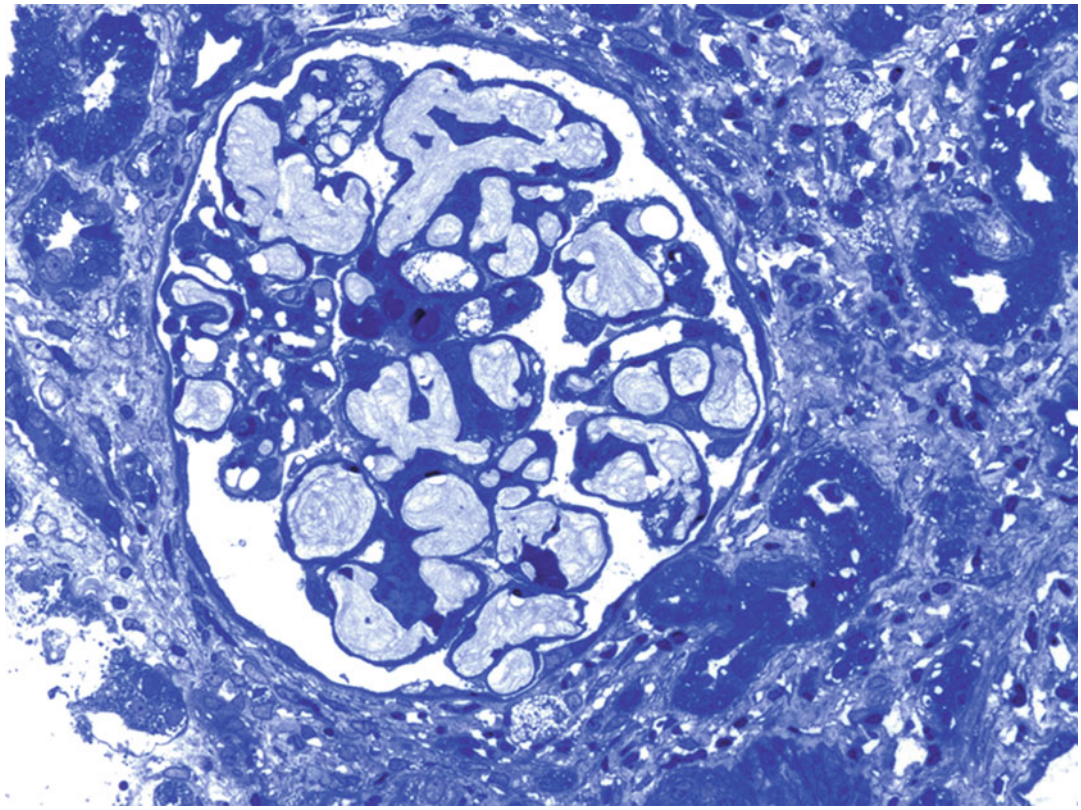

Fig. 3 Lipoprotein glomerulopathy. Capillary lumens are distended by lipid microthrombi. Toluidine blue, 400× (Image courtesy of Dr. Patrick Walker, Little Rock, AR)

On electron microscopy, the lipid microthrombi have a layered or lamellar appearance that has been compared to a fingerprint (Saito et al. 2014) (Fig. 4).

Therapy and Prognosis

Due to the rarity of lipoprotein glomerulopathy, established treatment approaches based in large clinical trials are not available. The most promising results to date have been obtained by using lipid-lowering drugs that contain fibrates (Matsunaga et al. 2009; Ieiri et al. 2003). Several such reports demonstrated marked reduction in proteinuria, and serial biopsies showed loss of the glomerular lipid microthrombi. Because these findings were obtained over a short time period, whether fibrate therapy remains an effective approach over the long term has not yet been proven. Another report showed reduced proteinuria after LDL-apheresis therapy in a patient with the unique apoE Modena mutation which leads to ApoE dimerization (Russi et al. 2009). Finally, a series of 13 patients with lipoprotein glomerulopathy was given a trial of immunoadsorption over a protein A substrate. The result was a reduction in proteinuria and creatinine, with subsequent renal biopsy showing reduction in the glomerular microthrombi. The mechanism by which immunoadsorption with protein A, which binds the Fc region of IgG, is effective in treating lipoprotein glomerulopathy is unclear. In patients receiving kidney allografts, the disease invariably recurs as would be expected from a systemic lipidosis (Xin et al. 2009).

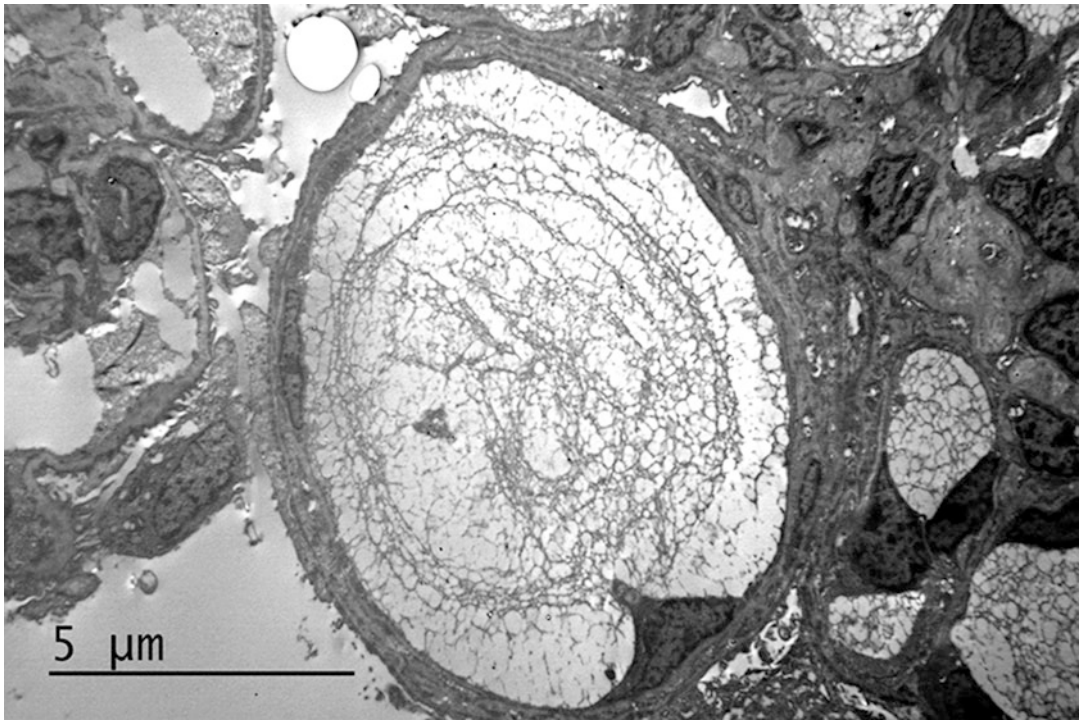

Fig. 4 Lipoprotein glomerulopathy. On electron microscopy, lipid microthrombi have a lamellated or fingerprint-like appearance. Electron micrograph, 8000× (Image courtesy of Dr. Patrick Walker, Little Rock, AR)

Pathophysiology

Lipoprotein glomerulopathy was first described in a report from Japan in 1989, in which a patient with resistant nephrotic syndrome was found to have glomerular lipid thrombi and type III hyperlipidemia. Characterization of this unique entity allowed subsequent identification of additional patients, most of whom were from Asian countries. Investigations have focused on ApoE because of its characteristic elevation in these patients, and because type III hyperlipidemia is associated with homozygosity of an infrequent isoform called ApoE2. Patients with lipoprotein glomerulopathy, however, instead of having homozygous ApoE2, were discovered to have heterozygosity at this locus with only one apparent ApoE2 by isoelectric focusing. Further, genetic sequencing revealed this ApoE2-like species to be a novel mutation, named ApoE Sendai. Since then, many additional ApoE mutations have been discovered in patients with lipoprotein glomerulopathy, most bearing the name of the cities where the patients were found. While most mutations have been found in patients with Asian descent, a few have been identified in Caucasians (e.g., ApoE Modena, ApoE Las Vegas).

The mechanism by which these ApoE mutations cause lipoprotein glomerulopathy is not fully understood. Inheritance of the disease follows an autosomal dominant pattern with variable penetrance, as there are some carriers of ApoE Sendai who do not have the disease. Thus there must be other unidentified environmental or genetic components underlying expression of the disease phenotype. ApoE is a component of lipoprotein particles and acts as a ligand for LDL receptors to facilitate lipoprotein transport and metabolism. Mutations associated with lipoprotein glomerulopathy are found in the LDL receptor binding region, but also outside this region, and some are deletions. Introduction of ApoE Sendai into mice reproduces the glomerular disease phenotype. Hypotheses under investigation include increased binding affinity to

the endothelial cell surface favoring thrombus formation, and altered protein folding that would favor aggregation and potentially formation of a lipoprotein thrombus. Whatever the mechanism, it must account for the striking glomerulocentricity of the lesion (Saito et al. 2014).

Idiopathic Nodular Glomerulosclerosis

Like many terms used in the practice of pathology to characterize and classify the morphologic lesions seen in diseased tissue, "nodular glomerulosclerosis" describes an injury pattern rather than specifying an etiology. Because the kidney may respond in similar ways to disparate sources of injury, in theory multiple clinical conditions can give rise to a single injury pattern such as nodular glomerulosclerosis. Thus the injury pattern previously thought to be pathognomonic for diabetic nephropathy, characterized by basement membrane thickening, nodular mesangial expansion, and exudative lesions, was reported in 1989 and 1999 to be present in rare patients without diabetes (Herzenberg et al. 1999). These cases were placed in a category termed "idiopathic nodular glomerulosclerosis." Several studies have examined series of patients with idiopathic nodular glomerulosclerosis and found an association with histories of smoking and hypertension, raising the hypothesis that at least some of these lesions are attributable to chronic smoking- and hypertension-related damage to endothelium (Nasr and D'Agati 2007).

Histopathologic Findings

Essentially indistinguishable from diabetic glomerulosclerosis at the level of light microscopy, glomeruli show mesangial sclerosis with variable nodule formation (Fig. 5). There may be microaneurysm formation, capillary hyaline insudation, and hyalinosis of Bowman's capsule. Capillary walls are thickened. An interesting feature which may be somewhat more prominent as compared with diabetic glomerulosclerosis is the presence of small vascular channels within sclerotic nodules. Just as diabetic nephropathy demonstrates a range of mesangial sclerosis severity and in some biopsies well-formed nodules may not be present, some cases attributed to smoking-related glomerulopathy have shown a pattern of diffuse rather than nodular mesangial sclerosis, and some with findings similar to chronic thrombotic microangiopathy. Immunofluorescence may demonstrate weak linear IgG staining of glomerular and tubular basement membranes, similar to that seen in diabetic nephropathy, but is otherwise negative or nonspecific. On electron microscopy, there is marked glomerular basement membrane thickening and mesangial matrix increase. There may also be variable subendothelial expansion and basement membrane duplication. Endothelium-lined small vascular channels may be seen within the expanded mesangial matrix (Nasr and D'Agati 2007; Li and Verani 2008).

Pathophysiology

The similarity of the lesion in patients with idiopathic nodular glomerulosclerosis with that of diabetic glomerulosclerosis suggests the possibility of similar pathophysiologic mechanisms. The mechanisms involved are likely complex and multifactorial. The hyperglycemic conditions of diabetes produce advanced glycation end products (AGE), altering cellular functions and the extracellular matrix. AGE are also increased in some tissues in tobacco smokers. Pentosidine, an AGE species detectable by immunohistochemistry, is present in the mesangium in biopsies with idiopathic nodular glomerulosclerosis and in diabetic nephropathy. A common pathogenic pathway active in both diabetic nephropathy and in cigarette smoking-related injury is oxidative stress, which among myriad other effects results in increased extracellular matrix production as seen in the expanded mesangium and thickened basement membranes seen in these lesions (Tanji et al. 2000).

Non-AL Amyloidosis

Amyloidosis is a group of diseases caused by the pathological deposition in various organs of misfolded protein with characteristic biochemical

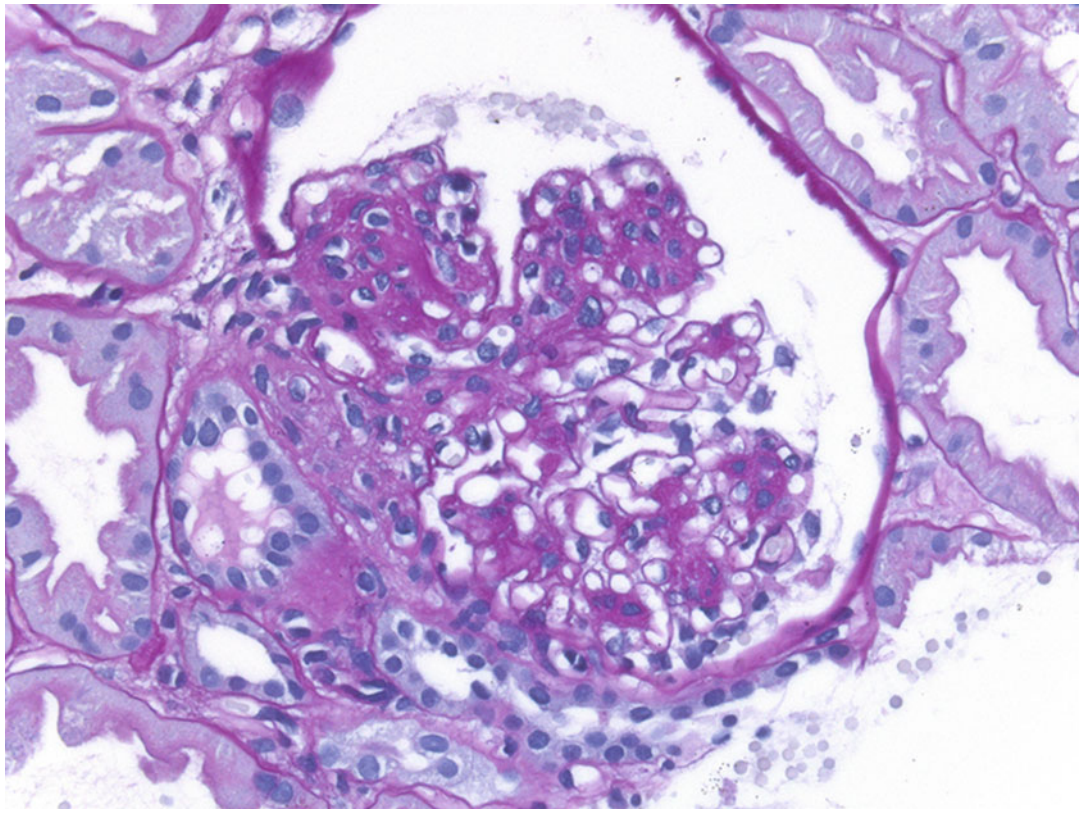

Fig. 5 Idiopathic nodular glomerulosclerosis. Mesangial areas are expanded in a nodular pattern, and there is capillary wall thickening. Small vascular channels are visible in some mesangial sclerotic areas. PAS, 400×

and biophysical properties. Amyloid deposits result from mutations or increased concentrations of one of an increasingly identified number of different proteins (Table 1) having in common the propensity to aggregate as insoluble fibrils of 8–10 nm width. The pathogenesis of the amyloidoses differs depending on the identity of the precursor protein and includes hereditary pathogenic mutation, somatic mutation, overproduction of wild type protein, or reduced excretion of wild-type protein. Amyloidosis nomenclature identifies the precursor protein preceded by the letter A. Amyloidosis type AL, or light chain amyloidosis, is the most common type of amyloidosis and is reviewed in ▶ Chap. 33, "Light Chain (AL) Amyloidosis and the Kidney." Here we review the non-AL amyloidoses with attention to their clinical characteristics and pathophysiology. While clinical features vary depending on the amyloid subtype (Table 2), pathologic diagnosis of all types follows a similar approach.

Histopathologic Findings

Rudolf Virchow in 1854 first used the term "amyloid" to describe these organ deposits, due to their gross appearance and chemical reactivity having similarities to starch. In the 1920s, it was discovered that Congo red dye, initially used in textiles, preferentially stained amyloid deposits and causing them to exhibit birefringence under polarized light. When electron microscopy later found amyloid deposits to be composed of randomly arranged fibrils 8–10 nm thick, these properties of Congo red avidity, birefringence, and fibrillary ultrastructure became the defining criteria for the

Table 1 Different types of renal amyloidosis

Renal amyloidosis		
Fibril protein	Precursor soluble protein	Non-renal target organs
AL, AH, AHL[a]	Ig light, heavy and heavy. light chains	All organs except CNS
AA	Serum amyloid A	All organs except CNS
ATTR	Transthyretin	Heart, ligaments, PNS, ANS, eye, leptomeninges
Aβ2M[b]	β2-Microglobulin	Musculoskeletal system, ANS
AApoAI	Apolipoprotein A I	Heart, liver, PNS, testis, larynx, skin
AApoAII	Apolipoprotein A II	Adrenal glands and small vessels
AApoAIV	Apolipoprotein A IV	Kidney medulla and heart
AApoCII	Apolipoprotein C II	Kidney
AApoCIII	Apolipoprotein C III	Kidney
AGel	Gelsolin	PNS, cornea, and skin
ALys	Lysozyme	Liver, GI tract, spleen, lymph nodes, skin, and salivary glands
ALECT2	Leukocyte chemotactic factor-2	Lungs, liver, adrenal glands, spleen ad colon
AFib	Fibrinogen Aα	Adrenal gland, spleen, and PNS

Abbreviations: *Ig* immunoglobulin, *CNS* central nervous system, *ANS* autonomic nervous system, *PNS* peripheral nervous system, *GI* gastrointestinal

[a]Reviewed in ▶ Chap. 33, "Light Chain (AL) Amyloidosis and the Kidney"

[b]Causes dialysis-related amyloidosis; no known kidney involvement

tissue diagnosis of amyloidosis. The recent application of mass spectrometry to characterize the amyloid protein deposits in microdissected glomeruli and other tissues has found a specific profile of amyloid-associated proteins whose detection may potentially identify and subtype amyloid with greater sensitivity than traditional histologic and immunostaining techniques. This amyloid proteomic signature includes Serum Amyloid P, ApoAIV, and ApoE, in addition to the amyloidogenic protein itself.

Light microscopic examination of tissue sections shows deposits of lightly eosinophilic material that appears glassy or fluffy. The material is weak to negative on Jones silver stain, and purple to gray on trichrome. Congo red stains amyloid deposits a salmon pink color (Fig. 6), while also conferring birefringence under polarized light that is usually light green to yellow, but other colors are also possible (Fig. 7). Staining of sections with Thioflavin T is another method of identifying amyloid, which gives a fluorescent reaction when bound to amyloid. In the kidney, deposits are most commonly found in the glomeruli, arterial walls, and interstitium. There is typically no cellular inflammatory reaction to the deposits, which appear to expand and distort tissue structures. Immunohistochemistry or immunofluorescence stains amyloid according to the identity of the amyloidogenic protein with variable success depending on the antibody and antigen, yielding a stain that is sometimes described as "smudgy" (Fig. 8). Electron microscopy shows deposits in glomerular basement membranes, mesangium, vessel walls, and interstitium. The deposits are composed of randomly oriented fibrils of varying lengths but with characteristic width of 8–10 nm (Fig. 9).

Epidemiology and Pathophysiology

AL and AA are the most common forms of amyloidosis. In the largest series from the USA, the following relative frequencies were reported: AL (85.9%); AA (7.0%), ALECT-2 (2.7%); AFib (1.3%); Apo AI, Apo AII, or Apo AIV (0.6%); and unclassified (2.3%) (Said et al. 2013). With the advances of mass spectrometry, some of this distribution is expected to change since some rare forms of hereditary amyloidosis were misclassified as AL. The incidence of AA is decreasing in developed countries, and some series are starting to show an incidence of ALECT-2 equal to or higher than AA. AA amyloidosis continues to be the most prevalent form of amyloidosis in developing countries where limited access to care for chronic infection and chronic inflammatory disease leads to prolonged

Table 2 Distinctive characteristics of non-AL amyloidosis

Types	Pathogenesis	Histology	Clinical presentation	Therapy
AA	Chronic infections or inflammatory disease Sustained production of the inflammatory protein SAA	Glomerular, interstitial, and arterial deposits rare medullary involvement	CKD Severe proteinuria	Supportive Treatment of the underlying inflammatory/infectious process
AApoAI	Mutation of ApoAI gene	Inner medulla peritubular amyloid deposits	Older patients Progressive CKD with minimal proteinuria	Statin therapy Liver transplantation is curative
AApoAII	Mutation of ApoAII gene	Mainly glomerular	Older patients CKD and proteinuria	Statin therapy Liver transplantation is curative
AApoAIV[a]	No mutation identified Kidney restricted	Medullary deposits	Progressive CKD with minimal proteinuria	Supportive therapy
AApoCII	Mutation of the ApoCII gene	Mainly glomerular Some vascular and interstitial involvement	Older patients CKD and proteinuria	Fibrate therapy
AApoCIII	Mutation of the ApoCIII gene	Mainly glomerular Some vascular and interstitial involvement	Older patients CKD and proteinuria Frequent extra-renal involvement (e.g., sicca)	Fibrate therapy
AGel	Gelsolin mutation	Glomeruli restricted deposits	Nephrotic range proteinuria	Supportive therapy
ALys	AD mutation of the lysozyme gene	Glomerular, vascular and interstitial deposits	CKD and mild proteinuria	Supportive therapy
ALECT2	No mutation identified Hispanic ancestry (recently ALECT2 reported in other ethnicities)	Mainly glomerular and interstitial deposits	CKD +/− proteinuria	Supportive therapy
AFib	Mutation of fibrinogen A α-chain AD with variable penetrance	Mainly glomerular	Older with CKD and proteinuria High incidence of cardiovascular disease	Supportive Recurs in the kidney allograft Combined liver-kidney transplant is curative but with high mortality

Abbreviations: *CKD* chronic kidney disease
[a]ApoAIV is co-expressed with other amyloid proteins; in AApoAIV, mass spectrometry fails to identify other amyloidogenic protein other than ApoAIV

inflammation. Because hereditary amyloidoses are due to mutations, their geographic distributions can be heterogeneous.

The mechanisms underlying formation of amyloid deposits differ somewhat across amyloidosis subtypes. In general, amyloidosis is a problem of misfolded proteins assuming a beta-pleated repeating structure, rendering them resistant to proteolytic degradation. Misfolding may be a function either of protein mutation or concentration. Molecular chaperones to some extent are able to recognize and bind amyloid, but the system for proper

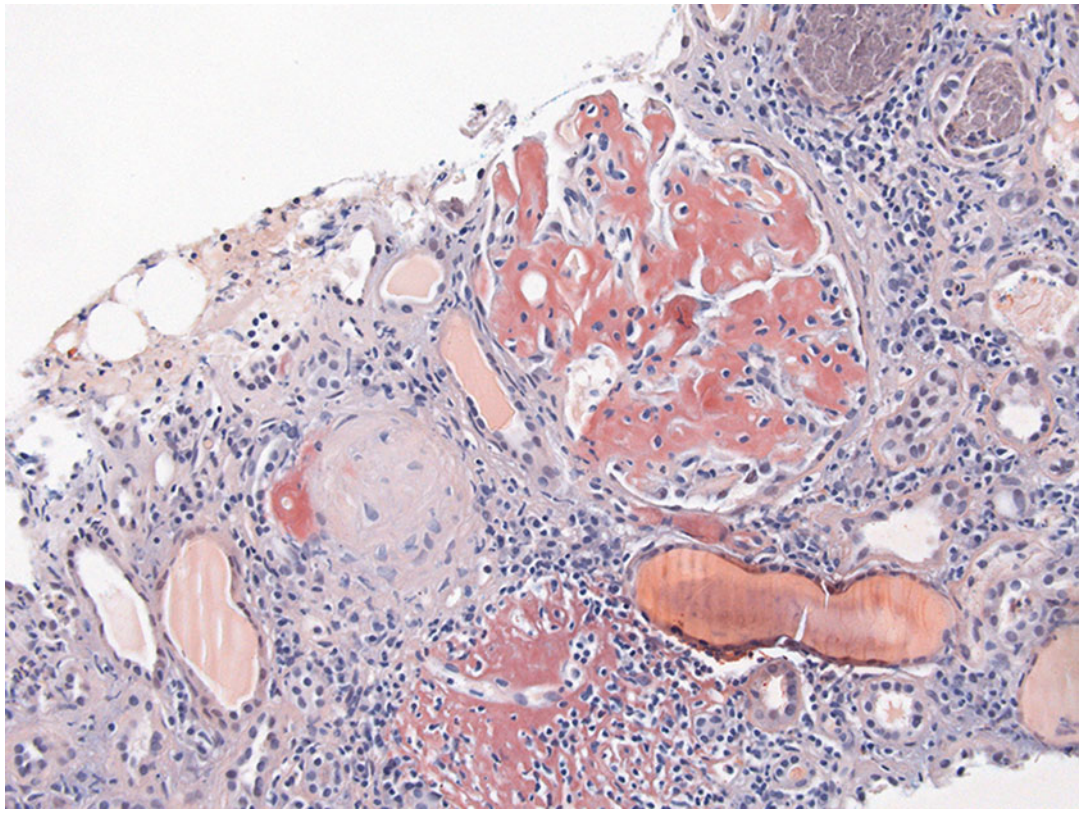

Fig. 6 Amyloid deposits appear salmon pink when stained with Congo red, and are seen throughout the glomerular mesangium and capillary walls, as well as interstitium and a vessel wall. Congo red, 200×

subsequent trafficking and degradation is either overwhelmed or otherwise dysfunctional. These chaperone proteins make up part of the proteomic signature that is detected in mass spectrometric analysis of amyloid deposits.

AA Amyloidosis

The epidemiology of AA amyloidosis has a regional variation and is the second most common form of amyloidosis in Europe and the United States after AL. In developing areas of the world, AA amyloidosis is the predominant type (Larsen et al. 2016) and the most common form of amyloidosis in children worldwide (von Hutten et al. 2009).

There is a median lag of 17 years between the onset of the inflammatory disease and the diagnosis of AA amyloidosis (Lachmann et al. 2007). Up to 97% of AA patients present with kidney disease. Since the deposits are predominantly glomerular, the proteinuria is pronounced with nephrotic syndrome in more than half of patients. An unusual finding in amyloidosis, crescentic glomerulonephritis was described in AA associated with RA or its variants (Uemichi et al. 1994; von Hutten et al. 2009). The reason for an aggressive crescentic presentation in these cases is unclear.

The amyloid fibrils of AA are derived from Serum Amyloid A (SAA) protein, which is an apolipoprotein component of HDL. SAA is produced in the liver and is an acute phase reactant (Simons et al. 2013). The underlying inflammatory stimuli associated with development of AA amyloidosis include chronic inflammatory arthritis, infection, periodic fever syndromes (such as familial Mediterranean fever), inflammatory bowel disease, neoplasia, and Castleman disease.

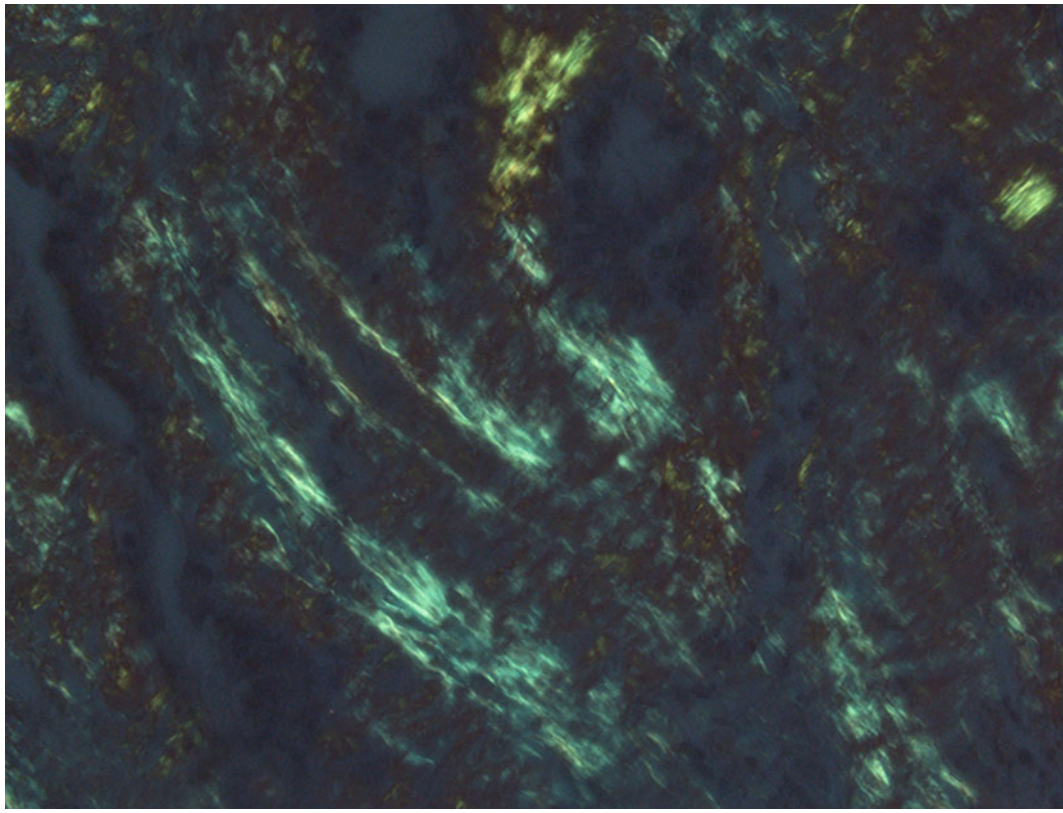

Fig. 7 Amyloid deposits stained with Congo red exhibit green to yellow birefringence when viewed under polarized light. Congo red with polarizer, 400×

AA treatment is primarily directed at the underlying chronic inflammatory condition. By treating the inflammation, SAA production was decreased and the amyloid deposits may regress over months or years (Lachmann et al. 2007). Another strategy is exemplified by Eprodisate, which disrupts the interaction between amyloid fibrils and glycosaminoglycans, thereby inhibiting the formation of tissue deposits (Dember et al. 2007). Recurrence of AA in the renal allograft is a potential risk if the underlying inflammatory process is not addressed.

ALECT2 (Leukocyte Chemotactic Factor-2) Amyloidosis

Leukocyte chemotactic factor-2 amyloidosis (ALECT2) is a recently described form of amyloidosis whose recognition is increasing with expanded application of mass spectrometry. In developed countries, ALECT-2 (2.7%) was the third leading cause of amyloidosis following AL (85.9%) and AA (7%) (Said et al. 2013). Initial reports from the USA showed a higher frequency of this disease in Hispanic patients with Mexican ancestry (Nasr et al. 2015). More recent studies show other ethnicities affected, such as in Egypt where ALECT-2 is the second leading cause of amyloidosis after AA (AA (48%); ALECT-2 (31%); AL (20%) (Larsen et al. 2016). ALECT-2 is becoming recognized as the most frequent of the rare types of amyloidosis (Hutton et al. 2014; Said et al. 2014; Larsen et al. 2014; Kulkarni et al. 2015; Holanda et al. 2011; Wang et al. 2015).

ALECT2 presents with slowly progressive renal failure, with 40% of patients also having proteinuria. The age range of presentation varies

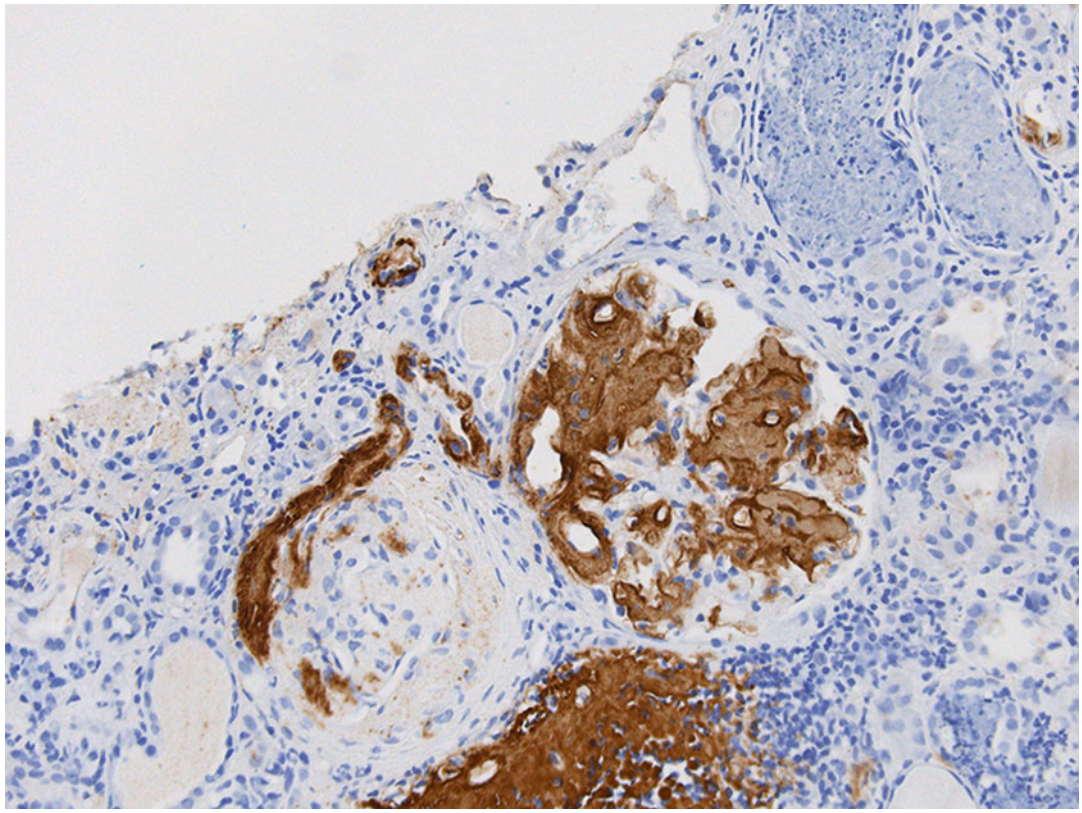

Fig. 8 AA amyloidosis. Deposits in AA amyloidosis stain positively with antisera against serum amyloid A protein, and are seen here in the glomerulus, interstitium, and vessel wall. Immunohistochemistry for SAA, 200×

from the early 30s to late 80s. This variation in age at presentation may be a reflection of differing thresholds for kidney biopsy performance across institutions in this slowly progressive kidney disease. Although LECT-2 amyloid deposits may be present in other organs, kidney involvement is the main reason for evaluation in most patients.

LECT-2 is primarily produced and secreted by hepatocytes and acts as a neutrophil chemotactic factor (Yamagoe et al. 1998). LECT-2 is also implicated in tissue repair processes (Nagai et al. 1998). The mechanism underlying ALECT-2 amyloidosis is unknown. While no causative LECT-2 gene mutation has been identified, there is some evidence of a genetic predisposition. First, there is a high prevalence in some ethnic groups (Mexicans and Egyptians). Second, in a series of Mexican patients with ALECT2, a SNP at position 172 (SNP rs31517) was found. However, this polymorphism is more frequent than the disease, suggesting possibly a necessary but not sufficient condition (Murphy et al. 2010).

No specific therapy is available for ALECT-2. Most patients have a progressive decline of kidney function, leading to end-stage renal disease (ESRD) in 30% (Larsen et al. 2014). The presence of comorbidities (e.g., diabetes and hypertension) was predictors of rapid progression and worse outcomes.

ATTR (Transthyretin) Amyloidosis

ATTR presents most commonly with peripheral neuropathy and dysautonomia. Other sites of involvement include the heart, skin, gastrointestinal tract, and kidneys. The age of onset can be quite variable, from 17 to 80 years, depending on

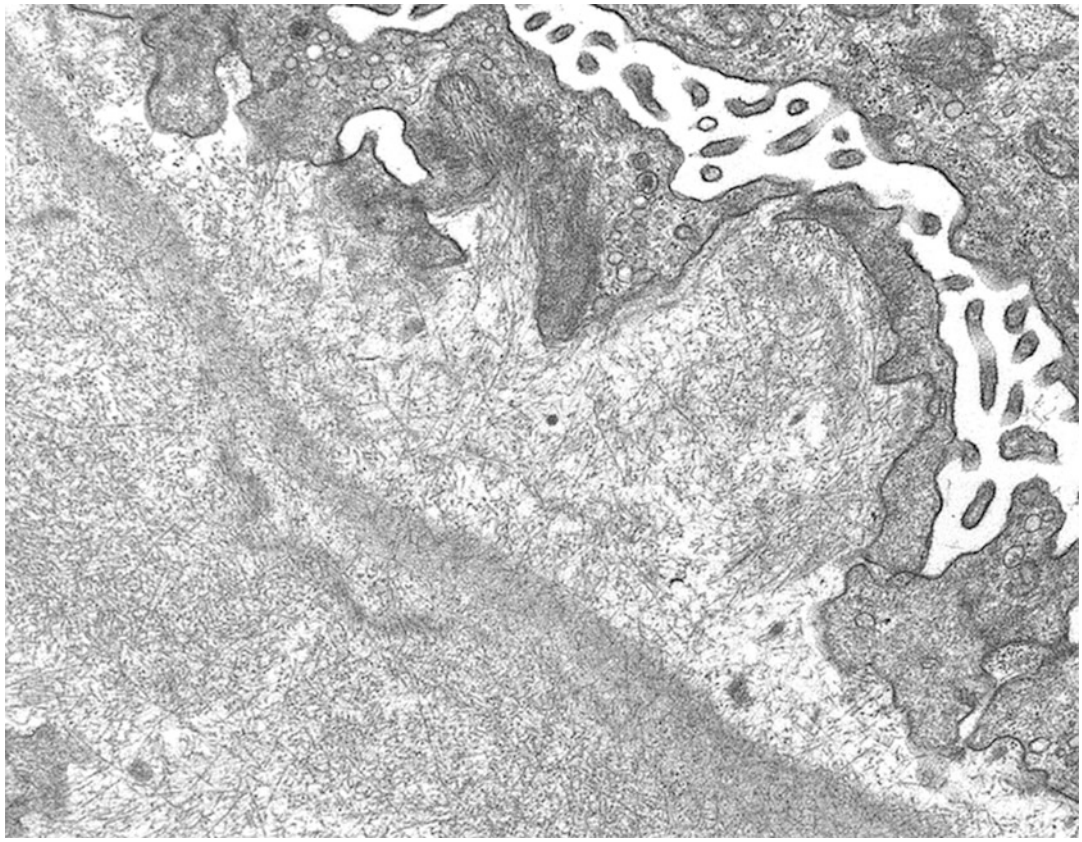

Fig. 9 Amyloid deposits appearing as fine, randomly oriented fibrils, massively distending a glomerular capillary wall. At upper right, there is podocyte injury with foot process effacement and microvillous transformation. Electron micrograph, 20,000×

the underlying mutation. When the kidney is involved, ATTR nephropathy presents with proteinuria and progressive renal disease. Nephropathy does not correlate with age, duration of disease, or severity of neuropathy.

Transthyretin (also known as prealbumin) is synthesized mainly in the liver. More than 100 amyloidogenic mutations have been described, of which 15 are nephropathic variants (Lobato and Rocha 2012). ATTR has an autosomal dominant inheritance pattern with variable penetrance, with higher penetrance associated with maternal inheritance (Bonaiti et al. 2010). Due to the often late age of onset, family history can be difficult to identify. Some cases of ATTR are thought to be senile amyloidosis (age-related) where no causative mutation is identified.

Definitive therapy requires liver transplantation to prevent production of mutated transthyretin. Combined liver–kidney transplantation is a treatment option for patients with ESRD (Lobato et al. 2011). RNA interference is an interesting emerging therapy for ATTR, in which interfering small RNA's targeting TTR suppress its expression in the liver (Coelho et al. 2013).

AFib (Fibrinogen Aα) Amyloidosis

Among the hereditary amyloidoses, Afib is the most common type in Europe and likely one of the most common in the United States. AFib presents with proteinuria and progression to renal failure with a median age at diagnosis of approximately 58 years. The proteinuria is an early and

constant feature in all AFib, and accordingly, the deposits are predominantly found in glomeruli on biopsy. Extra-renal manifestations are rare and include peripheral neuropathy and involvement of vascular walls and atheromatous plaques. The progression to ESRD is relatively fast compared to the other forms of hereditary amyloidosis, but slower compared with AL amyloidosis, with a median time from presentation to ESRD of 4.6 years (Gillmore et al. 2009).

AFib is inherited in an autosomal dominant fashion, with highly variable penetrance, so that some patients may not have family histories despite having inherited a mutant allele. At least 13 mutations of the fibrinogen Aα gene are known, including substitutions and premature stop codons. The precise mechanism of amyloidogenesis is not known. Since fibrinogen is produced entirely by the liver, the possibility of curative therapy includes combined liver and kidney transplantation (Mousson et al. 2006; Zeldenrust et al. 2003). In renal allografts without a liver transplant, the AFib tends to recur in the graft after a median of 6.7 years.

AApoAI (Apolipoprotein A I) and AApoAII (Apolipoprotein A II) Amyloidosis

Apolipoprotein AI may deposit as amyloid in atherosclerotic plaques in its wild type form, causing an acquired amyloidosis mainly involving arterial plaques. On the other hand, mutations in ApoAI cause familial systemic amyloidosis, so far attributed to at least 19 different mutations. ApoAII amyloidosis is also a genetic disease, caused by mutations in the stop codon that result in an extended protein. Both forms of familial amyloidosis are inherited as autosomal dominant traits. For AApoAI, hypogonadism due to testicular ApoAI deposition can be the initial clinical presentation (Scalvini et al. 2007). When renal disease is present, it is slowly progressive with minimal proteinuria since much of the deposition occurs in the medullary interstitium. Other extra-renal sites of involvement may be the heart, liver, peripheral nervous system, larynx, and skin. AApoAII disease tends to have mainly a renal presentation with progressive renal failure and proteinuria.

Apolipoproteins AI and AII are synthesized in the liver and are structural components of HDL. The mechanism by which mutant forms of ApoAI and ApoAII cause amyloid is incompletely understood. Interestingly, amyloidogenic mutations in ApoAI are associated with reduced rather than increased levels of circulating ApoAI. Amyloid deposits of ApoAI contain N terminal fragments of the protein, where most of the described mutations reside. This indicates a role for proteolysis of ApoAI in generation of amyloid. However, modeling analysis of ApoAI crystal structure and that of its mutants shows that misfolding may occur at certain N terminal "hot spots" in the intact polypeptide, and proteolysis may thus not be required for misfolding and aggregation. In AApoAII, amyloidogenic mutations result in an extended protein that is hypothesized to bind less avidly to HDL and to confer a propensity for altered conformation and amyloid formation.

No specific treatment is available for AApo AI or AII amyloidosis. Fibrates were suggested to be potential therapy of all AApoAI and AII, by shifting the apoproteins from the free (labile, prone to misfolding) to the HDL-bound (protected from misfolding) state (Jayaraman et al. 2017). Because of the slowly progressive natural history of most cases, renal and renal/liver transplantation is beneficial with recurrence usually occurring late.

AApoAIV (Apolipoprotein A-IV) Amyloidosis

AApoAIV is a very rare form of amyloidosis described in only a few case reports, the largest of which includes 11 patients (Murphy et al. 2010). AApoAIV presents with slowly progressive renal failure, with a mean age at diagnosis of 63.5 years. A distinctive feature in AApoIV is the absence of proteinuria. Consistent with this observation, the amyloid deposits are restricted to the medullary interstitium with no cortical involvement. Involvement may also be seen in the small intestine, heart, lung, and skin.

ApoAIV is another of the HDL-associated circulating lipoproteins (Kalogeris et al. 1997). The pathogenesis of ApoAIV is not known, and there are no associated mutations identified. The disease could be the result of prolonged deposition (age-related) of ApoAIV in the kidney. As with all circulating lipoproteins, ApoAIV is metabolized by the kidney and is present there at high concentration. The propensity to deposit in the medulla could be related the acidic and hypoxic medullary environment (Obici et al. 2016).

Diagnosis of ApoAIV amyloidosis presents a particular problem, since ApoAIV is one of the proteins found in amyloid deposits of all types. As such, immunohistochemistry will be diagnostically unhelpful. Mass spectrometry, with its ability to provide semiquantitative information about the relative abundance of amyloid constituents, will likely be necessary for diagnosis.

AApoCII (Apolipoprotein C II) and AApoCIII (Apolipoprotein C III) Amyloidosis

AApoCII and AApoCIII are very rare forms of amyloidosis described in isolated series. AApoCII was described in a case series of eight elderly patients (mean age of 70) with progressive renal failure and nephrotic-range proteinuria. Deposits of AApoCII were present in the glomerular mesangium and medullary interstitium (Nasr et al. 2017a). Other organs were not involved. By contrast, AApoCIII, reported in a French family, presented initially with extra-renal symptoms including sicca syndrome and esophagitis (Valleix et al. 2016) in the third decade of life. Kidney involvement became prominent later, with proteinuria and progressive renal failure.

AApoCII and AApoCIII are constituents of circulating lipoprotein particles involved in lipid metabolism. Mutations in each are hypothesized to facilitate amyloid formation by favoring dissociation from the lipoprotein particle and by conferring a propensity for misfolding. Fibrates may potentially slow progression of these diseases, in part by reducing hepatic *APOCIII* transcription (Haubenwallner et al. 1995).

AGel (Gelsolin) Amyloidosis

AGel is rare form of amyloidosis also known as familial amyloidosis of the Finnish type (Meretoja 1969). This disease usually presents as an autosomal dominant neuropathy syndrome, although renal involvement has been rarely described and arises later in life (sixth decade and older). Those with kidney disease present with progressive renal failure and severe nephrotic range proteinuria (Sethi et al. 2017). On kidney biopsies, AGel amyloid deposits preferentially involve glomeruli, occasionally with the unusual electron microscopic appearance of wavy or storiform fibrils in addition to the typical configuration. There is no specific therapy available for this disease.

Gelsolin is a calcium-dependent regulator of cytoskeletal actin. There is also an extracellular pool of gelsolin that scavenges the extracellular actin left after cell death (Sun et al. 1999; Yin et al. 1984). Several mutations in the gelsolin gene are associated with amyloidosis, all of which are in the calcium-binding domain. It is hypothesized that these mutations interfere with calcium binding which then allows for misfolding and amyloid generation.

ALys (Lysozyme) Amyloidosis

ALys is a very rare autosomal dominant hereditary amyloidosis (Nasr et al. 2017b) caused by mutations in the gene-encoding lysozyme. There is multisystemic involvement including progressive renal failure with proteinuria, gastrointestinal symptoms, skin petechiae, sicca syndrome, peripheral neuropathy, and cardiomyopathy.

Lysozyme is a secreted enzyme with bactericidal activity, expressed by hepatocytes, macrophages, and neutrophils. Several mutations have been described. There is heterogeneity in the rate of clinical progression that may be related to different mutations, but even within the same family, there is variation in presentation and severity. Renal allograft survival of greater than 10 years after transplant has been reported, and liver transplantation may ameliorate progression.

Aβ2M (β2 Microglobulin) or Dialysis-Related Amyloidosis

Dialysis-related amyloidosis (DRA) occurs in patients with ESRD treated with both hemodialysis (HD) and peritoneal dialysis (PD). The amyloidogenic protein is β2 microglobulin (β2M), a protein that is normally eliminated through glomerular filtration. Previously, an incidence of DRA as high as 95% was reported after 15 years of dialysis (Jadoul et al. 1997). However, with increased use of high-flux dialysis membranes, the incidence of DRA is decreasing.

Risk factors for DRA include the duration of dialysis, age of onset of ESRD (elderly patients are at higher risk of DRA) (van Ypersele de Strihou et al. 1991), loss of residual kidney function, and the type of dialysis membrane. Low-flux dialyzers have poor clearance of β2M, and bioincompatible dialyzers also have lower clearance and can stimulate inflammation, cytokine formation, and increased production of β2M (Memoli et al. 1991). DRA predominantly involves the joints of extremities and cervical neck. Less commonly, intestinal pseudo-obstruction has been described. Cardiac involvement is rare. The symptoms are mainly related to musculoskeletal involvement, frequently presenting as osteoarticular pain, carpal tunnel syndrome, and joint contractures.

The concentration of β2M increases up to 60-fold in ESRD, though increased concentration alone may not fully explain the pathogenesis of DRA. β2M has an affinity for binding collagens found in articular cartilage. Modifications of β2M, such as certain truncations (perhaps due to complement activity) or glycation to form advanced glycation end products, are found within the amyloid deposits and in circulation of dialysis patients. These modified forms of β2M are hypothesized to promote amyloid formation. Higher β2M levels were found to be a predictor of higher mortality (Cheung et al. 2006).

Prevention of DRA is based on providing dialysis using high-flux, biocompatible membranes. Increasing the frequency and the duration of dialysis is beneficial. Maintenance of residual kidney function is the optimal approach to minimizing levels of β2M levels (Ikegaya et al. 1995), so all measures should be taken to preserve the residual kidney function for as long as possible. Kidney transplantation may facilitate regression of already established β2M deposits (Campistol 2001).

Cross-References

► Light Chain (AL) Amyloidosis and the Kidney

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Fibronectin Glomerulopathy

50

Guillermo A. Herrera

Contents

Abstract

Fibronectin glomerulopathy is a rare renal disorder which is found most commonly in family clusters, though in some instances isolated cases with no family history have been documented. Diagnosis requires a renal biopsy which typically shows a mesangiopathy with increased matrix rich in fibronectin which may impart to the glomeruli a lobular appearance. While the ultrastructural findings can suggest and in some cases can be used to make a presumptive diagnosis, immunohistochemical stain for fibronectin is absolutely essential for making a definitive diagnosis. There is no real treatment for this condition, except for measures to delay progression of renal damage. Renal transplantation provides a feasible treatment modality when renal failure ensues, though recurrence of fibronectin glomerulopathy in transplanted kidneys has been documented in the literature. Genetic evaluation and counseling should be part of the management of these patients to identify affected individuals who are asymptomatic or early in the disease process and carriers that are at risk

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to develop the disease later in life, as the disease displays an autosomal dominant pattern of inheritance in many families.

Keywords
Fibronectin · Glomerulopathy · Electron microscopy · Immunohistochemistry · Genetics

Introduction/Historical Perspective

Fibronectin glomerulopathy is a hereditary disorder which has also been referred to as familial lobular glomerulopathy. This entity was first reported by Burgin in 1980 when he reported three siblings and a first-degree cousin affected by this condition (Burgin et al. 1980). Few other families, as well as sporadic cases, have been reported with this very unusual condition. It affects both sexes with no apparent predilection. Though Burgin et al. described what is believed the first case of fibronectin glomerulopathy (Burgin et al. 1980), Mazzucco et al. (1992) were the first to test for the presence of fibronectin in this entity. Strøm et al. examined the morphological and immunohistochemical alterations in patients from six unrelated families with similar renal biopsy findings and found excessive mesangial fibronectin deposition in all affected members (Strøm et al. 1995) bringing to the literature recognition of this unusual disorder in 1995. Since then about 30 cases of this entity have been published highlighting the spectrum of morphologic features in this rare disease.

Clinical Presentation/Epidemiology

The clinical presentation is characterized by proteinuria which is frequently in the nephrotic range, edema, microscopic hematuria, renal tubular acidosis, type IV, and hypertension. No systemic manifestations have been reported in these patients. The pattern of inheritance has been determined to be autosomal dominant in the majority of the affected families (Strøm et al. 1995). Patients have presented initial symptomatology at different ages but mostly between 15 and 30 years of age. At the time of clinical presentation, about half of these patients exhibit some degree of renal insufficiency. Fibronectin serum levels are typically normal. Diagnosis relies on evaluation of the renal biopsy specimen. The findings that are required for a diagnosis are detailed in the text of the chapter. Family history is helpful when confronted with a possible diagnosis of fibronectin glomerulopathy.

The more recent studies have focused on the pathogenesis of the disease process and in identifying candidate gene/s responsible for this condition. These subjects will be described in detail in specific assigned sections of this chapter.

Histology/Pathologic Findings/ Differential Diagnosis

Gross Pathology

There are no studies addressing the gross pathological findings in these patients.

Light Microscopy

The characteristic finding is enlarged glomeruli with mesangial expansion (Burgin et al. 1980; Strøm et al. 1995; Mazzucco et al. 1992; Assman et al. 1995; Gemperle et al. 1996; Hildebrandt et al. 1996; Hildebrandt and Vollmer 1998; Niimi et al. 2002; Tuttle et al. 1987; Abt et al. 1991; Sato et al. 1991; Uesugi et al. 1999; Chen et al. 2015; Herrera and Turbat-Herrera 2010; Howell et al. 2003; Iskandar and Herrera 2014) associated with accentuated glomerular lobularity in some cases (Abt et al. 1991) and even partial, sometimes segmental obliteration (Fig. 1a) of capillary spaces in some instances. The increased mesangium (Fig. 1a) is commonly (not always) PAS positive (Fig. 1b) and strikingly red with the trichrome stain (Fig. 2), depending on the amount of the deposited material present. Trichrome stain may be suggestive of the diagnosis, as red staining material in glomeruli is most commonly associated with hyalinosis than with other immunoglobulin-containing deposits of the immune type.

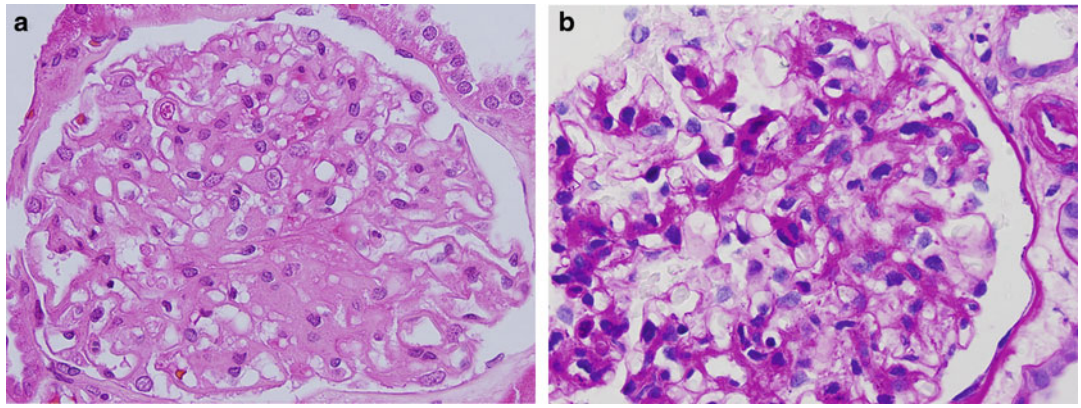

Fig. 1 (**a**, **b**) Hematoxylin and eosin and PAS stains, X750 and X750, respectively: early segmental mesangial expansion (**b**) and advanced disease with rather diffuse mesangial expansion with partial obliteration of capillary spaces and segmentally thickened peripheral capillary walls (**a**)

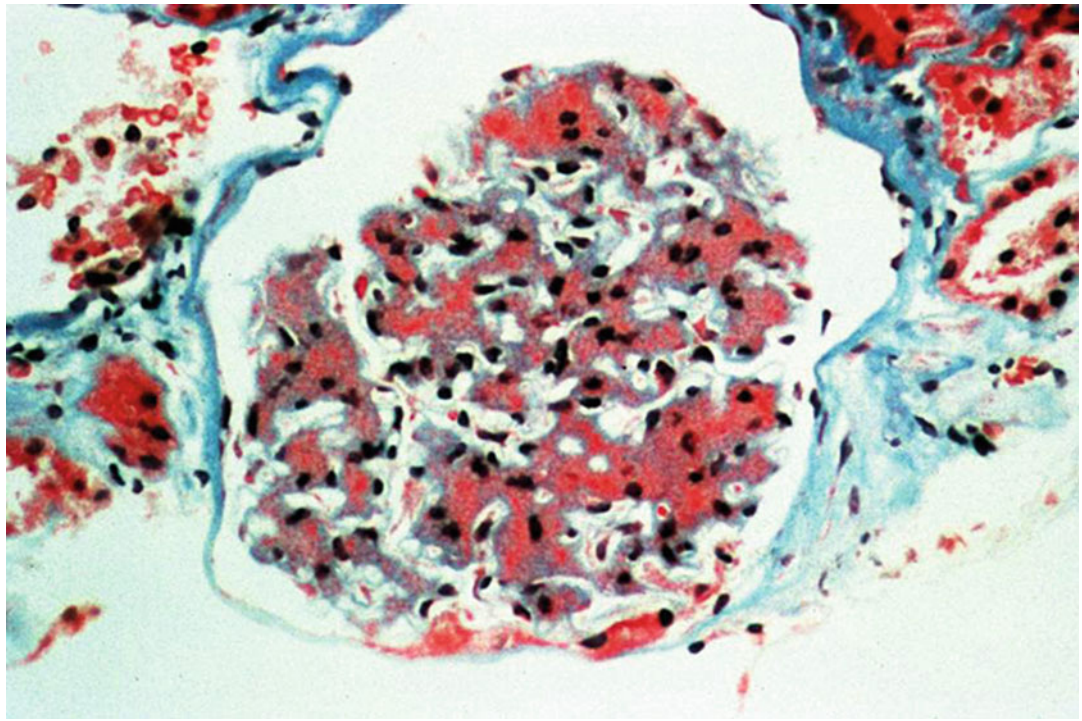

Fig. 2 Trichrome stain, X750: striking red staining of expanded mesangial areas

Staining with Jones silver methenamine stain is often prominent in the expanded mesangium (Howell et al. 2003), while no staining is characteristics in other mesangiopathies where the normal mesangial matrix is replaced. The problem is that in some cases decreased to absent mesangial staining has been reported. In some cases there is also segmental thickening of peripheral capillary walls. Mesangial cell cytoplasm interposition and splitting of glomerular basement membranes is not present in the great majority of the cases. Glomerular hypercellularity, necrosis, and crescents are not

features associated with this disease. There are no specific tubulointerstitial or vascular changes directly related to the pathology of this disease process, but as the disease advances and glomerulosclerosis ensues, interstitial fibrosis and vascular sclerosis accompany the progressive glomerular damage. No Congo red or thioflavin T or S staining is present.

Immunofluorescence

There is no consistent pattern of staining using the routine panel used for immunofluorescence evaluation. Most cases are negative for the usual battery of immunofluorescence stains including IgG, IgM, IgA, C1q, C4, C3, albumin, fibrinogen, and kappa and lambda light chains (Burgin et al. 1980; Mazzucco et al. 1992; Assman et al. 1995; Gemperle et al. 1996; Hildebrandt et al. 1996; Hildebrandt and Vollmer 1998; Niimi et al. 2002; Tuttle et al. 1987; Abt et al. 1991; Sato et al. 1991; Uesugi et al. 1999; Chen et al. 2015). However, a subset of the cases reported have demonstrated granular mesangial staining for IgG, IgM, IgA, C1q, C3, and albumin (Strøm et al. 1995; Abt et al. 1991; Yong et al. 2010). The staining is generally weak and likely non-specific. In all cases immunohistochemical stain for fibronectin displays striking mesangial labeling (Fig. 3).

Electron Microscopy

At the time of diagnosis in the majority of the cases, the ultrastructural findings are characterized by the presence of large, poorly circumscribed subendothelial and mesangial

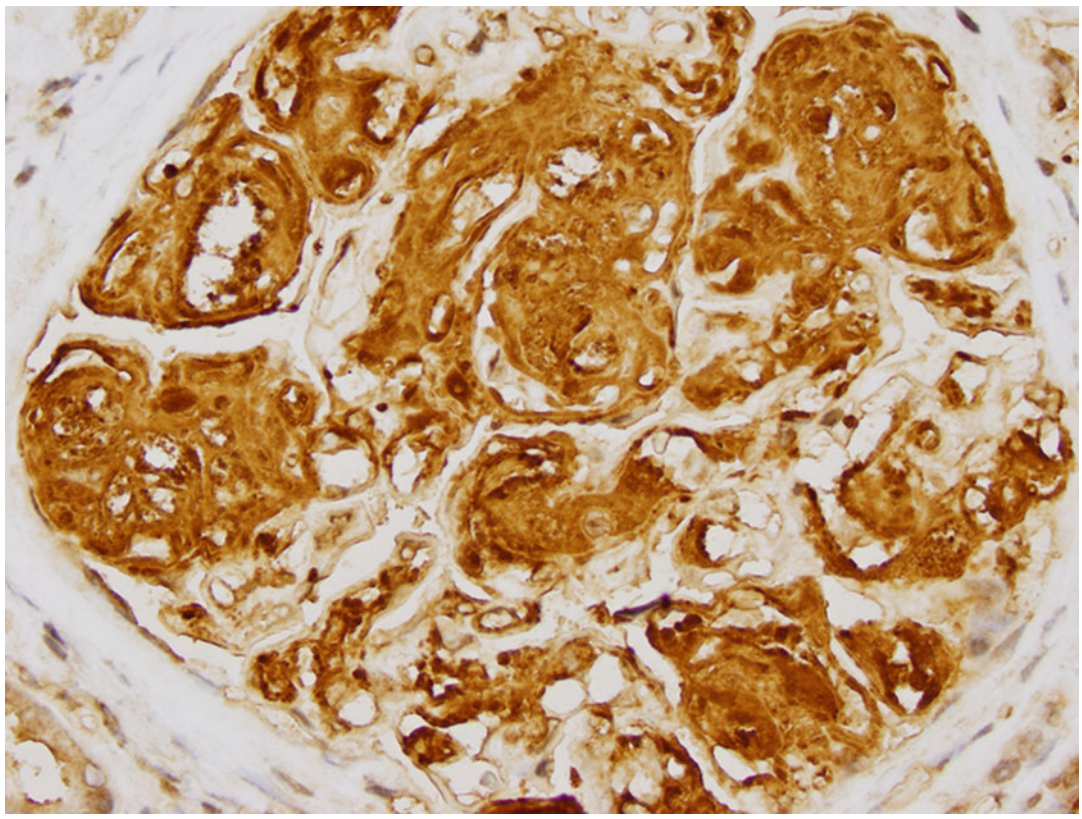

Fig. 3 Immunohistochemical stain for fibronectin, peroxidase-anti-peroxidase stain, X750: strong glomerular staining, mostly in mesangial areas

electron-dense deposits (Burgin et al. 1980; Strøm et al. 1995; Mazzucco et al. 1992; Assman et al. 1995; Gemperle et al. 1996; Hildebrandt et al. 1996; Hildebrandt and Vollmer 1998; Niimi et al. 2002; Tuttle et al. 1987; Abt et al. 1991; Sato et al. 1991; Uesugi et al. 1999; Chen et al. 2015; Herrera and Turbat-Herrera 2010; Howell et al. 2003; Iskandar and Herrera 2014) (Fig. 4a). The amounts of the electron-dense material deposited in the mesangium are somewhat variable from case to case; however, it is massive in some instances (Fig. 4b). These deposits replace the normal mesangial matrix. In cases where there is deposition of similar material along peripheral capillary walls, the mesangium is mostly full of the same material. Infrequently, deposits in intramembranous and subepithelial locations have also been documented. Extraglomerular deposits have been described in a few cases along Bowman's capsule and tubular basement membranes.

The electron dense deposits are generally composed of marked electron-dense material that is either amorphous/granular (most cases) (Fig. 4b) or fibrillary, and in selected cases, both types are noted intermingled. Fibrillary material is often seen only focally in a background of amorphous to granular electron-dense material. The fibrils are generally short, compactly disposed, and measure between 10 and 14 nm in diameter (Strøm et al. 1995; Mazzucco et al. 1992; Assman et al. 1995; Gemperle et al. 1996; Hildebrandt et al. 1996; Hildebrandt and Vollmer 1998; Niimi et al. 2002; Tuttle et al. 1987; Abt et al. 1991; Sato et al. 1991; Uesugi et al. 1999; Chen et al. 2015; Herrera and Turbat-Herrera 2010; Howell et al. 2003; Iskandar and Herrera 2014; Herrera 2017).

Ultrastructural immunogold labeling techniques have shown the expanded mesangial matrix to contain almost exclusively fibronectin replacing the collagen IV that is present in the normal mesangium (Yong et al. 2010).

Differential Diagnosis

Because the main finding is mesangial expansion and associated accentuated lobularity, there are many diseases that can mimic fibronectin glomerulopathy at the light microscopic level. Because this disease is rare, it is not suspected unless family history of a confirmed case is available. It is important for the renal pathologist to consider this entity in the differential diagnosis of

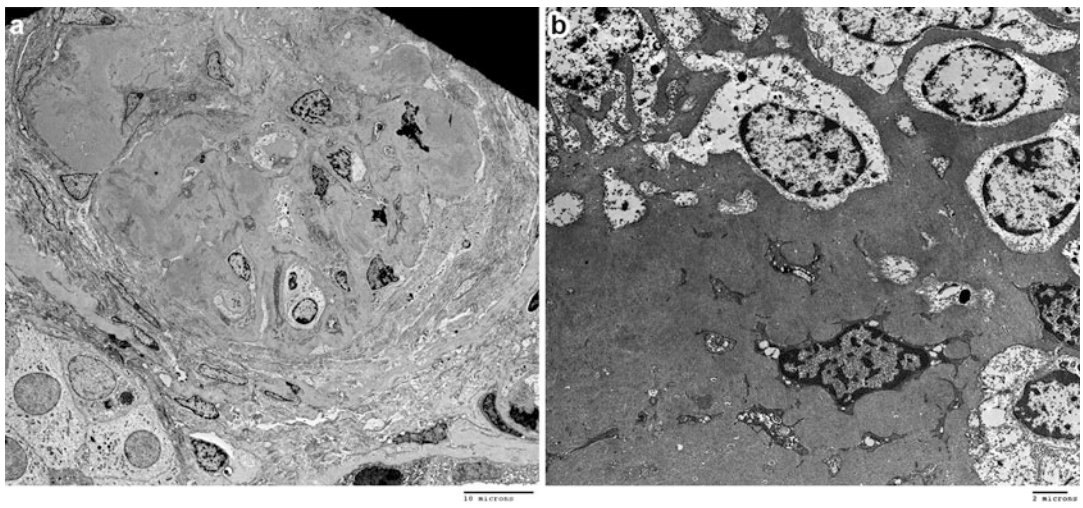

Fig. 4 Transmission electron microscopy; uranyl acetate and lead citrate, left X 8500 and right X13 500: almost completely destroyed glomerulus with abundant electron-dense material and essentially obliterated capillary spaces (**a**). Abundant electron-dense material in the mesangium replacing normal mesangial matrix. Material is granular with no fibrillary component (**b**)

mesangiopathic disorders. The diagnosis of this entity is entirely based on the renal biopsy findings.

The immunofluorescence findings using the routine battery of stains are also non-specific and do not provide any specific indication as to the diagnosis. The main reported staining patterns are for IgM and C3 and entirely non-specific and most suggestive of trapping.

The main diagnostic features which would suggest this entity are observed at the electron microscopic level where the findings are frequently striking. However, in the early stages of fibronectin glomerulopathy, they may be subtle, and it would be easy to miss the correct diagnosis. Usually the electron microscopic findings and/or knowledge of a family member affected by this disease triggers the request for a fibronectin stain.

Immunohistochemical/immunofluorescence stains for fibronectin demonstrating intense mesangial staining clinch the diagnosis, confirming the ultrastructural suspicion.

Pathogenesis

While the kidney produces fibronectin that accumulates in the mesangium, the liver generates circulating fibronectin. Fibronectin is an adhesive multifunctional, large dimeric glycoprotein consisting of two similar subunits, each approximately 250 kD in weight which participates in a number of functions in the kidney. Fibronectin characteristically exists in a soluble circulating (plasma) form and in an insoluble (cellular) form which is detected in basement membranes and in the extracellular matrix.

Production of fibronectin occurs in the mesangium by mesangial cells, and its production is a common finding accounting for expansion of the extracellular matrix in experimental platforms. Upregulation of fibronectin production has been documented to occur in several glomerular diseases in humans (Assad et al. 1993; Buyukbabani and Droz 1994). The increased fibronectin in these conditions is a result of excess production by mesangial cells, and it accumulates in mesangial areas (Border et al. 1990). Mesangial cells via stimulation of transforming growth factor (TGF)-β have been determined to be responsible for the production of the fibronectin that accumulates in the glomeruli in most other renal disorders (Yong et al. 2010; Assad et al. 1993; Buyukbabani and Droz 1994; Border et al. 1990) but not in fibronectin glomerulopathy (Strøm et al. 1995). Part of the evidence that has been used to reach this conclusion is the fact that fibronectin glomerulopathy has been seen to recur in a transplanted kidney (Strøm et al. 1995). Also in most renal diseases, except for fibronectin glomerulopathy, co-expression with other matrix proteins such as collagen IV and tenascin occurs (Strøm et al. 1995). In contrast, in fibronectin glomerulopathy, the deposited fibronectin in the glomerulus is derived mainly from the soluble plasma isoform. Plasma levels of fibronectin are not elevated in patients with fibronectin glomerulopathy (Vollmer et al. 2000); therefore, this disease appears to result from a primary renal problem. There is either a problem with clearing of fibronectin, perhaps due to the formation of a variant of fibronectin that cannot be cleared, or, alternatively, a circulating factor becomes attached to the circulating fibronectin moiety making clearance impossible (Vollmer et al. 1998). This has been observed to occur in the uteroglobin knockout mouse model (Zhang et al. 1997), though involvement of the uteroglobin gene has been ruled out to play a role in humans with this condition (Vollmer et al. 1998). One proposed mechanism that has acquired some support is that there is a defect in the catabolism of fibronectin.

In summary, the pathogenetic mechanisms involved in this disorder remain equivocal at the present time. This disease has been observed in clusters of family members indicating a genetic component in at least a subset of these cases. The pattern in some families is consistent with an autosomal dominant type of inheritance with age-associated penetrance. Sporadic cases have also been reported (Vollmer et al. 2000). Vollmer et al. mapped the gene to 4.1 cM interval on chromosome 1q32, in the region of the regulation of complement activation gene cluster, and they have proposed a candidate gene localized to this region (Vollmer et al. 2000).

Amyloid P has been localized to the fibrillary deposits in this condition in one case suggesting a probable connection between this finding and the fibrillogenesis that is seen in this disorder (Mazzucco et al. 1992).

Proteomic analysis using laser capture microdissected glomeruli from renal biopsies of patients with fibronectin glomerulopathy has demonstrated the accumulation of fibronectin and fibulin in the mesangium (Satoskar et al. 2012). Mutations in fibronectin have been proposed to play a role in the abnormal deposited fibronectin (Ertoy Baydar et al. 2013). Work by Castelleti et al. has shown that in about 40% of the families the disease is caused by mutations in the FN1 gene (2q34) encoding fibronectin. This mutation was identified in affected individuals from six unrelated families (Castelleti et al. 2008). In spite of this evidence, genetic heterogeneity is highly suspected in this condition.

Therapeutics: Treatment and Prognosis

There is no specific treatment for this condition. Only supportive care can be provided to ameliorate proteinuria and control hypertension using corticosteroids and ACE inhibitors or anti-AT1R antagonists to slow down the disease progression. Slowly, progressive deterioration of renal function occurs in the majority of the cases, but patients may end up in end-stage renal disease as early as in the second and as late as in the sixth decade. Thirteen affected members of a kindred all progressed to end-stage renal disease (Assman et al. 1995), but this is not the case in other families where the progression to renal failure is inconstant and impossible to predict.

For the most part, good results have been obtained with kidney transplantation in these patients. There are two cases in which recurrence of the disease in the transplanted kidney has been documented in the literature, in one of these only 19 days after transplantation (Otsuka et al. 2012), and in another case fibronectin deposits appeared in the transplanted kidney 29 months after transplantation with eventual loss of the allograft (Gemperle et al. 1996). A third patient who received a kidney from a cadaver enjoyed adequate renal function for 4 years until fibronectin glomerulopathy was noted to have recurred, confirmed with a renal biopsy (Tuttle et al. 1987).

Conclusions

Fibronectin deposition in the mesangium is not uncommonly seen in a number of glomerulonephritis. However, when it is deposited in large quantities in the absence of other recognizable glomerular disorders, a diagnosis of fibronectin glomerulopathy must be seriously considered. Because routine staining for fibronectin is not performed in renal biopsies, this condition must be suspected in order to be correctly diagnosed. Ultrastructural evaluation reveals deposition of a peculiar electron-dense material in expanded mesangial areas that should generate concern for this entity and trigger staining for fibronectin, either using immunohistochemistry or immunofluorescence techniques, depending on the antibody available. Final diagnosis depends on the demonstration of large amounts of fibronectin in the mesangial deposits.

There are situations where significant fibronectin deposits coexist with other renal disease processes on the same renal biopsy samples such as in association with IgA/C1q deposits (Yoshino et al. 2013) and systemic lupus erythematosus (Mene 2008). The significance of fibronectin deposition in these settings remains unclear at this time deserving further evaluation.

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Collagenofibrotic Glomerulopathy

51

Guillermo A. Herrera

Contents

Abstract

Collagenofibrotic glomerulopathy is a very rare condition with a genetic component. In most cases, the inheritance pattern has been autosomal recessive which is consistent with the usual onset of symptoms in early childhood. Less than 50 cases have been described in the literature under several names including primary glomerular fibrosis, collagen III glomerulopathy, and collagenofibrotic glomerulopathy. It was initially considered a variant of nail-patella syndrome, but it is now recognized as a specific entity. Manifestations of renal dysfunction may occur in childhood or later in life. Renal biopsy is required to make a diagnosis. A high index of suspicion and recognition of the rather characteristic ultrastructural findings is needed for the pathologist to suspect the diagnosis and order the stain for collagen III to confirm the diagnosis. This condition in at least a subset of the patients is a progressive disease, and no specific treatment is available at the present time.

Keywords

Collagen III glomerulopathy · Collagenofibrotic glomerulopathy · Electron microscopy · Light microscopy · Immunohistochemistry

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Introduction/Historical Perspective

This entity was first reported by Arakawa in 1979 (Arakawa et al. 1979). Dombros and Kats published a case in 1982 which they thought was a variant of nail-patella glomerulopathy without skeletal abnormalities (Dombros and Katz 1982), and a second case was published 2 years later (Salcedo 1984). Ikeda recognized the peculiar fibers present in glomeruli in 1990 (Ikeda et al. 1990). In 1995, collagenofibrotic glomerulopathy was first included in the World Health Organization classification of glomerular diseases. Since then, more than 40 cases have been published, and understanding of this disorder has been significantly advanced (see Pathogenesis). Most cases have been identified in Asia, and the first patients in Latin America were reported in 2009 (Ferreira et al. 2009).

Clinical Presentation/Epidemiology Initial presentation of this disease is quite variable. The patients have ranged from 6 to 72 years with no sex predilection. Familial occurrence of this disorder has been documented, and an autosomal recessive pattern of inheritance has been proposed. Extrarenal symptoms and findings are almost always absent. The first symptoms of this disease may appear in early childhood or in late adulthood. The most common clinical presentation is persistent proteinuria with or without associated nephrotic syndrome with minor alterations in renal function. These patients can also exhibit varying degrees of hematuria (though hematuria is often absent) and hypertension (Duggal et al. 2012; Patro et al. 2011; Imbasciati et al. 1991; Gubler et al. 1993; Tamura et al. 1996; Yoshioka et al. 1989). No skeletal manifestations are present. Renal function deterioration appears to be a late event.

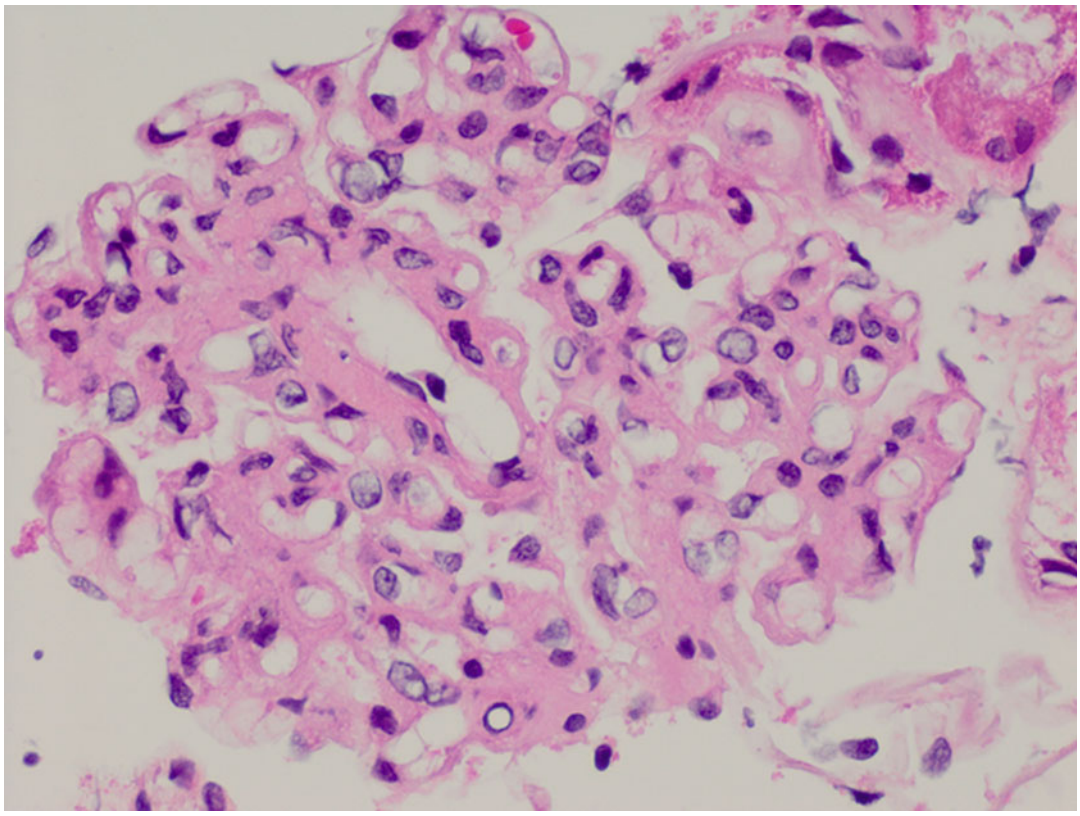

Fig. 1 Collagenofibrotic glomerulopathy, early stage. Hematoxylin and eosin stain. X750. Segmentally expanded mesangium with increased matrix

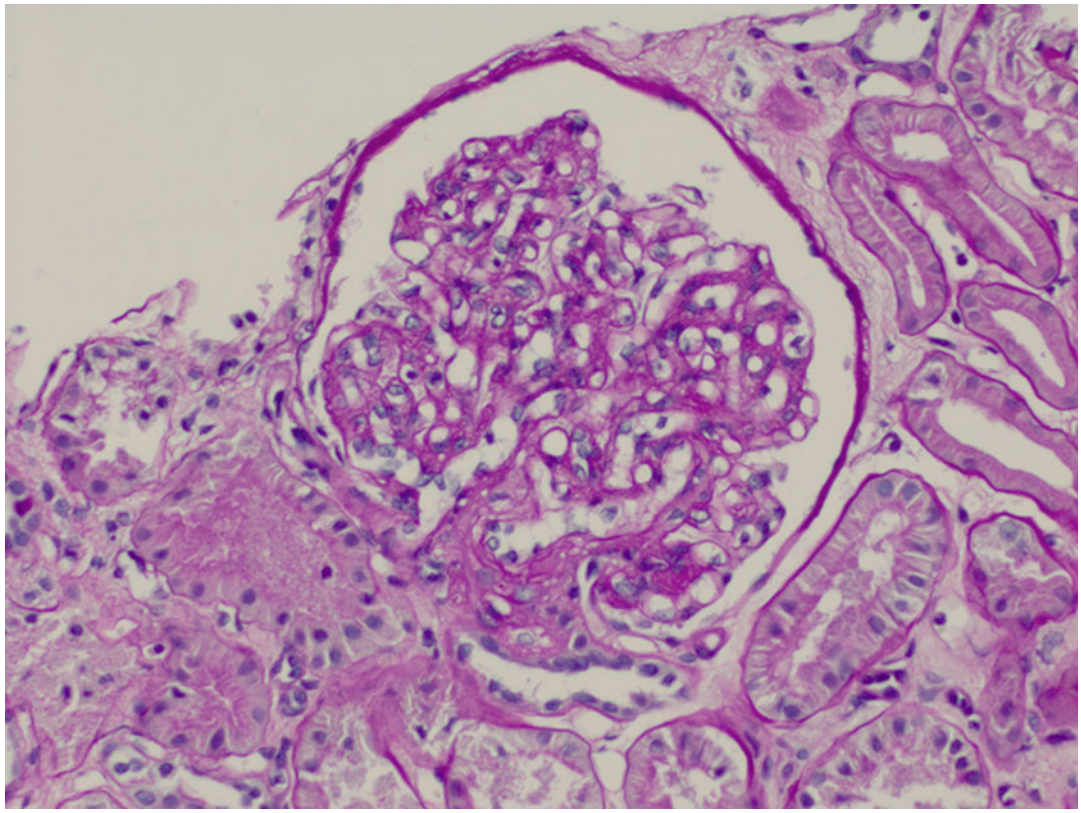

Fig. 2 Collagenofibrotic glomerulopathy. PAS stain. AX750. Note weak staining in expanded mesangial areas and segmentally expanded subendothelial zones

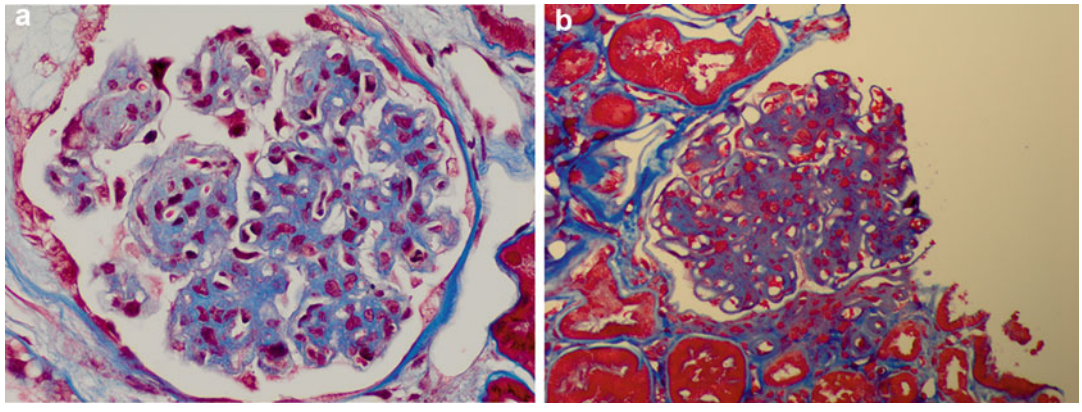

Fig. 3 Collagenofibrotic glomerulopathy. Trichrome stain. AX750, BX750. Note blue mesangial staining with increment from an early case (**a**) to a well-developed case with distinct mesangial expansion with increased matrix/nodular appearance (**b**)

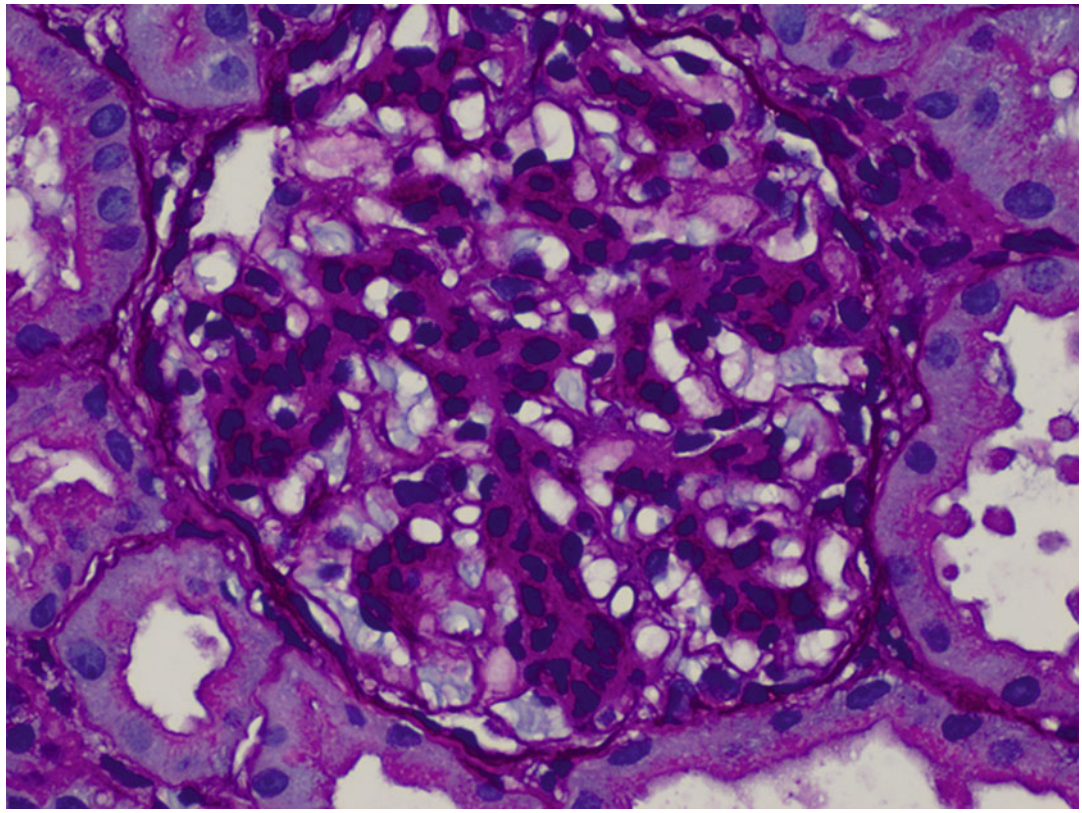

Fig. 4 Collagenofibrotic glomerulopathy. PAS stain. X750. Mesangial hypercellularity is present in selected cases

The disease appears to be primarily a renal process, but in one case, liver involvement with perisinusoidal fibrosis has been reported (Mizuiri et al. 1993). Collagen III deposition may be detected in other organs including the heart, liver, spleen, and thyroid gland, among other sites (Yasuda et al. 1999).

Hemolytic anemia, hemolytic uremic syndrome, and unexplained respiratory symptoms have been reported (Gubler 2008). A few cases have been associated with factor H deficiency (Gubler 2008; Vogt et al. 1995). A link between collagenofibrotic glomerulopathy and complement system defects has been proposed.

Many of the cases have been reported in Japan suggesting racial and geographic predilection; however, sporadic cases continue being reported (Tamura et al. 1996; Yoshioka et al. 1989).

Histology/Pathologic Findings/ Differential Diagnosis

Gross Pathology

There are no gross descriptions of the kidneys in this disorder.

Light Microscopy

The glomerular compartment is the one typically affected in this condition. Glomerular findings are generally diffuse and generalized. The glomeruli appear enlarged predominately as a result of mesangial expansion. Nevertheless, the light microscopic findings of this condition are rather non-specific with an increase in

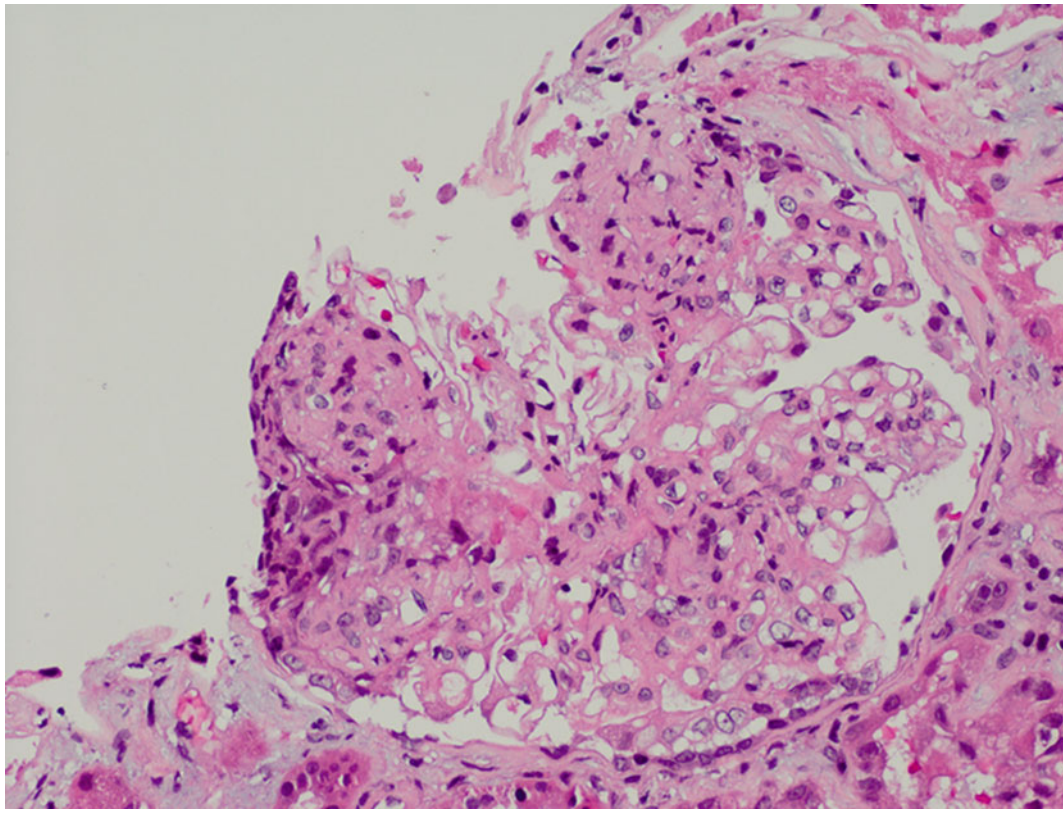

Fig. 5 Collagenofibrotic glomerulopathy, advanced stage. Hematoxylin and eosin stain. X750. Expanded mesangial areas with increased matrix acquiring a lobulated appearance segmentally

mesangial matrix (Fig. 1) which shows enhanced argyrophilia and occasional thickening of peripheral capillary walls, especially in early manifestations of the glomerular process. Weak PAS positivity is seen in the expanded mesangial areas and in the expanded subendothelial zones (Fig. 2). Trichrome stain highlights collagen deposition (Fig. 3a) and eventual mesangial nodularity (Fig. 3b). Mesangial hypercellularity may be identified in some cases (Mizuiri et al. 1993; Vogt et al. 1995) (Fig. 4). No glomerular necrosis and no crescents are observed. The expanded mesangial areas may compress the adjacent capillary spaces, and the glomeruli may acquire a somewhat lobulated appearance as the disease process advances and mesangial expansion becomes more pronounced (Fig. 5).

Immunofluorescence/ Immunohistochemistry

The typical immunofluorescence battery of stains is negative in the majority of the cases. Non-specific IgM and C3 deposition in mesangial areas has been reported.

Collagen III Immunohistochemical Stain

Collagen III immunohistochemical stain shows either focal, segmental, or diffuse, generalized mesangial staining (Fig. 6) primarily depending on the stage of the disease process, representing the hallmark of the diagnosis. The deposition of collagen III is impressive and far more than

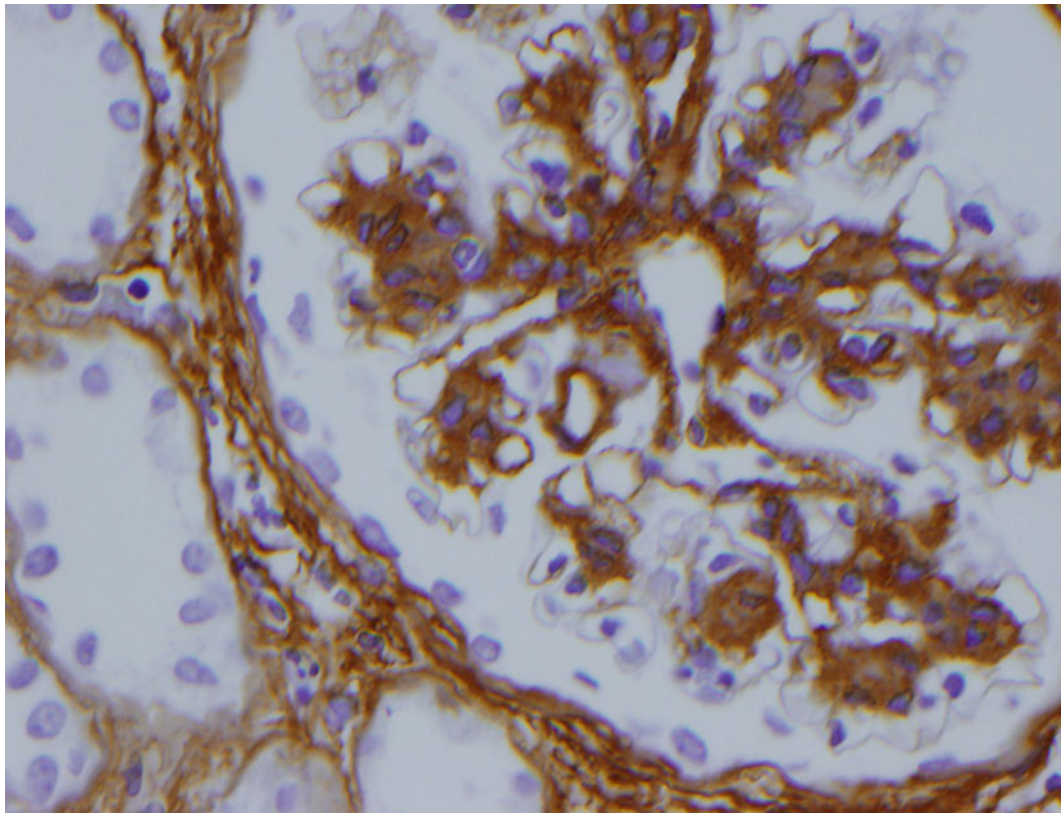

Fig. 6 Collagenofibrotic glomerulopathy. Immunohistochemical stain for collagen III. Peroxidase anti-peroxidase stain, diaminobenzidine. X750. Intense mesangial staining in expanded mesangial areas and also staining in the interstitium

can be seen in other glomerulopathies focally in mesangial areas (Salcedo 1984; Ikeda et al. 1990; Ferreira et al. 2009; Imbasciati et al. 1991; Gubler et al. 1993; Tamura et al. 1996; Yoshioka et al. 1989; Mizuiri et al. 1993; Yasuda et al. 1999; Gubler 2008; Vogt et al. 1995; Striker et al. 1984).

Reliable antibodies to collagen III are commercially available. Normal human glomeruli do not have or reveal minimal amounts of collagen III (D'Ardenne et al. 1983; Razzaque et al. 1994), but collagen III may be found in the interstitium, especially when fibrosis is present; however, this finding is of no specific diagnostic importance, as has nothing to do with making a diagnosis of collagenofibrotic glomerulopathy.

One case in the literature documented widespread staining for collagen V in glomeruli as well in a case of collagenofibrotic glomerulopathy (Morita et al. 2003). This may be an isolated incident or a feature of collagenofibrotic glomerulopathy. The significance of this finding is unclear at the present time.

Electron Microscopy

However, the ultrastructural findings are quite characteristic and characteristic enough to make a presumptive diagnosis in most instances. The mesangial areas and affected peripheral capillary walls show a clear to mottled appearance, and phosphotungstic or tannic acid treatment of the electron microscopy sections enhances the collagen fibers making them much easier to identify in areas where they are not abundant (Alchi et al. 2007). The electron microscopic findings will

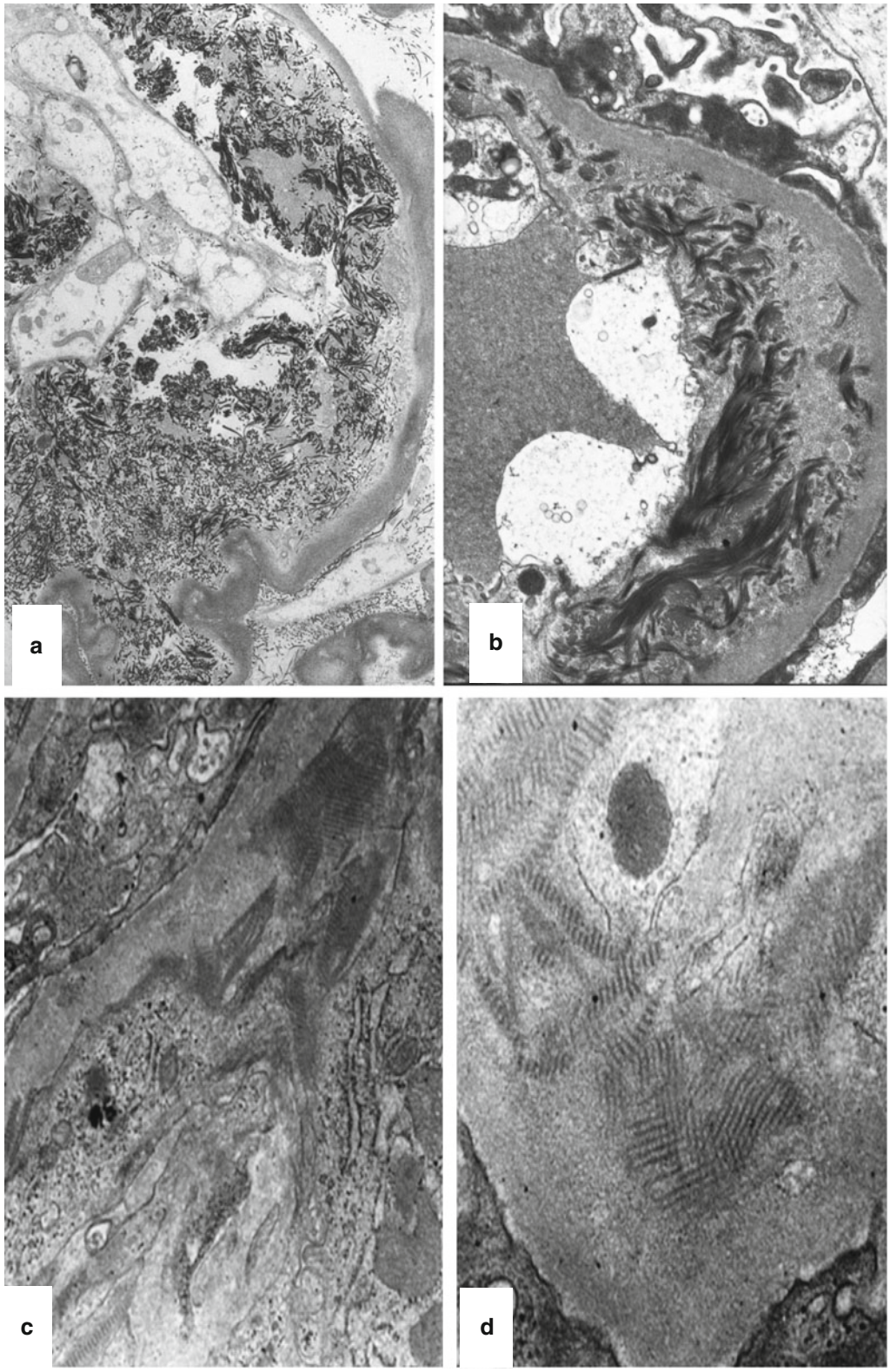

Fig. 7 (continued)

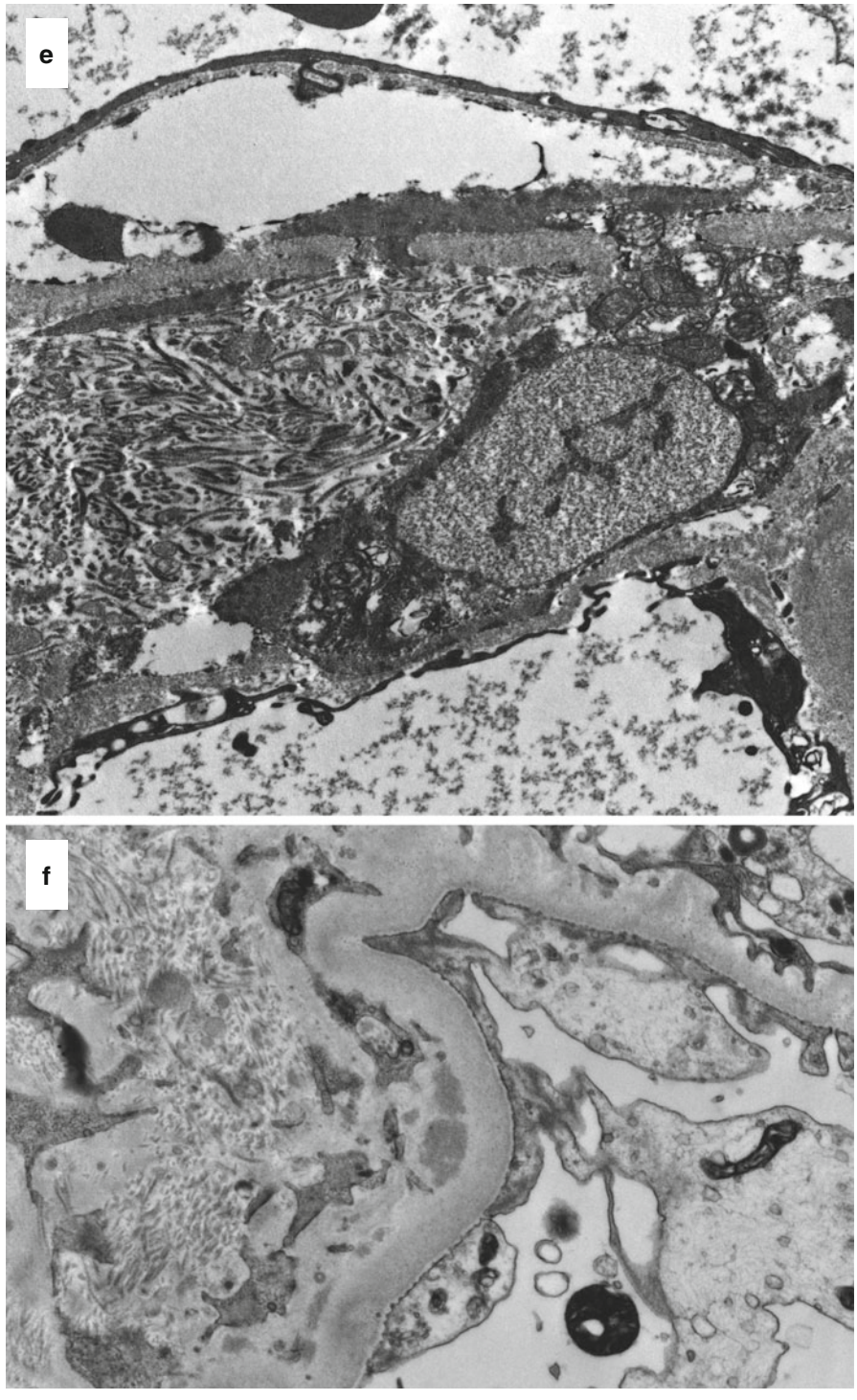

Fig. 7 (**a**–**f**) Collagenofibrotic glomerulopathy. (**a**, **b**, **c**, **d**) Collagen III in mesangium and along peripheral capillary walls. Collagen IV with different ultrastructural appearances. (**e**) Nonimmune complex-mediated glomerulopathy and (**f**) IgA nephropathy. AX12 500, BX 155000, CX9500, DX 27700. Transmission

prompt the request for a collagen III stain to confirm the suspected diagnosis (Gubler 2008; Vogt et al. 1995; Striker et al. 1984; Herrera 2016; Iskandar and Herrera 2014). The fibers deposited predominantly in the mesangium and to a lesser extent in the subendothelium reveal unusual features ultrastructurally (Fig. 7a, b). The fibers appear curved, frayed, spiraled, or worm or comma shaped when sectioned transversely and show a distinct periodicity from 43 to 65 nm. The fibers typically arrange in irregular bundles when cut longitudinally. In some cases, the collagen III fibers form peculiar lattices as they arrange in bundles that intersect (Fig. 7c, d). In contrast to nail-patella syndrome, the lamina densa of the glomerular basement membranes almost always remains intact with no collagen fibers deposited in this location (Herrera 2016; Iskandar and Herrera 2014). However, there have been two children with collagenofibrotic glomerulopathy that have exhibited abnormal collagen fibers in the lamina rara interna and externa of glomerular basement membranes, creating some confusion with nail-patella syndrome glomerular lesions (Tamura et al. 1996; Gubler 2008).

Differential Diagnosis

Making a definitive diagnosis of collagenofibrotic glomerulopathy on the basis of light microscopic findings is impossible. Mesangial expansion, either focal, segmental (early), or diffuse and generalized (far more common), is the most characteristic finding. The expanded mesangium displays increased argyrophilia. Due to the expansion of subendothelial spaces and even double-contoured basement membranes, some cases may be confused with thrombotic microangiopathy.

Demonstration of abundant collagen III in the expanded mesangial areas is imperative to confirm the diagnosis (Herrera 2016; Cohen 2013). It is also common to find collagen III in the interstitium, but this is of no diagnostic significance. Immunohistochemistry or immunofluorescence stains are available for testing.

In some cases, membranoproliferative glomerulonephritis is also in the differential diagnosis, as well as diabetic nephropathy and even amyloidosis. Differential diagnosis in selected cases includes distinction of collagen III deposition in mesangium from other fibrillary collagens at the ultrastructural level that can also be identified in the same location. Non-collagen III fibrillary collagen generally appears composed of straight fibrils with periodicity at 65 nm when sectioned longitudinally and circular when cut transversely. These collagen fibers typically dispose themselves in an organized parallel arrangement and, in rare cases, represent the main extracellular material in the mesangium. This type of fibrillary collagen is most commonly observed in focal, segmental glomerulosclerosis in segmentally sclerosed glomerular areas and in diabetic glomerulosclerosis in mesangial nodules (Fig. 7e). It is unusual to see fibrillary collagen in subendothelial zones, unless glomerular remodeling has occurred, but it is not uncommon to identify it in collagenofibrotic glomerulopathy. Rarely, in immune complex-mediated glomerular processes, there can be focal mesangial deposition of fibrillary collagen (Fig. 7f) in expanded mesangial areas.

Differentiation from nail-patella syndrome is also important in some instances (Salcedo 1984). The clinical manifestations of the latter disorder are rather specific in the great majority of the cases, but skeletal manifestations may be absent in selected cases. Ultrastructurally, the collagen fibrils are of

Fig. 7 (continued) electron microscopy. Uranyl acetate and lead citrate. In (**a** and **b**), the collagen fibers are located subendothelially and display curved, frayed appearance. In (**c** and **d**), they are in an expanded mesangium and display a peculiar lattice arrangement. Compare with well-aligned collagen fibers (not collagen III) in nonimmune complex (**e**) and immune complex-mediated glomerulopathies (**f**) (**a** and **b**, courtesy of Kensuke Joh, MD)

the classical type with the usual periodicity and are found along the glomerular basement membranes rather than in the mesangium.

Pathogenesis

The pathogenesis of this disorder remains unclear. Mesangial cells appear to be the most reasonable candidates for the overproduction of collagen III, but systemic overproduction of collagen III has also been suggested as an etiologic factor. Serum procollagen III is usually significantly elevated in these patients and could be considered a marker for this disease when interpreted in the proper clinicopathologic context (Vogt et al. 1995).

Collagen III glomerulopathy has been documented to occur in monkeys, dogs, pigs, and cats (Adachi et al. 2005; Fujisama-Imura et al. 2004; Kamiie et al. 2009; Kobayashi et al. 2009; Shirota et al. 1995; Nakamura et al. 1996). A naturally occurring autosomal recessive model of collagen III glomerulopathy has been published. This model displays morphologic features similar to those seen in humans with this condition. This animal model has shown that the canine Col3A gene is not involved in the pathogenesis of this disorder. It also demonstrated with the use of in situ hybridization analysis that mesangial cells are engaged in the production of de novo collagen III in this disease (Rorveit et al. 2012).

Therapeutics: Treatment and Prognosis

There is no specific treatment for this disorder. Renal failure was reported within 3 years of diagnosis in one patient (Ikeda et al. 1990). In other patients, symptomatology has progressed steadily to an increase in clinical manifestations, renal insufficiency, and, eventually, failure (Imbasciati et al. 1991; Yasuda et al. 1999; Kurasawa et al. 1984). The severity of the disease at presentation is highly variable and its pace of progression unpredictable. However, progression appears to be more severe when the first symptoms occur in early childhood (Salcedo 1984; Gubler 2008; Vogt et al. 1995). In some cases, abrupt deterioration of renal function may be a result of hemolytic uremic syndrome (Gubler 2008). Successful renal transplantation has been reported with no recurrence 3 years later (Suzuki et al. 2004).

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Index

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