Glomerular Disease

12

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Renal Anatomy

The kidneys receive approximately 25 % of the cardiac output. This blood is delivered via the renal arteries, which very rapidly divide into segmental arteries, lobar arteries, interlobar arteries, and finally the arcuate arteries before delivering blood to individual nephrons. The parenchyma of the kidney can be divided into the outer renal cortex—which houses approximately one to two million glomeruli per kidney—and the inner renal medulla, which is imperative in urinary concentration and water conservation.

The renal medulla can be appreciated macroscopically as the renal pyramids. These pyramids orient the final collecting ducts of the individual nephron subunits toward the renal calyces which then drain into the renal pelvis and into the lower genitourinary system.

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The Nephron

The basic functional unit of the kidney is the nephron. These can be divided into two subtypes: the cortical nephrons, which have relatively short loops of Henle, and the juxtamedullary nephrons, which have long loops of Henle that dive to the deepest parts of the medulla. The latter play a significant role in renal concentrating capacity.

Individual nephrons can be divided into several individual segments, each with unique transport and functional characteristics and susceptibility to injury. These include the glomerulus, proximal tubule, loop of Henle, distal convoluted tubule, the connecting segment, and finally the collecting duct, which delivers the tubular filtrate to the renal calyx [1, 2].

The Glomerulus

All serum filtration is performed in the glomerulus. The glomerulus consists of an afferent arteriole which branches into the glomerular tuft before coalescing back into a single efferent arteriole. The glomerular tuft is a delicate bouquet of capillaries that is composed of a specialized fenestrated endothelium, which is surrounded by a basement membrane and a layer of epithelial cells that are unique to the glomerulus called podocytes. The tuft is supported by the mesangium, which is made up of cells and matrix. The

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mesangial cells provide mechanical structure to the glomerular capillaries and may have other nutritive or hormonal roles.

The glomerular filtration apparatus is highly specialized and creates a size and charge barrier that allows blood filtration to occur. The barrier is composed of three layers. The endothelium of the glomerular capillary tuft is considered the first layer. It is one of the few capillary beds in the body that is fenestrated, with pores that measure approximately 70–100 nm across [3]. Given that platelets are approximately five- to tenfold larger that those pores, this layer provides an important barrier to cellular elements found in the blood.

Deep to the basal side of the fenestrated epithelium lies the glomerular basement membrane. The basement membrane is the fusion product of the endothelial basement membrane and the basement membrane from the podocyte [3]. Morphologically, it is composed of three layers: the lamina rara interna adjacent to the endothelial cell, a dense inner layer called the lamina densa, and the lamina rara externa adjacent to the podocyte. The composition of the basement membrane is also unique from other basement membranes, being composed primarily of type IV collagen. The meshwork of collagen fibers provides the superstructure of the basement membrane and generates smaller pores than those found in the fenestrated endothelium. These collagen fibers are then further modified with the addition of specific proteins that help maintain adhesion to the overlying cellular products and, more importantly, modify the barrier to limit the passage of charged particles [4].

On the urinary side of the glomerular tuft, deep to the basement membrane lies the podocyte. This is a highly specialized epithelial cell type that provides the final specificity to the filtration of blood. The podocytes spread out over the basement membrane in interdigitated foot processes that abut the membrane itself. In between these foot processes, several protein products coalesce into the slit diaphragm. This is believed to primarily add to the charge selectivity of the filtration barrier. This is highlighted in states of disease, namely, focal segmental glomerulosclerosis and minimal change disease, wherein the podocytes lose their structure and the foot processes lose cohesion, the result being the loss of charge selectivity and large protein losses in the urine; this will be further discussed later [3, 4].

The Proximal Tubule

The glomerulus is surrounded by Bowman's capsule, which collects the glomerular filtrate and shuttles it toward the tubule. The normal adult human filters approximately 160–170 L of ultrafiltrate daily. Most of this is reabsorbed through the length of the nephron, with the proximal tubule doing much of this work. In addition to reabsorption of valuable water and important solutes, it is also the site responsible for secretion of drugs, secretion of acids, as well as having some important metabolic activities [5].

The proximal tubule reabsorbs nearly all of the amino acids, glucose, and bicarbonate that are filtered through the glomerulus each day. This is largely through secondary active transport, with a favorable electrochemical gradient established by the Na-K ATPase found on the basal membrane driving sodium reclamation along with other solutes of interest. Since total body water is largely dependent on sodium balance, the reclamation of sodium also facilitates substantial resorption of water from the tubular ultrafiltrate, with approximately 66 % of the filtered water volume being recovered in this segment [5].

The proximal tubule also houses specialized active transporters for secretion of proteins and molecules that would otherwise not be adequately secreted into urine; the most common example of this is the secretion of pharmaceuticals into the urine through organic anion transporters. It is also the site for some of the renal metabolic functions such as vitamin D activation.

The Loop of Henle

The tubular filtrate not reabsorbed in the proximal tubule enters the loop of Henle. This segment can be divided into its descending limb, the thin ascending limb, and the thick ascending limb, each with a specific role. This segment is largely focused on managing water balance. Much of

this function is through the establishment of the medullary concentration gradient against which water can be reclaimed later in the nephron at the level of the collecting duct.

The loop is best described by beginning distally at the thick ascending limb (TAL). The TAL is considered to be water impermeable—that is, there are no aquaporins found in the TAL and the tight junctions limit paracellular movement of water. Here, the Na-K-2Cl transporter facilitates sodium reclamation from the tubular lumen into the medullary interstitium and begins the process of countercurrent exchange. Again, the reclamation of sodium here is considered a secondarily active process, with subsequent water reabsorption from the descending limb driven by the local increases in interstitial osmolarity. Because of the hairpin design of this segment, the local increases in sodium concentration at the beginning of the descending limb lead to water reclamation as the descending limb moves further into the interstitium, increasing the osmolarity of both the tubular and interstitial compartments down the length of the segment. In times of water avidity (dehydration, hypotension, etc.), this apparatus works maximally and can generate a medullary osmolarity of ~1200 mOsms which facilitates maximal water reclamation in the collecting duct.

It is important to appreciate the specialized arrangement of blood flow through this region as well. The efferent arteriole for a given glomerulus leads to the vasa recta for *that same glomerulus.* So the juxtamedullary glomeruli with long loops of Henle have vasa recta that follow them into the papillary medulla. Branching anastomoses in these vasa recta prevent high blood flows in the area and therefore prevent high blood flow at the deepest layers of the medulla, thereby preventing medullary washout, which impairs the nephron's concentrating ability.

Distal Convoluted Tubule and Connecting Segment

The remaining tubular filtrate then moves to the convoluted tubule. This is the home of the Na-Cl cotransporter. This site is responsible for approximately 5 % of the sodium reclamation in the kidney. This reabsorption is also by secondarily active transport with the favorable gradient being established by the basal Na-K ATPase. It is also one of the primary sites for calcium reabsorption from the urinary filtrate, an important factor in the generation of nephrolithiasis, considered elsewhere.

Collecting Duct

The distal-most tubular segment is responsible for final refinement of the tubular filtrate. Only about 5 % of the total filtered sodium and water enter the collecting duct. The cortical segment of the collecting duct houses two cell types, each with a specific role. The principal cell modulates potassium secretion via an aldosterone-sensitive pathway. The intercalated cell facilitates hydrogen secretion and therefore influences a patients' acid–base status.

The principal cell houses apical epithelial sodium channels (ENaC), which are aldosterone sensitive. In times of high aldosterone output—in general, periods of intravascular volume depletion—aldosterone both increases nuclear transcription of ENaC and facilitates the intracellular movement of preformed ENaC to the apical surface of the principal cell. This then allows sodium to move down its concentration gradient into the principal cell where it can be recovered through the Na-K ATPase. Concurrently, apical potassium channels allow for potassium secretion into the tubular filtrate in order to maintain electroneutrality.

The more distal collecting duct houses more of these cell types but becomes increasingly sensitive to circulating antidiuretic hormone (ADH). This circulating hormone increases the insertion of apical aquaporin 4 channels, which in times of volume depletion dramatically increase water recovery in this segment against a very favorable osmotic gradient that was established by countercurrent exchange in the loop of Henle. In that setting, urinary osmolarity will be very high, approaching 1200 mOsms, reflecting the water reclamation in this region.

The renal pelvis, ureters, and bladder are largely impermeable to water and solutes, though

Table 12.1 Indications and contraindications to renal biopsy

	Contraindications	
Indications	Relative	Absolute
Nephrotic syndrome	Severe azotemia	Uncooperative patient
Routinely in adults	Renal anatomic abnormalities	Uncontrollable hypertension
If atypical for MCD in children	Antiplatelet therapy or anticoagulation	Uncontrollable bleeding diathesis
Nephritic syndrome	Solitary native kidney	
Systemic disease with renal insufficiency	Skin infection over the biopsy site	
Unexplained CKD	Active kidney infection	
Familial renal disease	Pregnancy	
Renal transplant dysfunction		

MCD minimal change disease, *CKD* chronic kidney disease

in low flow states, some water and urea reclamation can occur. In animal models, this has been shown to change the urinary composition by approximately 7–15 % [6].

Renal Biopsy

The processing of renal tissue for pathologic review is somewhat different than typical tissue preparation that may be used for other biopsy samples. The nature of the diseases that can be detected through pathologic evaluation demands that optimal preparative technique be used. Proper handling at the time of biopsy facilitates light microscopy, immunofluorescence evaluation, electron microscopy (EM), and—where necessary—immunohistochemical staining.

Tissue adequacy has historically been a limiting factor in renal biopsy, though with newer technologies and safer sampling techniques, that issue has become less prevalent [7]. In order to make an accurate diagnosis of native renal disease, a minimum of 10 glomeruli are required, though to ensure a 95 % sensitivity for more focal lesions, 20–25 glomeruli are recommended [8].

Presently, the standard of care for outpatients who need renal tissue sampling for diagnosis of their underlying renal disease is the percutaneous renal biopsy. There are both relative and absolute contraindications to this procedure that would preclude percutaneous sampling, and in those instances CT-guided renal biopsy, laparoscopic or open renal biopsy, or transvenous renal biopsy can be considered (Table 12.1) [8].

Percutaneous Kidney Biopsy

The percutaneous renal biopsy has been adopted as the principal technique for sampling renal parenchyma. When doing percutaneous biopsy, most renal pathologists agree that at least two core samples are necessary for adequate sampling and to avoid missed diagnoses. Where available, it is also useful to hand tissue directly to a trained technician at the time of biopsy for review under either a dissection or light microscope to evaluate for tissue adequacy based on the number of observed glomeruli [9].

This procedure is typically done with the patient awake and in the prone position. CT or ultrasound is used to locate the desired target—typically the lower pole of either kidney. The patient is given instructions on breath holding and regional anesthetics are used to numb the patient from the skin to the renal capsule. Since renal parenchyma lacks sensory innervation, there is no need to anesthetize deeper renal tissues. A biopsy needle is passed through the anesthetized tract and core samples taken with the patient instructed to hold their breath during period when the biopsy will be taken. Typically precautions are taken following the procedure to

decrease the risk of bleeding and provide time for hemostasis to occur. Patients are maintained in the supine position with frequent vital sign monitoring for the ensuing 8–24 h. Urine collections are also preserved for physician review to ensure that gross hematuria, if present initially, improves during that same period.

A number of clinical studies have tried to address the exact amount of time that a patient should be observed for complications following the procedure. Early literature on the topic suggested that most complications would be noted by 12 h, thus perhaps eliminating the need for overnight hospitalization [10]. More recent data suggests that it may take longer to recognize complications, with one observational study noting that while 46 % of complications were noted before 4 h and 67 % by 8 h, 89 % could be identified by 24 h [11]. Presently, consensus recommendation is to observe patients in the inpatient setting for 24 h post procedure.

Open Kidney Biopsy

Laparoscopic and open biopsies have been shown to be largely safe and well tolerated. In the largest case series of 934 patients, a modified laparoscopic approach with general anesthesia had 100 % tissue adequacy for diagnosis, no major complications, and only one minor complication related to anesthesia [12].

However, given the invasive nature of the procedure, the risks of general anesthesia on a population basis, and the prolonged recovery time, open biopsy is typically only used in patients who have either an absolute or relative contraindication that precludes percutaneous biopsy [13].

Transvenous Kidney Biopsy

The transvenous—transjugular or transfemoral—approach is a procedural technique first described by Mal in France in 1990 [14]. Various reasons have been cited as prompting this choice of procedure, including need for other organ biopsies (heart, liver), bleeding diatheses, and uncontrolled hypertension, among others. Since that time a number of studies have been published reviewing the adequacy of this technique as well as their complication rates [13, 15]. Studies have reported adequate parenchymal sampling, with rates ranging from 73 to 97 %. In the published literature, no patient has died or required dialysis after these procedures [13]. Comparison to the other available biopsy options is difficult because of inherent selection bias. At present, the use of this technique largely depends on local availability and patient-specific factors that would preclude percutaneous biopsy.

Tissue Fixation and Preparation

The fixatives used for preserving the tissue vary by microscopy modality. It is important that the proceduralist be familiar with the handling preferences of their renal pathology lab in order to ensure appropriate handling once collected. Here we will discuss the handling of the percutaneous biopsy, given its prevalent use in parenchymal sampling.

The core samples taken by percutaneous biopsy are typically divided into portions destined for the varying histologic uses. Samples are taken from both the cortical end of the tissue and the medullary end for use in electron microscopy. The remaining tissue from each tissue core is divided for use with immunofluorescence of light microscopy.

Light Microscopy

Most pathology laboratories prefer light samples to be collected and stored in 10 % aqueous formaldehyde solution (formalin). Formalin is safe and readily disposed of and preserves morphologic features for review. It also allows for additional tissue processing using immunohistochemical techniques or molecular studies to be used if necessary. Alternative solutions include Bouin's, Duboscq-Brazil, Zenker's, or 4 % paraformaldehyde fixatives, each with varying uses [9].

Slide preparation also varies according to pathology laboratory, but typically includes sectioning of the preserved tissue into 2 μm slices and serial staining with hematoxylin and eosin (H&E) stain, periodic acid-Schiff reaction (PAS), silver stain, or trichrome stain [9].

Electron Microscopy

Tissue fixation for EM requires fixation in either 2–3 % glutaraldehyde or 1–4 % paraformaldehyde. This provides the greatest degree of structural preservation. It is occasionally necessary to reprocess samples stored in either the frozen section or the paraffin-embedded section if glomeruli are not available on the EM processed sections. This can lead to cellular artifact, but generally is considered acceptable for review of the GBM for both structural integrity and for immune deposition [9].

Immunofluorescence or Immunoperoxidase

Some pathology laboratories have gone to immunoperoxidase (IP) staining for review of immune deposition due to relative ease of processing. However, most renal pathologists agree that dark field imaging with IF is the preferred modality to identify immune deposition in pathology samples. The processing of these materials is laboratory dependent, though formalin fixation is typically adequate with freezing and subsequent sectioning used to label the immune complexes [9].

Glomerular Syndromes and Mechanisms of Injury

Medical renal disease affects the kidneys in a variety of ways and can manifest clinically as any number of clinical syndromes. Each of the individual classes of renal disease has their own hallmarks; here, however, we will be focusing diseases primarily affecting the glomerulus.

The glomerular diseases manifest according to the pattern of underlying injury, which we will briefly review, before discussing specific clinical syndromes.

Structural Patterns of Injury

As discussed previously, the glomerular tuft houses the filtration apparatus that generates the tubular ultrafiltrate and is composed of three layers: the fenestrated endothelium, the glomerular basement membrane, and the podocytes. Each of these layers can suffer injury and the nature of that injury correlates closely with the observed clinical syndrome.

Immune conditions or vasculitis conditions that affect the endothelium lead directly to a robust inflammatory cascade that typically leads to endothelial proliferation and filtration barrier disruption. That disruption can be detected clinically as the nephritic syndrome with loss of both protein and cellular elements (typically red blood cells) into the urinary space with concomitant changes in filtration efficacy as detected by changes in the glomerular filtration rate (GFR).

Conditions that affect the glomerular basement membrane include both congenital and acquired conditions. The congenital disorders tend to be more indolent with adaptive changes in the associated glomerular cell types and long latency to diagnosis. These include disease like thin basement membrane disease and Alport's disease. The acquired types can lead directly to disruption of the GBM and has implications for both the size and charge selectivity of the filtration barrier. These acquired conditions, like anti-GBM disease, typically lead to robust immune activation and consequences similar to those seen with endothelial diseases.

The podocytopathies are a family of disease that classically disrupt the cellular architecture of the podocyte leading to breakdown of the interdigitated foot processes with associated loss of charge selectivity. That loss of charge specificity leads to robust proteinuria, but relatively limited, if any, hematuria.

Each of these will be discussed in more detail below.

Nephritic Syndromes

The nephritic syndrome is a collection of signs and symptoms that denote underlying glomerular injury, the hallmark of which is the presence of

both proteinuria and hematuria in the urine. The classic nomenclature is used to describe a limited amount of protein, with any amount of glomerular hematuria. This contrasts with the nephrotic syndrome, which denotes a disease wherein there is significant proteinuria and no hematuria. Some providers also discuss the nephritic/nephrotic syndrome where there are significant hematuria and nephrotic-range proteinuria, though this is better described as an advanced nephritic syndrome, given that the underlying mechanism of injury, as discussed above, mandates endothelial injury in order to facilitate the observed hematuria.

Rapidly Progressive Glomerulonephritis

The most striking examples of the nephritic syndrome are the crescentic glomerulopathies, which frequently present as rapidly progressive glomerulonephritis (RPGN). RPGN does not refer to a single disease process; rather, it describes a clinical syndrome of rapidly progressive acute renal failure associated with hematuria and proteinuria, which is typically caused by advanced histologic injury to the glomerular tuft.

Clinical Presentation

Clinically, this collection of diseases share certain features, namely, the presence of a nephritic sediment with red blood cells either in red cell casts or with dysmorphic characteristics, some amount of proteinuria, and rapid loss of renal function. Renal failure with oliguria, severe azotemia, and hypertension are the hallmark of the initial presentation and typically lead to progression to ESRD within 3 months of diagnosis if left untreated [16]. Patients may also have evidence of hypertension—owing to disrupted sodium regulation and possibly renin-mediated mechanisms—and edema. There are of course more distant or systemic effects that can be seen as well, though these are generally a characteristic of the underlying disease. An example would be the pulmonary hemorrhage seen in anti-GBM disease (Goodpasture's disease) [17].

The number of disease conditions that are known to cause RPGN is limited. Each has a specific pathogenic mechanism by which it leads to glomerular capillary injury and disruption, outlined separately, but they can be organized according to their pattern of injury. The first and most straightforward is anti-GBM disease, the second group being a far more heterogeneous array of disease wherein immune complexes in the glomerular capillary tuft lead to local injury, and the last being the pauci-immune vasculitides wherein no immune depositions can be detected, but pathogenic antineutrophil cytoplasmic antibodies (ANCA) lead to notable inflammatory activation which can be observed histologically. The latter is the most common form of crescentic glomerulonephritis, accounting for approximately 60–80 % of all cases [16].

Pathogenesis

While the underlying pathogenesis of the specific disease entities is reviewed below, their progression to an RPGN is typical and includes necrotizing inflammation which leads to GBM disruption and leakage of serum proteins including fibrin and fibronectin into the urinary space which generates a robust activation of both the visceral and parietal epithelial layers in Bowman's space. In turn, these cells dedifferentiate and proliferate and lead to the formation of the prototypical crescent (Fig. 12.1) [16].

The crescents themselves are a histologic signal of injury; the association of this pattern of injury with the clinical manifestations of the RPGNs has led to these terms being considered near synonymous [18].

Treatment

Despite their differences, the initial treatment of these diseases is similar, largely because of the incredibly high risk of irreversible renal injury and risk of other morbidities and mortality [19].

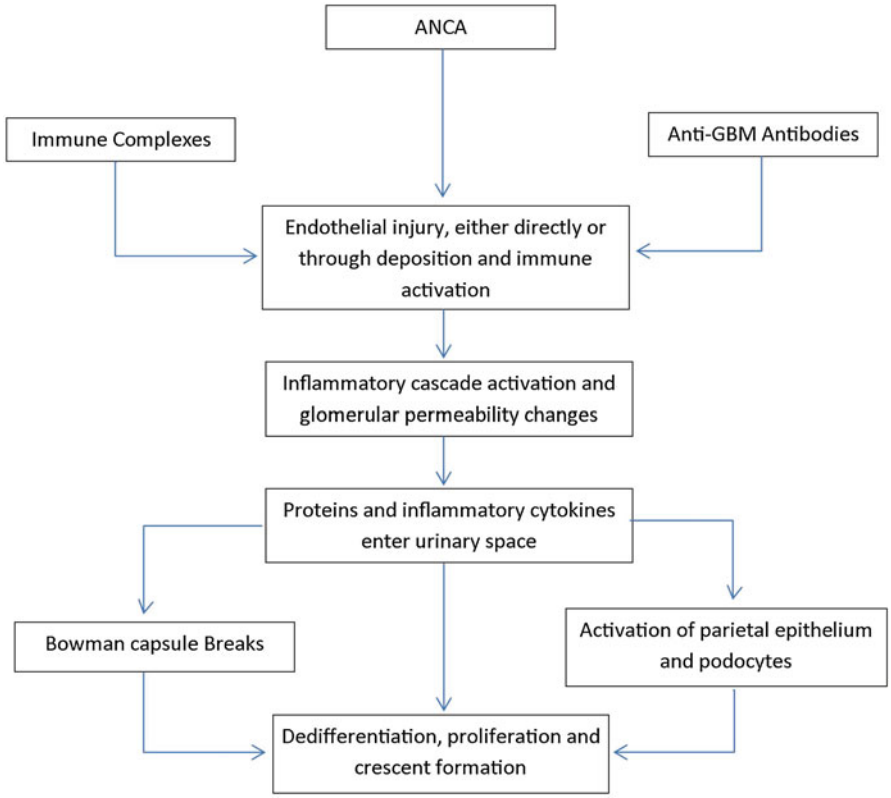

Fig. 12.1 Pathogenesis of crescent formation

Typically the treatment of any of these diseases is divided into induction and maintenance phases. Induction therapy is often initiated in advance of definitive diagnosis. Sometimes this is with serologic evidence, but often, even that is not yet available. The cornerstones of treatment have been steroid therapy and plasma exchange for nearly 40 years [20]. Recent meta-analysis on the topic has shown that the use of adjunct plasma exchange can reduce the rate of progression to ESRD in these patients, noting that ESRD rates are reduced at both 3 and 12 months [21]. Pulse glucocorticoid therapy is also typically started at the time of clinical presentation. While subject to varying patterns of administration, typically 500–1000 mg of methylprednisolone is given over 2–3 days as initial therapy to help calm the inflammatory cascades active in the tuft. Lastly the use of immunosuppression therapy is used to reign in the production of the injurious autoantibodies. The classical treatment for RPGN has been oral or intravenous cyclophosphamide (CYC) administered according to a variety of protocols either as continuous oral therapy or as pulse intravenous therapy [21]. With the advent of newer immunosuppressive therapies, the treatments used in practice have increased, though the details of their selection are outside the scope of this publication.

Anti-glomerular Basement Membrane Disease

Typically this disease presents as a pulmonary renal syndrome with acute onset of both lower respiratory complaints and changes in urinary character [17, 19]; however, more subtle cases can be seen. Because of its tendency to rapidly

progress, it should be considered in all cases of acute pulmonary renal disease, and coordination with a nephrologist is recommended for urgent initiation of plasmapheresis if needed in the setting of diffuse alveolar hemorrhage [21, 22].

Pathogenesis

The GBM is formed through the fusion of the endothelial and podocyte basement membranes. The normal GBM is a tight meshwork of collagen fibers, with alpha 3, alpha 4, and alpha 5 subtypes of type IV collagen fibers forming hexamers that then crosslink through their non-collagenous (NC1) domains. In patients with anti-GBM disease, immunoglobulin G (IgG) can be identified on immunofluorescence overlying all of the glomerular basement membrane, and the causative antibodies have been found to be directed against those NC1 domains of alpha 3 or alpha 5 type IV collagen [23].

Recent work has demonstrated that the disease is one of quaternary conformational change—the specific cause of which is unknown, though it has been linked to smoking, viral infections, and solvent exposure—which leads to molecular conformational shifting and exposure of the normally sheltered NC1 domains with subsequent autoantibody formation. Those autoantibodies then bind to the NC1 domains and lead complement fixation and to a type II hypersensitivity reaction with robust inflammatory recruitment and consequent local injury [22, 23].

This disease manifests as the nephritic syndrome due to the ongoing glomerular injury, and patients have pulmonary symptoms as well given that the alpha-3 subunit is also expressed in the alveoli of the lungs. This can lead to a very dramatic clinical presentation of the disease with diffuse pulmonary hemorrhage as the initial presenting symptom. Prior to the use of the above-described therapies, anti-GBM disease was nearly universally fatal, though with the use of modern treatments, the 5-year survival now exceeds 80 % [22].

Pathology

Anti-GBM disease has characteristics on light microscopy that are typical for RPGN, typically with areas of GBM destruction with nearby fibrinoid necrosis. In early disease, there may not be evidence of crescent formation on the biopsy sample, though in more advanced cases, lymphoplasmacytic infiltration and endocapillary proliferation may become apparent. Immunofluorescence is diagnostic with smooth GBM staining for IgG and c3. IgG is usually more positive than c3 staining. Electron microscopy reveals the absence of immune deposits and can highlight the broken GBM with associated fibrin tactoids notable in areas of discrete necrosis.

Management

The challenges present in diagnosing this disease combined with its rarity make this a challenging disease on which to do randomized clinical trials. However, given that it is understood to be an immune-mediated disease, immunosuppressive therapies are considered necessary as part of its treatment. If diagnosed during its fulminant phase, plasmapheresis is often indicated. At the same time, induction is achieved, as described above for all of the RPGNs, classically done with CYC and high-dose glucocorticoid therapy [16, 19, 22]. The introduction of anti-CD20 monoclonal antibody (rituximab) therapies has been used as well in small patient cohorts, the largest a series of eight patients who had received steroids and CYC as well as plasmapheresis. All were started on rituximab within 2 months of diagnosis. At approximately 2 years follow-up, patient and renal survival were 100 and 75 %, respectively [24].

The prognosis for patients affected by anti-GBM disease is largely dependent on the promptness of the diagnosis and initiation of effective treatment. While historically the disease was considered fatal [25], the above therapies have led to a 5-year survival rate in excess of 80 %, and only about a third of patients require long-term dialysis [22].

Table 12.2 Features of ANCA-associated vasculitides

	Renal limited disease	Microscopic polyangiitis	Granulomatosis with polyangiitis	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Frequency of renal involvement	100	90	80	45
Frequency of ANCA positivity	80	90	95	70
MPO	60	50	25	60
PR3	40	50	75	40
Extrarenal manifestations	None	Musculoskeletal complaints, pulmonary	Pulmonary, sinus, head, and neck	Pulmonary, neurologic, allergy symptoms

ANCA antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *PR3* proteinase 3

Pauci-immune Glomerular Disease

Accounting for just over half of all diagnosed RPGN syndromes and sometimes recognized in more indolent circumstances, this group of diseases is characterized by necrotizing changes on biopsy in the absence of immune deposits [19]. This group of diseases includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), and microscopic polyangiitis (MPA). The bulk of these patients have circulating ANCA. Clinically they present in a variety of different ways, each of which is typically associated with a collection of extrarenal manifestations that can suggest which disease is causative, though it does require tissue biopsy to establish the definitive diagnosis. The varying extrarenal characteristics, as well as the frequency of specific ANCA subtypes with those diseases, are summarized in Table 12.2. These diseases do occasionally present with less fulminant disease. So-called early systemic disease is defined as serologic positivity, but with sCr below 1.7 mg/dL and no critical extrarenal organ dysfunction [26]. This distinction has implications for treatment.

Pathogenesis

The association of ANCA and necrotizing glomerular disease was first recognized by Davies in 1982 [27]; subsequent work has gone on to support a pathogenic mechanism for these autoantibodies. There are two identified culpable antibody subtypes, the anti-myeloperoxidase (MPO) subtype and the anti-proteinase 3 subtype (PR-3). These antigens are typically sequestered into neutrophilic granules and are exposed only during periods of inflammatory activation [17, 19]. Directly linking this antibody activity to the disease, however, has been proven difficult. Renal biopsies of affected patients are rife with activated neutrophils, and indeed, the number of activated neutrophils seen on biopsy has been correlated with the degree of renal insufficiency [28], but they do not have observable immune complexes attributable to ANCA, hence the name "pauci-immune." Additional evidence for a pathogenic role of ANCA has grown with ANCA being elutable from affected kidney tissue, and in the case of anti-MPO antibodies, necrotizing glomerulonephritis can be induced with infusion of ANCA [29]. Interestingly, anti-LAMP 2 (antibodies directed against lysosomal membrane protein-2) have been shown to be present in upward of 80 % of all active ANCA-associated vasculitides (AAV) [30, 31]. While the understanding of the disease is improving, there are many aspects of the pathogenesis that remain to be understood.

Pathology

The ANCA-associated vasculitides have similar histologic appearances. Common among all of them are segmental glomerular necrosis with

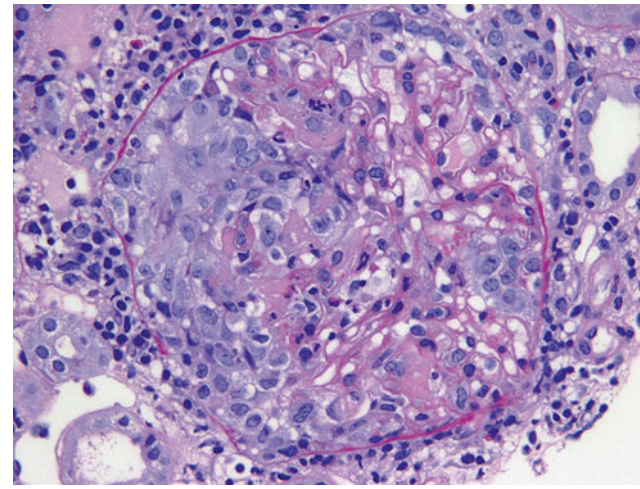

Fig. 12.2 A cellular crescent with fibrinoid necrosis is noted on the left side of this glomerulus in a patient with pauci-immune (ANCA-associated) glomerulonephritis (PAS)

crescent formation (Fig. 12.2) and the absence of either immunofluorescence findings or changes by electron microscopy. In GPA and microscopic polyangiitis, there is typically evidence of an active interstitial nephritis with or without larger vessel involvement. In EGPA there may or may not be an eosinophilic predominance in the interstitial infiltrate, and this does not have bearing on the pathologic diagnosis. The granulomatous changes seen in GPA are more typically identified in lung biopsy than in renal biopsy, and often the diagnostic distinction between these diseases (GPA/MPA/EGPA) is made clinically.

Management

Again, the induction therapy for this disease has included treatment as described for an RPGN with cyclophosphamide as the core of the induction immunosuppressive regimen since the 1970s. Typically, maintenance therapy is necessary due to high rates of relapse and has historically been accomplished with azathioprine. Recent studies have also set out to explore the utility of B cell-depleting agents like rituximab both as an alternative induction agent and a maintenance therapy.

In situations where patients may present with less threatening disease, so-called early systemic AAV, several studies have shown non-inferiority of methotrexate (MTX) as an induction agent. In one randomized controlled trial patients with confirmed ANCA positivity, sCr <1.7 mg/dL and no evidence of critical organ dysfunction were randomized to receive either oral cyclophosphamide or oral MTX for 12 months. There were similar rates of remission at 18-month follow-up, though the time to remission was longer in the MTX patients, particularly those with more extensive disease [26].

Cyclophosphamide is the historical gold standard for induction therapy. Oral or intravenous (IV) administration of CYC has also been extensively studied [32–34]. Indeed similar response rates were seen in patients receiving either oral or IV CYC, though the cumulative dose of those patients receiving IV therapy was less. Given that the complication profile of CYC is largely directed by its cumulative dose, there may be some long-term benefit to limiting the absolute amount of CYC administered. However, long-term follow-up of patients previously enrolled in the largest of these trials has failed to show a difference in treatment-related adverse events. It did, however, show a higher relapse rate among patients receiving the IV therapy, though this ultimately was not reflected in differences in the overall patient morbidity or mortality at just over 4 years [35].

Rituximab has also been used for both induction and maintenance in these patients as well with high efficacy. Two large, well-conducted trials have evaluated the use of rituximab for induc-

Table 12.3 Overview of the treatment of AAV according to EULAR recommendations

Disease stage	Treatment	Study/level of evidence, grade of recommendation
Induction of remission		
Early systemic	Methotrexate 15 mg/week (oral/parenteral), increase to 20–25 mg/week, folic acid + GC	NORAM (level 1B, grade B)
Generalized	Cyclophosphamide IV/oral + GC	CYCLOPS (level 1A/1B, grade A)
	duration: 3–6 months (oral) or 6–9 pulses (IV)	RAVE (level 1B)
	Rituximab 4 × 375 mg/m^2 in weekly intervals	
Severe (creatinine >500 μmol/L)	Standard therapy + plasma exchange	MEPEX (level 1B, grade A)
	Rituximab 4 × 375 mg/m^2 in weekly intervals (as substitute for cyclophosphamide)	RITUXVAS (level 1B)
Concomitant glucocorticoids (GC)	Prednisolone/prednisone 1 mg/kg/day oral taper to 15 mg/day or less within 3 months	(level 3, grade C)
Maintenance of remission		
Maintenance options	Azathioprine 2 mg/kg/day oral + low-dose GC	CYCAZAREM (level 1B, grade A)
	Methotrexate 20–25 mg/week + low-dose GC	WEGENT (level1B, grade B/A)
	Leflunomide 20 mg/day oral + low–dose GC	LEM (level 1B, grade B)
	Duration: at least 18 months	
Concomitant GC	Prednisolone/prednisone less than 10 mg/day	
Refractory, relapsing and persistent disease		
Options for refractory disease	IVIG 2 g/kg IV for 5 days	
	Rituximab IV	
	Infliximab 3–5 mg/kg IV 1–2 months	
	MMF 2 g/day oral	
	15-deoxyspergualin 0.5 mg/kg/day SUBQ until nadir; then stop until leucocyte recovery (six cycles)	
	Anti-thymocyte globulin 2.5 mg/kg/day IV for 10 days (adjusted to lymphocyte count)	

New trials have been incorporated into the overview and are presented in gray letters

Adapted with permission from Elsevier: Holle and Gross [39]

tion therapy with similar efficacy [36, 37]. Follow-up trials have gone on to show non-inferiority for maintenance therapy with rituximab as well [38]. The current treatment recommendations for AAV are summarized in Table 12.3.

Immune Complex Deposit Mediated Disease

This heterogeneous group of diseases is often consequent to ongoing immune activation with accumulation of immune elements in the glomerular tuft. Those immune complexes may form in circulation and deposit in the glomerular basement membrane, or they may be circulating antibodies which preferentially favor deposition in the glomerular tuft with in situ complex formation with circulating antigens.

These diseases can manifest as RPGN pictures depending on the variable amount of immune activation and tissue injury associated with that activation. They stem from a variety of underlying clinical illnesses ranging from the autoimmune condition systemic lupus erythematosus (SLE) to the mixed cryoglobulinemic conditions commonly associated with chronic viral infections like hepatitis C and Epstein-Barr virus. Here we will review the most common immune complex diseases and their pathology.

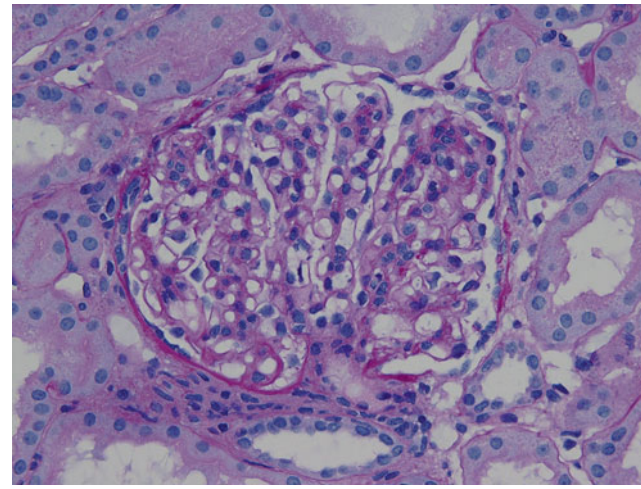

Fig. 12.3 There is segmental mesangial hypercellularity, which should be assessed in regions removed from the vascular pole, in this glomerulus from a patient with IgA nephropathy (PAS)

IgA Nephropathy

IgA nephropathy is the most common primary glomerulonephritis globally. First described in 1968 by Berger, it is also commonly referred to as Berger's disease. Clinically it most commonly presents as hematuria with or without overt proteinuria. It has a male predominance that ranges from 2:1 in Japan up to 6:1 in Europe and the United States [40]. It has long been considered a relatively indolent disease, but has recently been recognized to frequently lead to progressive CKD and ESRD and may present as a RPGN [40, 41].

Pathophysiology

Recent advances in the understanding of IgA nephropathy have led to a deeper understanding of the complex genetic and environmental interplay that are important in the development of this disease. Clinically, patients who manifest gross hematuria would note that hematuria would closely follow episodes of respiratory or gastrointestinal illness. Given that IgA is an important component of mucosal defense, this led to the hypothesis that it was primarily an overproduction of immunoglobulin with glomerular trapping that led to disease manifestations. While this may be true, we now recognize that aberrant *O*-galactosylation—a genetic phenomenon—in the hinge region of the immunoglobulin predisposes patients to the disease.

There are two subclasses of IgA: IgA1 and IgA2. Glomerular disease seems to be exclusively the consequence of IgA1, which houses a hinge region that IgA2 does not. This hinge region is heavily galactosylated. These carbohydrate modifications in patients with IgA nephropathy lack terminal galactose, which is considered to be the principal defect in the pathogenesis of this disease [42]. While IgA1 is dominantly in the mucosal tissues, some can be found in circulation. The galactosylation aberrancy is thought to lead either to easier trapping in the mesangium with in situ complex formation or to immune complex formation in circulation. These immune complexes lead to local inflammation and injury to the surrounding tuft [42].

Pathology

The most common finding by renal biopsy worldwide, IgA nephropathy is characterized by mesangial deposits of IgA that are readily apparent by immunofluorescence. As its name suggests, IgA is typically the dominant immunoglobulin identified by immunofluorescence, though it can be codominate with IgG. The deposits are readily apparent by electron microscopy in the mesangium—and occasionally at subendothelial deposits. Light microscopy varies and often correlates with the clinical findings observed (Fig. 12.3). It can range from normal histology to isolated mesangial proliferation and,

in very severe cases, can have focal or diffuse endocapillary proliferation with or without necrosis and crescent formation.

Management

Despite an expanding understanding of the pathogenesis of this disease, no specific disease-targeted therapy yet exists. In most cases management of this disease is conservative with emphasis on blood pressure and proteinuria management with renin-angiotensin-aldosterone system (RAAS) blockade. There have been a variety of treatments that have been considered but which have failed to show improvement in randomized studies (tonsillectomy, fish oil, immunosuppression therapy, etc.). If, despite conservative treatment for 4–6 months, proteinuria continues in excess of 1 g/day and the patient has preserved renal function, a course of high-dose oral steroids is often completed [43]. Patients that present with a crescentic RPGN are treated similar to other RPGNs with steroids and CYC.

Postinfectious Glomerulonephritis

Infection remains a common cause acute proliferative glomerulonephritis. Recognized and described first in the eighteenth century, the association between acute infection and subsequent renal manifestations is well known. In contrast to the renal manifestations that accompany IgA nephropathy, which are synpharyngitic, postinfectious glomerulonephritis (PIGN) typically presents 2–4 weeks after infection, earlier following upper respiratory tract infection, later after skin infections. Classically the patient is young with a recent infection with group A *Streptococcus pyogenes*, and they present with edema, oliguria, and hematuria. They have declining renal function and an active urinary sediment with dysmorphic red cells, red cell casts, and white cells in their urine. Evidence of complement activity is also an important clue to the diagnosis with low serum complement levels. The natural history is widely variable with some patients requiring renal replacement therapy and others recovering renal function relatively rapidly.

Pathogenesis

Multiple offending organisms have been implicated in the pathogenesis of acute PIGN. The most common among them is a streptococcal infection. Specific streptococcal Lancefield M types have been associated with PIGN and have been termed the "nephritogenic" strains. In patients who have disease that follows a typical upper respiratory or tonsillitis, types 1, 2, 4, and 12 have been implicated. In patients whose disease follows a skin infection, types 47, 49, and 57 have been shown to be associated [44]. That is not to suggest that *Streptococcus* is the only culpable organism, as *Staphylococcus* and many others have also been associated [45]. The antigenic organism forms circulating immune complexes that are then deposited between the GBM and the podocyte ("subepithelial") of the glomerulus. This leads to complement activation either through the alternative or lectin pathways and the proinflammatory milieu recruits additional immune cells to the area [44]. This robust activation leads to the endocapillary proliferation.

Pathology

Light microscopy is highly suggestive of postinfectious glomerulonephritis with diffuse endocapillary proliferation and infiltration with numerous polymorphonuclear cells (Fig. 12.4). Typically there are chunky subepithelial deposits, "humps" that can be seen along the capillary loops by electron microscopy, and these correlate with strong IgG and c3 staining by immunofluorescence. It is important to recognize that they will remain the longest in areas where the capillary loop meets the mesangium and these areas should be thoroughly investigated by electron microscopy if this diagnosis is suspected.

Management

Thankfully, in most children and young adults, the disease is self-limited. It can be more prolonged and have longer-lasting renal consequences in the elderly. This may be in part due to less renal reserve or perhaps due to a waning immune system unable to clear the immune mediators trapped in the glomerulus. In cases where there is pronounced activity on biopsy or where dialysis is

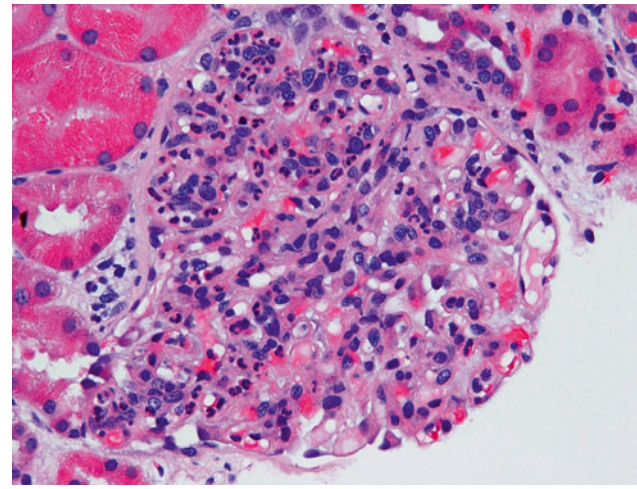

Fig. 12.4 Numerous neutrophils are present in the glomerular capillaries which are characteristic of postinfectious glomerulonephritis (H&E)

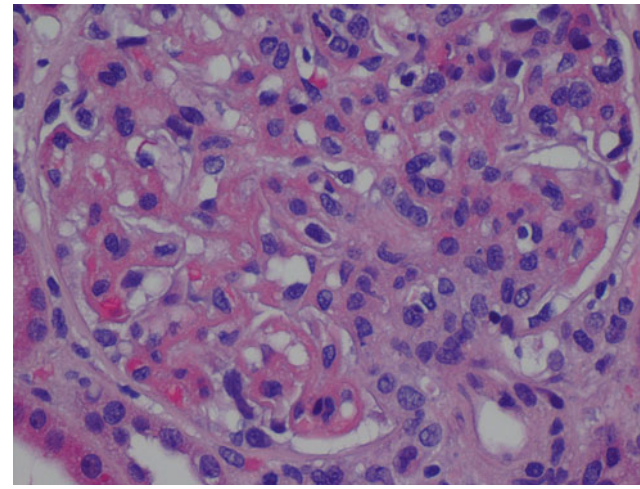

Fig. 12.5 This glomerulus from a lupus patient contains prominent immune complex deposition in the form of "wire-loop" deposits at the 4 and 6 o'clock aspects of this glomerulus, which is a feature of activity (H&E)

required, corticosteroids and sometimes immunosuppressants are used, though it is important to be sure the infection that led to the insult is cleared.

Lupus Nephritis

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease that has a number of implicated autoantibodies recognized to cause the disease. Those antibodies include antinuclear antibodies (ANAs), anti double-stranded DNA antibodies (anti-ds DNA), anti-histone antibodies, and anti-ribonucleoprotein antibodies (anti-RNP). The diagnosis is made clinically based on a variety of clinical, laboratory, and pathologic characteristics (Fig. 12.5). One of the end-organ injuries that can result from SLE is lupus nephritis, a varied disease entity with clinical manifestations that differ both between patients and across time.

Unfortunately there is no hallmark clinical presentation of lupus nephritis. It ranges from subnephrotic range proteinuria, to nephrotic syndrome, to the RPGN syndrome according to how the immune deposits culpable in the disease align within the glomerulus. Treatment is variable depending on the type of lupus nephritis.

Nephrotic Syndrome

The nephrotic syndrome is characterized by ≥3.5 g proteinuria per day, edema, and hypercholesterolemia. In this disease state, the primary defect driving the proteinuria—which may be secondary to a systemic disease process—is the loss of charge discrimination at the level of the glomerular filtration barrier.

As this charge barrier breaks down, small proteins, typically albumin, begin to move from the capillary into the urinary space where they are minimally reabsorbed, leading to microalbuminuria. This decline in serum colloid also leads to increased hepatic synthetic function, an increase that is thought to help rectify the hypoalbuminemia, but as an unintended side effect also leads to hypercholesterolemia as the hepatic apparatus also generates cholesterol.

The physiologic underpinning of edema development is felt to have both an "underfill" and "overfill" component. The "underfill" hypothesis describes the loss of albumin and decrease in intravascular oncotic pressure as being central to edema formation. It describes the loss of plasma proteins into the urine and the consequent decrease in intravascular oncotic pressure. This change in intravascular oncotic pressure leads to changes in the starling equilibrium such that there is a net ultrafiltration from the capillary to peripheral tissues. Early in the disease, lymphatic drainage is able to accommodate this increase in extravascular fluid, thus preventing tissue swelling, but as that system becomes saturated, edema develops.

Despite being a simple explanation, it is worth noting that experimental evidence has shown that there is a concurrent decrease in both intravascular and interstitial proteins. Classic literature on the topic has, in fact, shown that the difference in osmotic pressure between the intravascular and extravascular spaces is relatively constant across a wide array of serum albumins [46–48].

The "overfill" hypothesis explains the sodium avidity in these patients and helps to explain the process by which intravascular volume expansion occurs. Increased sodium retention in this hypothesis occurs at the level of the collecting duct via ENaC. Activation of ENaC appears to occur secondary to the filtration of proteinases into the urine that activate the channel and lead to sodium retention [49].

In addition to the classical features of the nephrotic syndrome, these patients are also at increased risk of both arterial and venous thrombosis, particularly renal vein thrombosis, due to loss of innate anticoagulant elements in the urine leading to an aberrant coagulation cascade [50]. They also are at increased risk of infection due to nonspecific loss of immunoglobulins in advanced nephrosis [51].

The Podocytopathies: Minimal Change Disease and Focal Segmental Glomerulosclerosis

The podocyte is the glomerular tuft cell with a complex array of microtubular arrays that create interdigitated foot processes along the GBM that are interconnected at the slit diaphragm. As noted previously, this structure is necessary to impose the final charge selectivity to the GBM. In recent years the importance of this cell has become increasingly apparent and, indeed, has realized a wealth of new insights, thanks to reliable mouse models allowing new investigation. Minimal change disease and focal segmental glomerulosclerosis (FSGS) are the two most common podocytopathies and we will review them here.

Minimal Change Disease

Minimal change disease is a major cause of nephrotic syndrome in children, with onset typically in childhood, after the first year of life with a peak incidence between 24 and 36 months of life. The disease seems to have a strong male predilection in children as well. In children between 85 and 95 % of cases of the nephrotic syndrome are due to minimal change disease. That frequency falls as children become adolescence, accounting for only 50 % in that age group. It can occur in adults, but other diseases, like focal segmental glomerulosclerosis, begin to also occur at higher frequencies.

Table 12.4 Secondary causes of minimal change disease

Drugs	Malignancy	Infection
NSAIDs	Hodgkin's disease	Tuberculosis
Lithium	Non-Hodgkin's lymphoma	HIV
Gold	Leukemia	Ehrlichiosis
Antimicrobials	RCC	Syphilis
Methimazole	Bronchogenic carcinoma	
Penicillamine	Colon CA	
Tamoxifen	Pancreatic CA	

The classic presentation, especially in the above-described age group, is significant proteinuria with advancing edema. In most patients, proteinuria and its associated edema are the dominant presenting complaints, often described as having arisen over a very short period of time. The incidences of associated hematuria, hypertension, or declining GFR are relatively uncommon. While any one of these abnormalities can be seen in approximately 15 % of patients with MCD, the presence of more than one should prompt consideration of another disease process. Its frequency in younger patients often leads to presumptive treatment with high-dose corticosteroids by the treating physician without a kidney biopsy. In adults, given the significantly lower pretest probability and the risks of inadequately treating other causes of the nephrotic syndrome, a biopsy is generally pursued before initiating therapy.

In adults, not only is the disease less frequently the cause of nephrotic syndrome, it is also less frequently considered idiopathic. There are a number of other drugs and primary or systemic disease that can manifest as minimal change disease in the kidney. A list of these is reviewed in Table 12.4.

Pathophysiology

The specific inciting factor in MCD is not known. In some inherited forms, specific defects have been identified in proteins that are integral for slit diaphragm function. In cases that are not inherited, it has been proposed that there is a circulating T cell-secreted factor that may be culpable [52]. While no such circulating factor has yet been positively identified, early work suggested a significant role for T regulatory (T_{reg}) cells, and indeed, studies have gone on to show that supplementing MCD patients with T_{reg} cells reduces proteinuria in mouse models [53]. Additional work has evaluated specific cellular markers, though these studies have thus far failed to provide a definitive answer.

Regardless of the specific inciting stimulus, the result is loss of cytoskeletal architecture of the podocyte. This decay leads to foot process effacement and disordered slit diaphragm proteins, without which protein efflux across the glomerular basement membrane is unimpeded. This disorganization is not visible at the level of the light microscope and, as such, was named "minimal change."

Pathology

As the name suggests, minimal change disease has a normal histologic appearance when reviewed by light microscopy (Fig. 12.6). Notably absent, especially if distinguishing between MCD and FSGS, are areas of focal sclerosis within glomerular tuft. Indeed, immunofluorescence also lacks positivity attributable to the condition. Electron microscopy, however, shows diffuse foot process effacement. If patients have been previously treated, the effacement can be incomplete.

Management

The mainstay of therapy is glucocorticoids. This treatment is highly efficacious leading to complete remission approaches 90 %. Indeed, even in adults, most patients will have a response to therapy, with approximately 80 % responding to treatment [54]. In two controlled studies in adults that evaluated the use of corticosteroids, significant

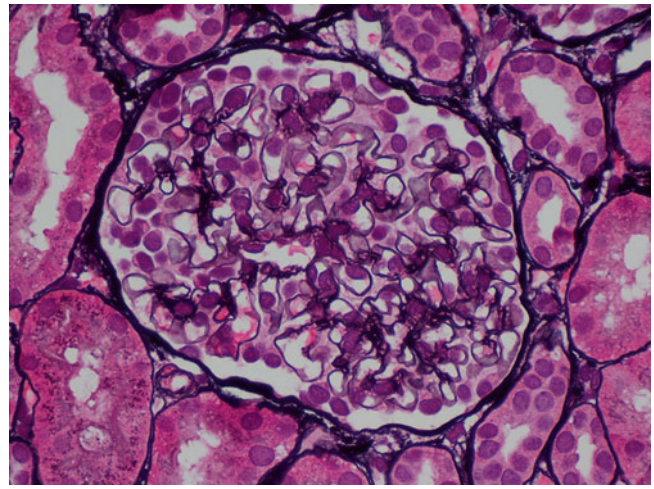

Fig. 12.6 This glomerulus appears normal by light microscopy and electron microscopy (not shown) revealed diffuse podocyte foot process effacement consistent with minimal change disease (Jones methenamine silver)

Table 12.5 Secondary causes of FSGS

Genetic mutations	Viral associations	Medications	Others
Podocin	HIV	Pamidronate	Obesity
α-Actinin 4	Parvovirus B19	Heroin	Sickle cell disease
		Interferon alpha	Reflux nephropathy
		Lithium	Renal agenesis
			Cholesterol atheroemboli

response rates were achieved at 2 months with complete resolution of proteinuria, though long-term follow-up showed similar rates of remission, suggesting that many patients will experience a spontaneous remission in time [55, 56].

In large part there continues to be debate regarding dosing frequency (daily versus alternate day dosing), though there may be some benefit, particularly in children, for preserving activity of the adrenal axis during growth periods [56, 57]. Oral dosing has been thought to be superior to intravenous dosing forms, largely because of the ease of use and evidence that trends toward higher rates of remission at 3 months. In children, current recommendations are for 6 months of therapy at a minimum given higher rates of relapse with shorter course [58]. In adults it is less certain, though current recommendations are for trials of at least 16 weeks prior to declaring the treatment a failure.

Focal Segmental Glomerulosclerosis

Similar to MCD, FSGS is a disease primarily of the podocyte. Its clinical presentation is similar, though it affects adolescents and adults more frequently than MCD. Unlike MCD, if left untreated it will progress to end-stage renal disease (ESRD). It is considered the most common cause of nephrotic syndrome among African Americans and, in some studies, the most common cause in all races.

Like MCD, it has both idiopathic forms wherein no underlying or associated disease can be identified as well as many different secondary forms, shown in Table 12.5. Many of these seen in patients seem to be related to the development first of hyperfiltration and associated glomerular hypertrophy. While the specific mechanism of how hyperfiltration causes sclerosis remains uncertain, it may be related to slow podocyte loss or insufficiency in those circumstances.

Table 12.6 FSGS subtypes and disease associations

Subtype	Histologic pattern	Disease associations
NOS, classical	Segmental sclerosis without features of subtype	
Collapsing	Glomerular tuft collapse with corrugated zGBM and podocyte proliferation	HIV, parvovirus, TB, hemophagocytic syndrome
Cellular	Endocapillary proliferation without evidence of collapsing or tip lesion	
Perihilar	Perihilar sclerosis and hyalinosis involving more than half of affected glomeruli	Nephron loss (HTNive disease, other causes CKD)
Tip variant	Glomerulosclerosis involving only the tubular pole of the glomerular tuft	

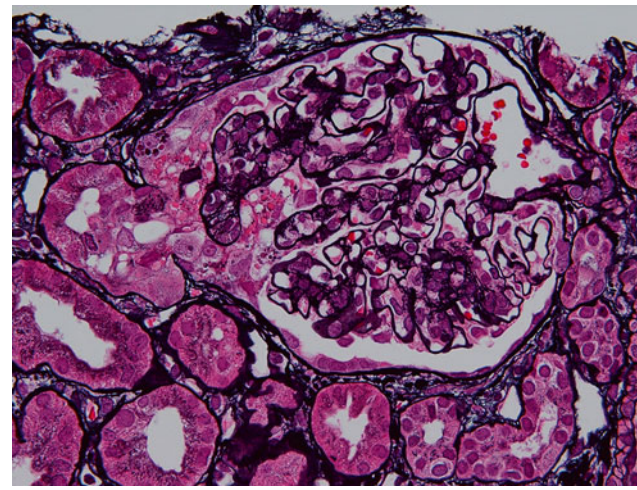

Fig. 12.7 The glomerular capillaries at the tip of this glomerulus demonstrate prominence of the visceral epithelial cells (podocytes), which also contain numerous protein reabsorption droplets, and there are some intracapillary foam cells. These findings are characteristic of the tip variant of focal segmental glomerulosclerosis (Jones methenamine silver)

Pathophysiology

Like many diseases, inherited forms of the disease allowed researchers to hone in on various key proteins in the podocyte that trigger FSGS. For example, mutations in the nephrin gene identified in congenital Finnish-type nephrotic syndrome have allowed researchers to appreciate the importance of slit diaphragm maintenance in podocyte health. However, many mouse models have identified other mutations both in proteins directly related to the slit diaphragm and in trafficking proteins. Whatever the error, there seems to be an association with progressive podocyte loss, podocyte effacement, and progressive sclerosis of portions of any given glomerular tuft.

And while the recognition of these congenital variants show that defects in the slit diaphragm are sufficient to cause disease, they are unlikely to explain idiopathic FSGS. Indeed, it has also been suggested that the different histologic variants of FSGS may be related to different pathophysiologic mechanisms. These are summarized in Table 12.6.

Pathology

Focal segmental glomerulosclerosis has a number of histologic subtypes that have important prognostic features for the patient (Fig. 12.7). The primary features are areas of sclerosis within the glomerular tuft (focal) that are apparent by light microscopy and associated foot process effacement of the podocytes that involve some but not all of the glomeruli (focal). As noted previously, this diagnosis is largely dependent on sample size given that even a single glomeruli with segmental sclerosis can distinguish between MCD and FSGS. Immunofluorescence may

reveal IgM and c3 deposition in the sclerotic segment.

The subtypes of FSGS can also be distinguished on their histology and are summarized in Table 12.6.

Management

Although the clinical course in FSGS varies between patients, the natural history is one of progressive glomerular sclerosis and loss. Unlike MCD, if left untreated, only 5–10 % of patients will experience a spontaneous remission in proteinuria. In early studies of the disease, only 10–30 % of patients treated with corticosteroids (or other early immunosuppressive regimens like azathioprine, chlorambucil, etc.) achieved a remission. Later observational studies suggested that while the response was not as robust as that seen in MCD, immunosuppressants did have an impact [59].

Presently, the standard of care in FSGS is to consider a trial of corticosteroids, with consideration of cyclosporine or cyclophosphamide if contraindicated to steroids or failure of corticosteroids (defined as lack of partial remission after 16 weeks of therapy). Mycophenolic acid has also been used, but is considered third-line therapy.

If the disease is known or presumed to be secondary, treatment and optimization of the underlying disease are recommended. In both idiopathic and secondary FSGS ongoing management of other risk factors for loss of renal function should be pursued (blood pressure management, RAAS blockade, etc.).

Membranous Nephropathy

Membranous nephropathy (MN) is a disease of IgG immune deposition between the GBM and the podocyte with reaction at the level of the podocyte leading to foot process effacement. Typically affecting men more than women (2:1) with a median age of onset in the mid-1950s, the disease often presents as isolated proteinuria that is incidentally detected. However, the disease can lead to profound protein losses in the urine with overt nephrotic syndrome manifestations.

Several genetic associations have been made with patients expressing HLA-DR3 having a threefold risk of the disease [60]. Other HLA subtypes have similarly been associated with increased disease risk, including HLA-DQA1 which seems to track with MN quite closely [61]. These risk factors may suggest a tendency toward autoantibody formation in these groups, although, until only the last decade, the specific antigens were largely unknown, with most cases of MN being dubbed idiopathic.

Patients with the disease have variable clinical courses with up to a third of patients exhibiting a spontaneous remission, even in the face of substantial of proteinuria. The remaining patients will have persistent proteinuria, with either preserved renal function or with progressive chronic kidney disease as a result with approximately 0.5 % of current US ESRD patients being dialysis-dependent from MN [62].

Pathophysiology

The pathology in the disease has long suggested in situ formation of immune complexes with resultant structural changes in the GBM. Those structural changes lead to loss of integrity of the overlying podocytes with effacement. While elusive up until the last decade, recent work has identified several target autoantigens including the best-described example, the M-type phospholipase A_2 receptor (PLA_2R) as a target for autoantibody formation. PLA_2R is a member of the mannose receptor family that is expressed as a transmembrane protein in the basolateral aspect of the podocyte [63]. Circulating autoantibodies against this protein likely migrate across the GBM and react with the membrane-bound PLA_2R protein.

There are a number of secondary causes of membranous nephropathy as well that range from viral infections to malignancies. While some of these may lead to autoantibody formation against proteins intrinsic to the podocyte, others are thought to lead to the formation of antigens that get trapped at the level of the podocyte [62]. Cationic antigens of the right size can easily traverse the GBM and then be targeted by autoanti-

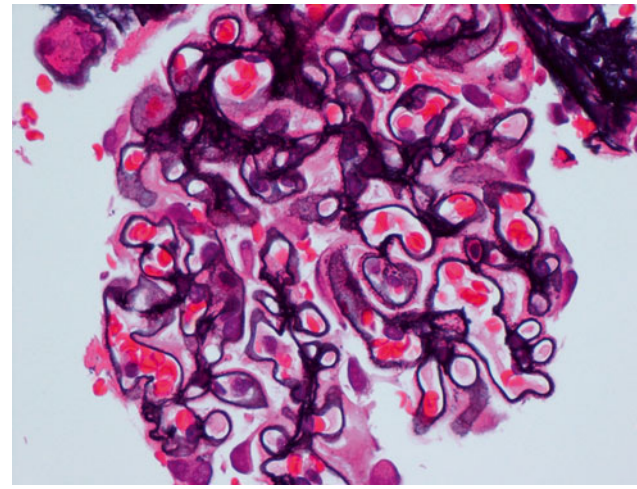

Fig. 12.8 Subepithelial "spike" formation is frequently observed along the capillaries due to membranous nephropathy

bodies. This is exemplified in mouse models of MN where the animal is immunized with cationized bovine serum albumin (cBSA) [62]. Planted antigens are thought to explain class V lupus nephritis and hepatitis B-associated MN [64, 65].

Pathology

MN is diagnosed by finding subepithelial and intramembranous immune deposits that can typically be seen (Fig. 12.8). The immune deposits give the GBM a rarefacted appearance on light microscopy—especially on silver stain, which stains for GBM—that can show the absence of immune deposit staining which appear as "holes." These can be seen early in the disease in tangential sections of GBM. As the disease progresses and the matrix reaction progresses, light microscopy can reveal "spikes" of basement membrane that reach outward toward the overlying podocytes. Immunofluorescence shows staining of the immunoglobulins present as a granular pattern along the length of the GBM. Most typically this is IgG, though other immunoglobulins can be appreciated in some cases and may bespeak a secondary cause of the disease.

Management

As noted previously, many cases of MN will spontaneously resolve if left untreated. Early trials evaluating prednisone, chlorambucil, or cyclophosphamide as therapy were mixed with some showing benefits in remission and renal survival and others showing no difference with increased adverse events from immunosuppressive therapy [66–68]. In the 1980s 140 cases of biopsy proven MN were reviewed and their clinical courses noted. Most of them, 83 % were nephrotic at the time of diagnosis. At last follow-up available, 57 % of the untreated group had achieved full remission. Indeed, at 10 years there was no statistical difference in either renal survival or mortality between the two groups [69]. All of these early randomized trials were limited by their follow-up, noting no difference over the short term. As time passed, though longer-term follow-up of treated cohorts became available, it

became apparent that in patients who had a high likelihood of progression, the use of an immunosuppression regimen was beneficial [70, 71].

Presently, most nephrologists attempt to stratify patients with MN according to their risk of progression, with low-risk patients (subnephrotic proteinuria with normal renal function) being treated conservatively and high-risk patients receiving immunosuppression. First-line therapy is cytotoxic therapy with cyclophosphamide or chlorambucil and glucocorticoids for 6 months of therapy. Calcineurin inhibitors have also been shown to be efficacious, but are considered to be second-line therapy.

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