Fundamentals of Renal Pathology

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Second Edition

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Part I

Renal Anatomy and Basic Concepts and Methods in Renal Pathology

Renal Anatomy and Basic Concepts and Methods in Renal Pathology

1

Normal Anatomy

Each kidney weighs approximately 150 g in adults, with ranges of 125–175 g for men and 115–155 g for women; both together represent 0.4 % of the total body weight. Each kidney is supplied by a single renal artery originating from the abdominal aorta; the *main renal artery* branches to form anterior and posterior divisions at the hilus and divides further, its branches penetrating the renal substance proper as *interlobar arteries*, which course between lobes. Interlobar arteries extend to the corticomedullary junction and give rise to *arcuate arteries*, which arch between cortex and medulla and course roughly perpendicular to interlobar arteries. *Interlobular arteries*, branches of arcuate arteries, run perpendicular to the arcuate arteries and extend through the cortex toward the capsule (Fig. 1.1). *Afferent arterioles* branch from the interlobular arteries and give rise to glomerular capillaries (Fig. 1.2). A *glomerulus* represents a spherical bag of capillary loops arranged in several lobules (Fig. 1.3); the capillaries merge to exit the glomerulus as *efferent arterioles*, which, in most nephrons, branch to form another vascular bed, peritubular or *interstitial capillaries*, which surround tubules. Efferent arterioles from juxtamedullary glomeruli extend into the medulla as vasa recta, which supply the outer and inner medulla. The vasa recta and peritubular capillaries collect, forming into *interlobular veins*; the veins follow the arteries in distribution, size, and course and leave the kidneys as *renal veins*, which empty into the inferior vena cava.

The kidneys have three major components: the cortex, the medulla, and the collecting system. On the cut surface, the cortex is the pale outer region, approximately 1.5 cm in thickness, which has a granular appearance because of the presence of glomeruli and convoluted tubules. The medulla, a series of pyramidal structures with apical papillae, numbers normally 8–18 and has a striped or striated appearance because of the parallel arrangement of the tubular structures. The bases of the pyramids are at the corticomedullary junction and the apices extend into the collecting system. Cortical parenchyma extends into spaces between adjacent pyramids; this portion of the cortex is known as the columns of Bertin. A medullary pyramid with surrounding cortical parenchyma, which includes both columns of Bertin and

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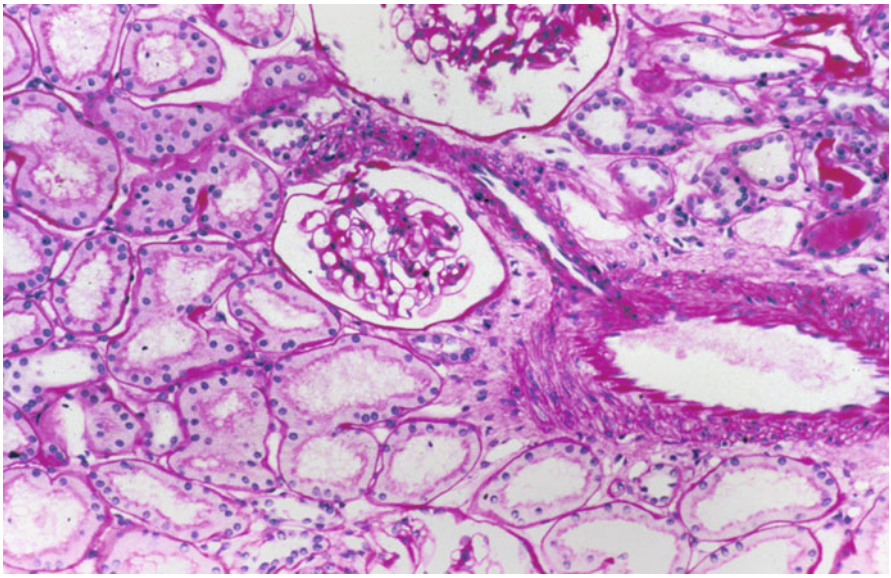

Fig. 1.1 Low magnification of cortex with portions of two glomeruli, tubules, and interstitium and interlobular artery with arteriolar branch [periodic acid-Schiff (PAS) stain]

the subcapsular cortex, constitutes a renal lobe. The collecting system consists of the pelvis, which represents the expanded upper portion of the ureter, and is more or less funnel shaped. Each pelvis has two or three major branches known as the major calyces. Each calyx divides further into three or four smaller branches known as minor calyces, each usually receiving one medullary papilla.

Each kidney contains approximately one million nephrons, each composed of a glomerulus and attached tubules. Glomeruli are spherical collections of interconnected capillaries within a space (Bowman's space) lined by flattened parietal epithelial cells (Fig. 1.3). Bowman's space is continuous with the tubules, with the orifice of the proximal tubule generally at the pole opposite the glomerular hilus, where the afferent and efferent arterioles enter and leave, respectively. A layer of visceral epithelial cells, also called podocytes, covers the outer aspects of the glomerular capillaries. Each podocyte has a large body containing the nucleus and cytoplasmic extensions, which divide, forming small fingerlike processes that interdigitate with similar structures from adjacent cells and cover the capillaries. These interdigitating processes, known as pedicles, are also called foot processes because of their appearance on transmission electron microscopy. The space between adjacent foot processes is known as the filtration slit; adjacent foot processes are joined together by a thin membrane known as the slit-pore diaphragm. The slit diagram is composed of a complex of the transmembrane proteins nephrin, NEPH1 through NEPH3, podocin, Fat1, VE-cadherin, and P-cadherin. Mutations in NEPH1 and podocin cause proteinuria. Epithelial cells cover the glomerular capillary basement membrane, a three-layer structure with a central thick layer slightly electron-dense

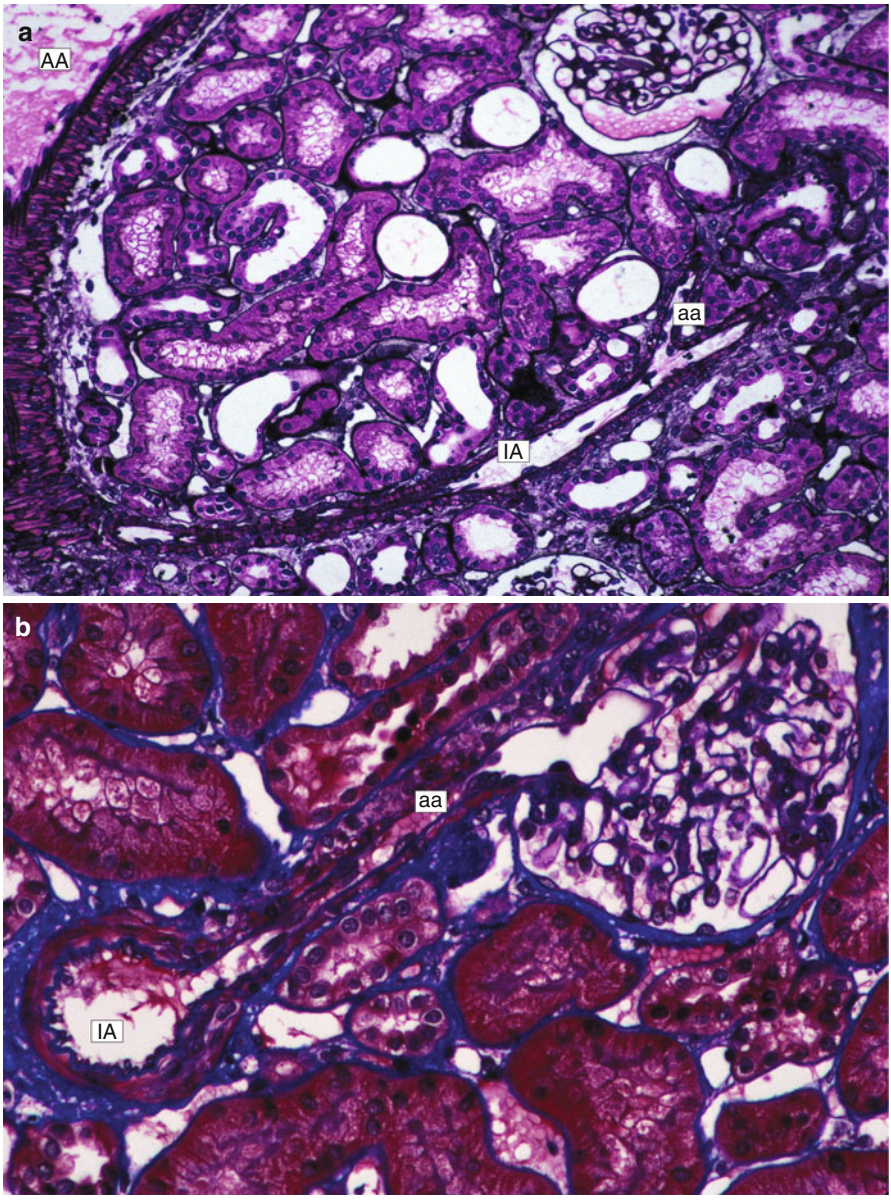

Fig. 1.2 (**a**) Low magnification of cortex. An arcuate artery (*AA*), interlobular artery (*IA*), and afferent arteriole (*aa*) are in continuity (Jones silver stain). (**b**) Interlobular artery (*IA*) with afferent arteriole (*aa*) extending into glomerulus (Masson trichrome stain)

(lamina densa) and thinner electron-lucent layers beneath epithelial and endothelial cells (lamina rara externa and lamina rara interna, respectively) (Fig. 1.4). The glomerular basement membrane is composed predominately of type IV collagen with

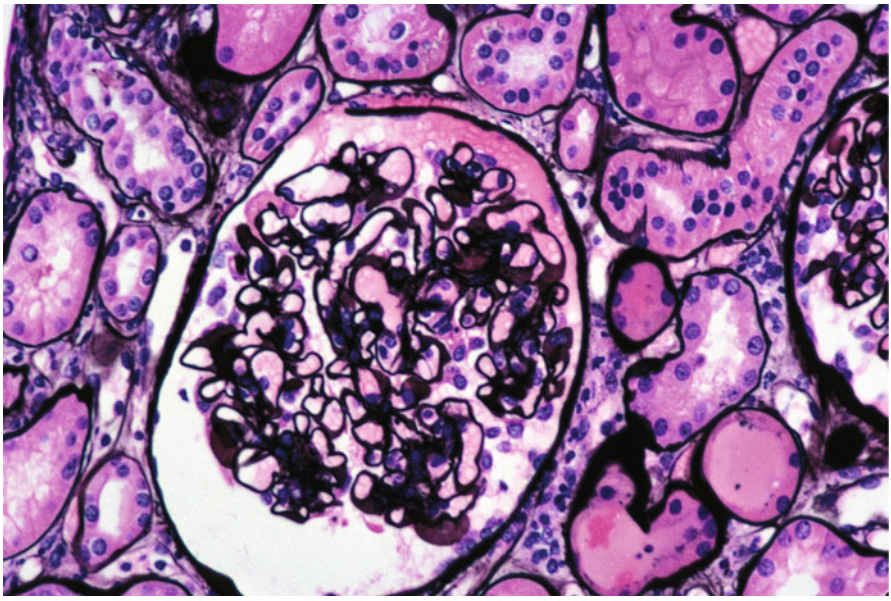

Fig. 1.3 Normal glomerulus with surrounding normal tubules and interstitium (Jones silver stain)

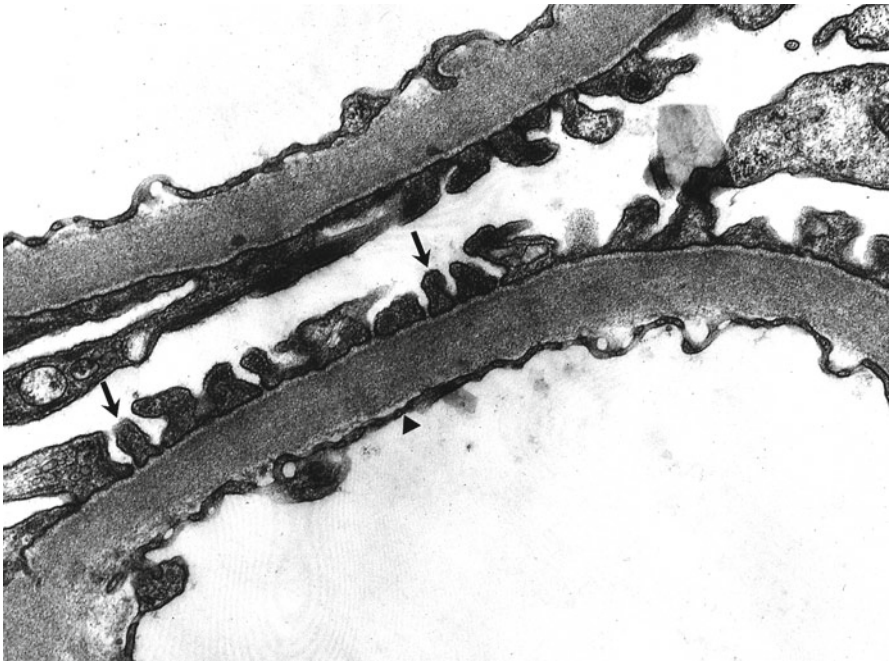

Fig. 1.4 Portion of glomerular capillary wall by electron microscopy. Individual foot processes of podocytes (*arrows*) cover the basement membrane and endothelial cell cytoplasm (*arrowhead*) lines the lumen

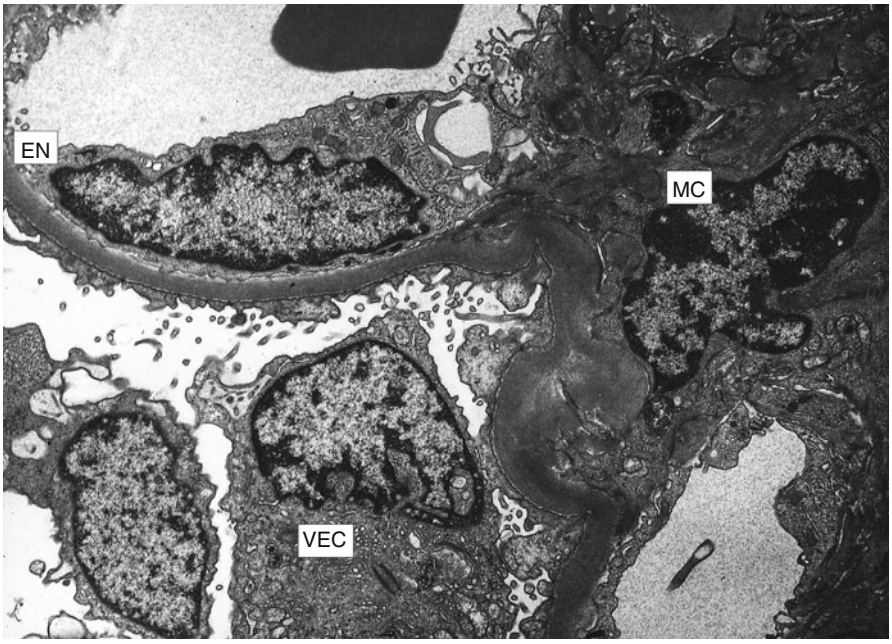

Fig. 1.5 Portion of glomerulus indicating different cell types: capillary endothelial cell (*EN*), visceral epithelial cell (*VEC*), and mesangial cell (*MC*) (electron microscopy)

six distinct λ chains, laminin 11, entactin, and sulfated proteoglycans. The glomerular basement membrane in adults measures approximately 340–360 nanometers (nm) in thickness and is significantly thicker in men than in women. The endothelial cells are thin and have multiple fenestrae, each measuring approximately 80 nm in diameter. The surface of endothelial cells is negatively charged, with a surface coat glycocalyx composed of anionic glycosaminoglycans and glycoproteins. The capillary tufts are supported by the mesangium, which represents the intraglomerular continuation of the arteriolar walls. The mesangium has two components. The extracellular one, *mesangial matrix*, has many structural, compositional, and, therefore, tinctorial properties similar to basement membrane. The cells of the mesangium are known as *mesangial cells*, of which there are two types: modified smooth muscle cells, representing greater than 95 % of the cellular population, and bone marrow-derived cells, representing the remainder. Mesangial cells have numerous functions including contraction, production of extracellular matrix, secretion of inflammatory and other active mediators, phagocytosis, and migration from the central zone where they are normally situated (Fig. 1.5).

The proteoglycans of the glomerular basement membrane are negatively charged; similarly, the surface of both epithelial and endothelial cells is anionically charged because of sialoglycoproteins in the cellular coats. Both of these negatively charged structures are responsible for the *charge-selective barrier* to filtration of capillary contents. The basement membrane, which, along with the fenestrated endothelial cell, allows for ready filtration of water and small substances, is known as the

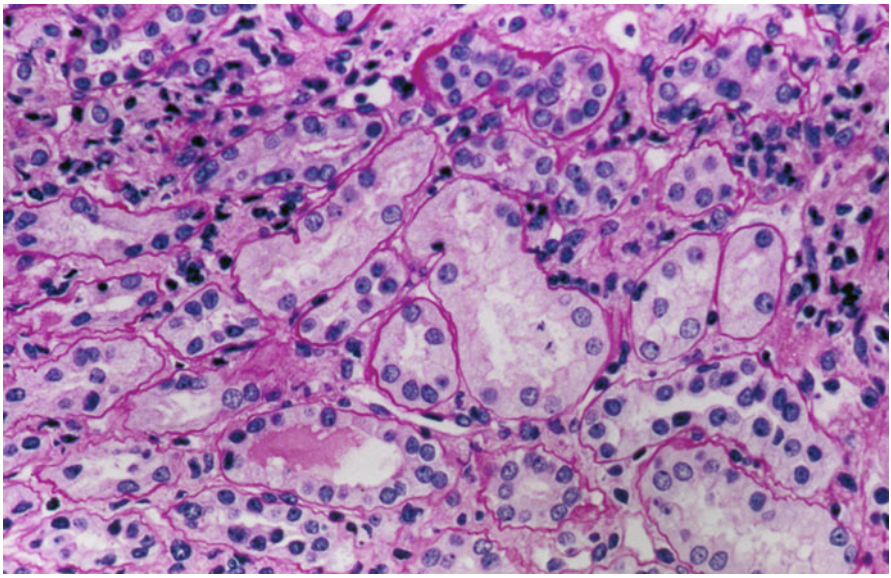

Fig. 1.6 Normal cortical tubules, interstitium, and peritubular capillaries; most of the tubules are proximal, with well-defined brush borders (PAS stain)

size-selective barrier. The podocyte in the adult is responsible for the production and maintenance of basement membrane.

The remaining portion of the nephron is divided into *proximal tubules*, which are often convoluted; the *loop of Henle*, with both descending and ascending limbs; and the *distal tubule*. The proximal tubular cells have well-developed closely packed microvillus luminal surfaces known as the brush border. The cells are larger than those of the distal tubules, which have relatively few surface microvilli. Each tubule is surrounded completely by a basement membrane. Adjacent tubular basement membranes are in almost direct contact with one another and separated by a small amount of connective tissue known as the interstitium, which contain peritubular capillaries (Fig. 1.6). At the vascular pole of the glomerulus and the site of entrance of the afferent arteriole, the cells of the arteriolar wall are modified into secretory cells known as juxtaglomerular cells; these produce and secrete renin, contained in granules. The macula densa, a portion of the distal tubule at the glomerular hilus, is characterized by smaller and more crowded distal tubular cells, which are in contact with the juxtaglomerular cells. Surrounding the macula densa and afferent arteriole are lacis cells, which are mesenchymal cells similar to mesangial cells.

Examination of Renal Tissue

Because of the types of diseases and the renal components that are abnormal, the preparation of tissue specimens for examination is somewhat complex considering the required methods of study. These include sophisticated light *microscopy*,

Table 1.1 Staining characteristics of selected normal and abnormal renal structures

	Stain		
	PAS	Jones	Masson's trichrome
Basement membrane	Red	Black	Deep blue
Mesangial matrix	Red	Black	Deep blue
Interstitial collagen	Negative	Negative	Pale blue
Cell cytoplasm (normal)	Negative (most)	Negative	Rust/orange granular
Immune complex orange deposits	Negative to slightly positive	Negative	Bright red-homogeneous
"Insudative lesions"	Negative to slightly positive	Negative	Bright red-orange homogeneous
Fibrin	Slightly positive	Negative	Bright red-orange fibrillar
Other			
Plasma protein orange precipitates (intra- or extracellular)	Slightly positive	Negative	Bright red-homogeneous
Amyloid (Congo red positive)	Negative/weakly positive	Negative (sometimes positive)	Light blue orange
Tubular casts (Tamm-Horsfall protein)	Red	Gray to black	Light blue

PAS periodic acid-Schiff

immunofluorescence, and electron microscopy. For light microscopy, the elucidation of lesions of glomeruli mandates that a variety of histochemical stains be used and that tissue sections be cut thinner than for other tissues. Furthermore, to take best advantage of the stains, many investigators and renal pathologists have found that formalin, Zenker's solution, or many of the more commonly used fixatives result in substandard preparations. Consequently, alcoholic Bouin's solution (Duboscq-Brasil) is the fixative of choice for superb morphology and stains. However, methods for many immunostains and molecular studies are based on formalin-fixed tissue and results are unreliable. Consequently, there has been a steady shift away from Bouin's and toward formalin in recent years. For the elucidation of glomerular structure and pathology, it is necessary that the extracellular matrix components (basement membrane, mesangial matrix) be preferentially stained. Table 1.1 indicates staining characteristic of normal and abnormal renal structures. In paraffin-embedded sections, the hematoxylin and eosin stain does not ordinarily allow for distinction of extracellular matrix from cytoplasm in a clear or convincing manner. Periodic acid-Schiff (PAS), periodic acid-methenamine silver (Jones), and Masson's trichrome stains all provide excellent definition of extracellular material. Each stain has its advantages and disadvantages, and, as a rule, all are used in evaluating renal tissues especially biopsies. The PAS reagent stains glomerular basement membranes, mesangial matrix, and tubular basement membranes red (positive), while the Jones stain (periodic acid-methenamine silver) colors the same

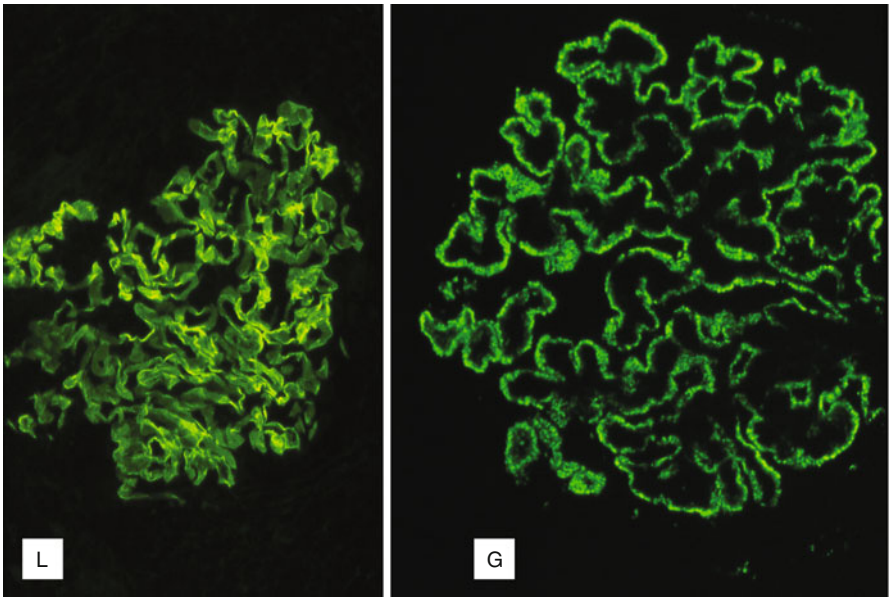

Fig. 1.7 Glomerular immunofluorescence indicating linear (*L*) and granular (*G*) capillary wall staining for immunoglobulin G (IgG)

components black, providing clear contrast between positively and negatively staining structures. Masson's trichrome colors extracellular glomerular matrix (capillary basement membranes, mesangial matrix) and tubular basement membranes blue, clearly distinguished from cells and abnormal material that accumulates in pathologic circumstances. Congo red, elastic tissue, and other stains are employed when indicated. The tissue sections should be no greater than 2–3 μm in thickness, for the definition of glomerular pathology, especially regarding cellularity, is dependent on sections of this thickness. The ability to detect subtle pathologic abnormalities is enhanced with thinner sections. Especially for glomerular diseases, *immunohistochemistry* is necessary for evaluation of renal tissues, especially for diagnosing glomerular diseases. Most laboratories utilize *immunofluorescence* for identifying and localizing immunoglobulins, complement, fibrin, and other immune substances within renal tissues; fluorescein-labeled antibodies to the following are used: immunoglobulin G (IgG), IgA, IgM, C1q, C3, albumin, fibrin, and kappa and lambda immunoglobulin light chains. For transplant biopsies, antibody to C4d is routinely utilized. Fluorescence positivity in glomeruli as well as tubular basement membranes is described as *granular* or *linear* (Fig. 1.7). Regardless of the immunopathologic mechanisms responsible for the granular deposits, there is an electron microscopic counterpart to granular deposits; by electron microscopy, extracellular masses of electron-dense material correspond to the deposits. The granular deposits can be appreciated in tissue prepared for light microscopy; this is best demonstrated and documented with the use of Masson's trichrome stain, where granular deposits

Table 1.2 Immune deposits

IF	LM	EM
Granular	Trichrome stain bright red orange	Electron dense
Linear	Not visible	Not visible

EM electron microscopy, *IF* immunofluorescence, *LM* light microscopy

appear as bright fuchsinophilic (orange, red orange) smooth homogeneous structures. There is no regular ultrastructural or light microscopic counterpart to linear staining (Table 1.2). Electron microscopy is routinely utilized in the study of renal tissues. For glomerular and some tubulointerstitial diseases, this method is mandatory and helps localize deposits, detects extremely small deposits, and documents alterations of cellular and basement membrane structure. Immunofluorescence and electron microscopy are also often necessary and helpful in diagnosing other tubular, interstitial, and vascular lesions.

The typical appearances and tinctorial properties with routinely used stains of normal and abnormal renal structures are provided in Table 1.1.

Tamm-Horsfall Protein (THP) (Also Known as Uromodulin)

Tamm-Horsfall protein is a large glycoprotein (mucoprotein) produced only by cells of the thick ascending limb of the loop of Henle and early distal convoluted tubule. While it has many physiologic functions, for the pathologist interested in renal tissue changes, it provides important information regarding tubular structure and integrity. This glycoprotein, when precipitated in gel form in distal tubules, forms a cast of the tubular lumen, which may be passed in the urine as a hyaline cast. Thus, Tamm-Horsfall protein is the fundamental constituent of urinary casts. In tissue sections, the casts are strongly PAS positive and can easily be recognized. The structural value of this feature is that the cast material, in a variety of pathologic states, may be found in abnormal locations and therefore may provide evidence regarding pathogenesis of certain diseases and their pathophysiologic consequences. Tamm-Horsfall protein has been identified primarily in three major abnormal sites: (1) the proximal nephron, (2) the renal interstitium and occasionally intrarenal capillaries and veins, and (3) in perihilar locations. It has been documented that with intra- or extrarenal obstruction and/or reflux, THP may be found in proximal tubules and in glomerular urinary spaces, the result of retrograde flow in the nephron. Escape of THP from within the nephron into the interstitium and peritubular capillaries has been documented to occur with tubular wall disruption. There are four major mechanisms proposed for this finding: (1) increased intranephron pressure (reflux, obstruction), which can cause rupture of the tubular wall and spillage of contents locally; (2) destruction of tubular walls by infiltrating leukocytes (as in any acute interstitial nephritis); collagenases produced by infiltrating cells, especially monocytes, can dissolve basement membranes and concomitant epithelial cell damage can result in tubular wall defects; (3) in acute tubular necrosis (especially of

ischemic type), both cell death and basement membrane loss have been described and interstitial and capillary and venous THP is uncommonly observed; and (4) intrinsic defects of tubular basement membranes (as in juvenile nephronophthisis), which likely result in loss of compliance of tubular walls and, in addition to cyst formation, may also lead to dissolution of part of the walls with escape of luminal contents. In all of the above, it is clear that while other tubular contents may also be in abnormal locations, it is Tamm-Horsfall protein that has the morphologic and tinctorial features that allow microscopists to identify it and use it as a marker of urine. Tamm-Horsfall protein is a weak immunogen; initially it was thought that its escape from tubules was, in large part, immunologically responsible for progression of chronic tubulointerstitial damage in the disorders characterized by this feature. However, despite the presence of serum anti-THP antibodies in patients with reflux nephropathy, the pathogenic role of THP in immunologic renal injury is uncertain and probably not very important. Tamm-Horsfall protein has been documented to bind and inactivate interleukin-1 (IL-1) and tumor necrosis factor (TNF).

General Pathology of Renal Structures

Before embarking on a consideration of various renal diseases, a discussion of basic abnormalities that characterize the renal structures is presented first.

Glomeruli

Increased cellularity (*hypercellularity*) may result from increase in intrinsic cells (mesangial, podocyte, parietal epithelial, or endothelial cells) or from accumulation of leukocytes in capillary lumina, beneath endothelial cells, or in the mesangium. Although not entirely correct, glomerular lesions with increased cells in the tufts are often known as proliferative glomerulonephritis. Accumulation of cells and fibrin within the urinary space is known as a crescent (see below).

Increase in extracellular matrix implies an increase in mesangial matrix or basement membrane material. In the former instance, this may be in a uniform and diffuse pattern in all lobules or in a nodular pattern in all or some lobules to the mesangium. Increased basement membrane material takes the form of thickened basement membranes, an abnormality that is best appreciated by electron microscopy.

Sclerosis refers to increased extracellular matrix and other material leading to obliteration of capillaries and solidification of all or part of the tufts. Sclerosis (glomerular scarring) may be associated with obliteration of the urinary space by collagen along with increased extracellular matrix in the capillary tufts. When the entire glomerulus is involved, this is known as global sclerosis; an older and less precise term is *glomerular hyalinization*. Segmental glomerulosclerosis implies a completely different pathologic process and often a disease. With segmental sclerosis, only portions of the capillary tufts are involved; capillaries are obliterated by

increased extracellular matrix and/or large precipitates of plasma protein known as insudates.

Crescents represent accumulation of cells and extracellular material in the urinary space. Crescents are the result of severe capillary wall damage with disruptions in continuity and spillage of fibrin from inside the damaged capillaries into the urinary spaces. This is associated with proliferation of podocytes and mostly parietal epithelial cells and accumulation of monocytes and other blood cells in the urinary space. The cellular composition of the crescent often varies depending on the type of disease and associated damage to the basement membrane of Bowman's capsule. Crescents most commonly heal by organization (scar formation). With an admixture of cells and collagen, the crescent is considered fibrocellular, and with only collagen in the urinary space, the crescent is designated as fibrotic.

Peripheral migration and interposition of cells: Mesangial cells and monocytes and often matrix extend from the central lobular portion of the tuft into the peripheral capillary wall, migrating between endothelial cell and basement membrane and causing capillary wall thickening with two layers of extracellular matrix. This two-layer or double-contour appearance may involve a few or all capillaries. Double contours also result from endothelial damage and consequent new subendothelial basement membrane formation. Distinction of one mechanism or the other requires electron microscopy.

Alteration in podocyte morphology: This abnormality requires the electron microscope to detect. In association with protein loss across the glomerular capillary wall, the epithelial cells change shape; the foot processes retract and swell, resulting in loss of individual foot processes and a near solid mass of cytoplasm covering the glomerular basement membrane. This loss or *effacement of foot processes* has also incorrectly been called fusion because it was initially thought adjacent foot processes fused with one another.

Tubules

Tubular cells may exhibit a variety of degenerative changes or may undergo acute reversible and irreversible damage (necrosis and apoptosis). The degenerative lesions are often in the form of intracellular accumulations, manifestations of either local metabolic abnormalities or systemic processes. For example, lipid inclusions in proximal and, less commonly, distal tubular cells result from hyperlipidemia and lipiduria of nephrotic syndrome, and protein reabsorption droplets ("hyaline droplets") accumulate in proximal tubular cells in association with albuminuria and its reabsorption by tubular epithelium. Additional locally induced abnormalities include uniform fine cytoplasmic vacuolization consequent to hypertonic solution infusion (e.g., mannitol, sucrose). Tubular cells may be sites of "storage" of hemosiderin in patients with chronic intravascular hemolysis, high iron load, or glomerular hematuria. Few metabolic storage diseases affect tubular epithelium; among others are cystinosis with crystals and glycogen storage diseases and diabetes mellitus with abundant intracellular glycogen. Vacuoles, especially large and irregular, may be associated with hypokalemia.

On the other hand, reversible and irreversible changes are features of acute tubular necrosis and injury. These include loss of brush border staining for proximal cells, diffuse flattening of cells with resulting dilatation of lumina, loss of individual lining cells, and sloughing of cells into lumina. Manifestations of repair or regeneration include cytoplasmic basophilia and mitotic figures.

The morphologic features of atrophy of tubules include not only diminution in caliber but more importantly irregular thickening and wrinkling of basement membranes. Adjacent tubules are invariably separated from one another in this circumstance. The intervening interstitium is almost always fibrotic, with or without accompanying inflammation. Other structural forms of tubular atrophy include uniform flattening of cells, hyaline casts in dilated lumina, and close approximation of tubules, resulting in a thyroid-like appearance to the parenchyma.

Interstitium

There are limited structural manifestations of interstitial injury. Commonly observed are edema, inflammation, and fibrosis. Both cortical edema and fibrosis are associated with separation of normally closely apposed tubules. With edema only, the tubular basement membranes are of normal thickness and contour. In contrast, with fibrosis, the tubules are invariably atrophied with thickened and irregularly contoured basement membranes. The distinction between an acute and a chronic interstitial process is made based on the presence of edema (acute) or fibrosis (chronic) regardless of the character of any infiltrating leukocytes. With interstitial inflammation, especially when acute, the leukocytes, which gain access to the interstitium from the peritubular capillaries, usually extend into the walls of tubules. During this process, there may be damage to and destruction of tubular basement membranes as well as degeneration of epithelial cells. This often results in spillage of tubular contents into the interstitium.

The type(s) of cells in an interstitial inflammatory infiltrate depends on the nature of the inflammatory process. For example, polymorphonuclear leukocytes, *as expected*, are present in early phases of many bacterial infections; however, they do not remain and are usually replaced by lymphocytes, plasma cells, and monocytes approximately 7–10 days following the onset of infection. On the other hand, other infectious agents may elicit only a mononuclear response. Cell-mediated forms of acute inflammation, even in very early stages, are characterized by lymphocytic infiltrate, with or without plasma cells, monocytes, and granulomata.

Besides inflammatory cells, the interstitium may be infiltrated by or contain abnormal extracellular material; this includes amyloid, immunoglobulin light chains (usually along tubular basement membranes), and immune complex deposits. This may be in association with similar infiltrates in glomeruli or, less commonly, may be restricted to the tubulointerstitium.

Pathogenic Mechanisms in Renal Diseases

Glomerular

Immunologic

Many glomerular and a small number of tubulointerstitial and vascular disorders are immunologically mediated. These may be the result either of antibody-mediated or cell-mediated processes. In most instances in humans, the immediate cause or antigenic stimulus for the immune reaction is not known. The detection of antibody-mediated damage in renal tissue depends on the use of immunofluorescence microscopy.

Most glomerulopathies are immunologically mediated and are the result of antibody-induced injury. This can occur as a consequence of antibody combining with an intrinsic antigen in the glomerulus or antibody combining either in situ or in the circulation with an extrinsic antigen, with immune complexes localizing or depositing in glomeruli. With circulating *immune complexes*, the antigens may be of endogenous or exogenous origin. Endogenous antigens occur in diseases such as systemic lupus erythematosus and include components of nuclei such as DNA and histones. Exogenous antigens are usually of microorganism origin and include bacterial products, hepatitis B and C viral antigens, and malarial antigen. Circulating immune complexes are trapped or lodge in glomeruli in the mesangium and subendothelial aspects of capillary walls. Less commonly, they may be found in subepithelial locations. It is the electron microscope that precisely localizes the deposits. Certain diseases are characterized by deposits in predominately one site, whereas other diseases may be characterized by deposits in more than one location. Once immune complexes are deposited, complement is fixed and often leukocyte infiltration follows. The white blood cells accumulate in capillary lumina and infiltrate into the mesangium; in addition, intrinsic mesangial cells may divide and may also extend into peripheral capillary walls. The leukocytes, in part, may be responsible for removal of deposited immune complexes. The names of the many glomerular disorders, diagnostic criteria, and prognostic and therapeutic implications depend on the correct localization and identification of the immune complexes in the glomeruli.

The other mechanism of antibody-induced injury results from in situ immune complex formation. This can occur in two major situations. The antibody can be directed against an intrinsic component of the glomerulus such as a portion of the basement membrane or a component of the podocyte foot process. Alternatively, antigen may arrive in the glomerulus from the circulation and be planted or trapped in a particular location. Antibody binds with the trapped antigen, forming immune complex locally.

In humans, antibody directed against the basement membrane component is known as antiglomerular basement membrane antibody. The pattern of fluorescence is of *linear* binding of the antibody to the basement membrane. Planted antigens and glomerular podocyte antigen when combined with antibody in situ result in a pattern of *granular* fluorescence similar to glomeruli with deposition of circulating immune complexes.

Cell-mediated immune injury in human renal disease is evident in acute interstitial disorders such as drug-induced acute interstitial nephritis and certain forms of transplant rejection. On the other hand, cell-mediated immune mechanisms in glomerular disease are postulated with sound experimental and clinical reasoning.

Complement components, especially C5b–C9, may have a large role in producing structural and functional damage, especially in glomeruli. Recent and continuing evidence has documented the important roles of cytokines, especially IL-1 and TNF as well as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) in the genesis and progression of glomerular disease.

Nonimmunologic

There are several important mechanisms that result in significant glomerular damage in a wide variety of circumstances that merit comment here.

Damage to glomerular visceral epithelial cells, from a wide variety of influences, causes cell swelling with loss of individual foot processes. Further damage results in vacuolization, accumulation of protein in lysosomes (protein reabsorption droplets), and detachment of cells from the basement membrane.

With significant loss of functioning nephrons, the remnant nephrons undergo hypertrophy. While initially an adaptive process, these changes are associated with the ultimate development of segmental glomerulosclerosis, diminution in glomerular filtration, and heavy proteinuria.

Tubular and Interstitial Injury

Pathogenic mechanisms in tubulointerstitial injury include immunologic processes (antibody-mediated and cell-mediated immunity) with cytokine expression and release and action of inflammatory mediators. Chronic changes (interstitial fibrosis and tubular atrophy) are also the result of cytokine (PDGF and TGF-β) and complement (C5) fibroblast chemoattraction and of interaction of fibroblasts with metalloproteinases and interleukin-1 (IL-1), tumor necrosis factor (TNF)-α, and epidermal growth factor. Fibroblasts produce collagen types I, III, IV, and V; tubular cells are capable of synthesizing types I and III collagens as well as type IV (basement membrane) collagen.

Vasculature

In general, the renal arteries and arterioles respond to injuries in a manner similar to other vascular beds. However, the kidneys are frequent targets of vascular injury because of their high blood flow (approximately 25 % of cardiac output); furthermore, kidney function is critically dependent on blood pressure and flow and any interference to either may have profound effects.

The major lesions affecting renal vasculature include (1) thrombosis and embolization; (2) fibrin deposition in the walls of arteries, arterioles, and glomerular

capillaries; (3) inflammation and necrosis of vascular walls; and (4) arteriosclerosis. The basic pathologic features of these injuries are little different from those of vessels in other organs and tissues, and a comprehensive consideration, therefore, is not warranted except in lesions unique to renal vessels.

Perhaps the most important of these features is the vascular picture resulting from platelet activation and mural fibrin deposition. These result in different abnormalities in different-sized vessels. In small (interlobular) arteries, there is smooth muscle cell proliferation with intimal ingrowth of these cells and marked luminal narrowing. Fibrin in arteriolar walls is associated with endothelial damage and local thrombosis, often with extension of the thrombi into glomeruli. In these structures (glomeruli), endothelial cells are swollen, capillary walls are thickened with accumulation of fibrin beneath endothelial cells, and mesangial regions widened also because of fibrin deposition. Structural consequences include capillary microaneurysm formation. Healing results in varying degrees of mesangial sclerosis (increased matrix) and capillary wall double contours [1–6].

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Part II

Glomerular Diseases with Nephrotic Syndrome Presentations

Membranous Nephropathy

2

Introduction/Clinical Setting

Membranous nephropathy is a major cause of the nephrotic syndrome in adults [1, 2]. Only in the past decades has it been surpassed by focal and segmental glomerulosclerosis as the main cause of the nephrotic syndrome in this age group [3, 4]. Membranous nephropathy develops mostly as an idiopathic disorder but can also be seen secondary to hepatitis B and other virus infections; Sjögren's syndrome; transplantation; systemic lupus erythematosus; syphilis; exposure to certain drugs and heavy metals (e.g., penicillamine, bucillamine, gold, mercuric chloride); malignancies including carcinomas, carcinoids, sarcomas, lymphomas, and leukemias; and other systemic conditions [1, 5–7]. Idiopathic membranous nephropathy, which we now know to have an autoimmune origin, must be distinguished from membranous lupus glomerulonephritis [8], as discussed in Chap. 8. Synonyms for membranous nephropathy are membranous glomerulonephritis and membranous glomerulopathy.

Idiopathic membranous nephropathy occurs mostly in adults with a peak incidence in the fourth and fifth decades; at all ages men are more often affected than women. Patients present most often with a nephrotic syndrome (approximately 80 %), with an onset that is often more gradual than occurs with minimal change disease [6]. Microscopic hematuria is a common concurrent manifestation. Blood pressure and renal function are often normal at the time of presentation. The clinical course is often waxing and waning, as indicated by the level of proteinuria, and spontaneous remissions and/or remissions induced by therapy are common. Some patients present with only asymptomatic proteinuria or hematuria. In general the prognosis is excellent in children, whereas in adults approximately 30–40 % of patients progress to chronic renal failure with depression of the glomerular filtration rate (GFR) [6, 9]. In secondary membranous nephropathy the underlying disease determines the prognosis. The therapeutic approach to patients with membranous nephropathy remains suboptimal [10–13].

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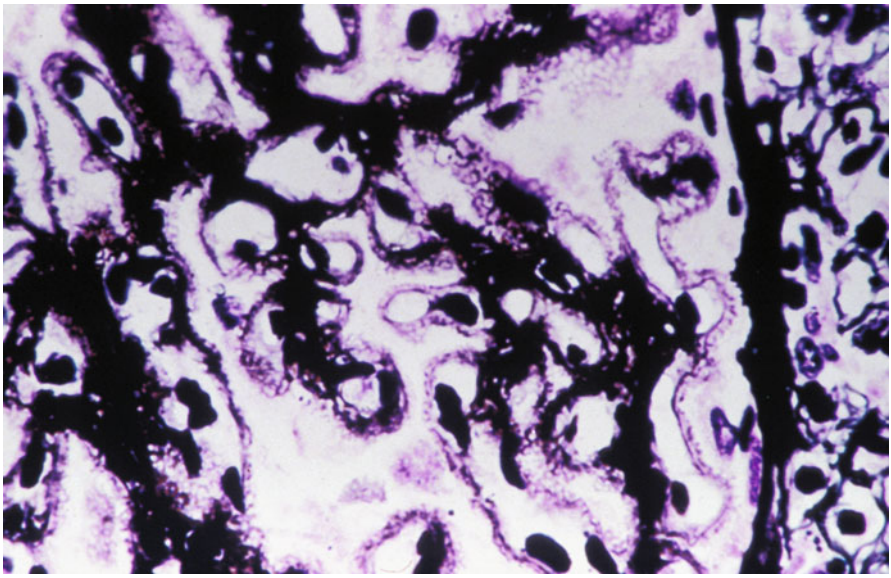

Fig. 2.1 Glomerulus showing thickening of glomerular basement membrane (GBM) and subepithelial "spikes" in membranous nephropathy (silver methenamine stain)

Pathologic Findings

Light Microscopy

Morphologic changes in membranous nephropathy are usually present in all glomeruli found in a biopsy, with little variation in the severity of the lesions between glomeruli. Morphologic lesions, however, can differ between patients or between biopsies taken from one patient at different time points. This is caused by the evolutionary pathologic changes occurring in the glomerular capillary walls over time. The histologic changes can be very subtle and sometimes are hardly or not at all visible, thereby illustrating the need for performing immunofluorescence and electron microscopic studies to establish the diagnosis.

In most cases the glomerular capillary wall is diffusely thickened as visualized by different histologic stains, as a result of the presence of nonargyrophilic, subepithelially localized immune deposits. In early stages a silver methenamine stain may reveal basement membranes completely normal in histologic appearance and thickness. Irregular thickenings of the glomerular basement membrane may grow around the immune deposits and appear in the silver-stained histologic sections as black "spikes" which project outwards to urinary space (Fig. 2.1). These are at first small and segmental, but they often grow in the course of the disease and increasingly serve to separate the deposits and incorporate them into basement membranes. Three dimensionally the spikes create

spaces in the capillary walls that can be likened to "craters," which appear as lucencies or rarefactions at sites where the capillary walls are cut tangentially. Spike formation results from the presence of subepithelial deposits, which trigger the overlying epithelial cells to increase their production of extracellular matrix, especially laminin [14]. The glomeruli in idiopathic membranous nephropathy typically lack inflammatory cell infiltration. Mesangial alterations such as proliferation are uncommon and should prompt a search for secondary causes of membranous nephropathy. Concurrent focal and segmental glomerulosclerosis, when present, imparts a worse prognosis [15, 16]. Segmental necrosis or crescent formation is not characteristic of this disorder and should prompt consideration of a concurrent disease process such as lupus nephritis, ANCA-associated glomerulonephritis, or superimposed anti-glomerular basement membrane antibody-mediated disease [17, 18].

In membranous nephropathy, there is a protein leak into the urinary space consequent to the structural alternations to the glomerular filtration barrier, and the tubules downstream of the glomeruli often contain protein reabsorption droplets. Foam cells may be present in the interstitium or between tubular epithelial cells and may be related to the hyperlipidemia and reabsorption of filtered lipoproteins, as can be seen also in nephrotic syndrome due to other causes. With progression of the glomerular lesions, nephron loss and interstitial fibrosis may occur. In late stages of cases of membranous nephropathy that have progressed to chronic kidney disease, a proportion of the glomeruli show nonspecific global sclerosis. Interstitial blood vessels are mostly without specific abnormalities in membranous nephropathy, though they may show changes such as arteriosclerosis that may be a consequence of concurrent injury processes such as hypertension on aging. The extent of interstitial damage correlates strongly with prognosis [19].

Immunofluorescence Microscopy

Immunofluorescence investigations in membranous nephropathy reveal granular deposits of immune reactants, typically with a uniform distribution and pattern in all of the glomeruli present in a specific biopsy, which follow the contours of the glomerular basement membranes. Immunoelectron microscopic studies have shown that these immune reactants are present in the electron-dense deposits described in Electron Microscopy below. The deposits can sometimes be very finely granular and extensively distributed, which may lead to the immunofluorescence pattern being falsely interpreted as linear. In a minority of cases, the deposits may be sparse or only segmentally distributed. Deposits in the mesangium are absent in most cases. The most commonly identified component in the immune deposits is immunoglobulin G (IgG) (Fig. 2.2), and in cases of idiopathic membranous nephropathy, the IgG is predominantly of subclass IgG4 [5, 20]. In addition, C3 is often present, while concurrent deposits of IgM and IgA are found in some cases. When IgG, IgA, IgM, C3, and C1q are all found ("full house"), suspicion of lupus membranous nephritis should arise [8].

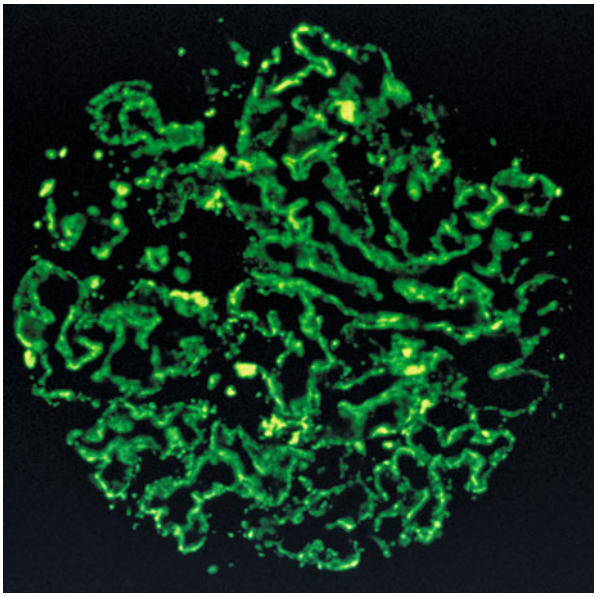

Fig.2.2 Immunofluorescence showing diffuse fine granular distribution pattern of immunoglobulin G (IgG) along the glomerular basement membranes in membranous nephropathy

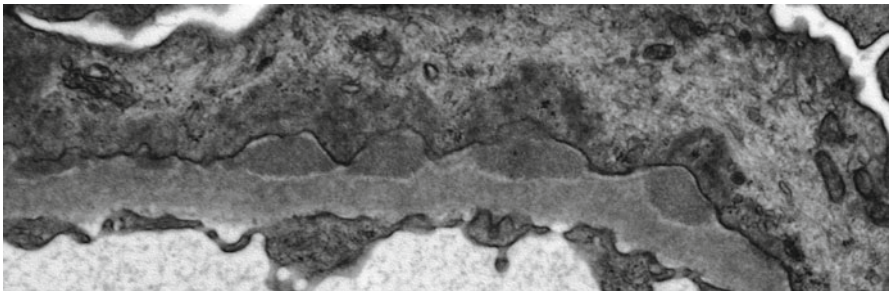

Fig. 2.3 Morphologically early stage of membranous nephrology with numerous discrete electron-dense deposits at the subepithelial surface of the glomerular capillary wall, accompanied by effacement of overlying epithelial cell foot processes. There is little or no basement membrane reaction ("spike" formation) at this stage, and capillary walls at this stage can appear normal by light microscopy

Electron Microscopy

The presence of subepithelial electron-dense deposits, whether widespread or sparsely distributed in the glomerular capillary walls, is the characteristic finding in membranous nephropathy (Figs. 2.3 and 2.4). The electron-dense deposits typically have a finely granular appearance without identifiable substructure. Electron microscopy also commonly demonstrates the basement membrane changes and "spikes" identified in silver-stained histologic preparations (Fig. 2.4). These changes contribute to progressive incorporation of the electron-dense immune deposits into

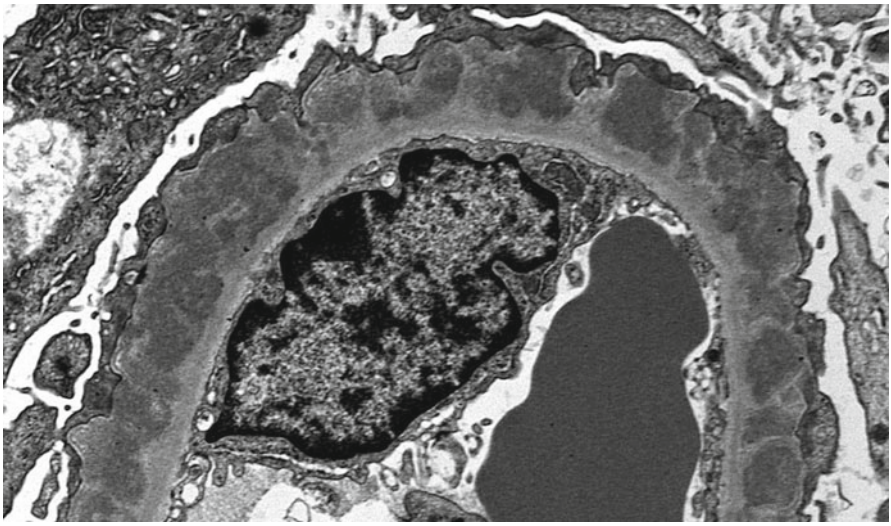

Fig. 2.4 Electron microscopy showing subepithelial electron-dense deposits with intervening spike formations of glomerular basement membrane matrices and effacement of overlying visceral epithelial cell foot processes in membranous nephropathy

the capillary wall, where the deposits may then occupy an intramenbranous location. Over time, the deposits can become less electron dense and even become electron lucent, presumably due to degradative processes that most likely are some form of proteolytic digestion. The spikes can be found in different stages of development, between and around the electron-dense deposits (Fig. 2.4). The subepithelial deposits are in contact with the glomerular epithelial cells, at least initially. In these cells the cytoplasm close to the deposits often shows condensation of intracytoplasmic actin filaments, and there is extensive effacement of the foot processes overlying the capillary walls (Figs. 2.3 and 2.4). The epithelial cells may also show reabsorption droplets and microvillus transformation as a nonspecific indication of cell injury. The changes in the distribution of deposits in the glomerular capillary wall, the progressive electron lucency of the deposits, and the thickening of the basement membranes as spikes of new basement membrane matrix are formed and as deposits are incorporated into the capillary wall are indicative of a sequence of events corresponding to early to late changes in the evolution of membranous nephropathy. This progressive evolution has been described in the classification of membranous nephropathy by Ehrenreich and Churg and has been generally divided into four stages of progression [21]. In stage I light microscopic changes are absent, but immunofluorescence shows granular aggregates of immunoglobulins, and electron microscopy shows subepithelial deposits without prominent basement membrane alterations (Fig. 2.3). In stage II spikes are present and the basement membrane matrices that progressively surround the immune deposits are visualized by electron microscopy. This may progress to stage III in which these spikes of basement membrane matrix surround the subepithelial deposits, with frequent incorporation of the

deposits into the capillary wall, leading to a thickened basement membrane. Stage IV is characterized by variation in electron density of the deposits and severe thickening and deformation of the glomerular basement membrane. Because of the aforementioned proteotypic digestion and degradation of the immune deposits over time, the deposits in stage IV may be less well recognized by the antisera used for immunofluorescence and the resultant staining patterns less prominent than for the other stages. Extensive effacement of foot processes, especially where they overly immune deposits, is typically present in all stages of this disorder. It should not be assumed that all cases of membranous nephropathy proceed through this sequence. For example, there may be cases of morphologic stage I that never proceed to other stages, and the occasional reports of clinical and pathologic resolution of membranous nephropathy indicate that there can be regression as well as progression, at least in the earlier stages of this process. This classification has been influential in shaping our understanding of membranous nephropathy, but it has not proven useful for guiding clinical management of patients or assessing prognosis.

Etiology/Pathogenesis

Membranous nephropathy continues to be a morphologic diagnosis. It is a disease characterized by a spectrum of changes in the glomerular capillary wall, initiated by the formation of subepithelial immune complexes [22]. Idiopathic membranous nephropathy is the result of an autoimmune disorder with immune complex deposition in glomeruli. Observations from animal models (especially the Heymann nephritis model in rodents) have long suggested that the production of antibodies directed at glycoproteins occurring on the podocyte surface results in in situ formation of subepithelial immune complexes, activation of complement, and glomerular damage [2, 5, 22]. The subepithelial location of the immune complexes in membranous nephropathy leads to complement activation, but not to chemotaxis and activation of inflammatory cells with subsequent glomerular cell proliferation, since the glomerular basement membrane acts as a barrier through which inflammatory cells cannot pass. This is believed to be the basis for the absence of glomerular proliferation and/or influx of inflammatory cells in membranous nephropathy [22]. For this reason, the term *membranous glomerulonephritis* has been regarded as a misnomer, and here the term *membranous nephropathy* has been used in its place. Subepithelial formation of immune complexes leads to podocyte damage with effacement of focal process and disruption of normal barriers to protein filtration such as the slit diaphragms of podocytes. In experimental membranous nephropathy, the onset of proteinuria is coincident with complement activation and loss of podocyte slit-diaphragm integrity [23].

Exciting advances in our understanding of membranous nephropathy have come from identification of previously unknown antigens that account for the great majority of idiopathic or primary membranous nephropathy. The first of these, neutral endopeptidase, is a rare cause of neonatal membranous nephropathy [2, 24]. Infants heterozygous for this peptide and who express this antigen on podocytes, when born

to a mother who is genetically deficient for this peptide but who possesses circulating antibodies to it as a result of prior exposure and sensitization, may develop immune complex deposition due to transplacental passage of the maternal antibodies that bind to the podocyte-expressed antigens [24]. More recently, about 70 % of patients with primary membranous nephropathy have been found to have circulating antibodies of IgG4 subclass to the M-type phospholipase A_2 receptor (PLA_2R), a podocyte surface protein whose normal function in the podocyte is unknown [20]. There is strong supporting evidence that the pathogenic immune complexes in glomeruli have PLA_2R as the target antigen [20]. The development of serologic assays to detect the presence and fluctuating titers of this anti-PLA_2R antibody in affected patients may lead to better therapeutics that target this antibody response. Such an assay may help in clinical management, by providing a good biomarker of disease activity and providing a dependable means of distinguishing primary from secondary forms of membranous nephropathy [2, 25].

Recent studies have also indentified a third etiologic mechanism based on the discovery of antibodies to bovine serum albumin in a small number of children with membranous nephropathy [26]. The antigen may be derived from intestinal absorption of cow's milk and subsequently become lodged in the glomerular capillary walls where it can serve as a foreign stimulus for antibodies and immune complex formation in situ. Other antigens have been occasionally identified in secondary forms of membranous nephropathy including nuclear matrix proteins and double-stranded DNA in lupus membranous nephritis and hepatitis B antigens that may get deposited ("planted") from the circulation in patients infected with this virus.

Clinicopathologic Correlations

The natural history of the untreated disease is variable. Complete or partial spontaneous remissions of proteinuria eventually occur in 40–50 % of patients, usually accompanied by stable renal function [10, 19]. The remainder slowly progress to end-stage renal disease or die of complications or from an unrelated disorder after 5–15 years [19]. Factors influencing the progression of membranous nephropathy are numerous and include age, renal function, and degree of albuminuria at the onset of nephropathy [6]. Pathologic factors such as concurrent focal and segmental glomerulosclerosis have been mentioned earlier.

Approximately 25 % of cases of membranous nephropathy are not "idiopathic" but have strong clinical and pathogenetic associations with other conditions. These include systemic lupus erythematosus (approximately 10–20 % of patients with lupus nephritis have membranous nephropathy), infections such as hepatitis B (the most common association with membranous nephropathy in children), hepatitis C, syphilis, graft versus host disease in patients who have received hematopoietic cell transplants, and malignancy [5, 6]. It has been estimated that between 5 and 20 % of patients with membranous nephropathy may develop a malignancy (typically a carcinoma) in a roughly similar time period [7, 27]. The strength of this association is unclear because of such confounding factors as the predilection of both processes

for an aging population, the wide variety of associated malignancies reported, and the relatively few instances where a specific tumor antigen has been implicated in the development of the membranous immune deposits. Nonetheless, the possibility of a malignancy must be considered in patients newly diagnosed with membranous nephropathy, especially in older patient populations.

The treatment of membranous nephropathy remains both controversial and suboptimal. For those patients who have persistent nephrotic proteinuria or manifest loss of renal function, steroids and immunosuppressive drugs are used, but their efficacy may be limited [6, 19]. Angiotensin II inhibition may slow progression, in part by controlling proteinuria [28]. Interventions directed towards inhibition of complement activation and specific components of the immune response are under active investigation at present [2, 22]. Treatment of secondary membranous nephropathy generally targets the disease rather than the renal lesion [29].

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Membranoproliferative Glomerulonephritis and C3 Glomerulopathy

3

Introduction/Clinical Setting

Membranoproliferative glomerulonephritis (MPGN) refers to a pattern of injury characterized by diffuse mesangial expansion due to mesangial and endocapillary proliferation and increased mesangial matrix, and thickened capillary walls, often with a double contour "tram-track" appearance [1, 2]. This pattern may be seen with immune complex deposition, or monoclonal proteins, or other organized deposits (as in fibrillary glomerulonephritis). The immune complexes may be undefined in terms of the inciting antigen ("idiopathic") or secondary to chronic infections [3]. Of note, glomerular basement membrane double contour appearance may be seen in other nonimmune complex injuries, such as the late phase of thrombotic microangiopathy (TMA) or in complement-mediated glomerulonephritides [3]. Although light microscopy may appear similar in these entities, immunofluorescence findings with staining for immunoglobulin and complement and corresponding deposits by electron microscopy readily allow recognition of the immune complexes in MPGN. In contrast, C3 glomerulopathies show C3 staining only, or dominant C3 without significant immunoglobulin, with deposits by electron microscopy, while chronic TMA shows no specific immunofluorescence findings and absence of deposits by electron microscopy. We and others prefer to use the term *membranoproliferative glomerulonephritis* only for immune complex glomerulonephritides with this pattern [1].

This type of immune complex MPGN has previously been referred to as MPGN type I. MPGN typically presents as combined nephritic/nephrotic syndrome with hypocomplementemia. Patients often have progressive renal disease, with about 50 % renal survival at 10 years. Idiopathic MPGN is more common in children and young adults, whereas MPGN-type lesions are more commonly secondary to chronic infections in adults. The so-called MPGN type III may not represent an entity separate from MPGN type I [4, 5]. C3 nephritic factor may be rarely found in these patients, but clinical distinction of this morphology, with frequent subepithelial deposits, has not been apparent.

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C3 glomerulopathies include dense deposit disease (DDD), also previously called MPGN type II. Patients with DDD typically have low serum complements, particularly C3, and nephrotic/nephritic syndrome. The majority develop chronic progressive kidney disease. Due to its similar light microscopic appearance, it previously has been classified with MPGN [6]. It is much more rare than MPGN type I, accounting for 15–35 % of total MPGN cases.

C3 glomerulopathies also include a group of patients with deposits with usual appearance by EM, but only C3, or dominant C3, by immunofluorescence. C3 glomerulopathy can affect patients from 7 to 70 years, with average age at presentation 30 years. Patients have proteinuria and microhematuria, with nephrotic syndrome present in around 15 %. The course is variable, with renal function preserved in about half, while about 15 % progress to end-stage kidney disease.

Pathologic Findings

Light Microscopy

Membranoproliferative glomerulonephritis type I characteristically has subendothelial deposits, resulting in a thickened capillary wall and a double contour of the glomerular basement membrane (GBM) by silver stains, and endocapillary proliferation [1].

This appearance results from the so-called circumferential cellular interposition, whereby infiltrating mononuclear cells or even portions of endothelial cells interpose themselves between the endothelium and the basement membrane, with new inner basement membrane being laid down [7]. A circumferential, or partial, double contour basement membrane results. Of note, in nonimmune complex diseases with this appearance by light microscopy (e.g., transplant glomerulopathy, chronic injury after hemolytic uremic syndrome), electron microscopy shows that the double contour results from widening of the GBM due to increased lucency of the lamina rara interna with new basement membrane formed underneath the endothelium. In MPGN type I, the glomeruli show endocapillary proliferation and increased mesangial cellularity and matrix and lobular simplification (Figs. 3.1, 3.2, and 3.3). The term *mesangiocapillary glomerulonephritis* has also been used for MPGN. Increased mononuclear cells and occasional neutrophils may be present. The proliferation is typically uniform and diffuse in idiopathic MPGN, contrasting the irregular involvement most commonly seen in proliferative lupus nephritis (Fig. 3.1). In secondary forms of MPGN, the injury may be more irregular. Crescents may occur in both idiopathic and secondary forms. Deposits do not involve extraglomerular sites. Lesions progress with less cellularity and more pronounced matrix accumulation and sclerosis over time [8]. Tubular atrophy, interstitial fibrosis, and vascular sclerosis proportional to glomerular scarring are seen late in the course.

Membranoproliferative glomerulonephritis type III shows, in addition to the subendothelial and mesangial deposits, numerous subepithelial deposits.

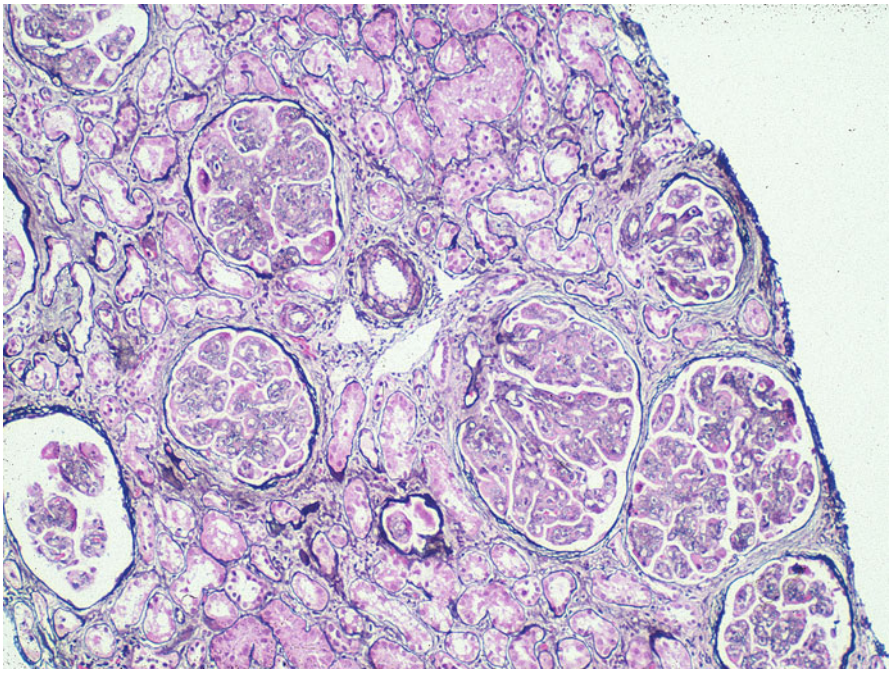

Fig. 3.1 Lobular appearance due to diffuse, global endocapillary proliferation of all glomeruli in immune complex-type membranoproliferative glomerulonephritis (MPGN) (Jones silver stain)

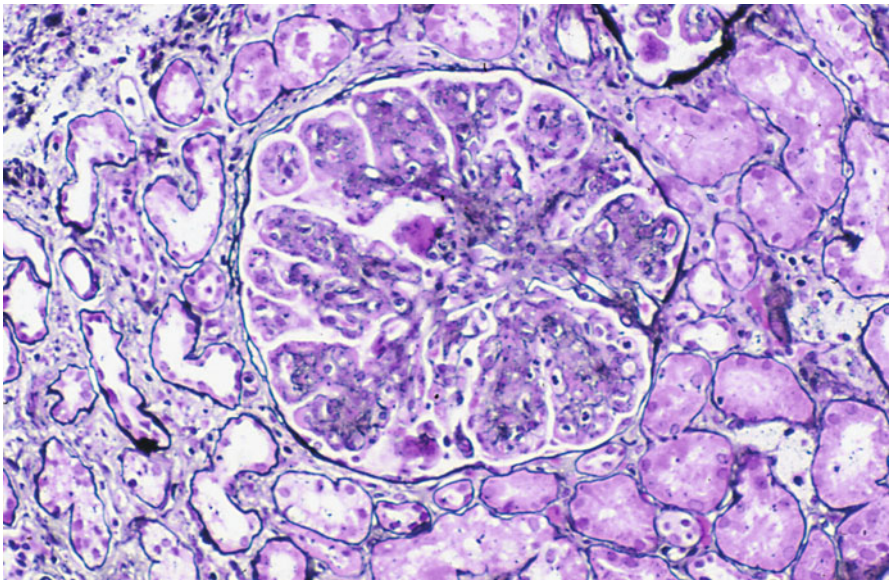

Fig. 3.2 Diffuse, global endocapillary proliferation with extensive glomerular basement membrane (GBM) double contours in immune complex-type MPGN (Jones silver stain)

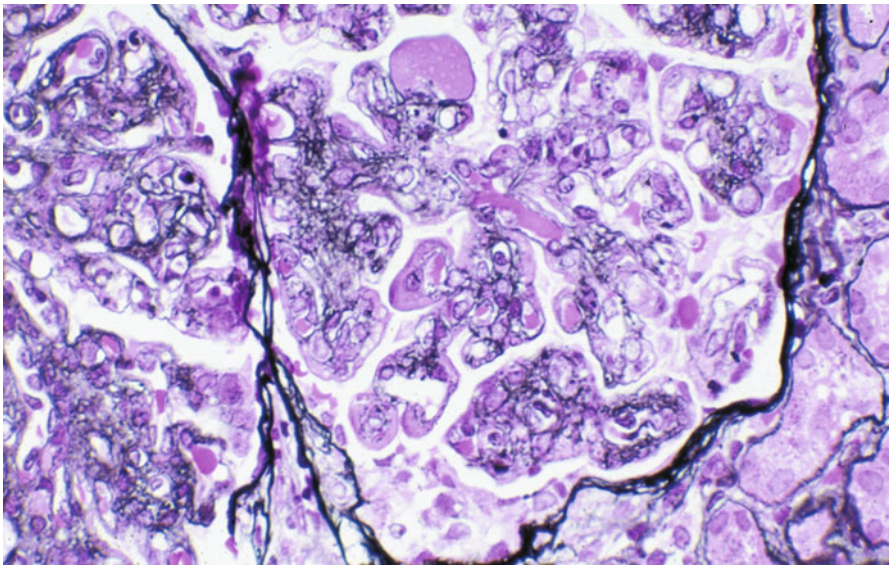

Fig. 3.3 Diffuse, global endocapillary proliferation with GBM double contours and visible large subendothelial deposits in immune complex-type MPGN (Jones silver stain)

Diseases with dominant C3 deposits include *the C3 glomerulopathies*. This group of disorders includes *dense deposit disease* (DDD, also previously called MPGN type II) and C3 glomerulonephritis [6, 9, 10]. The most common pattern of injury in DDD is mesangial proliferation, followed by endocapillary proliferation (Fig. 3.4) [9]. The basement membranes are thickened and highly refractile and eosinophilic, with involved areas with strings of deposits looking like a string of sausages. The deposits are periodic acid-Schiff (PAS) positive and stain brown with silver stain. Thickening also affects tubular basement membranes and Bowman's capsule. Crescents may be present. In some cases of C3 glomerulonephritis, the deposits lack the dense appearance by EM of DDD. In these cases, light microscopy most often shows membranoproliferative-type appearance with mesangial and endocapillary proliferation with a nodular appearance in about 20 % of cases.

Immunofluorescence Microscopy

The immunofluorescence findings are variable in immune complex-type MPGN. Typically, IgG and IgM and C3 are present in an irregular capillary and mesangial distribution (Fig. 3.5). IgA is present in only a small proportion of cases. When C3 staining is dominant, chronic infection or a C3 glomerulopathy should be considered.

In DDD, C3 staining outlines the capillary wall and may be smooth, granular, or discontinuous. Mesangial bright granular staining can be present. Immunoglobulin

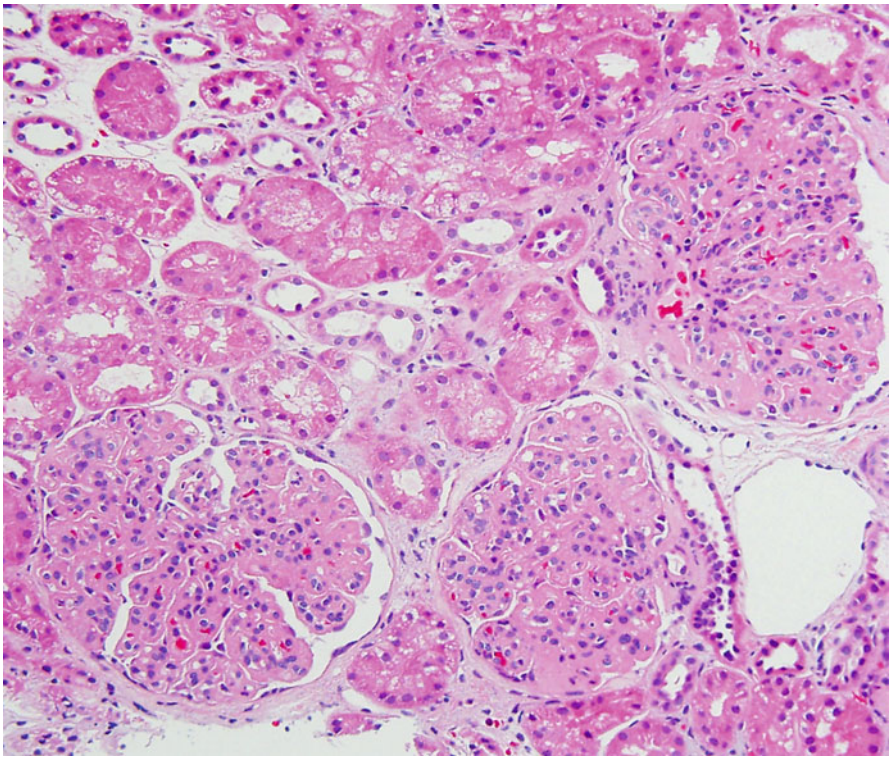

Fig. 3.4 Membranoproliferative pattern in C3 glomerulonephritis (H&E)

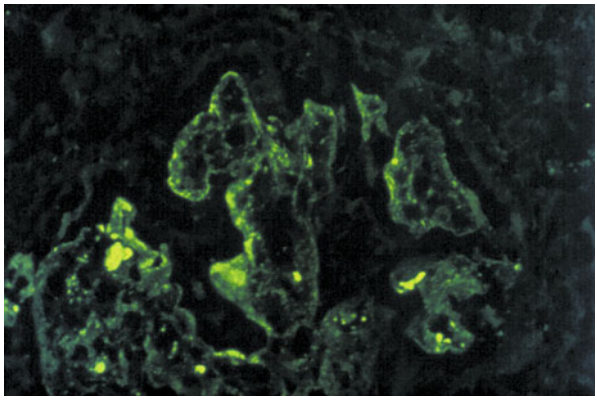

Fig. 3.5 Coarsely granular capillary loop and mesangial deposits in MPGN (anti-IgG antibody immunofluorescence)

is usually not detected, indicating the dense deposits are not classic antigen-antibody immune complexes. However, segmental IgM or less often IgG and very rarely IgA have been reported [11].

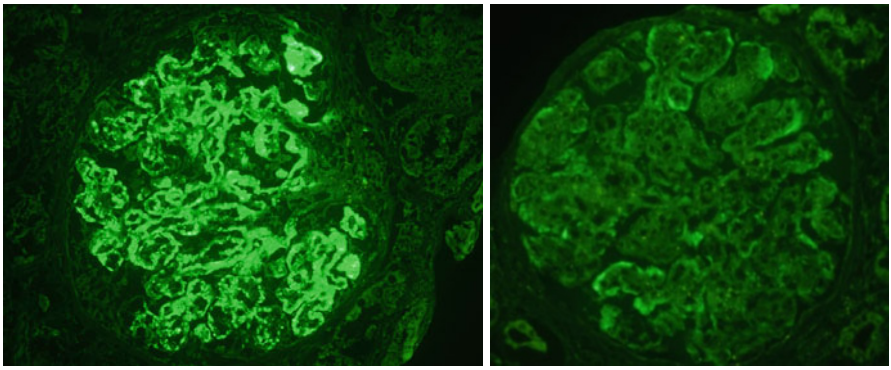

Fig. 3.6 Coarsely granular capillary loop and mesangial deposits in C3 glomerulonephritis, staining dominantly for C3 (*left*) with negligible staining for IgG (*right*) (immunofluorescence)

In non-DDD cases of C3-dominant glomerulonephritis, there are by definition isolated or dominant C3 deposits without significant C1q or immunoglobulin (Fig. 3.6). Deposits mirror the light microscopic pattern, with mesangial and scattered capillary loop deposits.

Electron Microscopy

By electron microscopy, immune complex-type MPGN shows numerous dense deposits in subendothelial and mesangial areas (Fig. 3.7). Vague wormy or microtubular substructure suggests a possible cryoglobulin component (Fig. 3.8). Cellular interposition is detected (Fig. 3.9), which refers to the interposition of cytoplasmic processes of mononuclear cells between the endothelial cell and the basement membrane. New basement material is present immediately under the swollen endothelial cells, resulting in the double contours visualized by light microscopy by silver stains [1].

In DDD, the lamina densa of the GBM and occasionally the tubular basement membranes show a very dense transformation without discrete immune complex-type deposits, with nodular dense ring-type deposits in the mesangium (Fig. 3.10) [6, 9, 12].

Similar dense material is often found in the mesangial areas in addition to increased matrix. Increased mesangial cellularity and/or cellular interposition are far less common than in immune complex-type MPGN. Podocytes show varying degrees of reactive changes, from vacuolization, to microvillous transformation, to foot process effacement. Tubular basement membranes and Bowman's capsule may show similar densities.

In C3 glomerulonephritis, there is no dense transformation of basement membranes. EM shows subendothelial and mesangial and less frequently subepithelial deposits, with reduplication of glomerular basement membranes (Fig. 3.11). These deposits may appear less well defined than usual immune complex-type deposits. About 30 % of these patients may demonstrate only mesangial and subepithelial

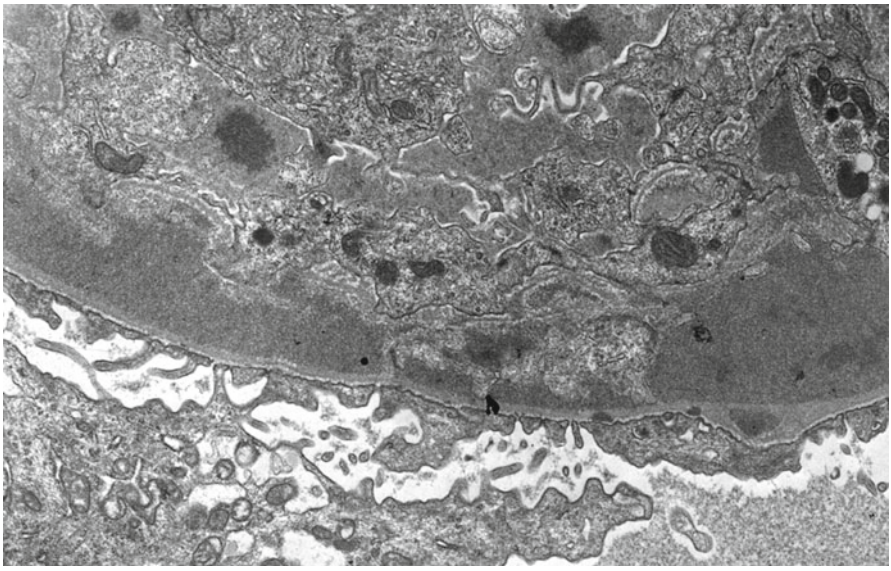

Fig. 3.7 Subendothelial immune complex deposits in immune complex-type MPGN (electron microscopy)

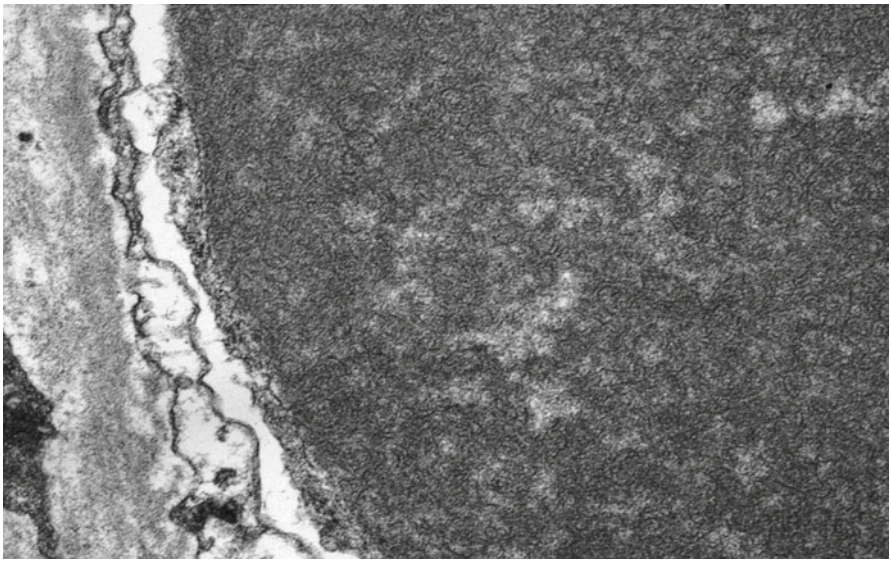

Fig. 3.8 Intracapillary deposits with vague, short fibrillary substructure, in MPGN caused by hepatitis C-associated cryoglobulin (electron microscopy)

deposits without subendothelial deposits or mesangial proliferation. Occasional subepithelial hump-type deposits may also be present. There is no dominant dense transformation of the glomerular basement membranes.

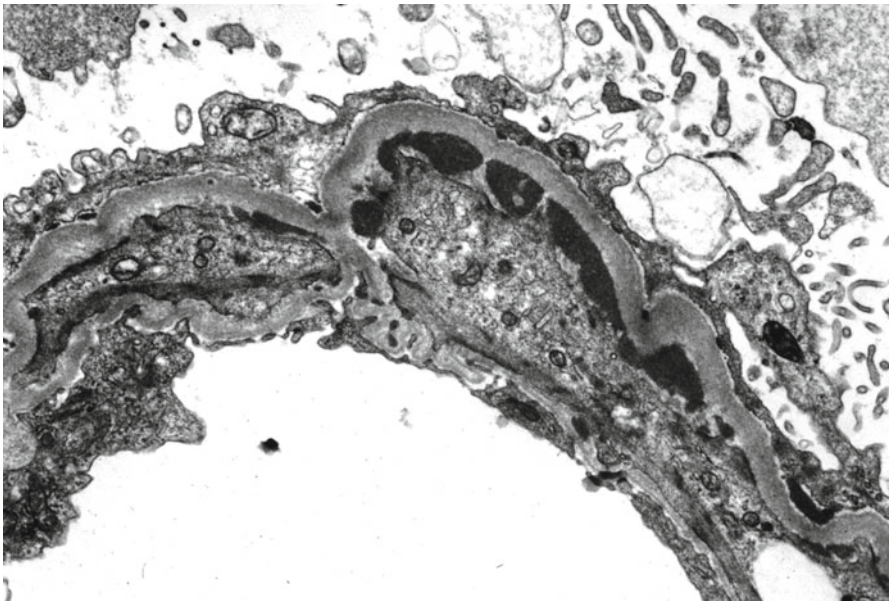

Fig. 3.9 Subendothelial deposits with underlying interposed cell (cellular interposition) and underlying new GBM formation, resulting in double contour appearance by light microscopy in MPGN (electron microscopy)

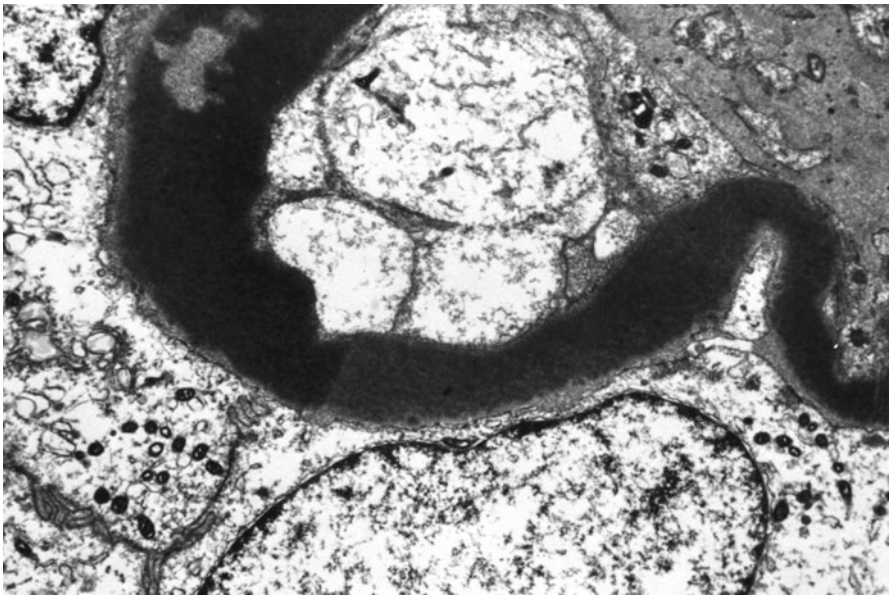

Fig. 3.10 Dense transformation of the GBM in dense deposit disease (electron microscopy)

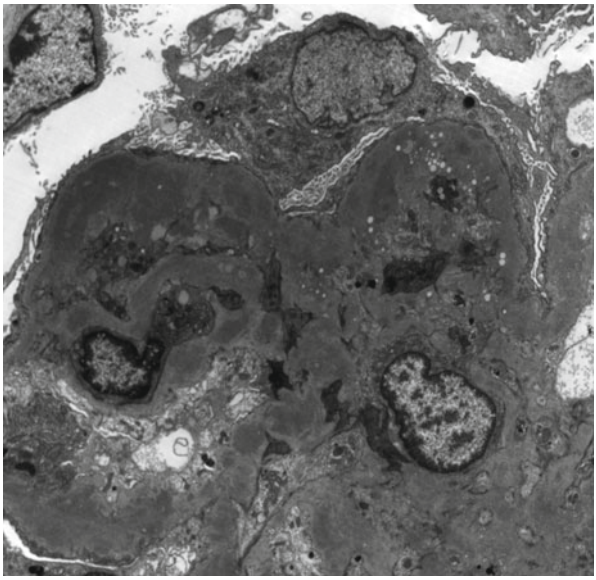

Fig. 3.11 In C3 glomerulonephritis, the deposits are typically mesangial and subendothelial/intramembranous, as in this case. Deposits often have a vague delineation from the GBM (electron microscopy)

Etiology/Pathogenesis

MPGN lesions have been recognized to occur secondary to a number of chronic infectious processes, including hepatitis B, hepatitis C, syphilis, and subacute bacterial endocarditis. If a chronic infection is causing MPGN-type lesions, hump-type subepithelial deposits may be present (see Chap. 5).

Generally, morphologic features do not allow precise classification of the underlying agent in most cases of immune complex-type MPGN. However, MPGN appearance may occur in settings other than immune complex injury. IF and EM can then classify MPGN-type lesions as immune-derived, monoclonal protein or other organized deposits, complement-related, or due to chronic endothelial injury [13]. A large number (~25 % in the United States) of previously idiopathic MPGN cases in adults have been associated with hepatitis C infection [14]. This association was not seen in a US series of children with MPGN. Morphologic features suggestive of hepatitis C with cryoglobulin as an underlying cause include vague substructure of deposits, with short, curved, vaguely fibrillar deposits (Fig. 3.6) (suggestive of mixed cryoglobulinemia), or rarely microtubular substructure, strongly PAS-positive cryo-"plugs" in capillary lumina (Fig. 3.12), vasculitis, and predominant IgM deposits, sometimes with clonality [15]. Cryoglobulinemia is commonly associated with hepatitis C, an RNA virus [16]. Approximately 150,000 cases of hepatitis C infection occur per year in the United States. Of these, approximately half have liver disease, with 15,000 developing chronic active hepatitis and/or cirrhosis. The prevalence of hepatitis C infection is approximately 0.6 % in the United States, reaching up to 6 % in Africa. In one large series of hepatitis C-positive cases

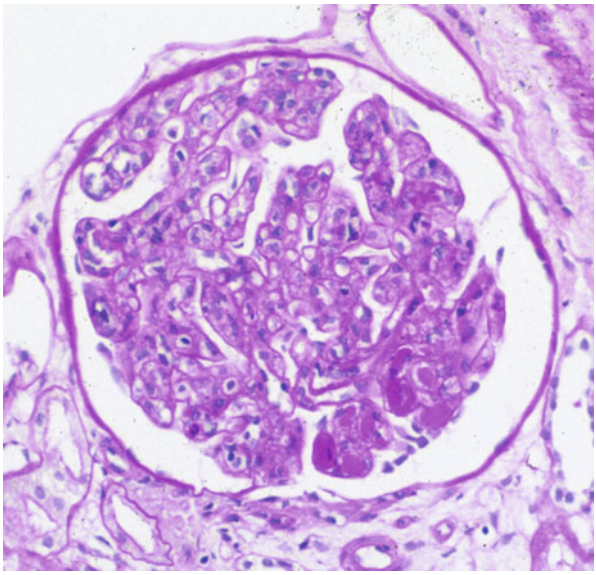

Fig. 3.12 Global endocapillary proliferation, double contours of GBM, and brightly PAS-positive so-called cryo-plugs in capillary lumina, characteristic of MPGN due to cryoglobulins (PAS)

affecting the kidney, 40 patients with an average age of 46 years were studied. The most common risk factors for infection in this series were intravenous drug abuse and blood transfusion. The mixed type 2 cryoglobulinemia associated with various infections is postulated to be due to the production of rheumatoid factor in response to complexes of IgG bound to foreign antigens [17]. Cryoglobulinemia may also manifest as a more acute glomerulonephritis and may even show strongly PAS-positive cryo-plugs (hyaline thrombi) visualized in capillary lumina (Fig. 3.12). Deposits of cryoglobulin typically show vague, short, fibrillary substructure by electron microscopy (Fig. 3.6). There may also be vasculitis involving medium-sized arteries in cryoglobulinemic glomerulonephritis.

In contrast, many patients with DDD show a distinct pathogenesis related to IgG autoantibodies (C3 nephritic factor, C3NeF) directed at C3 convertase, resulting in alternate pathway complement activation. C3NeF stabilizes the C3 convertase C3bBb, resulting in alternate pathway-mediated C3 breakdown and decreased serum levels of C3. Early components of the classic pathway, that is, C1q and C4, usually show normal serum levels. Sometimes DDD occurs in association with partial lipodystrophy, a condition with loss of adipose tissue, decreased complement, and the presence of C3NeF [6, 18]. Factor H inactivates factor C3bBb and may also be involved with DDD in some patients. Some patients with DDD show genetic deficiency or autoantibodies to complement factor H (*CFH*) or rarely mutations in C3 that promote fluid-phase activation [10]. Further, a porcine model of factor H deficiency has similarities to DDD, and additional studies also support that fluid-phase activation of C3 is linked to DDD [19]. These associations have suggested that abnormal complement regulation predisposes to DDD. However, clinical measures of complement, C3NeF, or

presence of partial lipodystrophy did not predict clinical outcome among patients with DDD, and some patients with apparent immune complex-type MPGN also have C3NeF. Some patients with partial lipodystrophy and C3NeF do not have DDD, a further indication that complement abnormalities alone are insufficient to produce the disease.

Mass spectrometry has shown that the dense deposits contain components of the terminal C5-9 pathway and alternative complement activation pathway [20].

C3 glomerulonephritis patients are now recognized to often manifest underlying complement dysregulation, with mutations described in key complement and complement-regulatory components, such as complement factor H or I, or complement factor H-related protein 5, resulting in the so-called CFHR5 nephropathy (*CFHR5*) [21]. Patients who are heterozygous for such complement mutations may have increased susceptibility to postinfectious glomerulonephritis and manifest a more prolonged course than typical for poststreptococcal glomerulonephritis [10, 22].

Clinicopathologic Correlations

Immune complex-type MPGN has an inexorable downhill course clinically [1, 18, 23]. Patients present with proteinuria, which reaches nephrotic levels in two-thirds. Renal disease associated with hepatitis C and cryoglobulin most often is manifest as MPGN, although membranous glomerulopathy has been described. Patients with cryoglobulins often have systemic disease in addition to renal involvement [24]. Necrotizing arteritis may also occur secondary to hepatitis C infection [25–27]. In these patients with renal disease and hepatitis C infection, purpura is frequently present. Sixteen percent showed signs of liver disease. Tests for cryoglobulins were positive at some point of the disease course in 80 % of patients. Most patients showed decreased complement (90 %). Demonstration of hepatitis C in kidney tissue has not been documented directly within deposits. However, hepatitis C virus-like particles have been identified within the dense deposits, and hepatitis C virus has been isolated from renal tissue [14].

Treatment so far has offered limited success. MPGN has recurred in up to 30 % of transplants in some series [18]. However, the disease may have a more benign clinical course when it recurs. Interferon-α therapy decreases symptoms of renal involvement in hepatitis C-associated MPGN, but relapses are prompt as soon as therapy is discontinued [14]. Improved antiviral therapies, sometimes in combination with immunosuppression, have led to improved outcomes. In DDD, crescents or glomerular PMNs were associated with worse prognosis, whereas focal segmental proliferative lesions were less frequently associated with progressive kidney disease. DDD has very frequent, near 100 % morphologic recurrence in the transplant, but loss of the transplant does not usually result [18, 28]. CFHR5 nephropathy also can recur in the kidney [29]. Novel therapies aimed at the abnormal complement activation are emerging and may lead to improved outcomes in these patients.

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Minimal Change Disease and Focal Segmental Glomerulosclerosis

4

Introduction/Clinical Setting

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are both common causes of the nephrotic syndrome. Minimal change disease accounts for greater than 90 % of cases of nephrotic syndrome in children vs. 10–15 % of adults with nephrotic syndrome [1]. Focal segmental glomerulosclerosis has been increasing in incidence in the United States in both African Americans and in Hispanics, in both adult and pediatric populations [2–4]. It is now the most common cause of nephrotic syndrome in adults in the USA. Patients with FSGS may have hypertension and hematuria. Serologic studies, including complement levels, are typically within normal limits in both MCD and FSGS.

Pathologic Features

Light Microscopy

Minimal change disease shows normal glomeruli by light microscopy (Fig. 4.1). In FSGS, sclerosis involves some, but not all, glomeruli (focal), and the sclerosis affects a portion of, but not the entire, glomerular tuft (segmental) (Fig. 4.2) [1, 5–7]. Sclerosis is defined as increased matrix with obliteration of the capillary lumen. Uninvolved glomeruli in FSGS show no apparent lesions by light microscopy; FSGS may also entail hyalinosis, caused by insudation of plasma proteins, producing a smooth, glassy (hyaline) appearance (Fig. 4.3). Adhesions (synechiae) of the capillary tuft to Bowman's space are a very early sclerosing lesion.

Focal segmental glomerulosclerosis is diagnosed when even a single glomerulus shows segmental sclerosis. Therefore, samples must be adequate to detect these focal and segmental lesions. A biopsy with only ten glomeruli has a 35 % probability of missing a focal (10 % involved) lesion, decreasing to 12 % if 20 glomeruli are sampled [8]. The juxtamedullary region also should be included in the biopsy for

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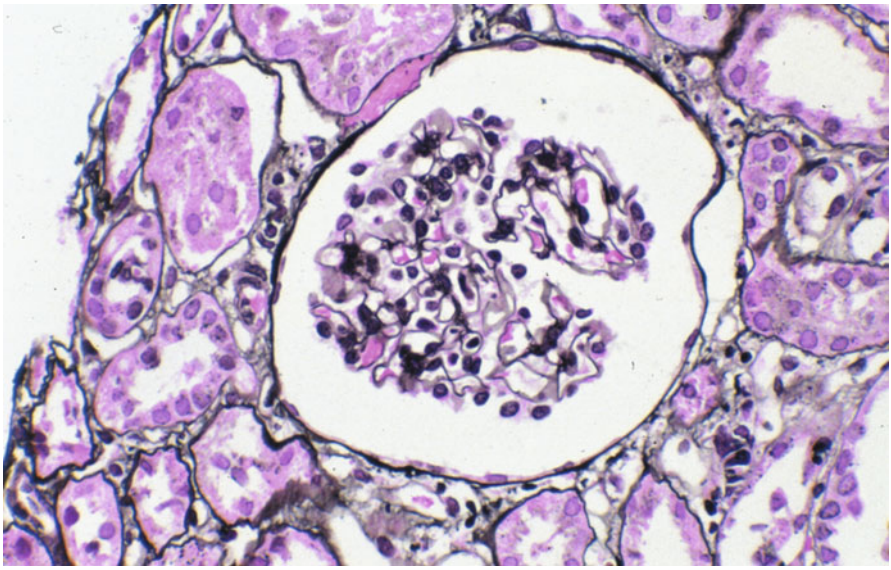

Fig. 4.1 Normal glomerulus in minimal change disease (Jones silver stain)

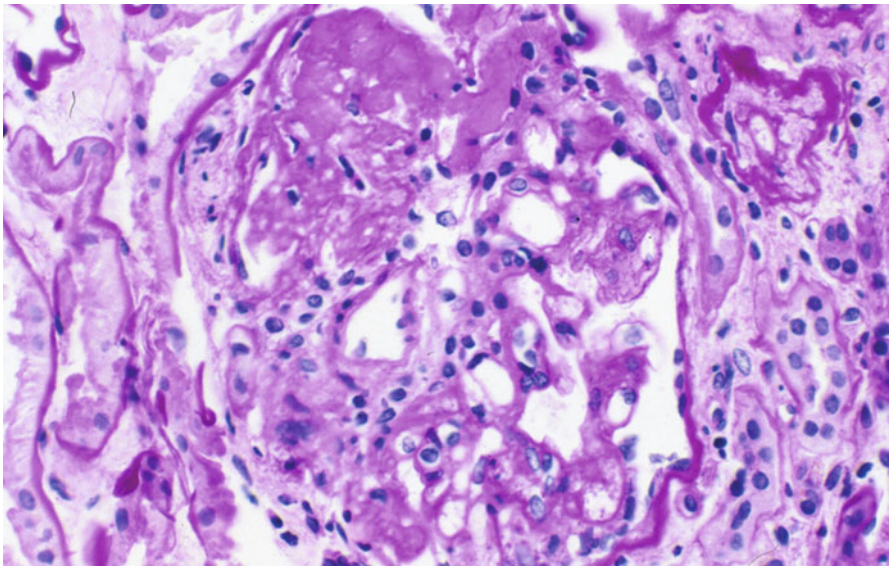

Fig. 4.2 Glomerulosclerosis in focal and segmental pattern in focal segmental glomerulosclerosis, not otherwise specified (FSGS NOS) type [periodic acid-Schiff (PAS)]

optimal sampling, because that is where FSGS starts [5]. Multiple-step sections should also be examined to detect the focal segmental lesions. As the disease process progresses, more glomeruli are involved more extensively, so that as the

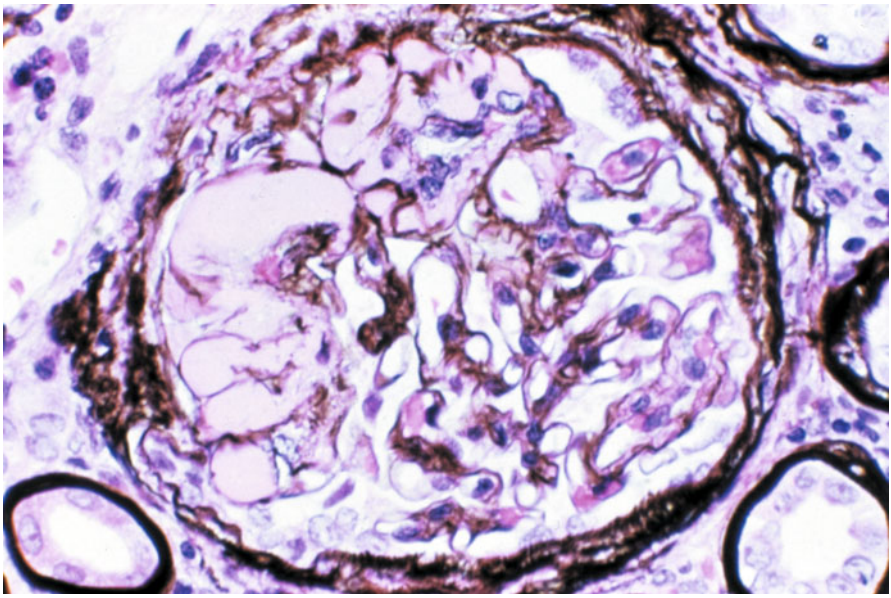

Fig. 4.3 Extensive hyalinosis and sclerosis in FSGS NOS type (Jones silver stain)

disease approaches end stage, all glomeruli may be involved with sclerosis, and the segmental sclerosis may then be extensive and global or near-global.

Global glomerulosclerosis, in contrast to the segmental lesion, is not of special diagnostic significance in diagnosing FSGS. Globally sclerotic glomeruli may be normally seen at any age. In children, less than 1 % global sclerosis is expected. The extent of global sclerosis increases with aging. Smith et al. [9] proffered the formula for normal percent of global sclerosis in adults of up to half the patient's age, minus 10, for example, up to 30 % by age 80.

Morphologic variants of sclerosis appear to have differing prognosis (see below) [12–16]. The most common type of FSGS, *FSGS not otherwise specified* (*NOS*), has no specific distinguishing features and is characterized by segmental sclerosis, defined as increased matrix and obliteration of capillary lumina, often with hyalinosis in the absence of underlying immune complexes or other indicators of a secondary etiology by complete immunofluorescence/electron microscopy (IF/EM) evaluation; FSGS NOS is diagnosed by exclusion of specific subtypes as follows (Fig. 4.4): Collapsing variant of FSGS is characterized by collapse of the capillary loops and overlying podocyte proliferation and has a particularly ominous prognosis (Fig. 4.5) [17, 18]. Even just one glomerulus with collapsing lesion is sufficient, we propose, to classify the process as collapsing variant FSGS. In the absence of collapsing lesions, the location of lesions, either peripheral or hilar, has significance as follows: The *glomerular tip lesion* is defined as sclerosis only affecting the tubular pole of the glomerulus, with adhesion of the tuft to the proximal tubule outlet (Fig. 4.6). There is often associated endocapillary hypercellularity and intracapillary foam cells [12, 19, 20].

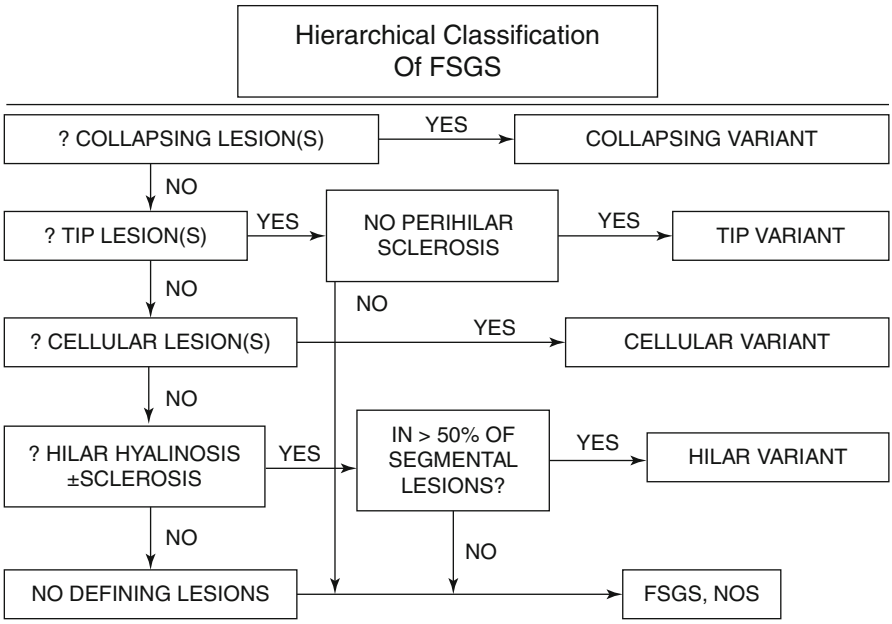

Fig. 4.4 Hierarchical classification schema for FSGS variants

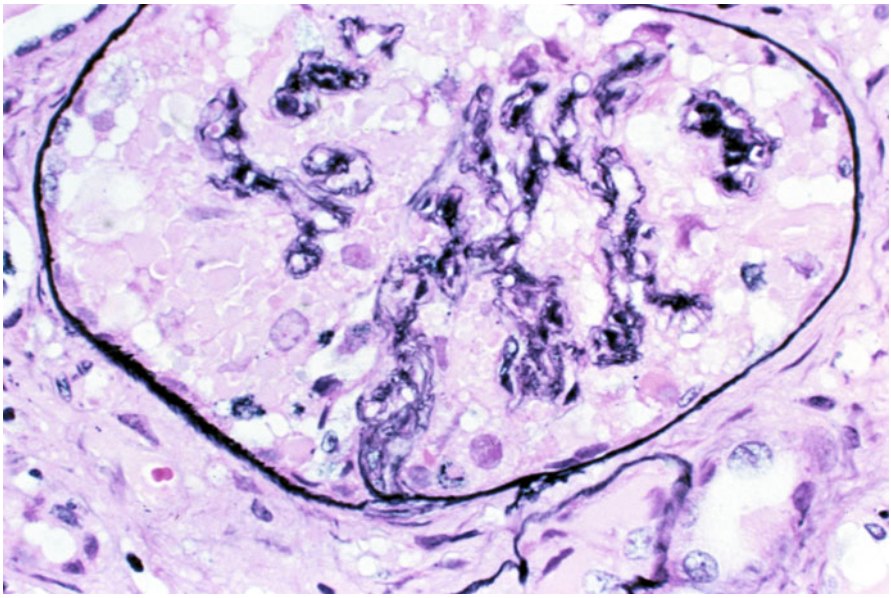

Fig. 4.5 Collapse of glomerular tuft with overlying epithelial cell hyperplasia in collapsing-type FSGS (Jones silver stain)

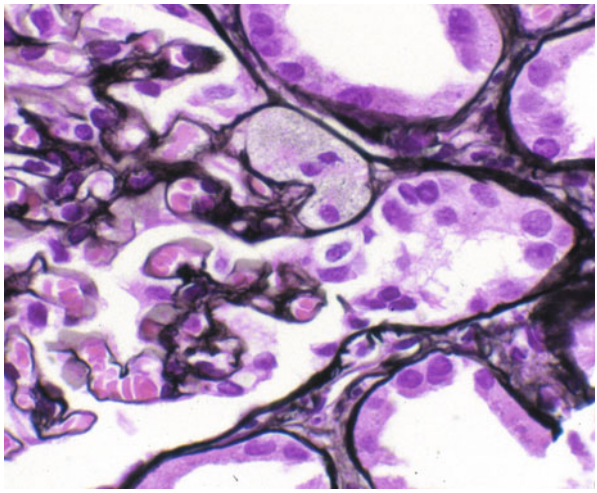

Fig. 4.6 Adhesion and endocapillary foam cells at proximal tubular pole in tip variant of FSGS (Jones silver stain)

The *cellular variant of FSGS* is characterized by segmental proliferative podocyte reaction associated with early sclerosis and/or endocapillary hypercellularity and often intracapillary foam cells [14]. It does not, per definition, involve the tubular pole. Predominantly *hilar lesions*, that is, more than half of sclerotic glomeruli with sclerosis with associated hyaline at the hilar pole, in the absence of collapsing lesions, have been proposed to represent a response to reduced renal mass and may also be associated with secondary FSGS seen with arterionephrosclerosis [10, 11].

Vascular sclerosis may be prominent late in the course of FSGS and is proportional to glomerular sclerosis. Tubular atrophy is often accompanied by interstitial fibrosis, proportional to the degree of scarring in the glomerulus. In HIV nephropathy and collapsing glomerulopathy, tubular lesions are disproportionally severe, with cystic dilation and a more prominent infiltrate [21].

The presence of acute interstitial nephritis (i.e., edema, interstitial infiltrate of lymphocytes, plasma cells, and often eosinophils) and apparent MCD glomerular lesion (i.e., complete foot process effacement, no light microscopic lesions) suggests a drug-induced hypersensitivity etiology, in particular nonsteroidal anti-inflammatory drug (NSAID)-related injury.

Surrogate markers of unsampled FSGS have been sought to suspect FSGS even when sclerosed glomeruli are not detected. Abnormal glomerular enlargement (see below) appears to be an early indicator of the sclerotic process preceding overt sclerosis [22]. Tubulointerstitial fibrosis in a young patient without evident glomerular sclerosis in the biopsy sample could also indicate possible unsampled FSGS.

Immunofluorescence Microscopy

There are no immune complex deposits in either MCD or FSGS. In FSGS, there may be nonspecific entrapment of immunoglobulin M (IgM) and C3 in sclerotic areas or areas where mesangial matrix is increased. IgM staining without deposits by EM does not appear to have specific diagnostic, prognostic, or etiologic significance [23].

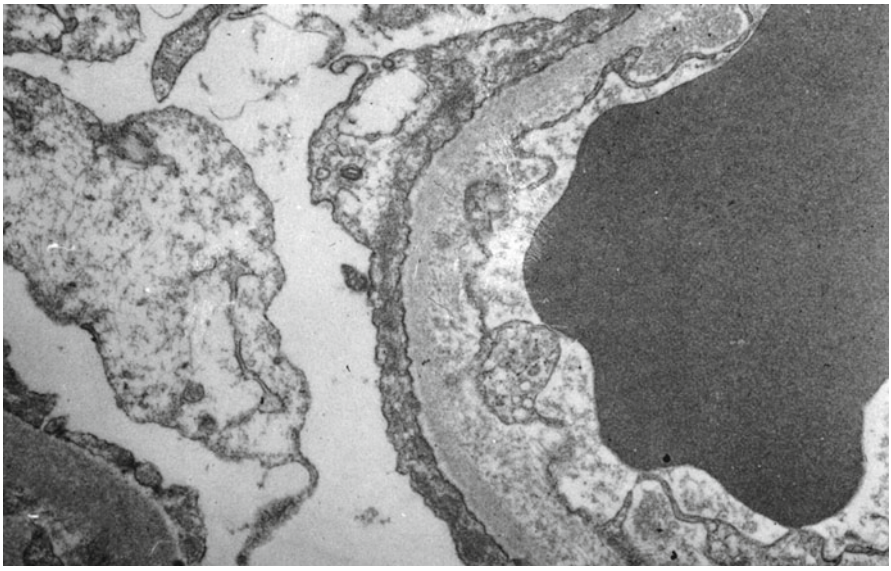

Fig. 4.7 Extensive foot process effacement is present in minimal change disease and also in FSGS. No immune complexes are present (electron microscopy)

Electron Microscopy

Electron microscopy shows foot process effacement, vacuolization, and microvillous transformation of epithelial cells in both MCD and FSGS. In MCD, foot process effacement is typically extensive (Fig. 4.7). Foot process effacement is often not complete in FSGS [23]. However, the extent of foot process effacement does not allow precise distinction between the two disease processes. In secondary FSGS, foot process effacement is generally less than in idiopathic forms. Thus, less than about 50 % foot process effacement is suggestive of a secondary etiology of the segmental sclerosis rather than idiopathic FSGS [24]. In HIV-associated nephropathy (HIVAN), there are reticular aggregates in endothelial cell cytoplasm.

Etiology/Pathogenesis

The pathogenesis of MCD appears related to abnormal cytokines, which only affect glomerular permeability and do not promote sclerogenic mechanisms. Urinary CD80 is increased in MCD but not in FSGS patients, suggesting that CD80 could be a marker or possibly contribute to pathogenesis of MCD [25]. CD80 is a transmembrane protein that provides a co-stimulatory signal for T cell activation and may be induced on podocytes in response to activated T cells or other injury. Minimal change disease has been associated with drug-induced hypersensitivity reactions, bee stings, Hodgkin's disease, and other venom exposure, implicating immune dysfunction as an initiating factor.

Glomerular hypertrophy may be a marker of early FSGS. Glomerular enlargement precedes overt glomerulosclerosis in FSGS [22]. Patients with abnormal glomerular growth on initial biopsies that did not show sclerotic lesions subsequently developed overt glomerulosclerosis, documented in later biopsies. A cutoff of glomerular area larger than 50 % more than normal for age indicated increased risk for progression. Of note, glomeruli grow until approximately age 18 years; so age-matched controls must be used in the pediatric population. Since tissue processing methods may influence the size of structures in tissue, it is imperative that each laboratory determines normal ranges for this parameter.

Recurrence of FSGS in the transplant has also shed light on its pathogenesis [26]. Most recurrences occur within the first months after transplantation, but recurrence may be immediate. Foot process effacement is present when proteinuria recurs and precedes the development of sclerosis, typically by weeks to months. The pattern of FSGS generally, but not always, is that of the original disease [27]. A circulating factor has been identified in patients with recurrent FSGS, which induces increased ex vivo glomerular permeability, and also a mild increase in proteinuria when injected in rats [28]. Plasmapheresis induced remission in some patients with recurrent FSGS, but more often relapse occurred when plasmapheresis was stopped. During the stage of foot process effacement in recurrent FSGS, but not in native kidney MCD, activated CD44-positive parietal epithelial cells were detected, both in a parietal and in a visceral location, suggesting that parietal epithelial cells are activated and perhaps migrating to sites of injury [29]. Parietal epithelial cells may act as stem cells to replenish podocytes, migrating along Bowman's capsule or adhesions to the glomerular capillary tuft [30]. Whether these cells with parietal epithelial cell markers and visceral location are reparative or profibrotic is not determined [31, 32].

Differentiation markers of podocytes, including the Wilms' tumor WT-1 protein, podocalyxin, and synaptopodin, are retained when proteinuria is caused by MCD or membranous glomerulopathy but disappeared (or were decreased in the case of synaptopodin) in the collapsing variant of FSGS or HIV-associated nephropathy, with lesser changes in typical FSGS, with gain of markers of activated parietal epithelial cells [29, 33, 34]. These observations point to a dysregulated phenotype of the visceral epithelial cell in the pathogenesis of the collapsing and HIV-associated forms of FSGS, perhaps with migration of activated parietal epithelial cells, or with transdifferentiation of the podocytes to a parietal phenotype [29, 33, 34].

Studies of the molecular biology of the podocyte and identification of genes mutated in rare familial forms of nephrotic syndrome or FSGS, e.g., *ACTN4*, *NPHS2*, *TRPC-6*, *PLCE1*, *INF-2*, *WT1*, *CD2AP*, *LAMB2*, and *NPHS1*, have given important new insights into mechanisms of progressive glomerulosclerosis [35, 36]. Congenital nephrotic syndrome of Finnish type (CNSF) is caused by mutations in nephrin (*NPHS1*) [37]. The common mutations in this syndrome are called *fin major and fin minor*. Nephrin localizes to the slit diaphragm over the podocyte and is tightly associated with CD2-associated protein (CD2AP) [38]. Nephrin functions as a zona occludens-type junction protein and along with CD2AP plays a crucial role in receptor patterning and cytoskeletal polarity. Nephrin also has signal transduction

functions. Some patients with CNSF develop nephrotic syndrome after transplantation, if the original disease was due to *fin major* mutations, which leads to complete loss of nephrin, with antibody to nephrin detected in the patient. Mice engineered to be deficient in CD2AP develop congenital nephrotic syndrome. Mutations of CD2AP, predicted to cause loss of function, have been detected in two adult patients with proteinuria and FSGS without a family history of the disease [39].

Autosomal dominant FSGS is caused by mutation in α-actinin-4, a key cytoskeletal protein (ACTN4) [40]. Patients with the ACTN4 mutation progress to end stage by age 30 years. Podocin, another podocyte-specific structural gene (*NPHS2*), is mutated in autosomal recessive FSGS with an early onset in childhood with rapid progression to end stage [41]. Importantly, patients with such podocin mutations are generally resistant to steroid therapy, whereas some patients with PLCE1 mutations may respond to steroids [36, 42]. Acquired FSGS also may involve alteration in expression of some of these key podocyte genes that confer increased susceptibility to injury and increased risk of FSGS. An allele variant of apolipoprotein L1 that is protective against trypanosomal disease has been linked to increased FSGS in African Americans [43]. The mechanisms for renal disease susceptibility remain unknown.

Additional observations underscore the importance of the interactions between the podocyte and the underlying basement membrane. Dystroglycan is an integral component of the GBM. Dystroglycan staining was decreased in patients with MCD and also in the proliferating epithelial cells in collapsing glomerulopathy [44, 45]. Dystroglycan expression was maintained in the nonsclerotic segments in FSGS NOS variant, suggesting that MCD and FSGS are indeed different disease processes and not different stages of one disease.

Germline mutations of the WT-1 (Wilms' tumor) suppressor gene are found in Denys-Drash syndrome (a rare childhood disease with diffuse mesangial sclerosis, male pseudohermaphroditism, and a high risk of Wilms' tumor, with mutations usually of exon 9) and in Frasier syndrome (a disease with FSGS, XY hermaphroditism, and a high risk of gonadoblastoma, with mutations of intron 9) [46]. Abnormal, lamellated basement membranes were observed in three patients with FSGS associated with Frasier syndrome, in whom studies for coexistent Alport syndrome were negative [47]. Abnormal splice variants of WT-1 have rarely been associated with nonsyndromal cases of FSGS [48].

Clinicopathologic Correlations

Minimal change disease patients typically respond to corticosteroids, with excellent long-term prognosis. In contrast, FSGS usually results in progressive decline of GFR. The finding of *mesangial hypercellularity* was proposed to indicate a subtype of primary MCD with poorer prognosis and increased risk for development of FSGS. However, several series have failed to confirm a definite clinical correlation of this morphologic variant. Thus, diffuse mesangial hypercellularity does not appear to impart a specific prognostic significance and is rather regarded as a manifestation of an earlier stage of disease.

Table 4.1 Working classification of focal segmental glomerulosclerosis (FSGS)

Type	Key histologic feature	Possible prognostic implication
FSGS NOS	Segmental sclerosis	Typical course
Collapsing FSGS	Collapse of tuft, visceral epithelial hyperplasia	Poor prognosis
Cellular FSGS	Endocapillary proliferation, often visceral epithelial hyperplasia	? Early-stage lesion ? Related to tip
Tip lesion	Sclerosis/adhesion at proximal tubule pole	Better prognosis
Perihilar variant	Sclerosis and hyalinosis at vascular pole	May reflect a secondary type of FSGS

NOS not otherwise specified

The proposed morphologic variants of FSGS appear to have prognostic significance (Table 4.1) [10, 11, 16]. Collapsing FSGS has a poor prognosis with rapid loss of renal function and virtually no responsiveness to corticosteroids alone [18]. Series of patients with collapsing FSGS show a strong preponderance of African Americans, and most patients were adults. FSGS in African Americans is tightly linked to risk allele variants of the apolipoprotein A1 gene [43]. Evidence of parvovirus infection was increased in patients with collapsing glomerulopathy compared to controls, usual-type FSGS and HIVAN [49]. The drug pamidronate and other bisphosphonates also have been linked to the development of collapsing glomerulopathy [41]. Collapsing lesions also have been seen in the transplant, linked to cyclosporine toxicity, with other causes of severe ischemia in lupus patients, and with exogenous interferon therapy [50].

Clinically, patients with the cellular variant of FSGS have an abrupt onset of nephrotic syndrome. This cellular lesion may be an early abnormality seen by light microscopy (LM) when FSGS recurs in the transplant. This morphologic appearance is postulated to represent an early, active lesion [10, 11]. With extensive serial sectioning, some of these cases ultimately are classified as tip lesions [12]. We speculate that the cellular lesion may be part of a continuum of that category of FSGS lesions.

Tip lesions, that is, glomerulosclerosis involving the proximal tubular pole of the glomerulus, and not extending past the mid-region, were proposed to represent an early lesion with good prognosis, although later follow-up has revealed a less than benign prognosis in some patients [12, 16, 19]. Review of autopsy cases of children with MCD who died of overwhelming infection showed rare tip lesions, suggesting that the lesion may not be disease specific [20]. Tip lesions can occur at any age. Patients typically present with nephrotic syndrome. In one recent series, patients with the tip lesion variant of FSGS were compared to FSGS NOS and MCD patients. After treatment with steroids alone in most of the tip lesion patients, with added cytotoxic therapy in about a third, over half had achieved remission, whereas only one of 29 in whom follow-up was available progressed to ESRD [12]. Thus, the tip variant appears to have a better prognosis than FSGS NOS and to be more similar to MCD.

Predominantly hilar lesions, with glomerulosclerosis located at the vascular pole with associated hyaline, have been proposed to represent a response to reduced renal mass and may also be associated with secondary FSGS seen with arteriolonephrosclerosis [16].

Some investigators have questioned the prognostic value of biopsy morphology in FSGS. The clinical trials of FSGS enrolled steroid-resistant patients with biopsy-proven FSGS and assessed response to treatment with cyclosporine, in addition to usual ACEI/ARB. Analysis of patient outcomes confirmed worst prognosis in those with collapsing FSGS and best in the tip variant group, with intermediate outcome in FSGS NOS patients [16].

Secondary and Other Variant Forms of Focal Segmental Glomerulosclerosis

C1q Nephropathy

C1q nephropathy presents most commonly as nephrotic syndrome, with variable morphologic lesions, which may include segmental sclerosis or proliferation, with abnormal complement C1q-dominant deposits in the mesangium and occasional subendothelial area [51, 52]. These patients are generally adolescent and steroid resistant. About a third of those with sclerosis at time of biopsy developed end-stage kidney disease. The median time to end stage from biopsy was 81 months in one recent series of 19 patients. In contrast, complete remission of the nephrotic syndrome occurred in 77 % of those with a minimal change-like lesion. Renal disease remained stable in just over half of those with proliferative lesions in the biopsy [53]. Clinical or morphological findings of lupus nephritis are absent [e.g., no reticular aggregates, no clinical evidence of systemic lupus erythematosus (SLE)].

By light microscopy, there may be no lesions or focal segmental sclerosis or focal mesangial or even endocapillary proliferation. Tubular atrophy and interstitial fibrosis are proportional to sclerosis.

Immunofluorescence microscopy may show staining with IgG, IgM, and C3 but by definition has prominent C1q. The pattern is most often mesangial, but capillary loop staining may also be present.

Electron microscopy shows electron-dense mesangial deposits, with occasional extension to subendothelial areas, and variable foot process effacement. In cases without proliferative lesions, foot process effacement was quite extensive, and these patients typically responded to steroids. There are no reticular aggregates.

The etiology and pathogenesis are unknown. C1q nephropathy appears to be heterogeneous, and those without proliferation may be viewed as an unusual lesion related to MCD-FSGS, whereas those patients with proliferative lesions behave more like immune complex disease. The deposition of C1q could suggest an abnormality of complement regulation.

Secondary Focal Segmental Glomerulosclerosis

Many insults to the kidney may result in secondary FSGS, either as the sole manifestation of injury or superimposed on other renal disease manifestations [6, 10]. The lesion of FSGS may be seen in association with, for example, substantial loss of nephron mass or very low birth weight, diabetes, obesity, HIV infection, interferon therapy, anabolic steroids, or heroin abuse [54, 57]. Hilar-type sclerosis may often manifest with these secondary forms of FSGS (see above). Secondary sclerosis also occurs in the chronic stage of many immune complex or proliferative diseases [58]. In some of these settings, the morphologic appearance of sclerosis can indicate the nature of the initial insult: Obesity-associated FSGS shows mild mesangial expansion, GBM thickening, subtotal foot process effacement, and marked glomerulomegaly [56]. The course is more indolent than for idiopathic FSGS with less frequent nephrotic syndrome. When segmental sclerosis is secondary to reflux nephropathy, there is frequently prominent periglomerular fibrosis and thickening of Bowman's capsule and patchy interstitial scarring, in addition to the heterogeneous glomerulosclerosis [58]. Segmental sclerosis may also be seen with arterionephrosclerosis, associated with hypertension (see Chap. 10) [58]. Focal segmental glomerulosclerosis associated with heroin use does not show pathognomonic features, although global glomerulosclerosis, epithelial cell changes, interstitial fibrosis, and tubular injury tend to be more prominent than in idiopathic cases of FSGS. In HIV-associated nephropathy, the tubules show severe injury, including cystic dilatation, out of proportion to the focal segmental glomerular scarring. Glomeruli show tuft collapse, and reticular aggregates are numerous in endothelial cells. FSGS can also develop in association with decreased renal mass, whether acquired or present at birth, the latter often associated with low birth weight in either term or very premature babies [55].

In summary, FSGS is a lesion with many manifestations and diverse mechanisms, including genetic, circulating factors, and environmental. Classification based on increasing understanding of these varying forms will likely lead to improved prognosis and, it is hoped, to treatments.

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Part III

Glomerular Disease with Nephritic Syndrome Presentations

Postinfectious Glomerulonephritis

5

Introduction/Clinical Setting

Acute postinfectious glomerulonephritis is a kidney disease that follows an infection. The most common and best-understood form of acute postinfectious glomerulonephritis is poststreptococcal glomerulonephritis, but other infectious organisms may also be the cause of this disorder.

A large number of bacterial and mycotic infections may be followed by acute glomerulonephritis. Especially after persistent extrarenal bacterial infections such as bacterial endocarditis, deep abscesses, cellulitis, and infected atrioventricular shunts in hydrocephalus or some chronic viral infections including some cases of Hepatitis B or C, proliferative and inflammatory patterns of glomerulonephritis can occur and these broadly can be categorized as infection-related glomerulonephritis. Acute postinfectious glomerulonephritis can be considered as a distinct subset within this group, characterized clinically by a preceding bacterial infection that is usually of streptococcal or staphylococcal type, a commonly self-limited course, and a typical constellation of pathologic findings. Most cases of acute poststreptococcal glomerulonephritis are caused by group A streptococci and follow upper airway infections, such as pharyngitis or tonsillitis, by 14–21 days [1]. Especially in warmer climates acute glomerulonephritis also may follow skin infections. In recent decades the number of patients with poststreptococcal glomerulonephritis has decreased considerably in the United States and Europe. In developing countries the incidence of poststreptococcal glomerulonephritis has remained high with an annual incidence that has been estimated to be in a range of 9.5–28.5 cases per 100,000 individuals [2–7]. In addition to the declining incidence, the number of biopsies demonstrative of acute postinfectious glomerulonephritis has decreased. In part this is due to the reluctance of clinicians to obtain a biopsy in a patient with classical or typical symptoms of acute postinfectious glomerulonephritis since the typical clinicopathologic features have become so well established, particularly in uncomplicated cases involving children, and because resolution of this disease commonly occurs within weeks of first presentation.

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The disease occurs most commonly in children between the ages of 2 and 12 years and young adults and more often in males than in females [2, 3, 8, 9]. Recently it has been appreciated that adult diabetics and the elderly also have increased risk for this disorder [5]. Clinically the disease is characterized by an acute nephritic syndrome (acute glomerulonephritis). The symptoms include an abrupt onset of macroscopic hematuria, oliguria, acute renal failure manifested by a sudden decrease in the glomerular filtration rate, and fluid retention manifested by edema and hypertension [8]. Edema probably results from renal sodium retention caused by the sudden decrease in the glomerular filtration rate, rather than occurring as a consequence of hypoalbuminemia as in the nephrotic syndrome [8, 9]. Milder clinical presentations, such as asymptomatic microscopic hematuria, also can occur. Laboratory studies are directed at the urine sediment, which reveals red blood cells (which may be dysmorphic) with or without red blood cell casts, and with proteinuria; at measures of impaired renal function; and at measures that establish evidence of an immune response to streptococcal or viral antigens. In cases of streptococcal infection, elevated titers of antistreptolysin O antibodies or other streptococcal antigens (streptozyme assay) often suggest or confirm the diagnosis, but these can be falsely negative in a minority of affected patients [8]. In most cases, complement levels (either C3 or CH50 as a measure of the total complement activity) are low [5]. However, many cases demonstrate concomitantly normal C4 levels, suggesting that complement activation in these cases occurs primarily via the alternative pathway.

Pathologic Findings

The classic pathologic alterations in glomeruli include an exudative component (a term which refers to an influx of neutrophils) and hypercellularity (due to the influx of leukocytes—both neutrophils and monocytes—and concurrent proliferation of intrinsic renal cells), all of which is readily identifiable by light microscopy. In conjunction with the histologic findings, there are accumulations of discrete subepithelial immune deposits in glomerular capillary walls that have a highly specific ultrastructural appearance as “humps” [7, 10, 11]. In viral, parasitic, or treponemal infections, membranous or membranoproliferative patterns of glomerulonephritis are seen more often.

Light Microscopy

In acute postinfectious glomerulonephritis usually all glomeruli are affected (“diffuse”) and generally all to a similar extent. The glomerular capillaries are dilated and hypercellular, without necrosis. In many cases there is an increase of endothelial and/or mesangial cells, and the endothelial cells in particular appear swollen (a constellation of findings termed “endocapillary proliferation”). Glomerular capillaries typically demonstrate a prominent influx of inflammatory cells, especially neutrophils and monocytes (Fig. 5.1). Because of the large numbers of neutrophils, the descriptive term *exudative glomerulonephritis* has been applied to these lesions.

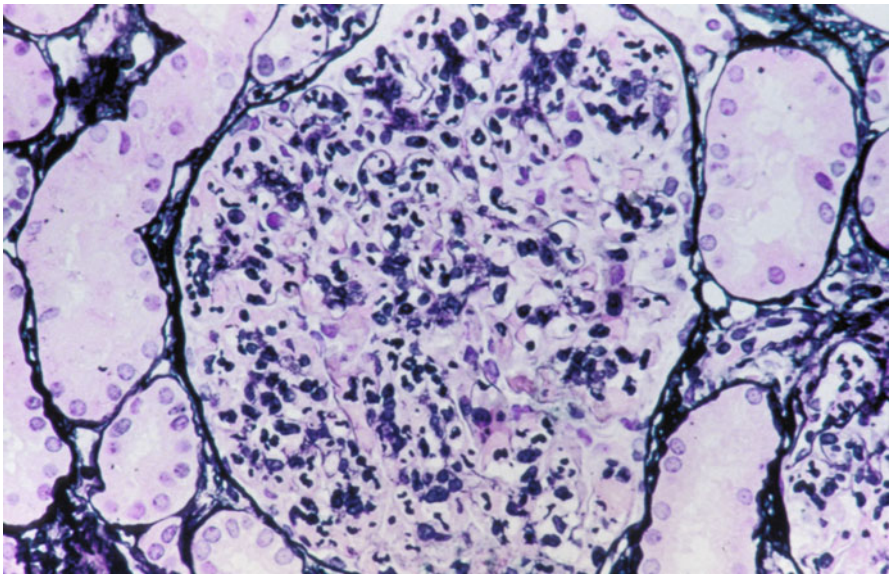

Fig. 5.1 Diffusely hypercellular glomerulus in acute postinfectious glomerulonephritis with massive influx of neutrophils (Jones silver stain)

Eosinophils and lymphocytes may be present, but they are usually scarce. The glomerular capillary walls are sometimes slightly thickened. In some biopsies, small nodules on the epithelial side of the glomerular capillary walls may be seen, when using high magnification in conjunction with trichrome or toluidine blue stains. These correspond to the subepithelial deposits ("humps") that are seen by electron microscopy (see below). In severe cases, extracapillary proliferation with formation of crescents and/or adhesions (synechiae) can be seen. Erythrocytes and sometimes neutrophils may be present in Bowman's space. In renal biopsies taken a few weeks after the appearance of clinical symptoms, the picture is often less inflammatory. The number of neutrophils will have decreased, the swelling of endothelial cells will have subsided, and the number of humps will have decreased. In this stage diffuse mesangial hypercellularity may still be seen, and this can remain for several months. Evidence of resolving or largely healed postinfectious glomerulonephritis may be overlooked or misdiagnosed as a mesangial proliferative glomerulonephritis resulting from a noninfectious etiology [12]. This supports the contention that postinfectious glomerulonephritis occurs more frequently than is clinically appreciated [13].

Tubular changes are less prominent than glomerular alterations. When proteinuria occurs, reabsorption droplets can be seen in the proximal tubular epithelial cells. Erythrocytes and sometimes neutrophils may be present in the lumen of some tubules. The extent of interstitial damage varies but is usually not extensive unless due to some other cause. Interstitial edema may be present, and mixed interstitial inflammatory cell infiltrates are common. Arteries and arterioles are usually unaffected.

Due to the combination of expansion of glomerular lobules, hypercellularity of the glomerular capillaries, and focal thickening of the capillary walls, postinfectious glomerulonephritis may be difficult to distinguish from membranoproliferative glomerulonephritis by light microscopy. Immunofluorescence and electron microscopy usually allow the distinction between the two diseases to be made. Other important considerations in the differential diagnosis include lupus nephritis, which usually can be distinguished on clinical grounds and by the constellation of associated immunofluorescence and electron microscopic findings. Some cases of acute glomerulonephritis morphologically indistinguishable from postinfectious glomerulonephritis but with an atypical, non-resolving clinical course have proven to be cases of the recently recognized entity C3 glomerulopathy [14] or, in cases of recurrent hematuria, IgA nephropathy (see Chaps. 3 and 6).

Immunofluorescence Microscopy

Immunofluorescence studies in biopsies taken during the first 2–3 weeks of the diseases most often show diffuse, irregular, coarse granular deposits of immunoglobulin G (IgG) and C3 along the glomerular capillary walls (Fig. 5.2). The C3 deposits resolve later than immunoglobulin, and so biopsies obtained late in the disease course may show predominantly or only C3 by immunofluorescence. In some cases IgM may be present, while C1q is most often absent. Based on the distribution pattern of the immune deposits, it has been proposed that postinfectious glomerulonephritis be divided into several histologic subtypes, but these are not clearly related to clinical behavior or prognosis [15, 16]. IgA-dominant postinfectious glomerulonephritis has been identified as a form of this disorder with classic ultrastructural findings (see below) but with deposits of IgA as the sole or

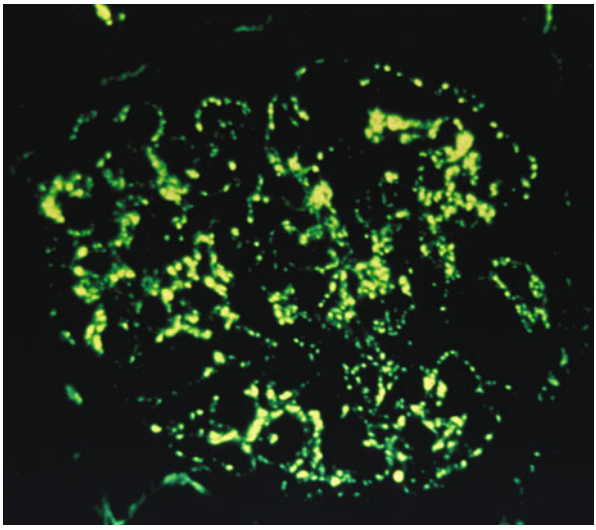

Fig.5.2 Immunofluorescence showing distribution of IgG in a "punctate" pattern in acute postinfectious glomerulonephritis

predominant immune reactant deposited [6, 17, 18]. These cases are usually associated with staphylococcal infection. Diabetes and older age have been identified as major risk factors for IgA-dominant forms of postinfectious glomerulonephritis [5].

Electron Microscopy

In acute postinfectious glomerulonephritis, swelling of glomerular endothelial cells and increased mesangial cellularity are often seen by electron microscopy. The glomerular basement membranes are usually of normal contour and thickness, although locally some thickening may occur. The glomerular basement membranes may also contain electron-lucent areas, possibly representing "resolving" deposits. The most consistent and classic change, however, is the presence of glomerular subepithelial cone-shaped electron-dense deposits, referred to as "humps." These are especially numerous during the first weeks of acute glomerulonephritis and their number decreases thereafter (Fig. 5.3). The humps are sometimes separated from the lamina densa by a lucent zone, which is in continuity with the lamina rara externa. Podocyte foot processes overlying the humps are often obliterated, with condensation of cytoplasmic microfilaments.

Early in the evolution of disease, the immune deposits may form in the subendothelial aspect of glomerular capillary walls and after undergoing some process of dissociation as the disease evolves reform at the subepithelial surface of the glomerular capillary walls. These early subendothelial deposits are uncommonly visualized in electron micrographs of renal biopsies, but in a minority of cases, these may be prominent and impart a predominantly membranoproliferative pattern of injury. Such cases require careful clinicopathologic correlation to distinguish them from other diagnostic entities, principally membranoproliferative glomerulonephritis of noninfectious origin, lupus nephritis, and rarely IgA nephropathy. In addition, some small irregular electron-dense deposits may be seen in the lamina densa of glomerular basement membranes and the mesangium.

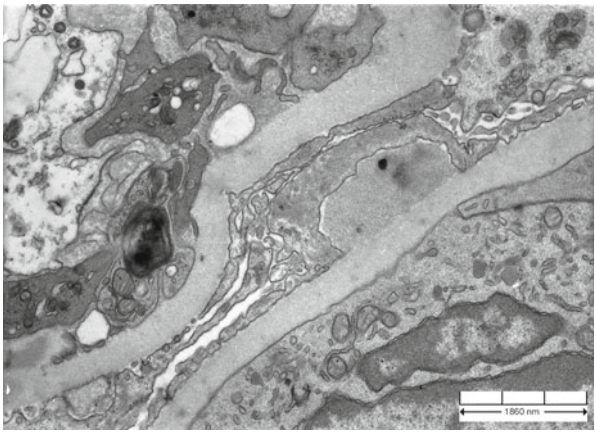

Fig. 5.3 Electron microscopy showing large subepithelial electron-dense deposits ("humps") and obliteration of overlying podocyte foot processes in acute postinfectious glomerulonephritis. Note the absence of glomerular basement membrane (GBM) thickenings and spikes

Etiology/Pathogenesis

The association between acute glomerulonephritis and preceding β-hemolytic streptococcal infections has been known for over 70 years [19]. Subsequently it became appreciated that this association was only limited to certain streptococcal strains, deemed "nephritogenic," and efforts continue to this day to identify host immune responses and unique characteristics of pathogenic organisms underlying this distinctive type of glomerulonephritis.

Many streptococcal antigens have been proposed as the essential mediator of poststreptococcal glomerulonephritis; current evidence is strongest that streptococcal pyogenic exotoxin B (SpeB) fulfills this role. This protein can directly activate complement and is commonly secreted by nephritogenic strains of streptococci [20]. Importantly, antibody titers to SpeB correspond to disease activity in many cases where these have been measured, and SpeB has been directly localized to the characteristic hump-like immune deposits seen by electron microscopy. However, evidence of SpeB involvement is not uniform in all cases of postinfectious glomerulonephritis nor is involvement of SpeB established in cases of postinfectious glomerulonephritis due to other organisms (e.g., staphylococci) and/or mediated by an IgA humoral response. Laboratory assays of antibody responses to SpeB are not generally available for use in clinical practice. Antigenic mechanisms underlying involved in the initiation of IgA-dominant postinfectious glomerulonephritis are particularly obscure.

Postinfectious glomerulonephritis is most essentially a disease caused by immune complex deposition in glomerular capillary walls. The complexes are formed in situ in the glomeruli and are the result of binding of circulating immunoglobulin (typically IgG but in some cases IgA as discussed above) to an antigen deposited in the glomerular capillary wall, with subsequent activation of complement. These immune deposits are not the result of deposition of circulating preformed immune complexes as was once thought. It is not certain whether local complement activation occurs by interactions with the immune complexes via the classical pathway or whether complement may be activated directly by deposited antigens, either through the mannose-binding lectin pathway or the alternate pathway. This latter possibility is suggested by the clinical observation of prominent deposition of C3 and late components of the complement pathway, but not necessarily C4 or other components specific to classical pathway activation. It is further supported by the observation that deposition of C3 may dominate the pathologic presentation of this disease, with IgG having limited extent and duration in many cases. Leukocyte recruitment is likely the result of complement activation with release of the anaphylatoxins C3a and C5a and as a result of engagement of immunoglobulin receptors (Fc receptors) on the surface of leukocytes. The release of inflammatory mediators by influxing leukocytes leads to many of the presenting nephritic features in patients as well as the features of glomerular endocapillary proliferation typically seen in renal biopsies demonstrative of postinfectious glomerulonephritis.

Clinicopathologic Correlations

The prognosis of postinfectious glomerulonephritis with respect to renal function is generally good. Over 95 % of pediatric patients recover spontaneously with return to normal renal function within 3–4 weeks [7, 8]. Most of those who recover quickly have no long-term sequelae, but some outcome data indicate a proportion of such patients will have abnormalities, usually subclinical, when measures of renal function are obtained [3, 6]. Treatment in most cases is supportive and usually directed towards correcting physiologic disturbances (e.g., volume overload) consequent to the glomerulonephritis. Adult patients fare less well, often because of comorbid conditions. Diabetes in particular has been shown to be a risk factor for progression to chronic kidney disease following an episode of postinfectious glomerulonephritis. The presence of proteinuria is prognostically a bad sign as well. The reported incidence of chronic renal insufficiency following an episode of postinfectious glomerulonephritis in adults ranges from 0 to 20 %.

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IgA Nephropathy and IgA Vasculitis (Henoch-Schönlein Purpura)

6

Introduction/Clinical Setting

Immunoglobulin A (IgA) nephropathy was first described by the pathologist Jean Berger [1, 2] and thus is sometimes called Berger's disease. IgA nephropathy is defined by the presence of IgA-dominant or codominant mesangial immunoglobulin deposits (Fig. 6.1) [3, 4]. Lupus glomerulonephritis, which may have IgA-dominant or codominant deposits, is excluded from this diagnostic category. IgA nephropathy also should be distinguished from IgA-dominant postinfectious glomerulonephritis (see Chap. 5) [5]. IgA nephropathy occurs as a primary (idiopathic) disease; as a component of IgA vasculitis (Henoch-Schönlein purpura), secondary to liver disease (especially alcoholic cirrhosis); and associated with a variety of inflammatory diseases including ankylosing spondylitis, psoriasis, Reiter's disease, uveitis, enteritis (e.g., *Yersinia enterocolitica* infection), inflammatory bowel disease, celiac disease, dermatitis herpetiformis, and HIV infection [6–10].

Pathologic Findings

Light Microscopy

IgA nephropathy and IgA vasculitis (Henoch-Schönlein purpura) nephritis can have any of the histologic phenotypes of immune complex-mediated glomerulonephritis other than pure membranous glomerulopathy, including no lesion by light microscopy with immune deposits by immunohistology, mesangioproliferative glomerulonephritis with mesangial but no endocapillary hypercellularity (Figs. 6.2 and 6.3), focal or diffuse proliferative glomerulonephritis with endocapillary hypercellularity (with or without crescents) (Fig. 6.4), overt crescentic glomerulonephritis with 50 % or more crescents, type I membranoproliferative (mesangiocapillary) glomerulonephritis (rare), and focal or diffuse sclerosing glomerulonephritis [4, 7–10].

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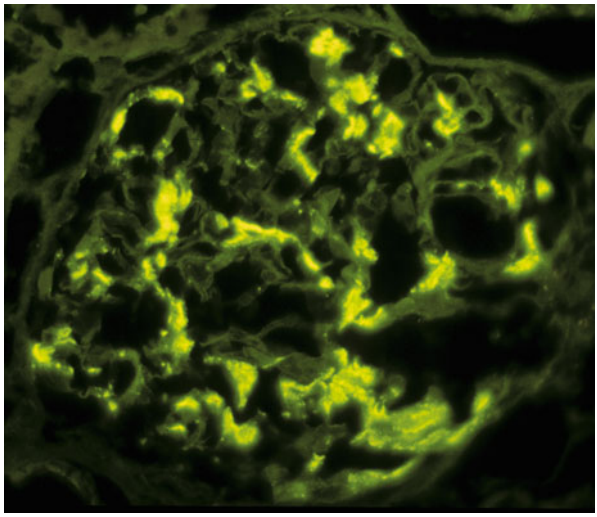

Fig.6.1 Immunofluorescence microscopy demonstrating glomerular mesangial staining for immunoglobulin A (IgA) in a patient with IgA nephropathy

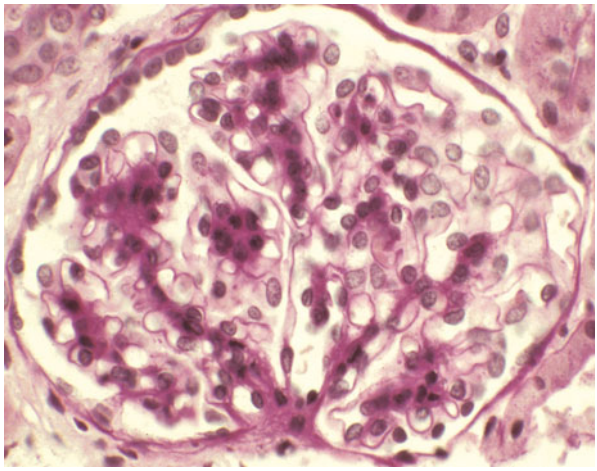

Fig. 6.2 Glomerulus from a patient with IgA nephropathy showing mild segmental mesangial hypercellularity in the upper left quadrant of the glomerulus [periodic acid-Schiff (PAS) stain]

A variety of classification systems have been used to categorize the light microscopic phenotypes of IgA nephropathy, such as those proposed by Kurt Lee et al. [11] and by Mark Haas [12] (Table 6.1). Another approach is to use the same descriptive terms (but not the numerical class designations) that are in the lupus classification system to categorize IgA nephropathy as well as other forms of immune complex glomerulonephritis. This terminology works as well for IgA nephropathy as it does for lupus and also has the advantage of not requiring knowledge of multiple different classification systems. Recently, a novel classification approach (the Oxford Classification System) has been developed [4]. This will be discussed later in this chapter.

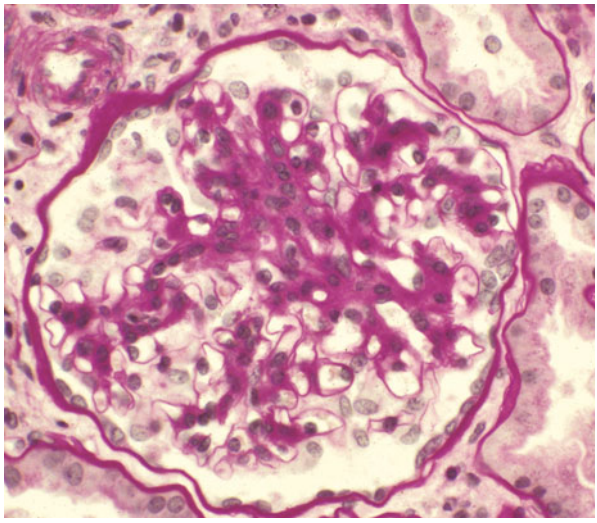

Fig. 6.3 Glomerulus from a patient with IgA nephropathy showing moderate segmental mesangial hypercellularity and increased mesangial matrix in the upper portion of the tuft (PAS stain)

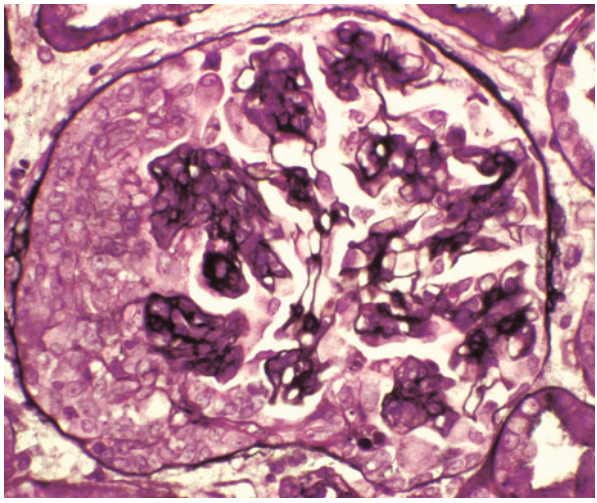

Fig. 6.4 Glomerulus from a patient with Henoch-Schönlein purpura showing a proliferative glomerulonephritis with endocapillary hypercellularity adjacent to a cellular crescent on the left of the tuft (Jones silver stain)

In patients whose renal biopsy specimens are referred to the University of North Carolina for evaluation, crescents are observed in about a third of patients with IgA nephropathy and two thirds of patients with IgA vasculitis nephritis (Henoch-Schönlein purpura) [13]. However, overt crescentic glomerulonephritis with 50 % more of glomeruli with crescents is uncommon (<5 % in IgA nephropathy and <10 % in IgA vasculitis nephritis). When substantial crescent formation is present, especially with conspicuous fibrinoid necrosis, the possibility of concurrent anti-neutrophil cytoplasmic antibody (ANCA) disease should be considered [14].

Table 6.1 Three different approaches to the histologic classification of IgA nephropathy

Lee system	Haas system	Lupus terminology
I: Focal mesangioproliferative	I: Focal mesangioproliferative	No lesion by light microscopy (I)
II: Moderate focal proliferative	II. Focal proliferative	Mesangioproliferative (II)
III: Mild diffuse proliferative	III: Focal sclerosing	Focal proliferative (III)
IV: Moderate diffuse proliferative	IV: Diffuse proliferative	Focal sclerosing (III C)
V: Severe diffuse proliferative	V: Chronic sclerosing	Diffuse proliferative (IV)
		Chronic sclerosing (VI)

Between 5 and 10 % of specimens with IgA nephropathy identified by immunohistology have focal segmental glomerulosclerosis as seen on light microscopy that is indistinguishable from idiopathic focal segmental glomerulosclerosis [12]. Most instances of this pattern of injury probably are glomerular scarring caused by earlier active focal segmental glomerular inflammation rather than another form of secondary focal segmental glomerulosclerosis (FSGS). However, at least some focal segmental glomerular sclerosis in IgA nephropathy may be caused by compensatory hemodynamic changes following loss of nephrons or through podocyte damage secondary to mediators released from activated mesangial cells [15, 16].

Immunofluorescence Microscopy

The sine qua non for a diagnosis of IgA nephropathy is immunohistologic detection of dominant or codominant staining for IgA in the glomerular mesangium (Fig. 6.1). A caveat to this is that the staining for IgA should at least be 1+ on a scale of 0–4+ or 0–3+. Trace amounts of IgA are not definitive evidence for IgA nephropathy [4]. The IgA is predominantly IgA1 rather than IgA2 [7, 17]. Capillary wall staining is observed in about a third of patients and is more common in IgA vasculitis (Henoch-Schönlein purpura) nephritis [10]. The mesangial immune deposits of IgA nephropathy stop abruptly at the glomerular hilum and are not observed along tubular basement membranes. Rare patients have IgA nephropathy concurrent with membranous glomerulopathy, and thus, their specimens show granular capillary wall IgG staining and mesangial IgA-dominant staining [18, 19].

Staining for IgA frequently is accompanied by staining for other immunoglobulins and complement components [3]. Staining for IgG and IgM often is present but at lower intensity compared to IgA. A very distinctive feature of IgA nephropathy compared to other immune complex diseases is the predominance of staining for lambda over kappa light chains in many specimens. C3 staining is almost always present and usually relatively bright. However, staining for C1q is uncommon and when present is typically of low intensity. The presence of substantial C1q should raise the possibility of lupus nephritis with conspicuous IgA deposition. This suspicion would be supported further by finding endothelial tubuloreticular inclusions by electron microscopy and antinuclear antibodies serologically. As in other forms of glomerulonephritis, staining for fibrin is seen at sites of

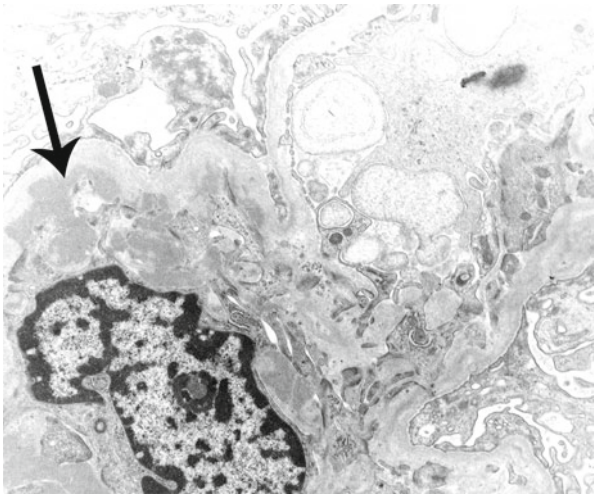

Fig. 6.5 Electron micrograph of a glomerulus from a patient with IgA nephropathy showing a moderate amount of electron-dense deposits (*arrow*) within the mesangium. The mesangium is on the *left* of the image and a portion of the capillary loop is on the *right*

necrosis and crescent formation. Depending in part on what reagent antibody is used, the immune deposits occasionally stain for fibrin, especially in patients with IgA vasculitis (Henoch-Schönlein purpura) nephritis [10]. The IgA deposits stain predominantly for IgA1 rather than IgA2 and also stain for secretory component in about a third of specimens [17].

Glomerular diseases other than IgA nephropathy that can have IgA-dominant or IgA-codominant deposits include lupus glomerulonephritis, rare examples of IgA-dominant anti-GBM disease [20, 21], and an IgA-dominant form of postinfectious glomerulonephritis that is usually caused by staphylococcal infections [5].

Electron Microscopy

The typical ultrastructural finding is immune complex-type electron-dense deposits in the mesangium (Figs. 6.5 and 6.6). Dense deposits most often are found immediately beneath the paramesangial glomerular basement membrane. The amount of deposits varies substantially, with occasional specimens having massive replacement of the matrix by the dense material (Fig. 6.6). Rare specimens that have well-defined IgA deposits by immunofluorescence microscopy do not have detectable mesangial dense deposits, which does not rule out a diagnosis of IgA nephropathy because the immunohistology is the defining feature. Capillary wall subepithelial, subendothelial, and intramembranous deposits are identified in approximately a quarter to a third of specimens with IgA nephropathy [3] and are more frequent in patients with IgA vasculitis (Henoch-Schönlein purpura) nephritis [10]. Capillary wall deposits are least frequent in histologically mild disease and most frequent in histologically severe disease, especially when crescents are present.

Focal areas of glomerular basement membrane thinning are observed in approximately a third of specimens with IgA nephropathy [22]. This structural abnormality

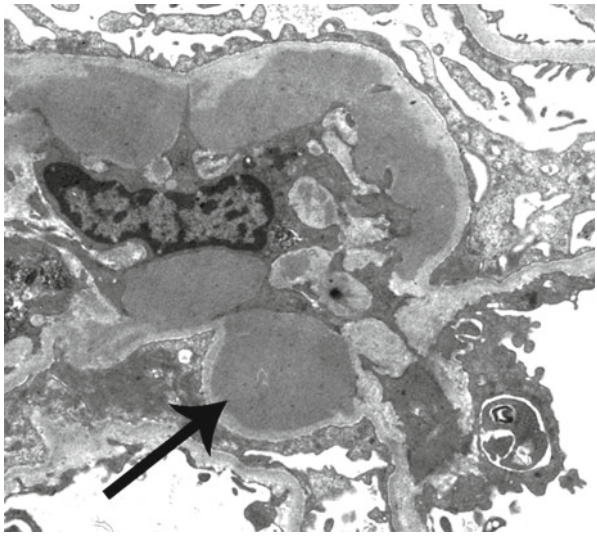

Fig. 6.6 Electron micrograph of a glomerulus from a patient with IgA nephropathy showing massive electron-dense deposits (*arrow*) within the mesangium. The mesangium is on the *left* of the image and a portion of the capillary loop is on the *right*

may contribute to the hematuria. Focal or diffuse podocyte foot process effacement often is present, especially in patients with nephrotic range proteinuria. Foot process effacement is particularly prominent in patients who have the syndrome of histologically mild IgA nephropathy with minimal change glomerulopathy-like features clinically [23]. Mesangial matrix expansion and mesangial hypercellularity parallel the mesangial changes seen by light microscopy.

Etiology/Pathogenesis

Multiple pathogenic factors and multi-hit combinations of factors probably contribute to the development of IgA nephropathy and IgA vasculitis [6, 7, 24, 25]. A frequent if not ubiquitous pathogenic factor is abnormal structure and function of IgA molecules resulting from aberrant glycosylation of IgA1 hinge regions [7]. This abnormality could result in mesangial IgA deposition by a variety of mechanisms including reduced clearance from the circulation because of lack of receptor engagement by the abnormal IgA, increased aggregation of IgA in the circulation resulting in mesangial trapping, development of immune complex-forming IgG autoantibodies directed against the abnormal IgA, increased affinity of the abnormal IgA for mesangial matrix, or combinations of these processes. Other factors could induce or act synergistically with this glycosylation abnormality. For example, a mucosal infection could induce excessive production of aberrant IgA1 in patients who are genetically determined to make abnormally glycosylated IgA1. Alternatively, mucosal infectious pathogens could release enzymes (e.g., neuraminidase, sialidase) that induce nephritogenic alterations in IgA1 glycosylation. These effects by infections could explain the close association between the onset and exacerbations of IgA nephropathy with respiratory and gastrointestinal tract infections.

Clinicopathologic Correlations

IgA nephropathy is one of the most common forms of glomerulonephritis in the world [6, 7]. The prevalence of IgA nephropathy varies among different racial groups, with the highest prevalence among Asians and Native Americans, intermediate prevalence among Caucasians, and lowest prevalence among individuals of African descent [26]. IgA nephropathy and IgA vasculitis are twice as common in males as females. On average, IgA vasculitis nephritis occurs at an earlier age than IgA nephropathy [9]. The onset and diagnosis of IgA nephropathy usually is in late childhood or early adulthood, whereas IgA vasculitis usually occurs in children younger than 10 years of age. IgA nephropathy can manifest any of the signs and symptoms caused by glomerular disease. The most common initial manifestations are asymptomatic microscopic hematuria or intermittent gross hematuria or both. Approximately 10 % of patients present with nephrotic syndrome and approximately 10 % have renal failure at initial presentation. Rare patients present with rapidly progressive glomerulonephritis or advanced chronic renal failure [7, 8]. Approximately 10–15 % of patients reach end-stage renal disease within 10 years of diagnosis and approximately 25–35 % within 20 years [7–10]. IgA nephropathy has a recurrence rate of greater than 50 % in renal transplants. Recurrent IgA nephropathy causes some graft dysfunction in approximately 15 % of patients after 5 years and graft loss in approximately 5 % after 5 years [27].

The glomerulonephritis of IgA vasculitis is not pathologically distinguishable from IgA nephropathy, although, as noted earlier, on average, IgA vasculitis nephritis tends to be more severe with a higher frequency of crescent formation [10]. In addition to nephritis, common clinical manifestations of IgA vasculitis include arthralgias, purpura caused by leukocytoclastic angiitis of dermal capillaries, and abdominal pain caused by involvement of small vessels in the gut and other abdominal viscera [28]. The presence of IgA deposits without vasculitis in systemic vessels is not adequate for a diagnosis of IgA vasculitis because some patients with IgA nephropathy have no evidence for systemic IgA deposits in extrarenal vessels, such as dermal venules. Patients with IgA vasculitis usually have only one episode of purpura that resolves completely. Persistent and progressive nephritis is the most important long-term complication and results in end-stage disease in 5–20 % of patients after 20 years [9].

The outcome of IgA nephropathy cannot be accurately predicted on the basis of clinical features; however, as with other glomerular diseases, there are trends toward worse outcomes with more severe renal insufficiency and greater proteinuria at presentation [6–8]. Although earlier pathologic classification systems had identified a correlation between more severe glomerular and tubulointerstitial lesions with worse outcome, this was recently refined by a Working Group of the International IgA Nephropathy Network and the Renal Pathology Society [4, 29, 30]. The resultant Oxford Classification System is based on four pathological variables that were found to have independent value in predicting renal outcome even after taking into account all clinical indicators at the time of biopsy as well as during follow-up: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental

glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T). MEST scores are determined based on clearly defined criteria and can be used to predict outcome. Multiple subsequent clinicopathologic studies have validated the utility of this system [31–34].

The treatment for IgA nephropathy and IgA vasculitis remains controversial [6–9]. There is general agreement that angiotensin-converting enzyme inhibitors (ACEI) are beneficial. Fish oil supplements with high concentrations of omega-3 fatty acids have been advocated by some investigators, but the evidence of their benefit is not conclusive. As with other forms of glomerulonephritis, corticosteroid treatment may be helpful, especially when there is substantial active glomerular inflammation or a syndrome of concurrent minimal change-like glomerulopathy. Treatment with cytotoxic agents generally has been reserved for patients with severe crescentic IgA nephropathy or IgA vasculitis [7]. The recently released KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for Glomerulonephritis makes specific recommendation for the management of IgA nephropathy and IgA vasculitis [35]. The guideline recommends long-term ACEI or ARB treatment when proteinuria is >1 g/day and suggests ACEI or angiotensin receptor blocker (ARB) treatment if proteinuria is between 0.5 and 1 g/day (in children, between 0.5 and 1 g/day/1.73 m^2). The KDIGO guideline suggests that patients with persistent proteinuria >1 g/day (in spite of 3–6 months of supportive care with ACEI or ARBs and blood pressure control) and GFR 450 ml/min per 1.73 m^2 receive a 6-month course of corticosteroid therapy. The KDIGO guideline supports the use of immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine) combined with corticosteroids for crescentic IgA nephropathy (with >50 % crescents). The KDIGO recommendations for IgA vasculitis nephritis are similar.

The rapidly emerging knowledge of the pathogenesis of IgA nephropathy and IgA vasculitis hopefully will lead to more effective treatment strategies that are targeted at the specific causes [6, 7].

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Thin Basement Membranes and Alport Syndrome

7

Alport Syndrome

Introduction/Clinical Setting

Classical Alport syndrome is an X-linked disease and is the most common form of Alport syndrome (90 % of patients), with an overall incidence of Alport syndrome in the United States of 1:5,000 to 1:10,000 [1–4]. Hematuria develops in early childhood in all male patients with X-linked Alport and in 95 % of female carriers of X-linked Alport and in nearly all autosomal recessive carriers. Affected males with X-linked Alport develop progressive hearing loss in one third and ocular defects and progression to renal failure in 30–40 % by early adulthood with more than 90 % with end-stage renal disease by age 40. Eye defects develop in 20–30 % of males with X-linked Alport, among which anterior lenticonus is the most common lesion. A large study of heterozygous female carriers of X-linked Alport syndrome demonstrated development of proteinuria in about 75 % and 30–40 % with end-stage renal disease after age 60.

Alport syndrome is due to mutations of collagen type IV [3–6]. The organs affected reflect the sites where collagen IV is crucial for function. Collagen type IV is made up of heterotrimers of alpha chains. These six alpha chains are encoded by genes arranged in pairs on three different chromosomes: *COL4A1* and *COL4A2* are on chromosome 13, *COL4A3* and *COL4A4* are on chromosome 2, and *COL4A5* and *COL4A6* are on the X chromosome. The mutation in the classic form of Alport occurs in the α5 (IV) collagen chain (*COL4A5*). The autosomal recessive form accounts for most of the remaining patients and is due to mutations in both alleles of α3 or α4 type IV collagen genes (*COL4A3* or *COL4A4*). Rare cases of autosomal dominant Alport due to heterozygous mutations in *COL4A3* or *COL4A4* also occur, with a highly variable clinical course and reduced penetrance [7]. Alport syndrome and coexisting diffuse leiomyomatosis are linked to large gene deletions that span the adjacent 5′ ends of the adjacent *COL4A5* and *COL4A6* genes [5].

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Pathologic Findings

Light Microscopy

There are no significant light microscopic abnormalities early in the disease [1]. At later stages, glomerulosclerosis, interstitial fibrosis, and prominent interstitial foam cells, nonspecific and just indicative of proteinuria, are typical. Glomeruli show varying stages of matrix expansion and sclerosis.

Immunofluorescence Microscopy

Standard immunofluorescence (IF) may show nonspecific trapping of immunoglobulin M (IgM) in the mesangium. Special IF studies for subtypes of type IV collagen on either skin or renal biopsy may be helpful in distinguishing between causes of thin glomerular basement membrane (GBM), which may be the only lesion in early Alport, the carrier state for X-linked Alport, or the so-called benign familial hematuria (see below) [3, 5, 8–11].

When any one of the three alpha chains, α3, α4, or α5, is mutated, the normal collagen IV (α3, 4, 5) heterotrimer cannot form. In kidney biopsies, about 70–80 % of males with X-linked Alport, where α5 is mutated, thus lack staining of the GBM, distal tubular basement membrane, and Bowman's capsule for α3, α4, and α5 (IV) chains [3, 10, 11]. In autosomal recessive Alport, where α3 or α4 is mutated, the GBMs usually show no immunostaining for α3, α4, or α5, because there is an inability to form the normal α3, α4, or α5 type IV collagen heterotrimer of the GBM. In these autosomal recessive cases, in contrast to X-linked cases, α5 remains normally expressed in Bowman's capsule and distal tubular basement membrane, because the α(1,1,2)/(5,5,6) heterotrimers can still be assembled in these patients. Female heterozygotes for X-linked Alport syndrome frequently show mosaic staining of GBM and distal TBM for α3, α4, and α5 (IV) chains and skin mosaic staining for α5 (IV). Patients with autosomal dominant Alport have not been studied immunohistochemically. Skin biopsies are thus only useful in diagnosis of classic X-linked Alport. In these affected patients, skin biopsy often shows absent staining for α5 type IV collagen. In contrast, α3 and α4 are not normally expressed in the skin, so this approach is not useful for diagnosis of recessive Alport [10, 12].

Of note, some cases with Alport syndrome clinically and by renal biopsy showed apparent normal α5 type IV immunostaining pattern. About 20 % of male classic Alport patients and affected homozygous autosomal recessive Alport patients show faint or even normal immunostaining of the skin or GBM for α5 [3]. This is postulated to reflect a mutation that results in protein that albeit abnormal still expresses the epitope recognized by the available antibodies. Thus, the absence or mosaic staining of α5 type IV in the biopsy is helpful in indicating a basement membrane abnormality, but an apparent normal staining pattern in either skin or kidney does not definitively rule out Alport syndrome [10, 11]. Further, many patients with apparent benign familial hematuria have thin basement membranes and are carriers of autosomal recessive Alport with normal immunostaining (see below).

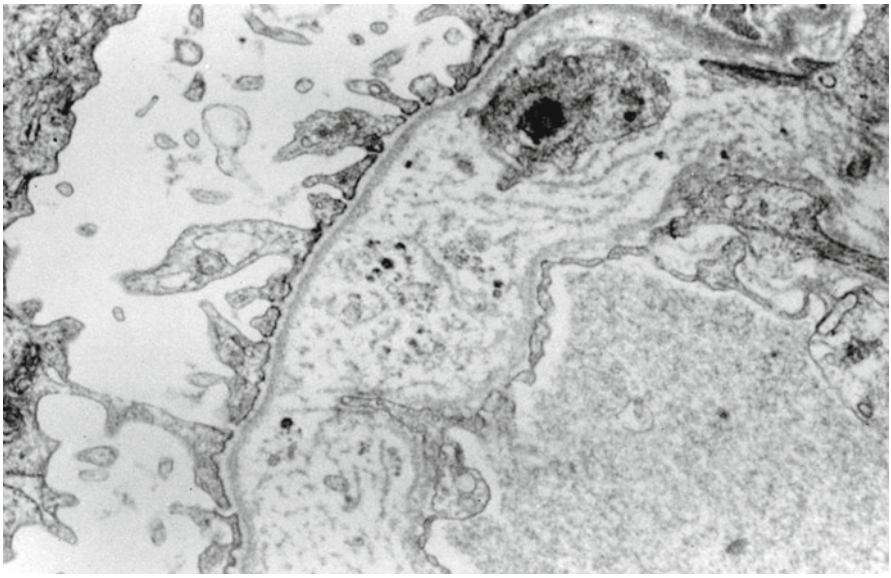

Fig. 7.1 The glomerular basement membrane (GBM) is thickened with "basket-weaving" appearance, diagnostic of Alport syndrome (electron microscopy)

Electron Microscopy

The diagnostic lesion consists of irregular thinned and thickened areas of the GBM with splitting and irregular multilaminated appearance of the lamina densa, the so-called basket weaving (Fig. 7.1) [2]. In between these laminas, granular, mottled material is present. In boys with early-stage classic Alport syndrome, the GBM may show only thinning rather than thickening. Female carriers of the *COL4A5* mutation also show only thin basement membranes, as do carriers of the autosomal recessive form of Alport. The GBM thickness normally increases with age [13–15]. Normal thickness in adults in one series was 373 ± 42 nm in men versus 326 ± 45 nm in women. Glomerular basement thickness <250 nm in adults has been used as a cutoff for diagnosis in many series. Of note, thinning of GBMs should be a diffuse lesion, affecting more than half the extent of the GBM, to consider a diagnosis of thin GBM and its differential. In children, the diagnosis of thin basement membranes must be made with caution, establishing normal age-matched controls within each laboratory. In our laboratory, we found a range of GBM thickness in normal children from approximately 110 nm at age 1 year to 222 ± 14 nm in 7-year-olds.

Etiology/Pathogenesis

Alport syndrome results from the inability to form normal type IV collagen heterotrimers. When α5 (or α3 or α4) is mutated, there is an inability to form the normal heterotrimers of the GBM. The organs involved in Alport syndrome reflect sites

where these type IV collagen chains are normally expressed and are essential for function, namely, the kidney, eye, and ear. In the kidney, heterotrimers of α3, α4, and α5 type IV collagen are expressed in the GBM, whereas α(1, 1, 2)/(5, 5, 6) heterotrimers are expressed in Bowman's capsule and in some tubular basement membranes [5]. At birth, α(1,1,2) heterotrimers are normally present in the immature glomerulus in the GBM, with gradual shift to the mature expression pattern. In the normal adult, α(1,1,2) remains expressed in the mesangium and also in Bowman's capsule. The switch to normal adult α(3,4,5) heterotrimers in the GBM cannot occur in Alport due to mutation in one of these chains.

The mechanism(s) of progressive renal scarring in Alport syndrome is unknown. In a report of seven patients with Alport syndrome, decreased proteinuria occurred in response to angiotensin-converting enzyme inhibitor (ACEI), and after an initial decrease of the glomerular filtration rate (GFR), renal function increased toward the starting levels by 24 months [16]. Larger retrospective analyses have shown benefit of angiotensin inhibition starting at early stages of disease [17]. Female carriers of X-linked Alport syndrome have variable outcomes. About 75 % of female carriers developed proteinuria, a risk factor for their eventual progression to end-stage kidney disease. About 30–40 % developed end-stage kidney disease by age 60, and about a quarter developed deafness [18].

Each Alport kindred reported thus far has presented its own unique mutation. More than 300 mutations in the *COL4A5* gene have been identified [4]. The rate of progression to end stage and deafness in hemizygous affected males are mutation dependent. Large deletions, nonsense mutations, or mutations that changed the reading frame were associated with 90 % risk of end-stage renal disease before age 30 in affected males with X-linked Alport, with only 50 % risk for patients with missense and 70 % risk for those with splice site mutations. Risk for hearing loss before age 30 was 60 % in patients with missense mutations versus 90 % risk for all other mutations [19]. Ultrastructural features do not strictly correlate with type of mutation, in that some patients with major gene rearrangements had no significant lesions, and varying ultrastructural abnormalities were present even within the same kindred [2].

Transplantation in patients with Alport syndrome has shed additional light on the molecular basis for this disease. Some patients with Alport receiving kidney transplants, probably around 5–10 %, develop antibodies to the normal GBM in the transplant. Occurrence of this posttransplant anti-GBM disease appears more frequent in patients with more extensive deletion of the α5 type IV gene [5].

Thin Basement Membranes

Introduction/Clinical Setting

This basement membrane abnormality is characteristic of the so-called benign familial hematuria and shows autosomal dominant or recessive inheritance [13–15]. The clinical manifestation is that of chronic hematuria, either macroscopic or

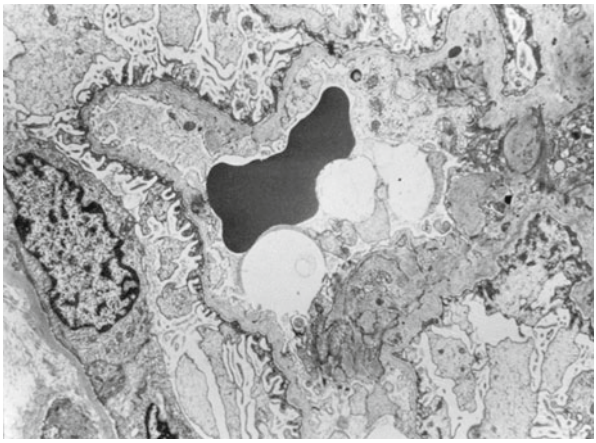

Fig. 7.2 The GBM is diffusely thin in this adult with hematuria. Family history and immunostaining were consistent with thin basement membrane lesion of benign familial hematuria (electron microscopy)

microscopic, intermittent or continuous. This lesion is common and is present in 20–25 % of patients biopsied for persistent isolated hematuria in some series and may occur in more than 1 % of the general population [20]. The lesion may also coexist with other glomerular disease, commonly diabetic nephropathy or IgA nephropathy [21, 22]. Occasionally patients with thin basement membranes have nephrotic range proteinuria, with five of eight such cases in one series showing additional focal segmental glomerulosclerosis (FSGS) lesions [23].

Pathologic Findings

Light Microscopy

The light microscopic appearance is unremarkable.

Immunofluorescence Microscopy

Standard IF is negative. Special IF studies for type IV collagen molecules (see above) may identify some of the patients with thin basement membrane lesions as female carriers of classic X-linked Alport or early-stage Alport [24, 25].

Electron Microscopy

Diffuse, greater than 50 %, thinning of GBM indicates possible thin basement membrane lesion, while small segmental areas of thinning are nonspecific (Fig. 7.2) [24]. The diagnosis of thin basement membranes is based on morphometric measurements from electron microscopic examination (see above). As mentioned above, thin basement membranes (without lamellation) may also be an early or only manifestation in some kindreds with Alport syndrome. Thus, the presence of thin basement membranes cannot per se be taken to categorically indicate a benign prognosis.

Etiology/Pathogenesis

Numerous studies indicate that autosomal recessive Alport syndrome and benign familial hematuria/thin basement membrane disease may represent a spectrum of severe to mild or carrier forms, respectively, of varying molecular defects in the same genes. Linkage of hematuria to mutations in either α4 type IV or α3 type IV has been documented in about 40 % of kindreds with apparent benign familial hematuria clinically [19, 25–27]. In remaining kindreds without apparent linkage, de novo mutations or incomplete penetrance of the hematuria phenotype is proposed to occur. In one study of patients with thin basement membranes, there was increased global sclerosis, with later development of hypertension and renal insufficiency in the patients and also in some relatives [28]. However, these patients were not defined molecularly and were presumed to not have fully developed Alport syndrome based on absence of hearing or eye abnormalities but may represent carriers of autosomal Alport. A large Cypriot cohort with familial hematuria has been described with heterozygous mutations in COL4A3/COL4A4 genes with significant progression to chronic kidney disease, further documenting the variable, not always benign, prognosis of these mutations in familial hematuria [29].

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Part IV

Systemic Diseases Affecting the Kidney

Lupus Nephritis

8

Introduction/Clinical Setting

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown cause that can occur at almost any age, although it affects mostly women in their 20s. The annual incidence of SLE is 50–70 people per million of the population, and prevalence is 500 per million [1]. The incidence of new cases and the survival of patients with SLE are both increasing [2]. The disease is characterized by a large variety of organ disorders involving many different immune mechanisms. The spectrum of kidney lesions predominantly involves the glomerulus and includes minimal mesangial alterations to florid proliferative lesions with necrosis and crescents but also extends to nonimmune complex lesions such as thrombotic microangiopathy (see Chap. 11) and direct podocyte injury. Correspondingly, clinical manifestations and course are equally diverse. Kidney disease develops in more than half of lupus patients and represents the first clinical manifestation of SLE in 15–20 % [3, 4]. Moreover, renal alterations are found in almost 90 % of lupus patients at autopsy. The lowest 5-year survival has been reported for patients with central nervous system and renal involvement [1].

The diagnosis of SLE is based on the documentation of multisystem involvement that meets at least 4 of 11 criteria established by the American College of Rheumatology [5]. Lupus nephritis is typically manifest by proteinuria, ranging from minimal to nephrotic and usually correlating with the histologic type of lesion. Severe glomerular lesions cause hematuria, a telescoped urinary sediment (i.e., red and white blood cells, as well as hyaline, granular, cellular, and broad casts), and renal insufficiency. Hypertension usually develops later in the course of the disease.

Classification of the renal pathology of lupus patients has been based on light microscopic changes, combined with immunohistochemical/immunofluorescent and ultrastructural observations. The classification was most recently revised in 2004 by a working group under the auspices of the Renal Pathology Society (RPS) and the International Society of Nephrology (ISN) (Tables 8.1, 8.2, and 8.3) [6].

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Table 8.1 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis [6]

Class I: minimal mesangial lupus nephritis Normal glomeruli by light microscopy (LM) but mesangial immune deposits by immunofluorescence (IF) and/or electron microscopy (EM)
Class II: mesangial proliferative lupus nephritis Mesangial hypercellularity or mesangial matrix expansion by LM with mesangial immune deposits; a few isolated subepithelial and/or subendothelial deposits may be present
Class III: focal lupus nephritis[a] Active (A) and/or inactive chronic (C) focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50 % of all glomeruli
Class IV: diffuse lupus nephritis[b] Active (A) or inactive chronic (C) diffuse, segmental (involving less than half of the glomerular tuft), or global endocapillary or extracapillary glomerulonephritis involving ≥50 % of all glomeruli This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50 % of the involved glomeruli have segmental lesions and diffuse global (IV-G) lupus nephritis when ≥50 % of the involved glomeruli have global lesions This class includes cases with diffuse wire-loop deposits but with little or no glomerular proliferation
Class V: membranous lupus nephritis Subepithelial immune deposits or their morphologic sequelae by LM and by IF or EM, involving ≥50 % of glomeruli and ≥50 % of capillary loops, 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

Note: See below Table 8.2 notes

Table 8.2 Abbreviated ISN/RPS classification of lupus nephritis

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis[a]
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis[b]
Class V	Membranous lupus nephritis[c]
Class VI	Advanced sclerosing lupus nephritis

Note: Indicate the grade (mild, moderate, severe) of tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis, or other vascular lesions

[a]Indicate the proportion of glomeruli with active and with sclerotic lesions

[b]Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents

[c]Class V may occur in combination with class III or IV, in which case both will be diagnosed

Table 8.3 Active and chronic glomerular lesions in lupus nephritis

Active lesions
Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction
Karyorrhexis
Fibrinoid necrosis
Rupture of glomerular basement membrane
Crescents, cellular or fibrocellular
Subendothelial deposits identifiable by LM (wire loops)
Intraluminal immune aggregates (hyaline thrombi)
Chronic lesions
Glomerular sclerosis (segmental or global)
Fibrous adhesions
Fibrous crescents

Pathologic Findings

Light Microscopy, Immunofluorescence, and Electron Microscopy

Mesangial Lupus Nephritis Classes I and II

Classes I and II lupus nephritis refer to mesangial lupus nephritis. These patients present clinically with mild hematuria, or proteinuria, or both. In general, this kidney lesion has a good prognosis, and the histologic alterations remain stable in the majority of cases. However, functional deterioration and progression of glomerular lesions to more active or generalized proliferative forms occur in about 20 % of cases. In the past decades, the availability of better supportive therapy and more selective use of immunosuppressive agents have led to improved survival of patients with mild forms of lupus glomerulonephritis, while new forms of immunosuppressive therapy are being developed [7, 8].

Class I minimal mesangial lupus nephritis refers to biopsies showing normal glomeruli by light microscopy but mesangial immune deposits by immunofluorescence and/or electron microscopy. Class II contains mesangial proliferative lesions characterized by mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy with mesangial deposits. In either class I or II mesangial forms of LN, there may be a few isolated subepithelial or subendothelial deposits by immunofluorescence and/or electron microscopy but without endocapillary, sclerotic, or crescentic reactions (Fig. 8.1). If the latter changes are present, then a diagnosis of focal LN (if less than half of glomeruli manifest these reactions) or diffuse LN (more than half) is warranted.

Focal Lupus Nephritis Class III

Focal lupus nephritis ISN/RPS class III entails *focal* (involving less than half of the glomeruli available for inspection) proliferative, necrotizing, or sclerosing lesions. These lesions may be either *segmental* (involving <50 % of the tuft area of the affected glomeruli) or *global* (involving ≥50 % of the tuft area of the involved

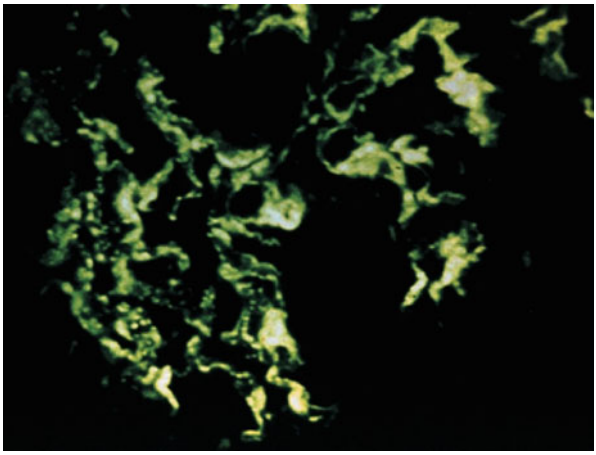

Fig. 8.1 Mesangial proliferative lupus nephritis ISN/RPS class II with granular mesangial immunoglobulin G (IgG) (immunofluorescence)

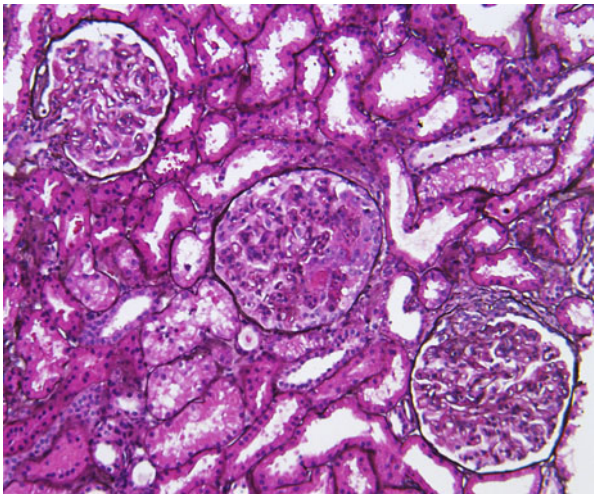

Fig. 8.2 Focal lupus nephritis ISN/RPS class III (A+C) with active endocapillary proliferation and an early necrotizing lesion with rupture of the glomerular basement membrane and early crescent formation in the middle glomerulus and a small adhesion and fibrocellular crescent in the lower right glomerulus. However, less than half of the glomeruli showed such lesions (Jones silver stain)

glomeruli). A subdivision is made according to the predominance of active versus sclerotic lesions as indicated in Table 8.1.

In the pathology report, the proportion of glomeruli with active and with sclerotic lesions and the proportion of glomeruli with fibrinoid necrosis or cellular crescents should be indicated. The proliferative lesions include variable mesangial proliferation and endocapillary proliferation with variable inflammatory cells. Double contours of the GBM on silver stain may be present. Necrotizing lesions with fibrinoid necrosis and crescent reaction are often present in active lesions (Figs. 8.2 and 8.3). In these areas, there is nuclear debris as well as influx of inflammatory cells. The inflammatory process may also lead to disruption of the glomerular basement membrane and fibrinoid necrosis. Fibrinoid necrosis appears as amorphous eosinophilic material staining bright red in trichrome staining, often

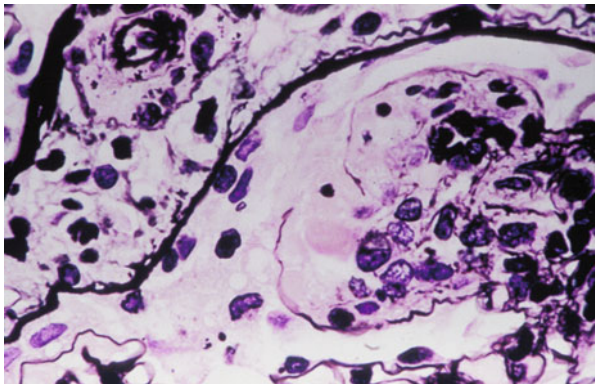

Fig. 8.3 Focal lupus nephritis ISN/RPS class III (A) with active endocapillary proliferation and an early necrotizing lesion with rupture of the glomerular basement membrane (Jones silver stain)

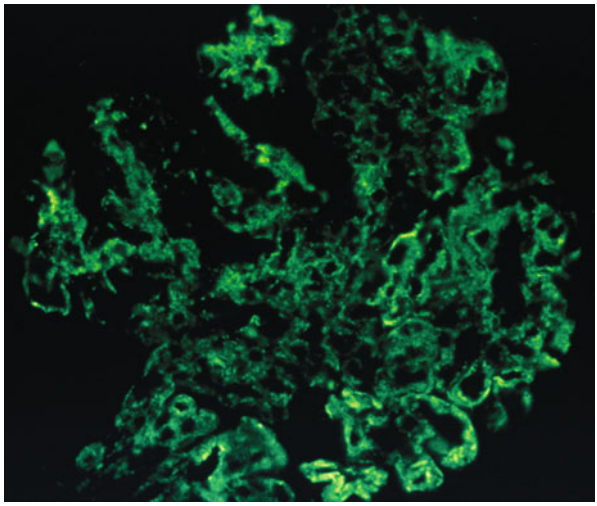

Fig. 8.4 Focal lupus nephritis ISN/RPS class III with diffuse, chunky pattern for IgG in mesangium and along capillary wall. Some of the capillary wall deposits have a smooth outer contour, reflecting their subendothelial location (immunofluorescence)

associated with GBM breaks and karyorrhexis. Interstitial inflammation may be marked adjacent to glomeruli disrupted by crescents and/or necrosis, particularly if Bowman's capsule is ruptured by the destructive lesion. Segmental sclerotic scars with broad-based adhesions to Bowman's capsule can develop from focal crescents with necrotic lesions. Tubular atrophy and interstitial fibrosis are proportional to glomerular scarring.

Immunofluorescent staining shows the presence of immunoglobulin G (IgG), IgM, IgA, and complement factors C3 and C1q ("full-house" immunofluorescence) in chunky granular and globular depositions along the glomerular capillary walls and in the mesangium (Fig. 8.4). These capillary wall deposits are largely subendothelial, seen by their smooth outer contour as they are molded under the GBM, and confirmed by electron microscopy. Although the light microscopic proliferative changes are focal, the immunofluorescence is usually positive in all glomeruli. Electron microscopy typically demonstrates deposits in the mesangium and also in

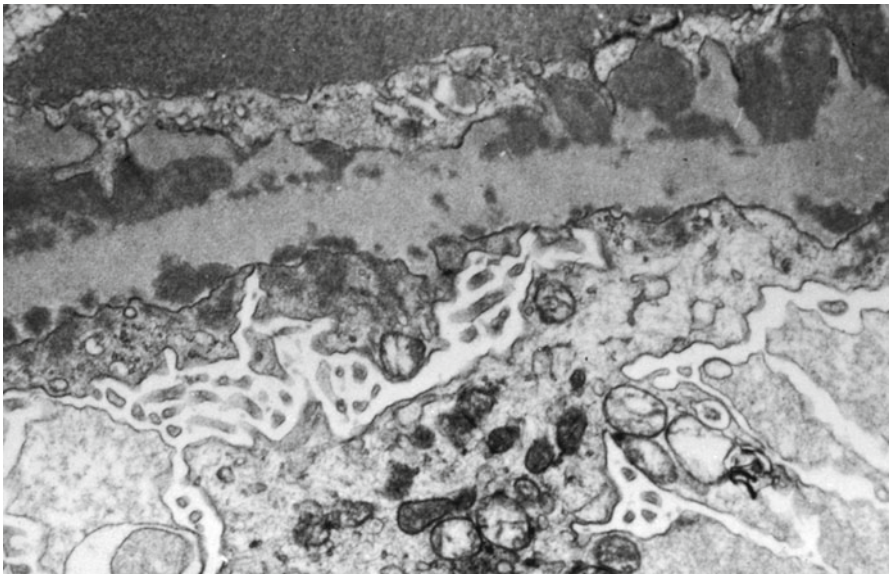

Fig. 8.5 Subendothelial (below the glomerular basement membrane, GBM) and subepithelial (above the GBM) electron dense deposits with irregular thickening of GBM and microvillous transformation of podocytes in focal lupus nephritis ISN/RPS class III (electron microscopy)

the subendothelial area. There may be scattered subepithelial deposits, but if these are extensive (i.e., >50 % of loops in most glomeruli), membranous LN should be diagnosed in addition to the proliferative process (Fig. 8.5) [6].

Patients with focal lupus nephritis class III present almost invariably with proteinuria and in the majority of cases with mixed findings of nephrotic and nephritic syndromes. The lesions can transform to diffuse proliferative (class IV) or membranous lupus nephritis class V.

Diffuse Lupus Nephritis Class IV

Patients with diffuse lupus nephritis class IV typically have increased renal dysfunction and significant proteinuria and active urine sediment. This class is the most common and severe form of lupus nephritis detected in renal biopsies. The biopsy shows *diffuse segmental* (IV-S) or *global* (IV-G) lesions, characterized by proliferative, sclerosing, and/or necrotizing lesions in more than 50 % of the glomeruli. The lesions may thus be either active or inactive and have a segmental or global distribution. There is variable mesangial and endocapillary proliferation. Cellular crescents and necrosis are frequently present in active cases, whereas broad-based adhesions with segmental sclerosis and fibrocellular to fibrous crescents characterize the chronic lesions. Some investigators revealed a poor outcome of diffuse "segmental" necrotizing glomerulonephritis involving over 50 % of glomeruli, as compared to other forms of class IV lupus nephritis [9]. Attempts to capture the possible significance of these severe segmental lesions were therefore made by dividing class IV

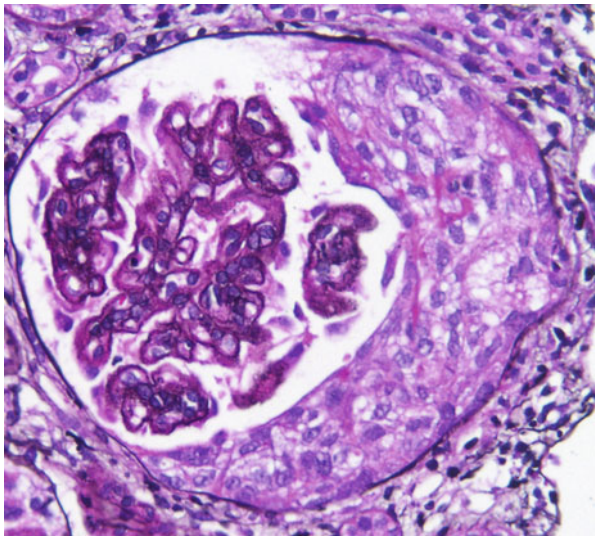

Fig. 8.6 Diffuse proliferative lupus nephritis ISN/RPS class IV with cellular crescent and segmental endocapillary proliferation and double contours of GBM (Jones silver stain)

diffuse lupus nephritis into diffuse segmental (IV-S) when ≥50 % of the involved glomeruli have segmental lesions and diffuse global (IV-G) when ≥50 % of the involved glomeruli have global lesions (Fig. 8.6) [6]. Furthermore, a subdivision is made according to the presence of active versus chronic lesions as was indicated for class III lesions (Table 8.1). However, the definition of "segmental" as <50 % of the tuft is not congruent with that used by the original investigators, who considered lesions "segmental" if even a single loop of the glomerular tuft was not involved. Thus, the ISN/RPS S versus G lesions may not adequately capture this subgroup of patients.

As in focal LN class III, the proportion of glomeruli with active and with sclerotic lesions and the proportion of glomeruli with fibrinoid necrosis or cellular crescents should be indicated in the pathology report. "*Wire-loop*" lesions, that is, local periodic acid-Schiff (PAS)-positive thickenings of the glomerular capillary walls, are characteristic of this form of lupus nephritis (Fig. 8.7). This thickening of the capillary walls is related to the presence of large, subendothelial electron dense deposits. Glomerular lesions run the gamut from diffuse hypercellularity to severe necrotizing "crescentic" glomerulonephritis or, in chronic cases, diffuse global glomerulosclerosis with loss of renal function. Tubular atrophy and interstitial fibrosis are often more extensive in diffuse LN, class IV than in focal LN, class III. The predictive value of these lesions with respect to renal function, however, is disputed [10, 11]. The tubular epithelium shows cytoplasmic hyaline droplets, hydropic degeneration, cytoplasmic vacuolization, hyaline protein cylinders, and, in more advanced stages, disease glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Arteries and arterioles may show varying lesions (see below).

Immunofluorescence in diffuse lupus nephritis class IV shows irregular "full-house" deposits of immunoglobulins and complements along the glomerular capillary walls and in the mesangium (Fig. 8.8). Ultrastructurally, electron dense deposits

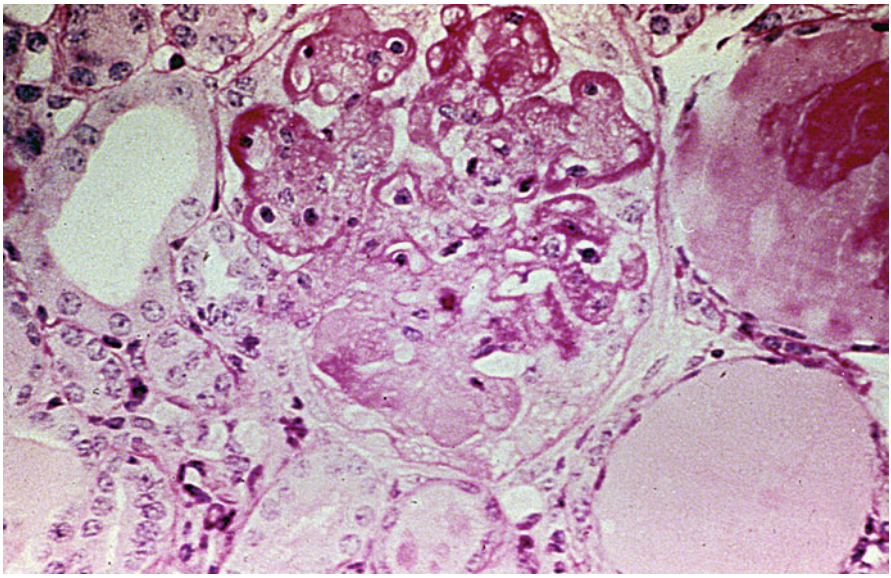

Fig. 8.7 Diffuse proliferative lupus nephritis ISN/RPS class IV with segmental endocapillary proliferation on left with early cellular crescent (Jones silver stain)

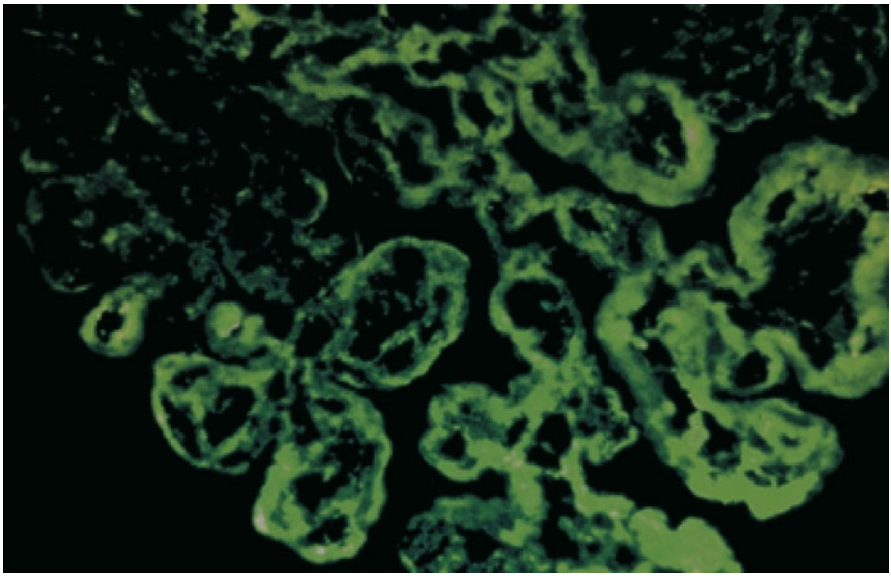

Fig. 8.8 Diffuse lupus nephritis ISN/RPS class IV with large confluent predominantly subendothelial IgG deposits along GBM, with smooth outer contours due to molding underneath the GBM (immunofluorescence)

are seen in the mesangium and subendothelially along the capillary walls, in larger quantities than in the other classes. There is frequent interposition of mononuclear cells with new GBM matrix laid down, resulting in double contours. By electron microscopy, frequent mesangial and subendothelial deposits are confirmed. Foot processes of podocytes are variably effaced.

Tubuloreticular inclusions (TRIs) (also called reticular aggregates) can be found in the cytoplasm of endothelial cells. These TRIs are not specific for SLE but are often seen in endothelial cells throughout the body in patients with AIDS and other viral infections or in patients receiving exogenous interferon therapy, reflecting high levels of interferon. Large and often confluent subendothelial deposits represent the ultrastructural analogue of the "wire-loop" lesions seen light microscopically. Variable subepithelial deposits are present but, if extensive, warrant concurrent diagnosis of additional membranous class V lupus nephritis (see below). As in the other classes of lupus nephritis, the electron dense deposits can show a typical fingerprint-like crystalline pattern, possibly representing the presence of cryoglobulins.

Patients with diffuse lupus nephritis class IV typically have marked proteinuria, an active urine sediment and decreased renal dysfunction.

Membranous Lupus Nephritis Class V

Membranous class V lupus nephritis is characterized by diffuse subepithelial deposits, involving ≥50 % of the loops in ≥50 % of the glomeruli. Among patients with lupus nephritis, the incidence of membranous nephritis varies between 8 and 27 %. The prognosis of patients with membranous lupus nephritis is relatively favorable, with a reported 10-year kidney survival of 91 % [12]. Still, one-third of patients with membranous lupus nephritis progress to proliferative lupus nephritis [13]. Patients most often present with marked proteinuria.

By light microscopy, there is variable mesangial expansion with diffuse thickening of the glomerular capillary walls in hematoxylin and eosin and PAS stains. With silver-methenamine staining, argyrophilic spikelike formations often can be seen along the glomerular basement membrane, corresponding to basement membrane reaction between and around the subepithelially localized immune deposits. By immunofluorescence, granular deposits of immunoglobulins and complement are present peripherally along the glomerular capillary walls and in the mesangium, corresponding to the presence of subepithelial and mesangial electron dense deposits. Membranous lupus nephritis is distinguished from idiopathic membranous nephropathy by full-house staining of deposits by immunofluorescence, reticular aggregates by electron microscopy, and most often mesangial deposits [14, 15]. Absence of staining for the phospholipase A2 receptor in the deposits, the antigen present in most cases of idiopathic membranous nephropathy, may also be useful [16]. Foot processes are diffusely effaced by electron microscopy.

Class V membranous lupus nephritis may occur in combination with classes III or IV (focal or diffuse lupus nephritis), in which case both are diagnosed. Patients with pure membranous lupus nephritis experience a relatively benign course, whereas those with mixed membranous and diffuse proliferative lesions have survival rates similar to those of patients with diffuse lupus nephritis alone. Likewise,

in a study of membranous lupus nephritis, patients with additional proliferative lesions had higher serum creatinine levels at entry and were more likely to experience a decline in renal function than those without proliferation [17].

Advanced Sclerosing Lupus Nephritis Class VI

This class refers to a late stage, resembling morphologically any late or end stage in chronic glomerulonephritis with global or extensive segmental sclerosis of >90 % of glomeruli without residual activity. Specific features of lupus nephritis are usually lacking. However, in patients with lupus nephritis such chronic end-stage glomerulosclerotic lesions are seldom seen. Patients with lupus nephritis who have been treated for longer periods may show chronic glomerular lesions at autopsy. These may be morphologically similar to other late stages of glomerulonephritis and of focal global sclerotic lesions that occur invariably at an older age [18–20].

Lupus Podocytopathy

Some patients with SLE may have only mesangial lesions but widespread foot process effacement and the nephrotic syndrome with extensive foot process effacement by EM [21–23]. Some of these patients have responded rapidly to steroid therapy, suggesting that the podocyte lesions are more like minimal change disease rather than related to consequences of immune complexes. It is not established whether such podocyte injury could reflect a second superimposed minimal change disease-type process or secondary injury related to cytokines activated by an immune complex process.

Vascular Lesions in SLE

Several types of vascular lesions may be seen in SLE patients [24]. Patients with SLE are not protected from banal vascular lesions related to hypertension and thus may show nonspecific sclerosis of arteries and arterials with associated hyaline. Uncomplicated vascular immune deposits also occur commonly in lupus nephritis and are highly specific for this condition (Fig. 8.9). Immune deposits may be detected by immunofluorescence and electron microscopy in arteries or arterioles within the media or along the intimal basement membrane, with staining for immunoglobulins as well as complement components, typically both C3 and C1q. These uncomplicated vascular immune deposits are not associated with any particular clinical manifestations.

In contrast, necrosis of arterioles and occasionally larger arteries without inflammation may occur in patients with severe lupus nephritis, a lesion called lupus vasculopathy. This fibrinoid material is present within the intima and stains eosinophilic with a smudgy appearance. The fibrinoid material may expand to the lumen. Vascular smooth muscle cells and endothelial cells often show necrosis, but there is no true vasculitis in that there are no inflammatory cells associated with this lesion. Immunoglobulins are detected by immunofluorescence. Electron microscopy has documented both hyaline-type material with insudated plasma proteins and immune deposits in addition to fibrin. This lesion has a poor prognosis [25, 26].

Patients with SLE may also have thrombotic microangiopathy with or without a detectable circulating lupus anticoagulant or antiphospholipid antibody. These lesions do not contain immune deposits but rather show fibrin within glomeruli and small

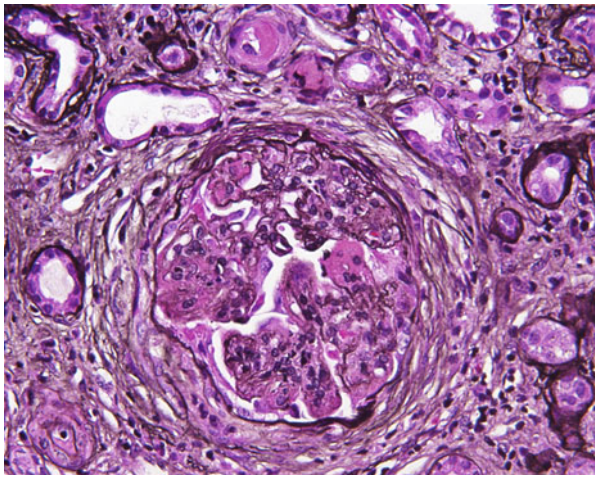

Fig. 8.9 Bland vascular deposits are evident in the arteriole at the top, documented to contain IgG and C3 by immunofluorescence. The glomerulus shows segmental endocapillary proliferation and a fibrocellular crescent with segmental adhesion and sclerosis and double contours of GBM in addition to mesangial proliferation (Jones' silver stain)

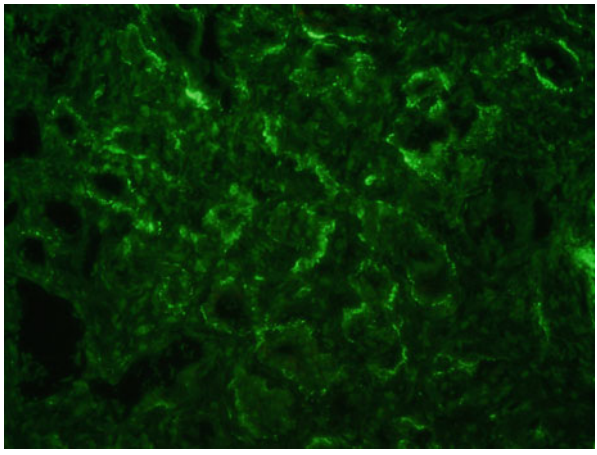

Fig. 8.10 Granular tubular basement membrane deposits staining for IgG are evident (immunofluorescence)

arteries, often with glomerular involvement manifest as mesangiolysis with fibrin thrombi in capillary loops. The glomerular capillary wall shows double contours in the more chronic state. Acutely, there is intimal proliferation of arteries and arterials and mucoid change with red blood cell fragments within the injured vascular walls.

Vasculitis is very rare in patients with SLE. This lesion is defined as fibrinoid necrosis with associated inflammatory infiltrate through the vascular wall, with or without immune complex deposits.

Tubulointerstitial Lesions in SLE

Deposits may be present along tubular basement membranes and can be diagnosed based on the presence of granular immunoglobulin and complement deposition (Fig. 8.10). Corresponding electron dense deposits are then visualized by electron microscopy. Such deposits are often, but not invariably,

associated with interstitial inflammation comprised predominately of lymphocytes, with scattered monocytes and plasma cells [27–29]. Of note, interstitial inflammation does not correlate directly with tubulointerstitial immune deposits. There may be active injury with tubulitis related to these deposits. More frequently, significant tubulointerstitial inflammation is associated with areas of glomeruli destroyed or injured by crescents. Tubular basement membrane deposits are detected in about half of biopsied patients with lupus nephritis and may be associated with any type of glomerular lesion but most frequently with class IV diffuse lupus nephritis. Deposits may also be present in peritubular capillaries [30].

Tubular atrophy and interstitial fibrosis develop most often in association with severe glomerular disease with marked chronicity. These tubulointerstitial chronic changes correlate well with degree of loss of GFR.

Additional Challenges

Although some incomplete definitions and distinctions of subclasses in previous WHO classifications have been clarified in the newer ISN/RPS classification [31], challenges and issues remain. The attempt to analyze segmental versus global class IV lesions does not quite recapitulate the important findings of the group of Lewis et al., in that the ISN/RPS classification divides segmental versus global lesions depending upon whether less than half or more than half of the tuft is involved [6, 9]. In contrast, the original observations were based on definition of "segmental" as a lesion where any part of the glomerulus was left uninvolved. When the original cases were reexamined based on the current ISN/RPS classification, designating classes as class IV segmental versus global indeed did not show significant differences in outcome. In contrast, when cases were divided according to the Lewis definition of segmental, meaning that only at least some part of the glomerulus remained uninvolved by injury, distinct differences in renal survival were noted [32]. Of interest, these segmental lesions have generally been found to have fewer immune deposits, more necrosis, and more crescents and have been postulated to be more vasculitic-like rather than immune complex driven, analogous to lesions of ANCA-associated glomerulonephritis and polyangiitis, with important potential implications for therapy.

In addition, activity and chronicity indices have not yet been shown to be reproducible and thus have not been incorporated into the ISN/RPS classification [11, 20]. Specific development of better indices of disease activity and chronicity is warranted. A further conundrum arises when nonspecific segmental or global scars are present in cases that otherwise show only mesangial or membranous-type lesions. Clearly, sclerosis may develop nonspecifically with aging, and even idiopathic membranous nephropathy may have segmental scars and global sclerosis. Whether such sclerosed glomeruli warrant additional diagnosis of class III or IV chronic lupus nephritis has not been established. Further, the assessment of whether more than half or less than half of glomeruli are involved with significant lesions to

differentiate class III versus class IV may be problematic with the presence of many remotely globally sclerosed glomeruli. Particularly with small sample sizes, this conundrum is amplified. Finally, the current classification does not account for extraglomerular lesions (see above), which may be present and important in patients with SLE.

Etiology/Pathogenesis

SLE has an autoimmune basis, and the disease can affect numerous organs, including the skin, joints, serous membranes, lungs, central nervous system, and kidney. SLE can affect the kidney in various ways. Lupus nephritis is used to describe the lesions related to immune complex-mediated injury in patients secondary to SLE. The commonly used classifications, including past World Health Organization (WHO) and the current International Society of Nephrology/Renal Pathology Society (ISN/RPS) classifications, only focus on the glomerular lesions. However, immune complexes maybe present along tubular basement membranes and blood vessels as well. Some renal lesions associated with SLE do not have an immune complex deposition etiology. The sites and nature of immune deposits also may vary, and disease manifestations may remit or flare, and the dominant pattern of immune complex localization and the subsequent pattern of injury may change either spontaneously or in response to treatment.

The precise etiology of SLE remains unknown. Autoimmunity is proposed to be related to dysregulated apoptosis with ineffectual clearance of apoptotic cell fragments [33]. There is important genetic susceptibility with increased risk if a family member is affected and HLA associations to DR2, DR3, and B8. SLE-like conditions and lupus nephritis-like immune complex deposits may also develop in patients with HIV infection, illustrating the importance of dysregulated immunity in the evolution of SLE and kidney disease. Immune complexes may be circulating and deposit in specific locations based on size, charge, affinity, and avidity or may form in situ in response to planted exogenous antigens with circulating immunoglobulins reaching the planted antigens or local endogenous antigens of specific cells. Circulating antibodies may also cross-react with antigens present within kidney parenchyma. Numerous antigens, including histones, or DNA bound to histones may be antigenic in SLE. When complexes are small and stable with high-affinity antibodies, these tend to localize in the mesangium and elicit a limited mesangial reaction with mesangial hypercellularity. Larger size or number of complexes with high-avidity antibodies may spill over to the subendothelial area, where inflammatory mechanisms are easily activated, including complement and leukocyte Fc receptors, resulting in infiltration of inflammatory cells and proliferation of endogenous cells, filling up the capillary lumens, so-called endocapillary proliferation. Over time, new matrix may be formed internal to the subendothelial deposits along with infiltrating interposed cells, resulting in the double contour visualized by silver stain. The presence of subepithelial immune deposits in lupus nephritis may result from dissociation of low-avidity and/or low-affinity complexes that reassemble

after passing through the GBM. These deposits activate complement and perturb the adjacent podocyte, resulting in foot process effacement, a leaky capillary wall and proteinuria, and a GBM reaction visualized as spikes by silver stain.

Clinicopathologic Correlations

Classification of lupus nephritis is considered useful to describe the patient's clinical status and for grouping patients with similar clinical profiles. For instance, membranous and diffuse proliferative forms usually present with proteinuria, and severe activity in a renal biopsy is usually associated with the clinical syndrome of a rapidly progressive glomerulonephritis. Moreover, the classification is related to prognosis with respect to renal function and patient survival [4]. The use of the lupus nephritis classification facilitates the ease and reliability with which nephrologists and nephropathologists communicate information and has improved standardization and reproducibility of biopsy interpretation [31]. In contrast, the prognostic value of the so-called activity and chronicity indices used by some in lupus nephritis is subject to discussion, and the utility of these indices is limited by concerns about their irreproducibility [6, 10, 11]. Nevertheless, distinguishing "active" and "sclerosing" lesions (Table 8.3) may help determine prognosis and sensitivity to treatment in both lupus and other glomerulonephritides [34–36]. In general, lesions that are potentially sensitive to treatment and reversible show activity, characterized by hypercellularity, leukocyte exudation, necrosis/karyorrhexis, cellular crescents, hyaline deposits, and interstitial inflammatory infiltrate. More chronic lesions less sensitive to treatment are glomerulosclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis [37]. Persistent macrophages in second biopsies after therapy portend worse prognosis [38]. Interstitial lesions are most severe in class IV. Interstitial inflammation, tubular atrophy, and interstitial fibrosis each have been independently associated with poor outcomes, and in turn, severe glomerular active lesions correlated with more interstitial inflammation. Sclerosis of glomeruli also correlated with tubular atrophy and interstitial fibrosis [29].

The persistence of subendothelial deposits has been associated with the progression of lupus nephritis, whereas a decrease in the amount of subendothelial and mesangial deposits was linked to a lower risk for renal impairment in SLE. Thus, patients with more proliferative lesions and more activity and chronicity had worse long-term outcomes [39].

Lupus lesions may not remain static over time in many patients. The type of glomerular lesion remains unchanged in about half of the cases. In the other half transformation occurs to either more ominous or more benign histologic patterns, the latter particularly under the influence of therapy. In patients with the most severe forms of lupus nephritis, a remission of clinical renal abnormalities, usually in response to aggressive treatment, is associated with dramatic improvement in long-term patient and renal survival [20, 40]. With current management strategies, in general the long-term outlook for patients with lupus nephritis has improved, but only a minority of patients are able to stop treatment altogether, and the incidence

of serious complications is high [37, 41, 42], infection being the leading cause of death. Trials are ongoing of novel immunomodulatory drugs such as rituximab, which depletes B lymphocytes [43, 44]. Overall, only 10–15 % of patients with lupus nephritis now go into end-stage renal failure, with 10–30 % of those with class III, IV, or V reaching end-stage kidney disease within 15 years [4, 45].

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Crescentic Glomerulonephritis and Vasculitis

9

Introduction/Clinical Setting

Crescentic glomerulonephritis is not a specific disease but rather is a manifestation of severe glomerular injury that can be caused by many different etiologies and pathogenic mechanisms. The major immunopathologic categories of crescentic glomerulonephritis are immune complex-mediated, anti-glomerular basement membrane (anti-GBM) antibody-mediated, and pauci-immune, which usually is antineutrophil cytoplasmic autoantibody (ANCA)-mediated [1]. Table 9.1 shows the relative frequency of these immunopathologic categories of crescentic glomerulonephritis. Crescentic glomerulonephritis can occur as a renal-limited process or as a component of systemic small-vessel vasculitis, such as IgA vasculitis (Henoch-Schönlein purpura), cryoglobulinemic vasculitis, Goodpasture's syndrome, or ANCA vasculitis [2–5]. In addition to small-vessel vasculitis, the kidneys also are a frequent site of involvement by other forms of vasculitis, such as polyarteritis nodosa, Kawasaki disease, giant cell arteritis, and Takayasu arteritis [3, 5] (Table 9.2).

Table 9.1 Frequency of immunopathologic categories of crescentic glomerulonephritis in over 3,000 consecutive native kidney biopsies evaluated by immunofluorescence microscopy in the University of North Carolina Nephropathology Laboratory

	Any crescents ($n=487$)	>50 % crescents ($n=195$)	Arteritis in biopsy ($n=37$)
Immunohistology			
Pauci-immune (<2+Ig)	47 % (227/487)	61 % (118/195)[a]	84 % (31/37)
Immune complex (>2+Ig)	49 % (238/487)	29 % (56/195)	14 % (5/37)[b]
Anti-GBM	5 % (25/487)[c]	11 % (21/195)	3 % (1/37)[d]

From Jennette and Falk [3]

[a]70 of 77 patients tested for ANCA were positive (91 %) (44 P-ANCA and 26 C-ANCA)

[b]4 patients had lupus and 1 poststreptococcal glomerulonephritis

[c]3 of 19 patients tested for ANCA were positive (16 %) (2 P-ANCA and 1 C-ANCA)

[d]This patient also had a P-ANCA (MPO-ANCA)

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Table 9.2 Names and definitions of vasculitis adopted by the 2012 Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis (partial modified listing)

Large-vessel vasculitis	Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected
Takayasu arteritis	Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50
Giant cell arteritis	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 and often associated with polymyalgia rheumatica
Medium-vessel vasculitis	Vasculitis predominantly affecting medium arteries defined as the main visceral arteries and their branches. Any size artery may be affected. Inflammatory aneurysms and stenoses are common
Polyarteritis nodosa	Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with ANCA
Kawasaki disease	Arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries. Coronary arteries are often involved. Aorta and large arteries may be involved. Usually occurs in infants and young children
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	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., PR3-ANCA, MPO-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 (Wegener's) (GPA)	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 (Churg-Strauss) (EGPA)	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

Table 9.2 (continued)

Immune complex vasculitis	Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent
Anti-GBM disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents
Cryoglobulinemic vasculitis (CV)	Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum. Skin, glomeruli, and peripheral nerves are often involved
IgA vasculitis (IgAV) (Henoch-Schönlein)	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gut and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur
Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis)	Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e., capillaries, venules, or arterioles) and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common

Each of these vasculitides can affect the kidneys. Large-vessel vasculitis usually presents as renovascular hypertension, medium-sized vessel vasculitis as renal inflammatory aneurysms and infarction, and small-vessel vasculitis as glomerulonephritis

Anti-Glomerular Basement Membrane Disease

Anti-GBM disease is a small-vessel vasculitis that affects the glomerular capillaries and pulmonary alveolar capillaries [6, 7]. It may occur as an isolated glomerulonephritis or as the renal component of a pulmonary-renal syndrome. In the latter instance, the term *Goodpasture's syndrome* is appropriate.

Pathologic Findings

Light Microscopy

By light microscopy, the acute glomerular lesion is characterized by segmental to global fibrinoid necrosis with crescent formation in over 90 % of patients [1]. Periodic acid-Schiff (PAS) and silver stains demonstrate breaks in the GBM in areas of necrosis (Fig. 9.1). Glomerular segments that do not have necrosis often are

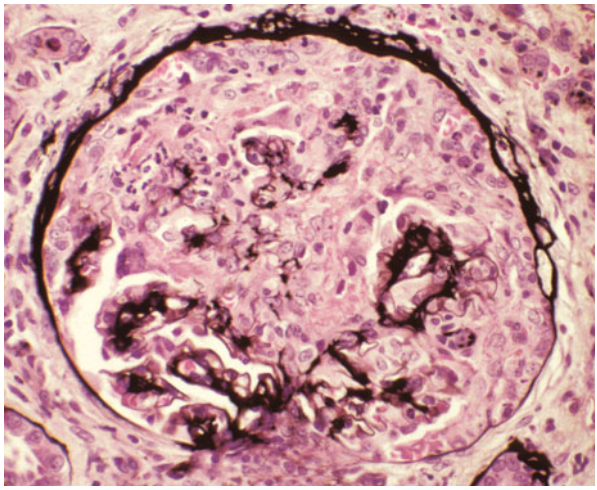

Fig. 9.1 Glomerulus from a patient with anti-glomerular basement membrane (GBM) disease showing a very large cellular crescent and extensive destruction of approximately 80 % of the tuft. A few silver-positive intact profiles of GBM are present at the hilum (Jones silver stain)

remarkably normal or have a slight increase in neutrophils. Marked neutrophil infiltration is observed in association with the necrosis in occasional specimens. Features of aggressive immune complex glomerulonephritis are notably absent, such as marked capillary wall thickening and endocapillary hypercellularity. Often there are breaks in Bowman's capsule, occasionally with associated reactive multinucleated giant cells.

With time, foci of glomerular necrosis evolve into glomerular sclerosis, and cellular crescents become fibrous crescents. Acute tubulointerstitial inflammation that is centered on necrotic glomeruli evolves to more regional or generalized interstitial fibrosis with chronic inflammation and tubular atrophy.

Immunofluorescence Microscopy

Immunohistology demonstrates intense linear staining of the GBM (Fig. 9.2), predominantly for immunoglobulin G (IgG) along with more granular and discontinuous staining for C3 (Fig. 9.3). Immunoglobulin A (IgA)-dominant anti-GBM disease is very rare [8]. Irregular staining for fibrin occurs at sites of fibrinoid necrosis and within crescents. In some specimens, the fibrinoid of glomeruli is so extensive that identification of linear staining along intact segments of GBM is difficult. Care must be taken not to misinterpret anti-GBM disease with extensive destruction of GBMs as pauci-immune disease.

Electron Microscopy

Electron microscopy reveals no immune complex-type electron-dense deposits unless there is concurrent immune complex glomerulonephritis. Glomerular basement membrane gaps are present in areas of necrosis and crescent formation. Cellular crescents typically contain electron-dense fibrin tactoid strands.

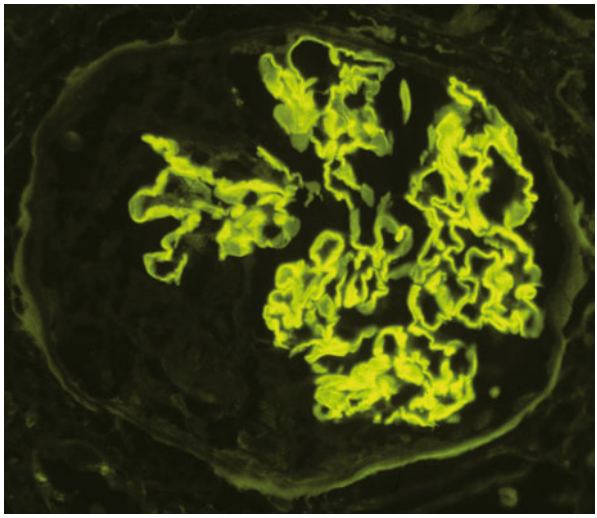

Fig. 9.2 Glomerulus from a patient with anti-GBM disease showing linear staining of the GBM by direct immunofluorescence microscopy using an antibody specific for immunoglobulin G (IgG)

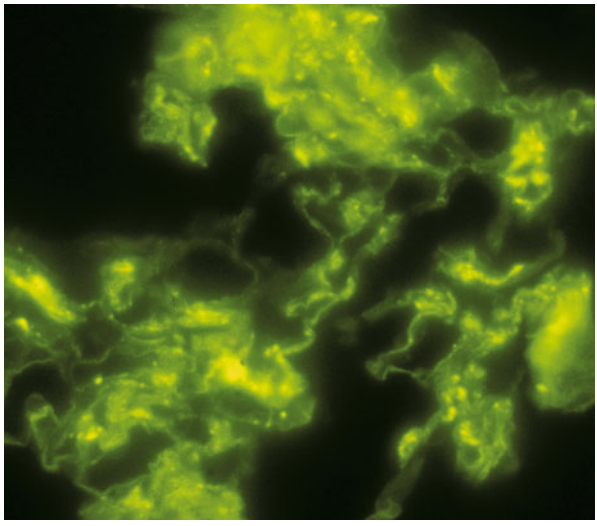

Fig. 9.3 Glomerulus from a patient with anti-GBM disease showing irregular granular staining of the capillary walls by direct immunofluorescence microscopy using an antibody specific for C3

Clinicopathologic Correlations

Anti-GBM disease is caused by autoantibodies directed against the α3 chain in the noncollagenous domain of type IV collagen [9]. Serologic confirmation of anti-GBM disease should be sought, but approximately 10–15 % of patients with anti-GBM disease have negative results. About a quarter to a third of patients with anti-GBM disease also have ANCA [10]. Thus, all anti-GBM patients should be tested for ANCA. Patients with both anti-GBM and ANCA have an intermediate prognosis that is worse than ANCA alone but better than anti-GBM alone. Anti-GBM antibodies

characteristically occur as one episode that clears with immunosuppressive therapy, whereas ANCA disease is characterized by more persistent antibodies and frequent recurrence of disease. Patients with combined disease may have permanent remission of the anti-GBM disease with recurrence of the ANCA disease alone.

Approximately half the patients with anti-GBM disease present with rapidly progressive glomerulonephritis without pulmonary hemorrhage, and the other half have pulmonary-renal syndrome (Goodpasture's syndrome). However, most patients with pulmonary-renal syndrome have ANCA disease rather than anti-GBM disease [11].

Anti-GBM is the most aggressive form of crescentic glomerulonephritis and has the worst prognosis, especially if aggressive immunosuppressive treatment is not instituted quickly before the serum creatinine is >6 mg/dL [1, 7, 12]. The serum creatinine at the time treatment is begun is a better predictor of outcome than any pathologic feature. The current approach to treatment uses high-dose cytotoxic agents combined with plasma exchange [6, 7, 12].

Pauci-immune and ANCA Glomerulonephritis and Vasculitis

Introduction/Clinical Setting

Antineutrophil cytoplasmic autoantibody disease is a form of small-vessel vasculitis [2–4, 13–15]. Small-vessel vasculitides have a predilection for capillaries, venules, and arterioles, although arteries may be affected [2, 13, 14]. The major immunopathologic categories of small-vessel vasculitis are anti-GBM disease, immune complex small-vessel vasculitis, and pauci-immune small-vessel vasculitis. Pauci-immune small-vessel vasculitis is characterized by an absence or paucity (<2+) of vessel staining for immunoglobulin, which is distinct from the conspicuous linear staining in anti-GBM disease and prominent granular staining in immune complex disease. Approximately 85 % of active untreated pauci-immune crescentic glomerulonephritis and vasculitis is associated with ANCA in the circulation. The major clinicopathologic expressions of pauci-immune and ANCA-associated vasculitis are renal-limited vasculitis (pauci-immune necrotizing and crescentic glomerulonephritis), microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (Table 9.2) [2, 3, 13, 14].

Pathologic Findings

Light Microscopy, Immunofluorescence, and Electron Microscopy

Histologically, the glomerular lesion in all four clinicopathologic categories is identical and is characterized by fibrinoid necrosis and crescent formation (Figs. 9.4, 9.5, and 9.6). In less than 10 % of specimens, the glomerulonephritis may be accompanied by necrotizing arteritis (Fig. 9.7) (usually in the interlobular arteries) or medullary angiitis affecting the vasa rectae (Fig. 9.8).

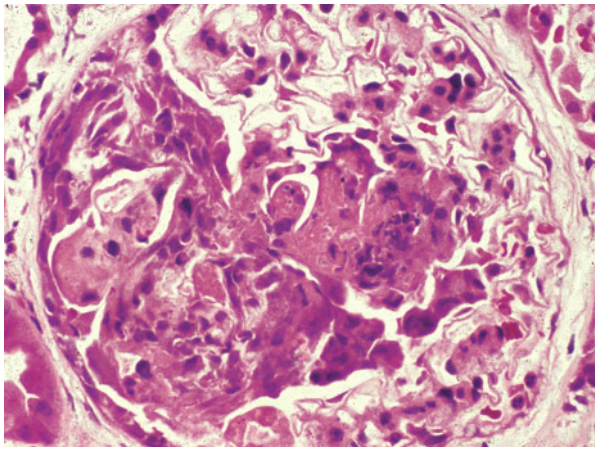

Fig. 9.4 Glomerulus from a patient with granulomatosis and polyangiitis (Wegener's granulomatosis) demonstrating segmental fibrinoid necrosis and early cellular crescent formation (H&E)

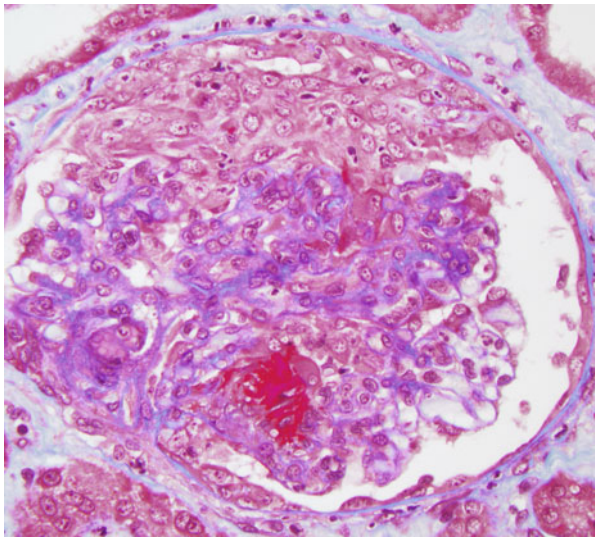

Fig. 9.5 Glomerulus from a patient with microscopic polyangiitis demonstrating a cellular crescent at the top of the image and a small irregular fuchsinophilic (*red*) focus of fibrinoid necrosis near the bottom of the image (Masson trichrome stain)

By light microscopy and electron microscopy, pauci-immune crescentic glomerulonephritis cannot be distinguished from anti-GBM crescentic glomerulonephritis; however, immunofluorescence microscopy readily distinguishes the two. Pauci-immune crescentic glomerulonephritis, by definition, has no or low-intensity immunostaining for immunoglobulin; however, often there is some staining for immunoglobulin [16]. A reasonable approach is to draw the line at 2+ or less immunoglobulin staining on a scale of 0–4+ for pauci-immune disease. Pauci-immune crescentic glomerulonephritis often has irregular segmental or global staining for fibrin at sites of fibrinoid necrosis and crescent formation (Fig. 9.9). Electron microscopy may show no electron-dense deposits, or there may be a few small electron-dense deposits,

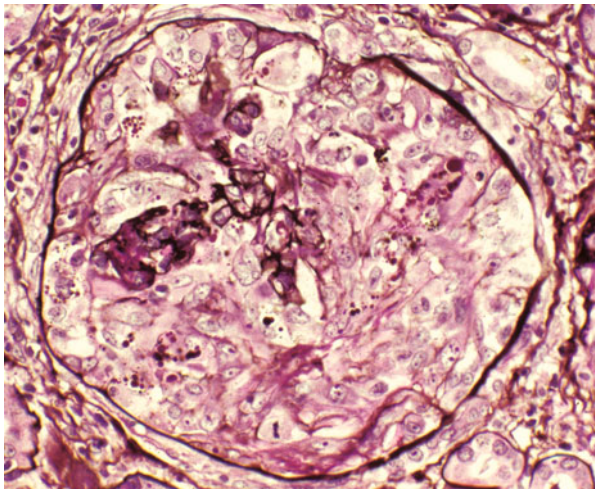

Fig. 9.6 Glomerulus from a patient with ANCA-positive renal-limited disease showing a large cellular crescent with extensive destruction of the glomerular tuft (Jones silver stain)

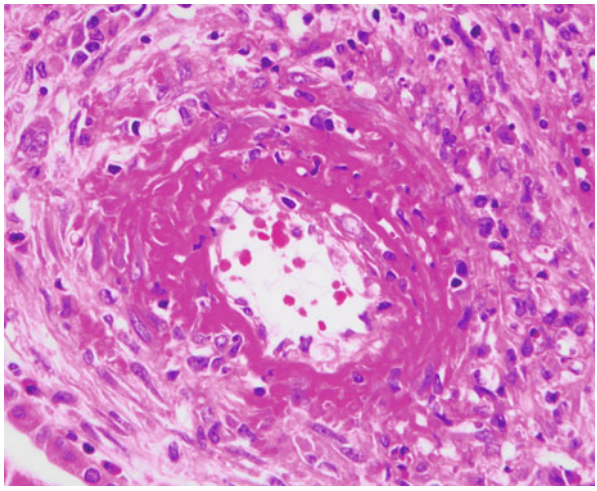

Fig. 9.7 Interlobular artery in a renal biopsy from a patient with microscopic polyangiitis showing circumferential fibrinoid necrosis with associated leukocyte infiltration and leukocytoclasia (H&E)

especially if immunofluorescence microscopy revealed staining for immunoglobulin. Glomerular basement membrane breaks often can be identified.

Microscopic polyangiitis (MPA) is necrotizing vasculitis with few or no immune deposits affecting small vessels, that is, capillaries, venules, or arterioles [4, 13, 14, 17]. Necrotizing arteritis occurs in some but not all patients. Approximately 90 % of patients with microscopic polyangiitis have glomerulonephritis. Hemorrhagic pulmonary alveolar capillaritis is common in patients with microscopic polyangiitis. Histologically, the acute vascular lesions, for example, affecting dermal venules or small visceral arteries, are characterized by segmental fibrinoid necrosis, and mural and perivascular neutrophilic infiltration with leukocytoclasia (Figs. 9.7 and 9.8). Within a few days, the predominant inflammatory cells in the vasculitic lesions

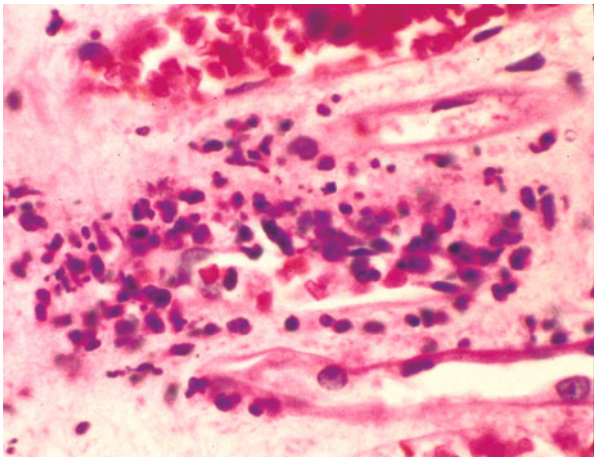

Fig. 9.8 Medullary vasa recta in a renal biopsy from a patient with granulomatosis with polyangiitis (Wegener's granulomatosis) showing angiitis with leukocytoclasia (H&E)

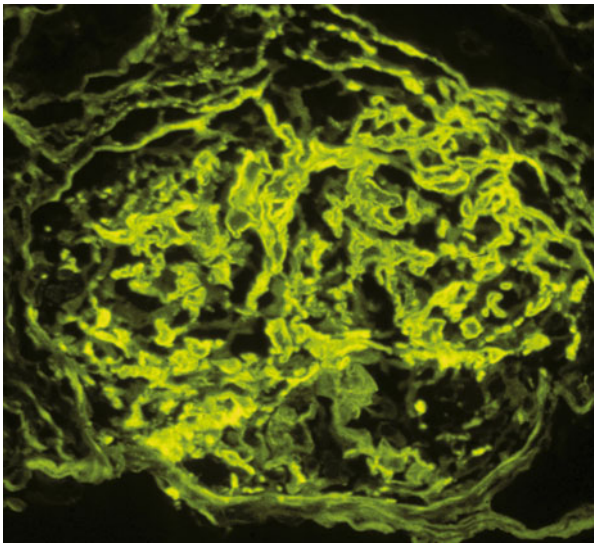

Fig. 9.9 Glomerulus from a patient with ANCA crescentic glomerulonephritis with irregular staining of a large crescent by direct immunofluorescence microscopy using an antibody specific for fibrin

evolve from neutrophils to mononuclear leukocytes, and the fibrinoid necrosis transforms into fibrosis.

Granulomatosis with polyangiitis (Wegener's granulomatosis) (GPA) is characterized by granulomatous inflammation that frequently is accompanied by necrotizing vasculitis affecting capillaries, venules, arterioles, and small- to medium-sized arteries [4, 13, 14]. Necrotizing granulomatous inflammation is observed most often in the upper and lower respiratory tract but occasionally in other tissues, such as the orbit, skin, and kidneys. The granulomatous lesions typically have extensive necrosis with infiltrating mononuclear and polymorphonuclear leukocytes with scattered multinucleated giant cells. Necrotizing glomerulonephritis is common (Fig. 9.4).

The vasculitis in the lungs and elsewhere can involve arteries, arterioles, veins, venules, and capillaries and can be granulomatous or nongranulomatous. The latter is histologically identical to the necrotizing vasculitis of MPA and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (EGPA).

EGPA is characterized by eosinophil-rich granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels that is associated with asthma and blood eosinophilia [13, 14]. The vasculitis of EGPA cannot be definitively differentiated by histology from the vasculitis of GPA or MPA; however, there is a tendency for more eosinophils among the infiltrating leukocytes. Likewise, the necrotizing granulomatous inflammation of EGPA resembles that of GPA but tends to have more eosinophils. The vasculitis of EGPA most often affects the lungs, heart, peripheral nervous system, skin, gut, and kidneys. The pauci-immune focal necrotizing glomerulonephritis of EGPA usually is less severe than the glomerulonephritis in GPA or MPA but is histologically indistinguishable.

Etiology/Pathogenesis

Overall, approximately 90 % of patients with pauci-immune crescentic glomerulonephritis or pauci-immune small-vessel vasculitis have circulating ANCA [4, 15]. The two major antigen specificities of ANCA are for proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). Either specificity can occur in any clinicopathologic variant of ANCA disease, but MPO-ANCA is most prevalent in renal-limited disease and PR3-ANCA is most prevalent in GPA. Overall, <50 % of patients with EGPA have ANCA; however, >90 % of EGPA patients with crescentic glomerulonephritis have ANCA, usually MPO-ANCA. In Asia, MPO-ANCA is much more frequent than PR3-ANCA in all clinicopathologic variants [18]. Genetic associates and important disease characteristics, such as response to therapy and frequency of relapses, correlate better with ANCA specificity than with clinicopathologic phenotype [19].

There is compelling in vitro and animal model experimental data showing that ANCA IgG causes glomerulonephritis and vasculitis, probably by direct interaction with neutrophils (and possibly monocytes) resulting in neutrophil activation with release of complement-activating factors, lytic enzymes, and reactive oxygen radicals that cause the inflammatory injury to glomeruli and vessels [20, 21]. Clinical support is provided by the observation that a neonate developed pulmonary hemorrhage and nephritis following transplacental transfer of maternal MPO-ANCA IgG [22] as well as the effectiveness of therapy that reduce circulating antibody levels, such as immunosuppressive drugs, anti-B antibodies, and plasma exchange [15].

Clinicopathologic Correlations

All variants of pauci-immune small-vessel vasculitis and glomerulonephritis are treated with high-dose corticosteroids and immunosuppressive agents when there is active and progressive glomerulonephritis [15, 23, 24]. Remission of

glomerulonephritis and other vasculitic manifestations can be induced in approximately 80 % of patients. However, a third or more of patients may have one of more relapses within 5 years. Nevertheless, the 5-year renal and patient survival approaches 80 % if treatment is instituted early enough. As with anti-GBM disease, the renal outcome in ANCA disease correlates best with the serum creatinine at the time treatment was begun. A pathologic classification system categorizes pauci-immune crescentic glomerulonephritis as focal (50 % or more histologically normal glomeruli), crescentic (50 % or more crescents), sclerotic (50 % or more global sclerosis), or mixed (<50 % normal, crescentic, and sclerotic glomeruli) [25]. Renal function at presentation and the outcome is best for the focal class and worst for the sclerotic class.

Polyarteritis Nodosa

Introduction/Clinical Setting

Polyarteritis nodosa is a medium-vessel vasculitis because it primarily affects medium-sized arteries rather than smaller vessels [3, 5, 13, 14]. The other major category of medium-vessel vasculitis is Kawasaki disease (Table 9.2). Medium-vessel vasculitides have a predilection for main visceral arteries, such as the coronary, hepatic, renal, and mesenteric arteries and their major first- and second-order branches. These same vessels, however, also can be involved with large-vessel vasculitides and small-vessel vasculitides. In the kidney, the major targets of polyarteritis nodosa and Kawasaki disease are the interlobar and arcuate arteries, whereas ANCA small-vessel vasculitis primarily targets interlobular arteries, arterioles, vasa rectae, and glomerular capillaries [3].

The term *polyarteritis nodosa* has been used quite variably over the years [2]. Some definitions have allowed involvement of vessels smaller than arteries, including glomerulonephritis. However, the Chapel Hill nomenclature system confined the term to necrotizing arteritis that affects arteries but does not involve vessels smaller than arteries and thus does not cause glomerulonephritis [13, 14]. If pauci-immune necrotizing arteritis is associated with glomerulonephritis, this would be categorized as microscopic polyangiitis by the Chapel Hill nomenclature system.

Pathologic Findings

Light Microscopy

By light microscopy, polyarteritis nodosa is characterized by segmental transmural fibrinoid necrosis and accompanying inflammation (Fig. 9.10), which initially has predominantly neutrophils and sometimes eosinophils but within several days has predominantly mononuclear leukocytes. The segmental inflammation and necrosis in artery walls may produce an aneurysm (actually a pseudoaneurysm) by eroding

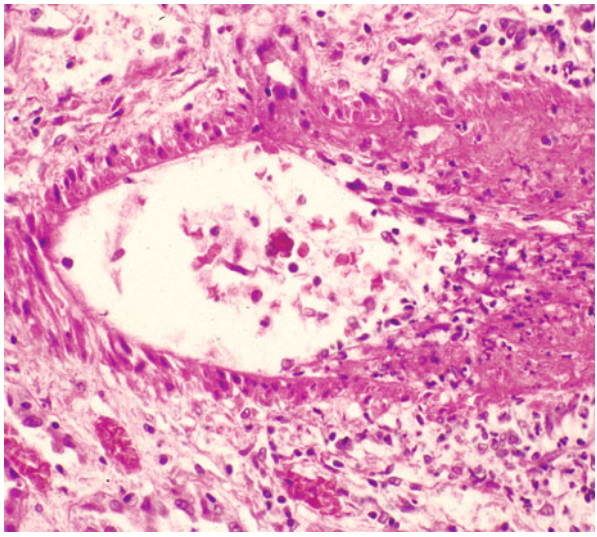

Fig. 9.10 Arcuate artery in a renal biopsy from a patient with polyarteritis nodosa showing segmental fibrinoid necrosis with associated leukocyte infiltration and leukocytoclasia (H&E)

through the artery wall into the perivascular tissue. Infarction and hemorrhage are the major consequences of renal involvement by polyarteritis nodosa.

Polyarteritis nodosa is treated with high-dose corticosteroids, often in combination with cytotoxic drugs such as cyclophosphamide [26]. Polyarteritis nodosa is less likely to recur after induction of remission than is microscopic polyangiitis.

Kawasaki Disease

The sine qua non of Kawasaki disease is the mucocutaneous lymph node syndrome, which includes fever, cutaneous and oral mucosal erythema and sloughing, and lymphadenopathy [5, 13, 14, 27]. Kawasaki disease is a disease of childhood that rarely occurs after the age of 5 years. The vasculitic lesions of Kawasaki disease involve predominantly small- and medium-sized arteries, with a special predilection for the coronary arteries [27]. The histologic lesions are characterized by segmental transmural edema and necrosis with infiltration by monocytes and neutrophils (Fig. 9.11). The necrotizing lesions of Kawasaki disease have less fibrinoid material and more edema than the necrotizing lesions of polyarteritis nodosa.

Kawasaki disease rarely causes clinically significant renal disease; however, postmortem examination demonstrates substantial involvement of renal arteritis in many patients who die from Kawasaki disease [27].

The arteritis of Kawasaki disease responds very well to treatment with aspirin and high-dose intravenous immunoglobulin [28].

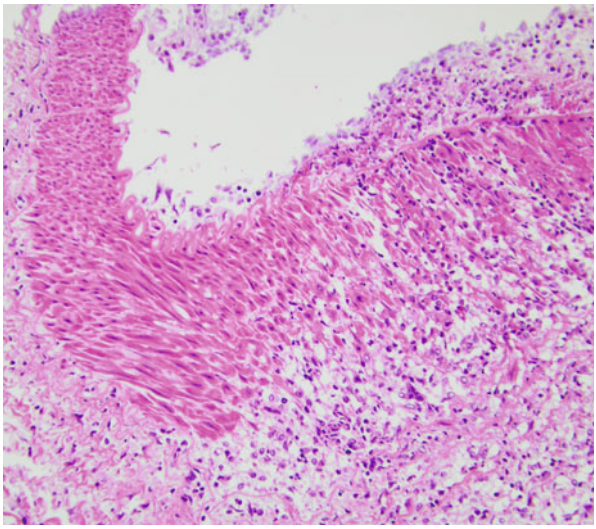

Fig. 9.11 Lobar artery in a postmortem kidney specimen from a patient with Kawasaki disease showing segmental necrosis with associated edema and leukocyte infiltration (H&E)

Large-Vessel Vasculitis

Introduction/Clinical Setting

Large-vessel vasculitis affects the aorta and its major branches with transmural chronic inflammation that is characterized even in the acute phase by infiltration of predominantly mononuclear leukocytes, often with accompanying multinucleated giant cells [5, 13, 14]. The two major clinicopathologic variants are giant cell arteritis and Takayasu arteritis. The best distinguishing feature between these two variants is the age of the patient [13, 14]. Giant cell arteritis rarely occurs before 50 years of age, and Takayasu arteritis virtually always occurs prior to the age of 50. Postmortem examination reveals that pathologic involvement of the kidneys by large-vessel vasculitis is much more common than clinically significant involvement [3]. The most common clinical manifestation is renovascular hypertension, which results from involvement of the main renal artery or its major branches, especially the lobar (interlobar) arteries [29].

Pathologic Findings

The pathologic hallmark of large-vessel vasculitis is transmural infiltration of artery walls by mononuclear leukocytes accompanied by variable numbers of multinucleated giant cells (Fig. 9.12) [5]. This often results in thickening of the intima and narrowing of the lumen, which causes ischemia to the tissue supplied by the artery.

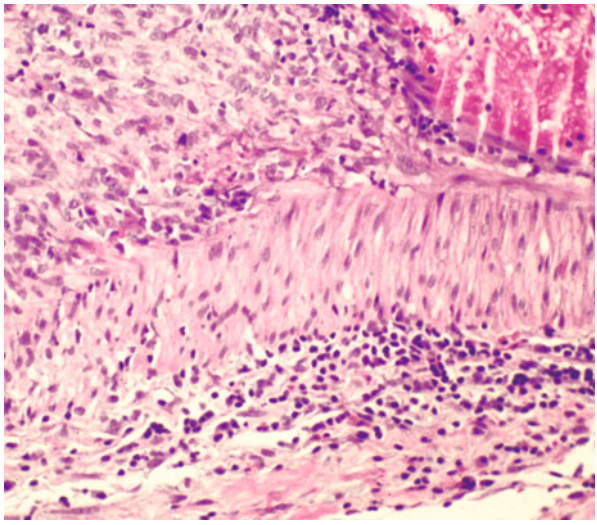

Fig. 9.12 Renal artery in a nephrectomy specimen from a patient with giant cell arteritis showing (on the *left*) transmural inflammation with a markedly thickened intima that is impinging on the lumen (H&E)

Involvement of the renal artery can cause a pattern of renal artery stenosis atrophy in the renal parenchyma that is characterized by marked reduction in the size of the tubules and resultant clustering of glomeruli close to one another. This pattern of atrophy has much less interstitial fibrosis and inflammation than the ischemic atrophy of hypertensive arterionephrosclerosis.

Large-vessel vasculitis that is causing substantial ischemic injury is treated with corticosteroids [30, 31]. Patients with severe disease or steroid toxicity require other immunosuppressive agents, e.g., cyclophosphamide, mycophenolate mofetil, or azathioprine. Reconstructive vascular surgery (stent or bypass) may be required to improve flow to ischemic tissues.

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Part V

Vascular Diseases

Nephrosclerosis and Hypertension

10

Arterionephrosclerosis

Introduction/Clinical Setting

Approximately 60 million people in the United States have hypertension. Many are undiagnosed or untreated. Different populations have different risks and different consequences of hypertension. Increased hypertension is seen with aging, positive family history, African-American race, and exogenous factors such as smoking. Although African-Americans make up only 12 % of the US population, they are fivefold overrepresented among patients with end-stage renal disease (ESRD) presumed due to hypertension [1, 2]. Hypertension is associated with significant morbidity and mortality due both to cardiovascular and renal diseases [1–5].

Essential hypertension is diagnosed when no cause is found. Hypertension may also be secondary to various hormonal abnormalities, including excess aldosterone, norepinephrine, or epinephrine, or produced from adrenal cortical, medullary, or other tumors; renin-producing tumors; or hypercalcemia or hyperparathyroidism. Other secondary causes include neurogenic, iatrogenic, and structural lesions (e.g., coarctation of the aorta).

Renal hypertension refers to hypertension secondary to renal disease. Chronic renal disease is the most common form of secondary hypertension (5–6 % of all hypertension). The kidneys modulate blood pressure in several ways: They modulate salt/water balance under the influence of *aldosterone*. The kidney is also a major site of renin production, which allows generation of *angiotensin II*, an important vasoconstrictor and stimulus for aldosterone secretion. In renovascular disease (i.e., stenosis of the renal artery), renal ischemia is thought to be the stimulus that increases renin-angiotensin system activity, thereby increasing systemic blood pressure. In renal parenchymal disease, multiple factors contribute to increased blood pressure. The decreased mass of functioning nephrons leads to a decrease in the glomerular filtration rate (GFR), leading to increased extracellular volume and increased angiotensin, aldosterone, and other vasoactive substances.

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The most common complications in untreated hypertension are cardiac, renal, and retinal disease. Half of hypertensive patients die of cardiac disease, 10–15 % of cerebrovascular disease, and about 10 % of kidney failure. Treatment to decrease blood pressure reduces mortality and especially reduces the incidence of cerebrovascular accidents. Hypertension accelerates the decline in GFR characteristic of many chronic kidney diseases, whether the primary cause is hypertension associated or not. Chronic kidney disease is common, affecting 195,000 Americans, with 45,000 new patients enrolled in end-stage treatment Medicare programs yearly. It has been postulated that direct transmission of increased blood pressure to the glomerulus increases injury. Other mechanisms may also play a role, however, since antihypertensive drugs have benefit even in nonhypertensive patients with chronic kidney disease (see below). Recent studies point to strong genetic factors linked to risk of hypertension-associated kidney injury, although mechanisms are not yet elucidated.

Pathologic Findings

Gross Findings/Light Microscopy

"Benign" nephrosclerosis results in small kidneys with finely granular surface and thinned cortex in late stages. Malignant (accelerated) nephrosclerosis grossly shows petechial hemorrhage of the subcapsular surface, with mottling and occasional areas of infarct. Microscopically, in "benign" arterionephrosclerosis there is vascular wall medial thickening with frequent afferent arteriolar hyaline deposits and varying degree of intimal fibrosis. The hyalinization is due to endothelial injury and increased pressure, leading to an insudate of plasma macromolecules. There are associated focal glomerular ischemic changes with variable thickening and wrinkling of the basement membrane and/or global sclerosis, tubular atrophy, and interstitial fibrosis (Fig. 10.1). Global sclerosis more commonly is of the obsolescent type, with fibrous material obliterating Bowman's space. Solidified glomeruli, where the tuft is globally sclerosed without collagen in Bowman's space, has been called "decompensated" arterionephrosclerosis. Secondary focal segmental glomerulosclerosis (FSGS) may also occur, often with associated glomerular basement membrane (GBM) corrugation and filling of Bowman's space with fibrous material [4–10]. These morphologic features hint that the segmental sclerotic process is secondary to hypertension-associated injury, rather than idiopathic FSGS. The lesions associated with accelerated hypertension consist of mucoid change of the arterioles, often with red blood cell (RBC) fragments within the wall. In malignant hypertension, arterioles show fibrinoid necrosis, and interlobular arteries have a concentric onion-skin pattern of intimal proliferation and fibrosis, overlapping with the appearance of scleroderma and chronic thrombotic microangiopathy (Fig. 10.2) (see below). There is proportional tubulointerstitial fibrosis in arterionephrosclerosis.

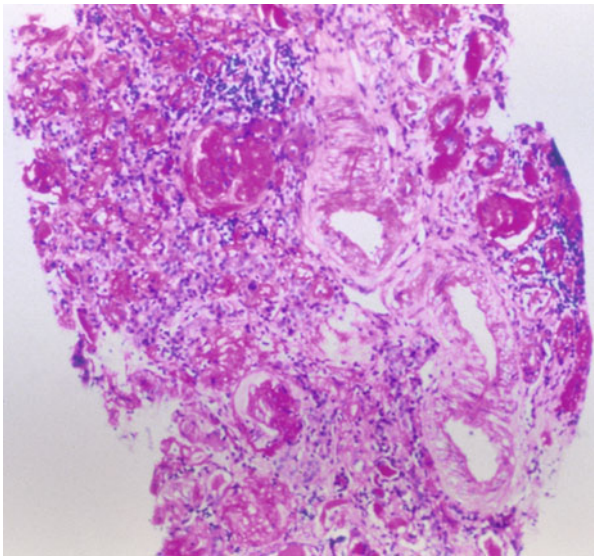

Fig. 10.1 Arterial and arteriolar medial thickening, intimal and interstitial fibrosis, tubular atrophy, and global sclerosis in arterionephrosclerosis (PAS)

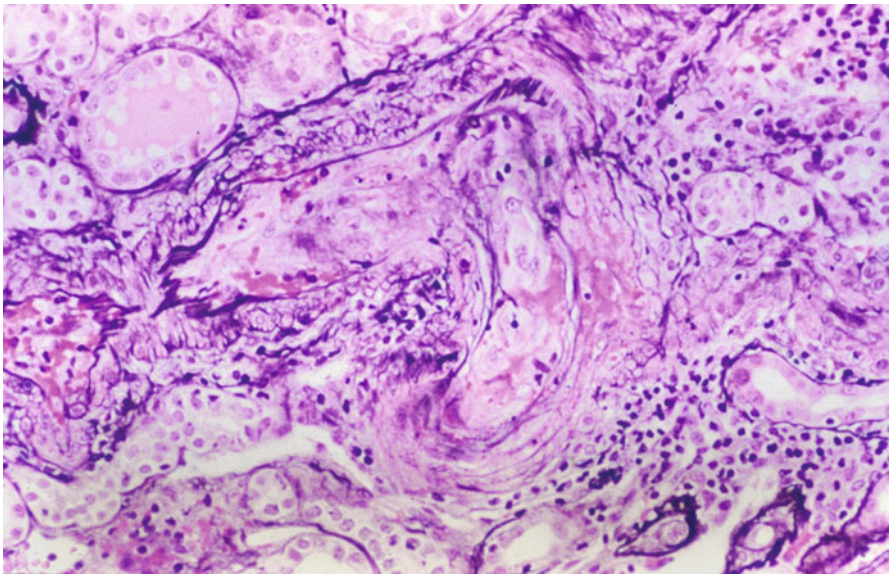

Fig. 10.2 Vascular fibrinoid necrosis and thrombosis in malignant hypertension (Jones silver stain)

Immunofluorescence may show trapping of IgM and C3 in glomeruli, but there are no immune complex-type deposits. In malignant hypertension, fibrin/fibrinogen staining may be present in necrosed arterioles/arteries and injured glomeruli.

Electron microscopy confirms the corrugated, wrinkled GBM and ischemic changes with increased lamina rara interna but without immune deposits. Hyaline may be present in sclerosed segments. Some foot process effacement of podocytes may also be present, but it is usually not extensive.

Although none of the above lesions are pathognomonic, the constellation of these changes in the absence of other lesions of primary glomerular disease is indicative of arterionephrosclerosis.

Etiology/Pathogenesis

Hypertension has been presumed to cause end-organ damage in the kidney, and hypertension undoubtedly accelerates progressive scarring of renal parenchyma, but the relationship of hypertension and arterionephrosclerosis is not simple and linear [11]. In a large series of renal biopsies in patients with essential hypertension, arterionephrosclerosis was present in the vast majority, and the severity of arteriolar sclerosis correlated significantly with level of diastolic blood pressure [9]. However, in several large autopsy series of patients with presumed benign hypertension, significant renal lesions were rare [4, 5]. Further, the level of blood pressure does not directly predict degree of end-organ damage: African-Americans have higher risk for more severe end-organ damage at any level of blood pressure [2]. The African American Study of Kidney Disease (AASK) trial showed that African-Americans with presumed arterionephrosclerosis indeed did not have other lesions, by renal biopsy, but the global sclerosis was severe and did not correlate with vascular sclerosis [12]. It is possible that underlying microvascular disease causes the hypertension and the renal disease in susceptible patients. In a large study of patients without clinically evident kidney disease at baseline, even relatively modest elevation in blood pressure was an independent risk factor for development of end-stage kidney disease [13]. Underlying causes in addition to direct hemodynamic injury could include possible genetic and structural components, such as decreased nephron number and consequently fewer, but enlarged glomeruli [14]. Whether hypertension can cause kidney scarring, or a primary microvascular renal injury causes the hypertension, which in turn accelerates the sclerosis, has not been proven. Apolipoprotein L1 allele variants are tightly linked to excess arterionephrosclerosis, focal segmental glomerulosclerosis, and HIV-associated nephropathy, but not diabetic nephropathy in African-Americans [15]. The ApoL1 allele variant confers protection against some trypanosomes, which could have a survival advantage and thus, by natural selection, have led to its high prevalence in African-Americans. The mechanisms of increased risk of kidney disease are unknown [16].

Our data suggest a different phenotype of scarring in hypertension-attributable nephrosclerosis in African-Americans vs. Caucasians, with solidified global glomerulosclerosis prevalent in the former, contrasting with the obsolescent type (see above) in Caucasians [17]. The AASK trial has shown that angiotensin-converting enzyme inhibitors (ACEIs) are effective in protecting renal function in African-Americans, although multiple additional drugs were needed to achieve blood pressure control [18].

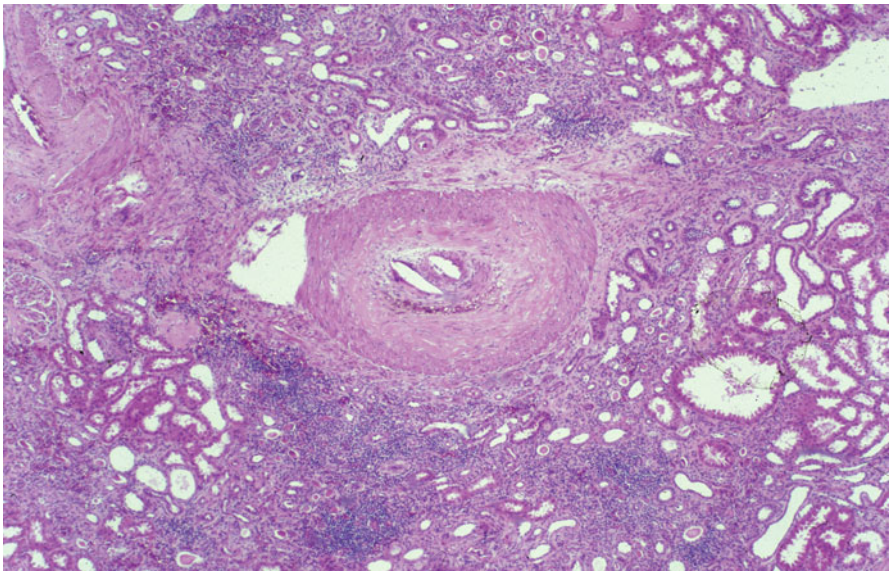

Fig. 10.3 Cholesterol emboli in artery with surrounding mononuclear and early fibrotic reaction (PAS)

Cholesterol Emboli

Introduction/Clinical Setting

Patients with significant atherosclerosis are also at risk for cholesterol embolization due to dislodgment of atheromatous plaque material. These emboli shower organs downstream from the site of origin in the aorta, and thus often involve the kidney, skin, gastrointestinal tract, adrenals, pancreas, and testes. Cholesterol emboli may occur spontaneously or after an invasive vascular procedure. This entity mimics vasculitis clinically and presents with acute renal failure, new-onset or exacerbated hypertension, and eosinophilia [19–21]. Cholesterol emboli may underlie 5–10 % of all acute renal failure cases [22]. In some patients, there is associated presumed secondary FSGS, with proteinuria. Prognosis is generally poor, with older series reporting about 60–80 % mortality at 1 year, with improvement with more aggressive supportive therapy in recent series [22].

Pathologic Findings

Cholesterol crystals usually lodge in and occlude interlobular size arteries (Fig. 10.3). The crystals themselves are dissolved by processing of tissue, but cleft-shaped empty spaces remain, with surrounding mononuclear cell reaction, which over weeks organizes to fibrous tissue. Vessels typically show associated arteriosclerosis, with proportional tubulointerstitial fibrosis and glomerulosclerosis

[20, 21, 23]. The cholesterol emboli are very focally distributed, and serial section analysis may be necessary to detect diagnostic lesions. Immunofluorescence and electron microscopy do not show any specific lesions.

Scleroderma (Progressive Systemic Sclerosis)

Introduction/Clinical Setting

Scleroderma is a multisystem disease that affects the skin, the GI tract, the lung, the heart, and the kidney. Scleroderma is classified as a limited or diffuse cutaneous type [24]. In the limited form, the disease manifests in hands, arms, and face with Raynaud's phenomenon preceding fibrosis. Diffuse cutaneous scleroderma involves the skin and one or more internal organs, most often kidneys, esophagus, heart, and lungs. Kidney involvement occurs in approximately 60–70 % of patients. Scleroderma renal crisis, manifest by malignant hypertension, acute kidney injury, and some even with infarcts, previously was observed in approximately 20 % of patients with scleroderma but may be decreasing due to widespread use of angiotensin-converting enzyme inhibitors in these patients [25, 26]. Age at onset of systemic sclerosis is 30–50 years, and females are affected more than males. Patients present with renal manifestations of acute kidney injury and malignant hypertension and may have significant proteinuria acutely.

Pathologic Findings

Gross Findings/Light Microscopy

Grossly, petechial hemorrhages or even renal infarcts may be present in patients with scleroderma renal crisis, similar to hemolytic uremic syndrome or malignant hypertension. Microscopically, there is fibrinoid necrosis of afferent arterioles. Interlobular arteries show intimal thickening, proliferation of endothelial cells, and edema. Red blood cell fragments are often present within the injured vessel wall, and there may be vessel wall necrosis and/or fibrin thrombi within vessels. Glomeruli may show ischemic collapse or fibrinoid necrosis. In chronic injury, arterioles show reduplication of the elastic internal lamina, the so-called onion-skin pattern (Fig. 10.4). Tubules may show degeneration and even necrosis, especially in scleroderma crisis. Tubulointerstitial fibrosis develops with chronic injury [23, 25].

Immunofluorescence Microscopy

There are no immune complexes, although sclerotic segments of glomeruli may show IgM and C3. Necrosed vessels may show fibrin and fibrinogen.

Electron Microscopy

There is corrugation of the GBM and increased lucency of the lamina rara interna, without immune deposits.

Thus, the pathologic appearance of scleroderma overlaps with that of malignant hypertension and thrombotic microangiopathy (TMA) as seen in hemolytic uremic

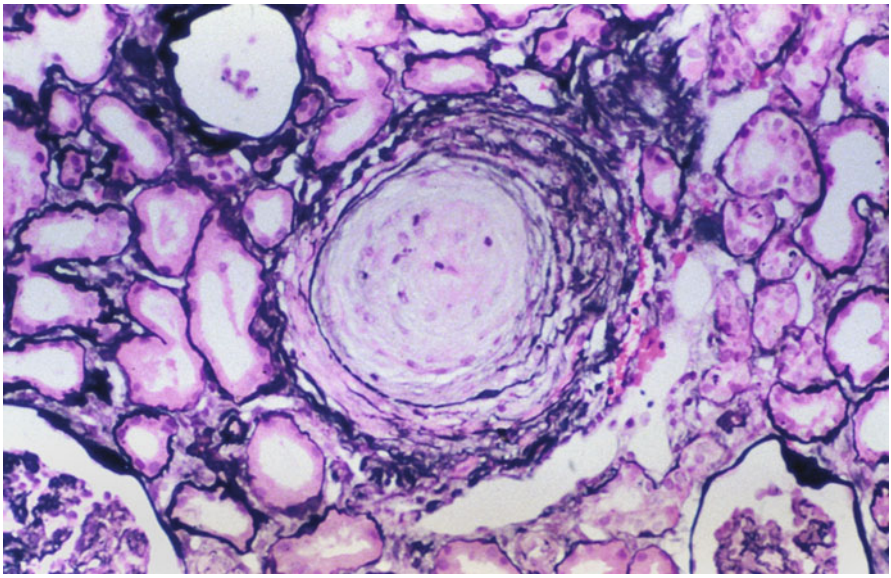

Fig. 10.4 Onion-skin appearance in scleroderma with concentric intimal proliferation and fibrosis and mucoid change (Jones silver stain)

syndromes (HUS) (see Chap. 11). Idiopathic malignant hypertension tends to involve smaller vessels, that is, afferent arterioles, whereas scleroderma may extend to interlobular size and larger vessels, and the TMA in HUS typically involves primarily glomeruli. However, distinction of scleroderma and malignant hypertension solely on morphologic grounds is not feasible, and clinicopathologic correlation is required for specific diagnosis.

Etiology/Pathogenesis

The pathogenesis of scleroderma is probably immune with unknown inciting events. Endothelial injury occurs early in scleroderma patients, although the inciting injury is unknown. Endothelial damage and vacuolization is followed by perivascular mononuclear infiltrates, obliteration of the microvasculature, and loss of capillaries. Excess collagen accumulation then ensues, linked to increased profibrotic factors. Autoantibodies are often present, including anti-topoisomerase I, anti-centromere, and anti-RNA polymerase, each present in 25 %. Only one of these markers may be positive in any one patient. Some studies have demonstrated cytotoxic anti-endothelial factors in serum from scleroderma patients. Imbalance of vasodilators (e.g., nitric oxide, vasodilatory neuropeptides such as calcitonin gene-related peptide and substance P) and vasoconstrictors (e.g., endothelin-1, serotonin, thromboxane A_2) has been described in scleroderma patients. Prolonged vasoconstriction could contribute to structural changes and fibrosis in the kidney as well. A defect in circulating endothelial progenitor cells in scleroderma patients has been proposed to underlie deficiency of vasculogenesis and repair in response to endothelial injury, contributing to sclerosis [24, 27].

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Thrombotic Microangiopathies

11

Introduction/Clinical Setting

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) share the morphologic lesion of thrombotic microangiopathy (TMA), characterized by thrombi occluding the microvasculature. The HUS and TTP syndromes overlap clinically [1–9]; however, there are differing pathogeneses (see below). TTP is more common in adults and is characterized by fever, bleeding, hemolytic anemia, kidney injury, and neurologic impairment. Hemolytic uremic syndrome is characterized by acute kidney injury, nonimmune hemolytic anemia, and thrombocytopenia, and it is most common in infants and small children. The renal manifestations at presentation include hematuria and low-grade proteinuria with elevated creatinine in severe cases. Intravascular hemolysis is evident by increased bilirubin and lactate dehydrogenase (LDH), reticulocytosis, and low haptoglobin. Both HUS and TTP cause thrombocytopenia. In our experience, and that of others, the peripheral blood manifestations may not be detected by the time a renal biopsy is performed, especially in the transplant setting [10].

Pathologic Findings

Light Microscopy

Fibrin and platelet thrombi are present, primarily in the glomeruli [1–4]. Fibrin is best visualized on hematoxylin and eosin or silver stains. Lesions may extend to arterioles, with some overlap with progressive malignant hypertension and scleroderma, where arteriolar and even larger vessel involvement occurs (Figs. 11.1 and 11.2). Mesangiolysis occurs frequently but is a focal, subtle lesion that may be overlooked [11]. Mesangial areas seem to "unravel," resulting in very long, sausage-shaped capillary loops due to the loss of mesangial integrity and coalescence of adjoining loops.

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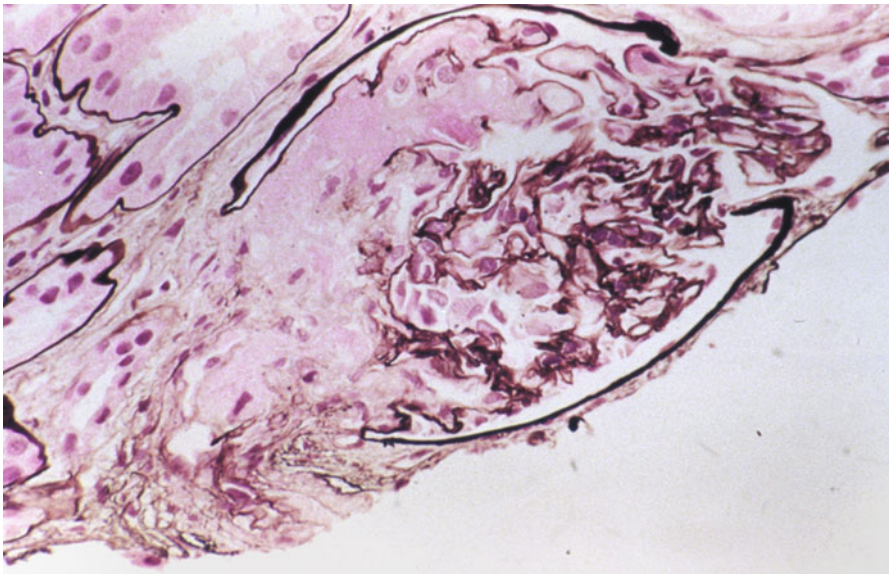

Fig. 11.1 Segmental red blood cells (RBCs) and fibrin in capillary loops and arteriole in glomerulus in thrombotic microangiopathy (Jones silver stain)

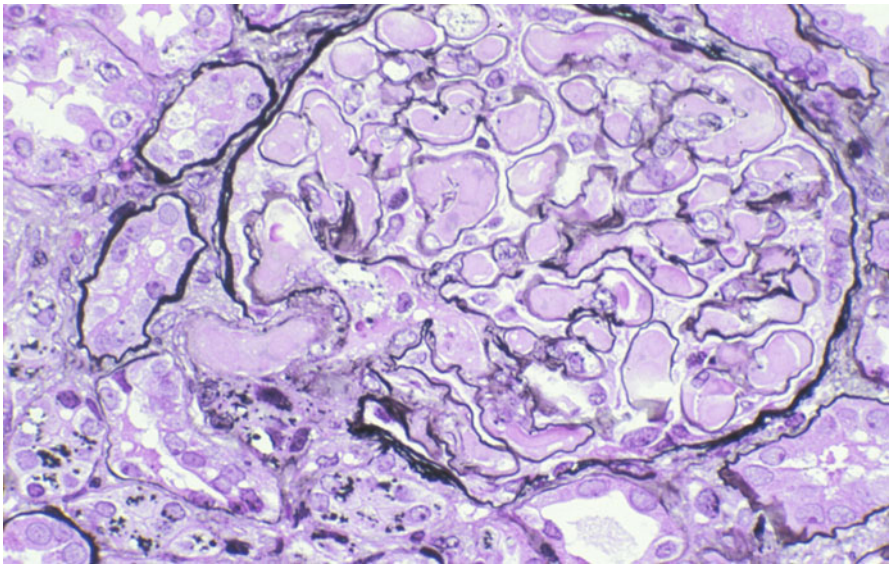

Fig. 11.2 Entire glomerulus and arteriole are filled with chunky, eosinophilic fibrin in this case of hemolytic uremic syndrome (HUS) (Jones silver stain)

In infants and young children, thrombotic lesions predominate [4]. In older children and adults, varied lesions occur. Many glomeruli may show only ischemic changes with corrugation of the glomerular basement membrane and retraction and

collapse of the glomerular tuft. Segmental glomerular necrosis may be seen with rare well-developed fibrin thrombi. Arterioles and arteries, when involved, show thrombosis and sometimes necrosis of the vessel wall, with intimal swelling, mucoid change, and intimal proliferation. Fragmentation of red blood cells within the vessel wall may also be present. Tubular and interstitial changes are proportional to the degree of glomerular changes. In severe cases, cortical necrosis can occur [12].

Secondary changes late in the course include glomerular sclerosis, either segmental or global. Reduplication of the glomerular basement membrane may occur in the late phase due to organization following endothelial injury.

Immunofluorescence Microscopy

Immunofluorescence studies show no immunoglobulin deposits. Complement and immunoglobulin M (IgM) may be present in sclerotic areas. Fibrin and fibrinogen are present in affected glomeruli and arterioles.

Electron Microscopy

Endothelial cells are frequently swollen, and detachment may be seen by electron microscopy. Fibrin tactoids may be present in affected glomeruli (Fig. 11.3). Mesangiolysis is a prominent finding in early phases [11].

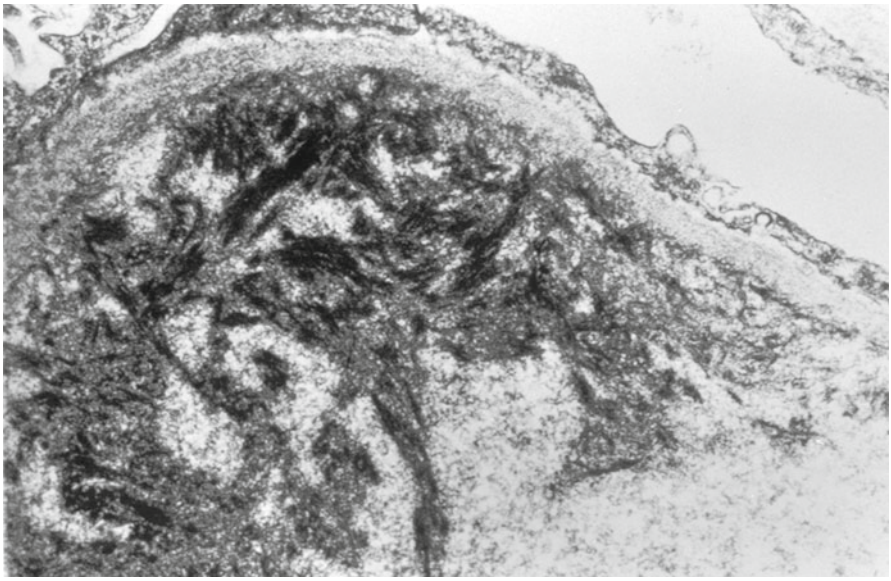

Fig. 11.3 Fibrin tactoids in subendothelial area in thrombotic microangiopathy (electron microscopy)

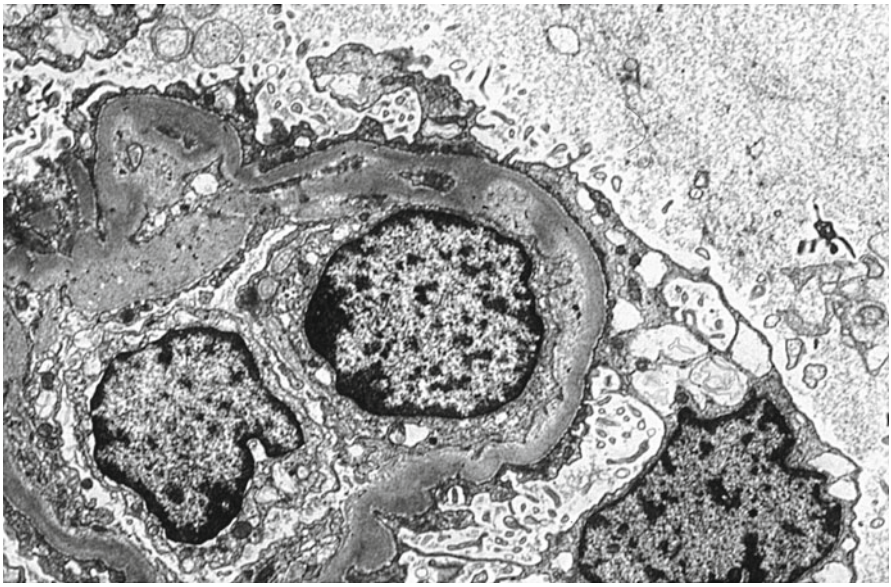

Fig. 11.4 Increased lucency of lamina rara interna and glomerular basement membrane (GBM) corrugation in HUS (electron microscopy)

In the subacute and chronic phase, the increased lucency of the lamina rara interna is in part correlated to breakdown of coagulation products (Fig. 11.4). This zone contains breakdown products of fibrin, laminin, and fibronectin [2].

Etiology/Pathogenesis

Thrombotic microangiopathy is the key lesion present in both HUS and TTP. Numerous etiologies are recognized (Table 11.1) [7, 13, 14]. HUS/TTP has also been classified as diarrhea associated or not, D+ or D–. The typical diarrhea-associated (D+) form of HUS accounts for the vast majority of HUS cases and is most often associated with Shiga-like toxin or verotoxin [4, 9, 12]. Most of these infections are due to the *Escherichia coli* serotype O157:H7. Verotoxin was associated with ~90 % of cases of HUS in children in North America and Europe. Undercooked hamburger meat is most closely associated with such outbreaks in North America, pointing to cattle as an important reservoir for the implicated *E. coli* serotype O157:H7. In addition, this *E. coli* strain can be transmitted from person to person, and outbreaks associated with swallowing contaminated lake water or ingestion of contaminated fruit or vegetables or cider have occurred. In a recent outbreak, Shiga-toxin-producing *E. coli* O104:H4 was identified and linked to contaminated sprouts, and most patients were adult [15].

The mature verotoxin has alpha and beta subunits. The beta subunits interact with the target cell, most often the endothelial cell, binding to the glycolipid Gb3

Table 11.1 Proposed classification of HUS/TTP

I. Etiology reasonably established:
(a) Infection-induced (e.g., Shiga toxin)
(b) Complement dysregulation (e.g., factor H, I, MCP-1 dysfunction)
(c) ADAMTS13 deficiency
(d) Antiangiogenic drugs
II. Associations, etiology unknown:
(a) HIV
(b) Malignancy, radiation/chemoRx
(c) Calcineurin inhibitors
(d) Pregnancy, OCP, HELLP
(e) Familial not included above
(f) Unclassified

Modified from Besbas et al. [13]
OCP oral contraceptive pills, *HELLP syndrome* hemolysis, elevated liver enzymes, low platelet count

protein. The alpha unit is cleaved and taken up by endocytosis, inactivating 60S ribosomes, thereby causing cell death. The Gb3 receptor for verotoxin is highly expressed in human kidney, perhaps underlying the susceptibility of the kidney to this toxin [16]. However, Gb3 levels were not different in normal children vs. adults, so the excess risk of children for D+ HUS cannot be simply explained by overexpression of Gb3 [17].

D(−) HUS, also called atypical HUS (aHUS), comprises about 10 % of cases of HUS/TTP. With atypical HUS (D–) no diarrheal prodrome is seen, and Shiga-like toxin is not identified. About half of these patients have an underlying genetic abnormality of key regulatory molecules of the complement cascade, such as factor H (CFH), factor I (CFI), or membrane cofactor protein (MCP) [18, 19]. Ongoing activation of complement injures the endothelium and thrombosis ensues. Disease has early onset, before 1 year of age with CFH and CFI defects, and is often relapsing and leads to end-stage kidney disease. In some patients there may be an autoantibody to factor H, with underlying defect of factor H, the so-called DEAP-HUS (deficient for CFHR proteins and factor H autoantibody positive) [19]. Plasmapheresis may be beneficial in these patients. Liver and kidney transplant may be needed for patients with defects in CFH or CFI, which are synthesized in the liver, whereas patients with defect of MCP, a factor synthesized systemically, may generate enough factor from kidney transplant. Eculizumab, a humanized monoclonal antibody against complement protein C5 that thus inhibits activation of the terminal complement pathway, has been used to treat the complement dysregulation [15].

Familial TTP is most often due to constitutional deficiency of a von Willebrand factor (vWF)-cleaving protease, whereas a nonfamilial form of TTP seems to be caused by an acquired inhibitor of this protease. This protease is now called ADAMTS13 (a member of the "*a d*isintegrin *a*nd *m*etalloprotease with *t*hrombo*s*pondin type 1 repeats" family of zinc metalloproteases) [7]. The long vWF multimers activate platelets and cause thrombosis when ADAMTS13 function is defective.

However, there is overlap with varying phenotypes of injury even within the same family and overlap of the HUS-TTP spectrum.

The lesion of thrombotic microangiopathy may also be seen in malignant hypertension; systemic lupus erythematosus, especially when antiphospholipid antibodies are present; pregnancy; scleroderma; and secondary to toxins and in HIV patients [8, 20–26]. Bone marrow transplant patients may develop HUS months after transplantation, with apparent multifactorial etiology. The etiology and pathogenesis of injury in these cases is incompletely understood.

Drugs, including cyclosporine and mitomycin and anti-vascular endothelial-derived growth factor (VEGF) agents, may also cause HUS [19, 27]. VEGF is produced by podocytes in the glomerulus and is necessary for integrity of the endothelial cells. Patients with anti-VEGF therapy, including bevacizumab, sorafenib, and sunitinib, may develop hypertension and proteinuria, presumably related to subtle endothelial injury, or frank TMA [19, 27].

Clinicopathologic Correlations

Histologic distribution of lesions may have some prognostic significance (see below). Age has a major impact on prognosis. Mortality of TTP in adults was nearly 100 % before advent of plasma therapy. Children have a much more benign course, with less than 10 % mortality even when only symptomatic treatment was given. Improved survival in the last 10 years is associated with use of a combination of antiplatelet agents and plasmapheresis [28]. In some series, plasma exchange has resulted in better prognosis than plasma infusion, but the results are not clear-cut. New molecular insights (see above) suggest that plasmapheresis and/or anti-B-cell therapy could be useful when acquired inhibitors of ADAMTS13 are present, whereas plasma replacement theoretically could be indicated in patients with deficiency of this protease or factor H mutation, with normal plasma presumably correcting the deficiency [16, 18]. ADAMTS13 testing has been advocated as a means to distinguish between HUS and TTP, with TTP proposed to result from ADAMTS13 mutation and resulting deficiency [7]. However, there may be overlap both clinically and at a molecular level. Hemolytic uremic syndrome accounts for about half of cases of acute kidney injury in HIV patients and has a poor outcome [22, 26]. The pathogenesis of this association is not known, but animal studies do not support direct HIV infection of intrinsic renal cells as a cause of this lesion.

Long-term follow-up 10 years after HUS has shown a decrease in the glomerular filtration rate (GFR) in half of patients [29]. Histologic distribution of lesions may have some prognostic significance. Degree of histologic damage, rather than initial clinical severity, was the best predictor of long-term prognosis in HUS [30]. Predominantly glomerular involvement has a better outcome than larger vessel involvement. Glomerular predominant injury is the most frequent pattern of injury in children. Hypertension is more frequent with larger vessel, rather than glomerular, injury. Poor prognosis was predicted by cortical necrosis or thrombotic microangiopathy involving >50 % of glomeruli at time of presentation.

Segmental sclerosis was associated with decreased GFR long term. Recurrence in the transplant is very common in familial forms of HUS and is most often associated with graft loss. Initial levels of serum plasminogen activator inhibitor-1 (PAI-1) in patients with HUS also correlated with worse long-term outcome, perhaps because high PAI-1 promotes thrombosis and also inhibits matrix breakdown [31].

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Diabetic Nephropathy

12

Introduction/Clinical Setting

Diabetic nephropathy is a clinical syndrome in a patient with diabetes mellitus that is characterized by persistent albuminuria, worsening proteinuria, hypertension, and progressive renal failure [1–3]. Approximately a third of patients with type 1 insulin-dependent diabetes mellitus (IDDM) and type 2 non-insulin-dependent diabetes mellitus (NIDDM) develop diabetic nephropathy [2]. The pathologic hallmark of diabetic nephropathy is diabetic glomerulosclerosis that results from a progressive increase in extracellular matrix in the glomerular mesangium and glomerular basement membranes [4]. Diabetic glomerulosclerosis is the leading cause of end-stage renal disease in the United States, Europe, and Japan [1].

Pathologic Findings

Light Microscopy

Diabetic nephropathy causes pathologic abnormalities in all of the major structural compartments of the kidney, including the glomeruli, extra-glomerular vessels, interstitium, and tubules [3–15].

The earliest glomerular change is enlargement (hypertrophy, hyperplasia, glomerulomegaly), which corresponds to the early clinical phase of elevated glomerular filtration rate. By the time albuminuria is detectable, there is generalized thickening of glomerular basement membranes (GBMs) and an increase in mesangial matrix material. In the earliest phase, morphometry is required to detect these changes, but eventually the GBM thickening and mesangial expansion is so pronounced that it can be readily discerned by routine light microscopy, especially if a special stain that accentuates collagenous structures is used [e.g., periodic acid–Schiff (PAS), Jones silver, Masson trichrome]. Mild mesangial hypercellularity occasionally accompanies the matrix expansion; thus, care must be taken not

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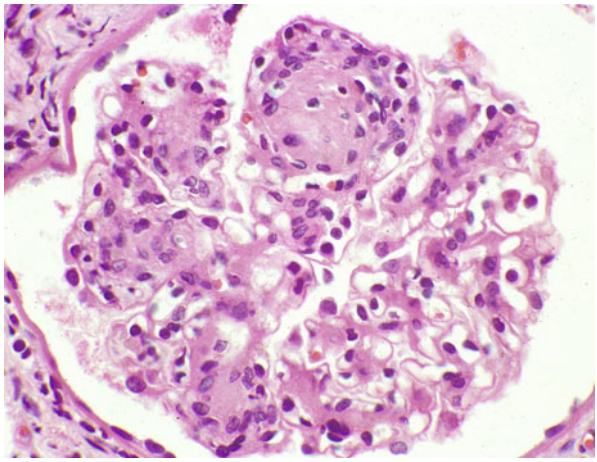

Fig. 12.1 Glomerulus from patient with diabetic glomerulosclerosis showing segmental mesangial matrix expansion and hypercellularity that is most pronounced on the left. The upper pole has a Kimmelstiel–Wilson (K–W) nodule [hematoxylin and eosin (H&E) stain]

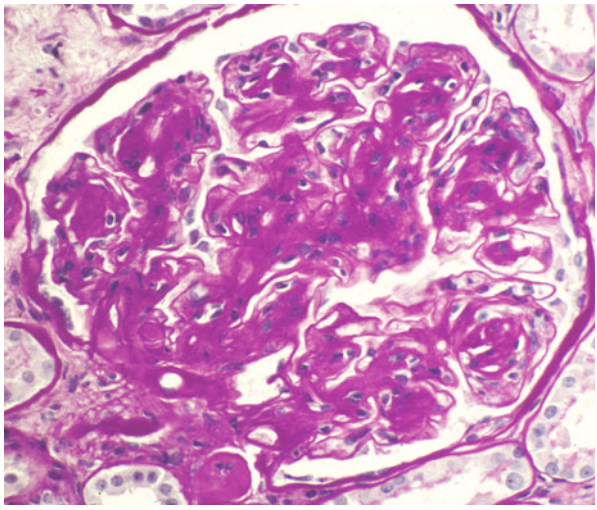

Fig. 12.2 Glomerulus from patient with diabetic glomerulosclerosis showing relatively diffuse mesangial matrix expansion, although there is slight nodularity in some segments [periodic acid–Schiff (PAS) stain]

to misdiagnose early diabetic glomerulosclerosis as mesangioproliferative glomerulonephritis.

Overt glomerular mesangial matrix expansion (glomerulosclerosis) manifests as diffuse mesangial matrix expansion or nodular mesangial matrix expansion or, most often, a combination of both (Figs. 12.1, 12.2, 12.3, 12.4, and 12.5). Glomerular basement membrane thickening usually accompanies the mesangial matrix expansion, but it may be somewhat discordant in severity [6]. The designations *diffuse versus nodular glomerulosclerosis* are primarily of descriptive value in the biopsy report and have no value in the diagnosis because the distinctions do not have clinical significance.

Diffuse diabetic glomerulosclerosis is less specific for diabetic glomerulosclerosis than nodular diabetic glomerulosclerosis. Especially if the clinical presence

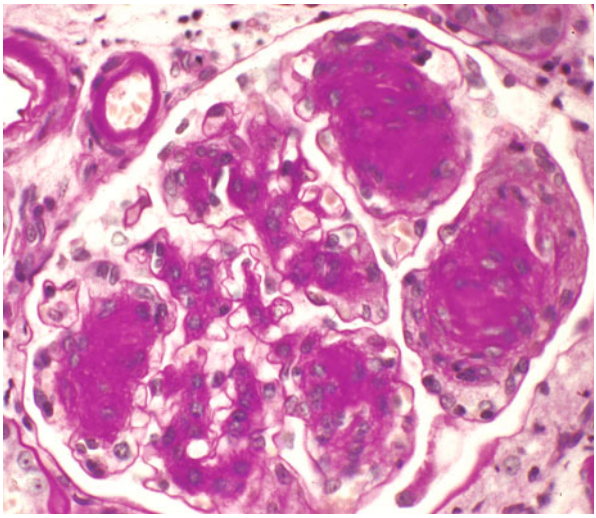

Fig. 12.3 Glomerulus from patient with diabetic glomerulosclerosis showing multiple K–W nodules (PAS stain). The afferent and efferent arterioles in the upper left corner both have PAS-positive hyalinosis

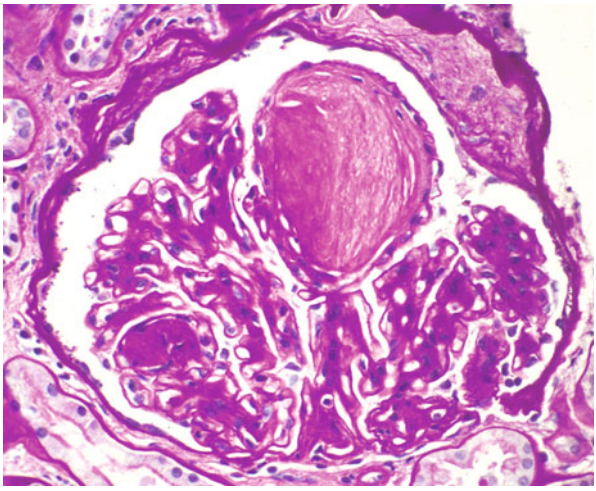

Fig. 12.4 Glomerulus from patient with diabetic glomerulosclerosis showing a large K–W nodule with vague lamination (PAS stain)

of diabetes is not known and there is accompanying mesangial hypercellularity, the light microscopic changes can be mistaken for a mesangioproliferative glomerulonephritis. Careful examination may reveal early mesangial nodules, which will suggest the correct diagnosis.

The nodular lesions of diabetic glomerulosclerosis were first described by Kimmelstiel and Wilson [5] and thus are called Kimmelstiel–Wilson (K–W) nodules. The nodules begin in the heart of the mesangial region of a segment. As the nodule of matrix accrues, there may be increased numbers of mesangial cells, especially at its leading edges (Fig. 12.1). The nodules often are focal and segmental, although occasional specimens have rather diffuse global nodularity. The nodules have the same tinctorial properties as normal mesangial matrix and thus are PAS

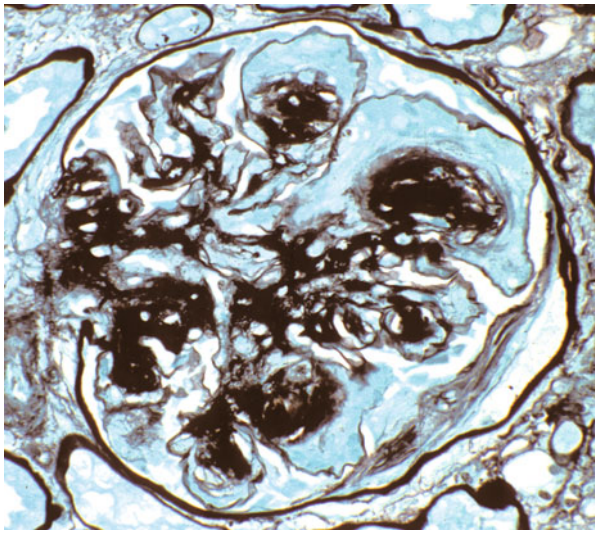

Fig. 12.5 Glomerulus from patient with diabetic glomerulosclerosis showing extensive capillary aneurysm formation as a result of mesangiolysis that has released the GBM from the mesangium (silver stain)

and silver positive (Figs. 12.3, 12.4, and 12.5). The matrix at the center of the nodules may be homogeneous or laminated (Fig. 12.4). K–W nodules may have a corona of capillary aneurysms that are formed as a result of mesangiolysis, which disrupts the attachment points of the GBM to the mesangium (Fig. 12.5).

Glomerular hyalinosis is common in diabetic glomerulosclerosis. These hyaline lesions putatively result from insudation or exudation of plasma proteins from vessels followed by entrapment in matrix. The hyalinosis can occur anywhere in the tuft, but there are two characteristic patterns: hyaline caps and capsular drops. The hyaline caps are produced when the hyalinosis forms arcs at the periphery of segments, sometimes appearing to fill the capillary aneurysms. Capsular drops are spherical accumulations of hyaline material adjacent to or within Bowman's capsule.

Crescent formation is identified in <5 % of specimens with diabetic glomerulosclerosis (Fig. 12.6). When crescents are observed, one should consider the possibility of a concurrent glomerulonephritis that is more often associated with crescents, such as antineutrophil cytoplasmic antibodies (ANCA) disease or anti-GBM disease. However, small numbers of crescents may result from diabetic injury alone, possibly as a consequence of rupture of peripheral capillary aneurysms.

Diabetic glomerulosclerosis is caused by both type 1 (IDDM) and type 2 (NIDDM). The latter is more heterogeneous in appearance [7, 10, 13, 15], in part because it often is altered by concurrent hypertensive and aging changes. At a comparable stage of diabetic nephropathy, the glomerular lesions in type 2 diabetes tend to be less severe than those in type 1 [9, 15].

Arteriolosclerosis and arteriosclerosis are typical accompaniments to diabetic glomerulosclerosis. Arteriolar hyalinosis at the glomerular hilum is ubiquitous with diabetic glomerulosclerosis and typically affects both the afferent and efferent arterioles [4, 12]. Hypertensive hyaline arteriolar sclerosis affects the afferent but not efferent arteriole.

The earliest tubular change is thickening of tubular basement membranes (TBMs) that is analogous to the GBM thickening (Fig. 12.7) [4]. With progressive chronic

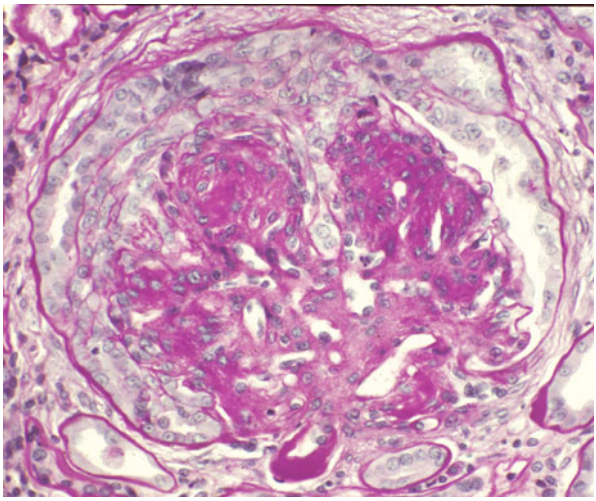

Fig. 12.6 Glomerulus from patient with diabetic glomerulosclerosis showing cellular crescent formation (PAS stain). No other glomerular disease was identified. Note the hyalinosis of the efferent arteriole

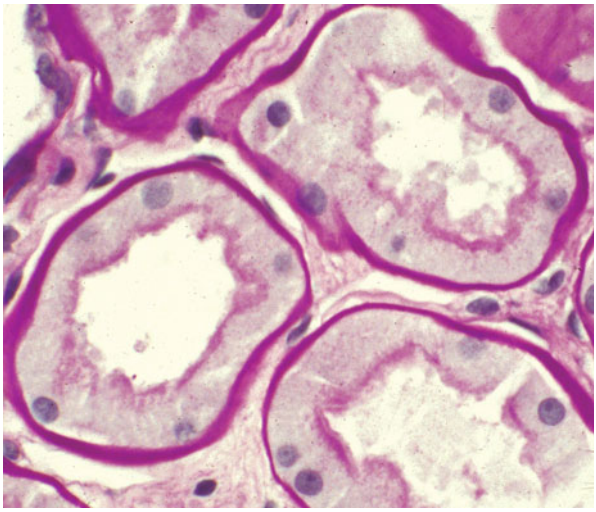

Fig. 12.7 Proximal tubules from patient with diabetic glomerulosclerosis showing markedly thickened tubular basement membranes even though there is no tubular atrophy or interstitial fibrosis (PAS stain)

disease, tubules become atrophic and the interstitium develops fibrosis and chronic inflammation. Except for the marked TBM thickening, these chronic tubulointerstitial changes resemble those seen with any form of progressive glomerular disease.

Immunofluorescence Microscopy

Typical diabetic glomerulosclerosis usually can be diagnosed with reasonable accuracy from the immunofluorescence microscopy findings alone. The characteristic feature is linear staining of GBMs with antisera specific for immunoglobulin G (IgG) and other plasma proteins, although the staining for IgG is usually brightest (Fig. 12.8). Kappa light chain staining usually is brighter than lambda light chain

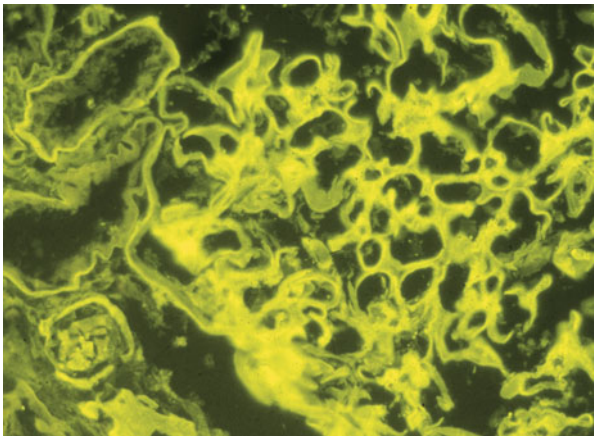

Fig. 12.8 Glomerulus from patient with diabetic glomerulosclerosis showing linear staining of glomerular basement membranes (GBMs) by immunofluorescence microscopy for immunoglobulin G (IgG). Note also the tubular basement membrane (TBM) staining on the left

staining. Immunofluorescence microscopy is useful for ruling out other glomerular diseases that can mimic diabetic glomerulosclerosis by light microscopy, such as monoclonal immunoglobulin deposition disease, membranoproliferative glomerulonephritis, fibrillary glomerulonephritis, and amyloidosis. Bowman's capsule and TBMs also often show linear staining.

In addition to the linear staining for IgG, the background fluorescence often allows identification of the typical nodular sclerosis because the mesangial nodules may also stain for IgG and other determinants.

The overall histology, not to mention the clinical features, usually preclude any confusion with anti-GBM disease as a result of the linear GBM staining for IgG.

Electron Microscopy

Ultrastructural examination confirms the structural abnormalities seen by light microscopy [4, 6, 11] and helps document that there is no other glomerular disease that is mimicking diabetic glomerulosclerosis by light microscopy. For example, monoclonal immunoglobulin deposition disease would have granular densities in the GBM, membranoproliferative glomerulonephritis would have subendothelial or intramembranous dense deposits, and fibrillary glomerulonephritis or amyloidosis would have deposits with a distinctive fibrillary substructure.

The typical finding is thickening of GBMs and mesangial matrix expansion (Fig. 12.9) [4, 11, 14, 15]. The protein insudation (hyalinosis by light microscopy) appears as electron-dense material and should not be misinterpreted as immune complex deposits. In line with the distribution of hyaline seen by light microscopy, this electron-dense insudative material may occur as capsular drops in Bowman's capsule (Fig. 12.9) or as extensive dense accumulations in aneurysmal capillaries forming caps on mesangial nodules. Arterioles with hyalinosis by light microscopy have extensive deposition of insudative homogeneous electron-dense material by electron microscopy [11, 12].

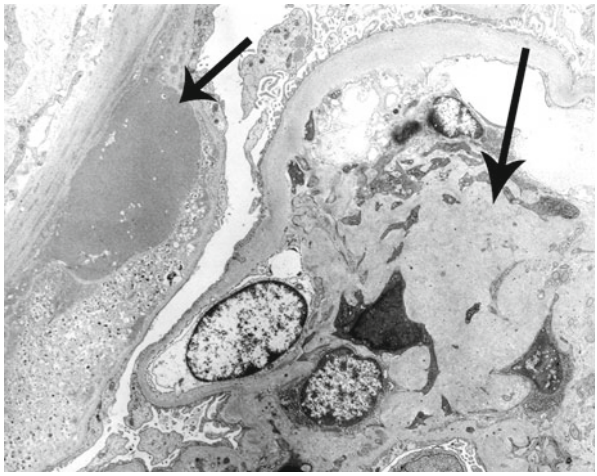

Fig. 12.9 Electron microscopy of a glomerulus from patient with diabetic glomerulosclerosis showing marked increase in mesangial matrix (*long arrow*, lower right quadrant), thickening of the GBM (especially at the *top* of the image), and a capsular drop of electron-dense insudative material (*short arrow*, upper left quadrant)

Table 12.1 Glomerular classification of DN

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 9 years of age and older
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–III

Pathologic Classification

An international collaborative group of renal pathologists under the auspices of the Renal Pathology Society has proposed a pathologic classification system for diabetic nephropathy (Table 12.1) [4]. Class I is characterized by GBM thickening and only mild, nonspecific changes by light microscopy. Class II has mild (IIa) or severe (IIb) mesangial but no nodular sclerosis (Kimmelstiel–Wilson lesions) or global glomerular sclerosis in more than 50 % of glomeruli. Class III has at least one glomerulus with Kimmelstiel–Wilson nodules without advanced glomerular sclerosis. Class IV has more than 50 % global glomerular sclerosis attributable to diabetic

nephropathy. The reproducibility of this classification was documented, but no correlation with outcome was determined [4]. Issues that have been raised concerning this system are that it does not incorporate vascular or tubulointerstitial lesions (although an approach for scoring these lesions is provided), and it does not take into account the different expression and evolution of lesion in type 1 versus type 2 diabetic glomerulosclerosis [13]. Nevertheless, now that a classification system has been proposed, its clinical utility can be tested.

Etiology/Pathogenesis

The etiology and pathogenesis of diabetic nephropathy is multifactorial [2, 16–20]. Contributing factors that could influence both the susceptibility to and the rate of progression of diabetic nephropathy include genetic, endocrine, metabolic, hemodynamic, and structural characteristics. Although the etiology of the diabetes is very different in type 1 and type 2 diabetes mellitus, the basic pathophysiologic events that lead to the nephropathy probably are very similar in both [17].

The importance of genetic factors is indicated by the observation that only about a third of diabetic patients develop nephropathy and that this is independent of the severity or control of hyperglycemia [2]. Some but not all of the genes that have been implicated in affecting the susceptibility for or progression of diabetic nephropathy are promoter of RAGE (receptor for advanced glycation end-product), histocompatibility antigen DR3/4, angiotensin-converting enzyme, angiotensinogen, bradykinin receptor, aldose reductase, transforming growth factor-β, and apolipoprotein E [17].

Experimental data indicate that many different cell types in all structural compartments of the kidney are stimulated or injured by hyperglycemia and other stimuli (e.g., advanced glycation end products and reactive oxygen species) to produce cytokines, growth factors (e.g., transforming growth factor-β, platelet-derived growth factor-β), and other humoral mediators that cause increased extracellular matrix production [2, 16–18]. Activation of the renin–angiotensin system and the kallikrein–kinin system by high glucose and altered hemodynamics (e.g., reduced blood flow caused by narrowed arteries, arterioles, and capillaries) also contributes to many pathophysiologic events including increased extracellular matrix accumulation [16–20]. Podocyte injury may be critically important for inducing structural and functional abnormalities [18, 20].

Monoclonal immunoglobulin deposition disease (MIDD) may provide insight into the pathogenesis of diabetic glomerulosclerosis. It is caused by the deposition of monoclonal immunoglobulin light chains or heavy chains or both in GBMs and mesangial matrix, resulting in nodular glomerulosclerosis that is identical to diabetic glomerulosclerosis by light microscopy. As in diabetic glomerulosclerosis, transforming growth factor-β is a mediator of the matrix increase [21]. This suggests that the IgG localization in GBMs in diabetic glomerulosclerosis might be the cause of the nodular sclerosis and not merely an epiphenomenon.

Clinicopathologic Correlations

Clinical manifestations of diabetic nephropathy do not occur until overt structural features of diabetic glomerulosclerosis have developed [6].

Patients with type 1 or type 2 diabetic nephropathy have a variable rate of decline in glomerular filtration rate that usually falls between 1 and 2 mL/min/year (median 12 mL/min/year) [1]. Proteinuria increases progressively, with approximately 50 % of patients becoming nephrotic. There is a strong correlation between the severity of diabetic glomerulosclerosis and the severity and progression of renal insufficiency and proteinuria [6, 8]. One hypothesis for the correlation between glomerular sclerosis and reduced renal function is that the mesangial expansion impinges on the capillary lumen and reduces the filtering surface area, which in turn reduces the glomerular filtration rate [6, 16]. The severity of arteriolar hyalinosis also parallels the severity of glomerulosclerosis and has a positive correlation with the severity of proteinuria and renal insufficiency [12]. Severity of proteinuria correlates better with mesangial matrix expansion than with GBM thickening [6]. Proteinuria in diabetic nephropathy may result more from direct toxic effects on podocytes than from alterations in the GBM alone [16, 18, 20].

Diabetic glomerulosclerosis recurs in renal allografts from 2 to 10 years after transplantation [22, 23]. In patients with type 1 diabetes, simultaneous pancreatic transplantation can protect against recurrent diabetic nephropathy. The earliest and most frequent change is arteriolar hyalinosis. Linear GBM staining for IgG also is an early marker of recurrence. Less than 10 % of kidneys develop overt nodular sclerosis.

Because hypertension, dyslipidemia, and poor glycemic control are important risk factors for progression of diabetic nephropathy, combined therapies to control these factors (including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) are the current management strategy for diabetic nephropathy [24]. In patients with type 1 diabetes mellitus, pancreas transplantation can reverse the pathologic lesions of diabetic nephropathy, although reversal requires more than 5 years of normoglycemia [25].

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Part VI

Tubulointerstitial Diseases

Acute Interstitial Nephritis

13

Introduction/Clinical Setting

Acute interstitial nephritis (AIN) may be the result of indirect injury by drugs, reaction to systemic infections, direct renal infection (viral and selected bacteria), humoral immune responses (anti-tubular basement membrane disease), hereditary and metabolic disorders, and obstruction and reflux in the acute stages. Similar changes can also be observed in the kidney in systemic diseases such as lupus erythematosus and in transplant rejection. Acute tubulointerstitial nephritis also occurs to varying degrees in association with glomerulonephritides. This section is largely confined to the drug-induced, reactive, idiopathic, and immunologic disorders inducing AIN. Acute interstitial nephritis usually presents with acute renal failure, often oliguric; it is sometimes associated with systemic manifestations, such as arthralgia, fever, eosinophilia, and rash, typically as a consequence of drug hypersensitivity [1–3].

General Pathologic Findings

On gross examination, kidneys with AIN are enlarged with a pale cortex and a distinct corticomedullary junction. Histologically, there is diffuse interstitial edema with an interstitial infiltrate of lymphocytes, monocyte macrophages, and plasma cells to varying degrees (Fig. 13.1). Eosinophils may comprise from 0 to 10 % of the infiltrate, depending on the etiology of the AIN. When there are many eosinophils, they may be focally concentrated (Fig. 13.2). The inflammatory cells are often prominent at the corticomedullary junction and are generally confined to the cortex. Neutrophils and basophils are infrequent; large numbers of neutrophils suggest a diagnosis of acute infectious interstitial nephritis. In some cases, granulomas may be found in the interstitium or around ruptured tubules. Glomeruli and vessels are usually uninvolved. The inflammation extends into the walls and lumina of tubules (tubulitis), with distal tubules more often affected than proximal tubules. There are varying numbers of degenerating and regenerating tubular epithelial cells;

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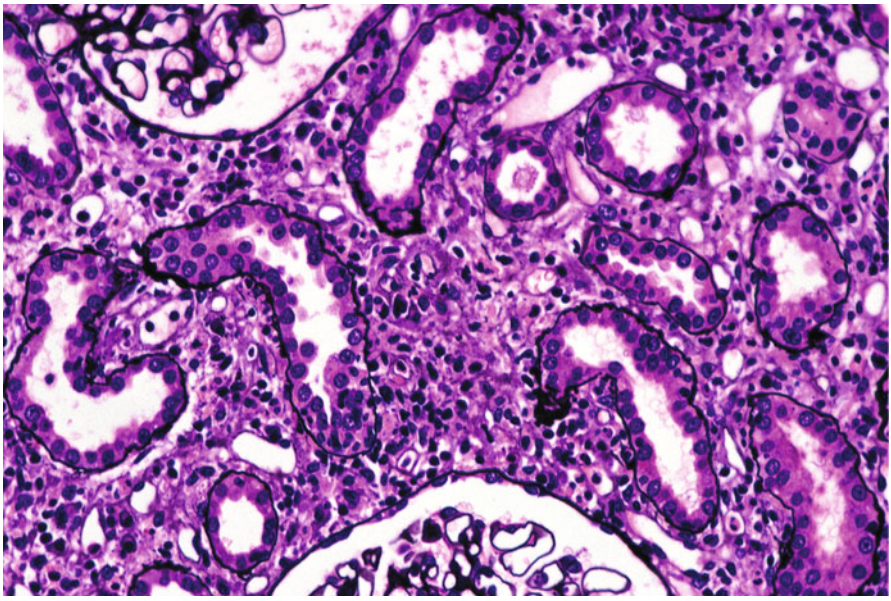

Fig. 13.1 The interstitium is edematous (tubules with normal basement membranes are separated) and infiltrated by lymphocytes, some of which are in the walls of tubules [periodic acid-Schiff (PAS) stain]

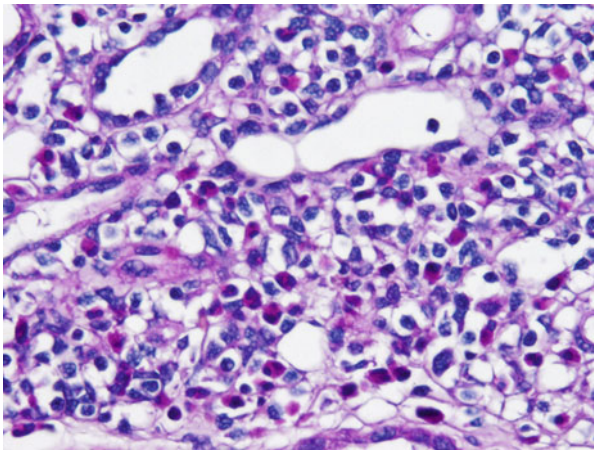

Fig. 13.2 There are numerous eosinophils in the interstitium along with lymphocytes and edema (H&E)

occasionally desquamated cells may be observed in tubular lumina. Proximal tubules often have focal loss of brush border staining. Immunofluorescence studies are usually negative but infrequently reveal granular deposits of complement in the tubular basement membranes (TBMs) and rarely fibrin in the interstitium. In cases of anti-TBM antibody formation, there is linear staining of TBMs for immunoglobulin G (IgG).

Etiology/Pathogenesis

Acute interstitial nephritis is a morphologic entity with many pathogenetic etiologies. These include cell-mediated immunity of the delayed hypersensitivity type and possibly direct cytotoxicity, humoral immunity such as anti-TBM antibody formation, and others possibly including complement activation and enhanced expression of major histocompatibility complex (MHC) class I or class II antigens. Some studies have reported drug-induced acute interstitial nephritis to represent approximately 6.5 % of nontransplant biopsies. Delayed hypersensitivity is the likely mechanism for AIN induced by drugs, particularly antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). T cells carrying both CD4 and CD8 antigens in varying proportions have been identified in kidneys with drug-induced AIN. This variability may be related to the offending agent or the time course of the biopsy. The T cells have been shown to carry activation markers and therefore are presumed to be effector cells in the hypersensitivity process. B cells are also present to some extent, more so with NSAID-induced AIN. This allergic form of AIN may be associated with a granulomatous response, particularly with sulfa-containing drugs and oxacillin, although it has been reported with a number of other medications. Delayed hypersensitivity is currently the most favored mechanism for the majority of drug-induced episodes of AIN and may be related to fixed antigens (drugs, metabolites, or either of these bound to tissue components or altered tissue components). This response is idiosyncratic and is not dose-related, although it may require up to 1 year of use to occur with NSAIDs. Other actions of drugs such as the nonsteroidals that result in acute renal failure include direct toxicity or functional abnormalities related to alterations in prostaglandin synthesis. Hypersensitivity may also account for the occurrence of AIN in kidneys of patients with systemic streptococcal, diphtheria, or measles infections in the absence of direct renal infection. This is more of historical importance as its occurrence is infrequent now; it produces a picture similar to that of the more often occurring drug-associated AIN.

Humoral immunity is a less frequent but in some ways better understood mechanism resulting in AIN. Rodent models of anti-TBM disease have been characterized by linear staining of TBMs with IgG and C3 with associated interstitial mononuclear inflammation, giant cells and edema, and tubular damage. The humoral immune role has been shown by the passive transfer of this process in animals with immune serum but not with immune cells.

In the setting of AIN, anti-TBM antibody formation is most often a secondary process and likely not responsible for significant renal injury. These antibodies are probably produced when drugs interact with a portion of the TBM, which macrophages then digest, presenting a new autoantigen; several antigens ranging from 48 to 70 kd are potential targets of the anti-TBM antibodies. Anti-TBM disease is rare. Anti-TBM antibodies uncommonly occur in association with membranous glomerulonephritis and may be genetically determined. Reaginic antibodies uncommonly may be induced during infections or by other agents and cross-react with renal elements or form immune complexes that deposit in the renal tubules or interstitium. Other suggested mechanisms for the induction of AIN include enhanced expression

of MHC antigens on renal cells such as tubular epithelium. Interferon and other cytokines associated with immunologically mediated processes are known to upregulate MHC expression, possibly eliciting an inflammatory response. Complement activation has been proposed as a possible source of continuing injury in AIN. Granular immune complex deposits in TBMs are common in systemic lupus erythematosus and when present invariably are accompanied by lupus immune complex glomerulonephritis. On the other hand, isolated TBM deposits are a feature of Sjögren's syndrome. Recently, another group of patients with extensive tubulointerstitial deposits with associated hypocomplementemia was described; it was suggested that this resulted from local immune complex formation.

Microscopic features reported as portending a worse prognosis in acute interstitial nephritis include presence of tubular atrophy with interstitial fibrosis, interstitial granulomata, and a greater inflammatory infiltrate.

Several forms of interstitial nephritis deserve further comment. Tubulointerstitial nephritis with uveitis (TINU) syndrome is a disease often with systemic manifestations presenting similar to acute interstitial nephritis either preceding, following, or coincident with eye pain and redness. Renal morphology is of a typical acute interstitial nephritis often with granulomata and eosinophils. Bone marrow granulomata may also be present. Pathogenic mechanism is not understood. Recent report suggests that modified C-reactive protein (mCRP), an autoantigen common to both renal tubular cells and uvea, may have a role as TINU patients have a higher prevalence of IgG antibodies to mCRP than a series of control patients [4, 5].

IgG4-related disease is a multisystem disorder with salivary and lacrimal gland and pancreatic, renal, and other organ involvement. It is characterized by a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells often with developing fibrosis. The kidneys are affected in approximately 30 % of the patients. While classified often as acute interstitial nephritis, it eventually has interstitial fibrosis sometimes forming pseudotumors. Membranous glomerulonephritis is sometimes an accompanying lesion [6–8].

Clinicopathologic Correlations

Acute kidney injury is correlated with interstitial edema and inflammation as well as tubular inflammation with associated acute tubular cell injury; up to 60 % of patients require dialysis [9]. Proteinuria is usually modest in the range of 1.0 g/24 h except when combined with minimal change disease-type lesion as a consequence of NSAIDs or other drug-induced damage. In these instances, nephrotic range proteinuria is observed [10]. The renal outcome, with or without corticosteroid therapy, is generally good. Modest stable chronic renal insufficiency is common, reflecting resolution of the acute inflammatory process.

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Chronic Interstitial Nephritis

14

Introduction/Clinical Setting

Chronic interstitial nephritis represents a large and diverse group of disorders characterized primarily by interstitial fibrosis with mononuclear leukocyte infiltration and tubular atrophy [1–3]. The chronic damage is unrelated to underlying glomerular or vascular processes. Among the many causes of chronic interstitial nephritis are high-grade vesicoureteral reflux, urinary obstruction, chronic bacterial infections, Sjögren's syndrome, drugs (lithium, Chinese herbs), radiation, and Balkan nephropathy [3]. Although the pathologic aspects by light microscopy have the abovementioned features in common, historical information, imaging data, familial history, and gross pathology features may help to distinguish one disease from another. Because it was once widely considered that most chronic interstitial nephritis represented chronic infection, the term *chronic pyelonephritis* was commonly used for this group of disorders [1, 2]. However, chronic pyelonephritis is a rare entity [4].

Pathologic Findings

Gross Findings

As high-grade vesicoureteral reflux is such an important and representative form of chronic interstitial nephritis, it will be a large focus of this discussion. However, it should be emphasized that there is controversy regarding whether high-grade reflux alone can lead to chronic and progressive renal disease or whether reflux is a marker for abnormal renal development, which is the reason for reduced parenchyma with scarring [5, 6]. When examined grossly, the kidney in patients with reflux and chronic interstitial nephritis (also called reflux nephropathy) has scarring primarily and initially at the poles with dilated calyces and overlying thinned pale parenchyma. These areas have irregular, broad, deep scars with contraction. The other areas of kidney may be less affected or may have a finely granular surface indicating

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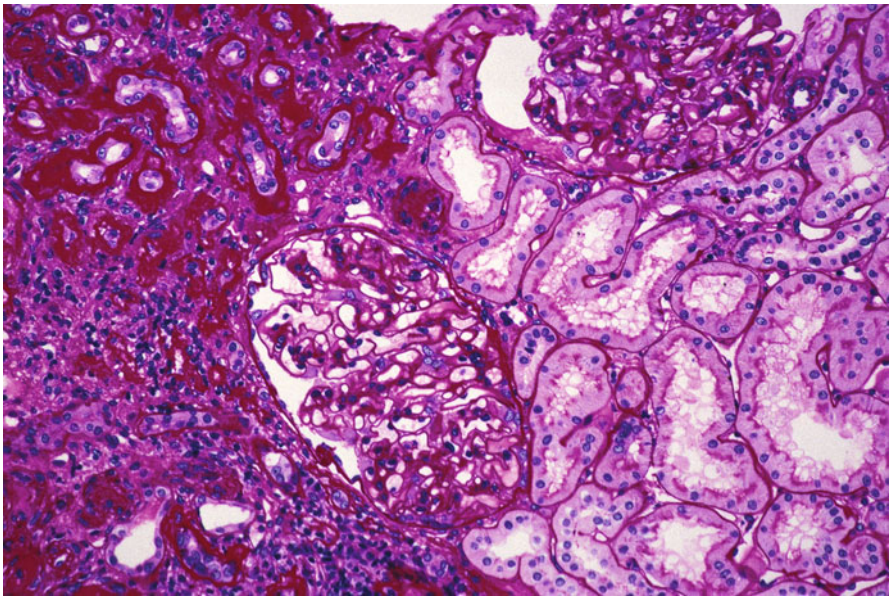

Fig. 14.1 In this low-magnification photograph, there is a large area of tubular atrophy, interstitial fibrosis, and lymphocytic infiltration; few completely sclerotic glomeruli are present [periodic acid-Schiff (PAS) stain]

ischemic effect. The walls of the affected calyces and pelvis are thickened. In contrast to reflux, with obstruction there are diffuse pelvicalyceal dilatation and uniform parenchymal thinning. Calculi may or may not be evident. The renal surface is smooth or finely granular with only shallow scars induced by ischemia.

Light Microscopy

Microscopically, there is tubular atrophy with associated interstitial fibrosis, with areas of tubular dropout in more severe cases. Foci of thinned dilated tubules containing cast material may be seen (thyroidization), particularly in the outer cortex. Tubules focally are ruptured, and Tamm-Horsfall protein and other intraluminal contents are in extratubular locations. Mononuclear inflammatory cells including lymphocytes, histiocytes, and plasma cells are throughout the interstitium in large numbers (Figs. 14.1 and 14.2); lymphoid follicles may be observed. If active infection is still present, neutrophils and a small number of eosinophils may also be found. The calyces and pelvis disclose submucosal mononuclear leukocytes, fibrosis, and hypertrophy of the smooth muscle; the overlying transitional epithelium may be hyperplastic or display glandular or squamous metaplasia. Renal arteries often have intimal fibrosis and muscular hypertrophy, while glomeruli show ischemic collapse and periglomerular fibrosis. Glomeruli may have Tamm-Horsfall

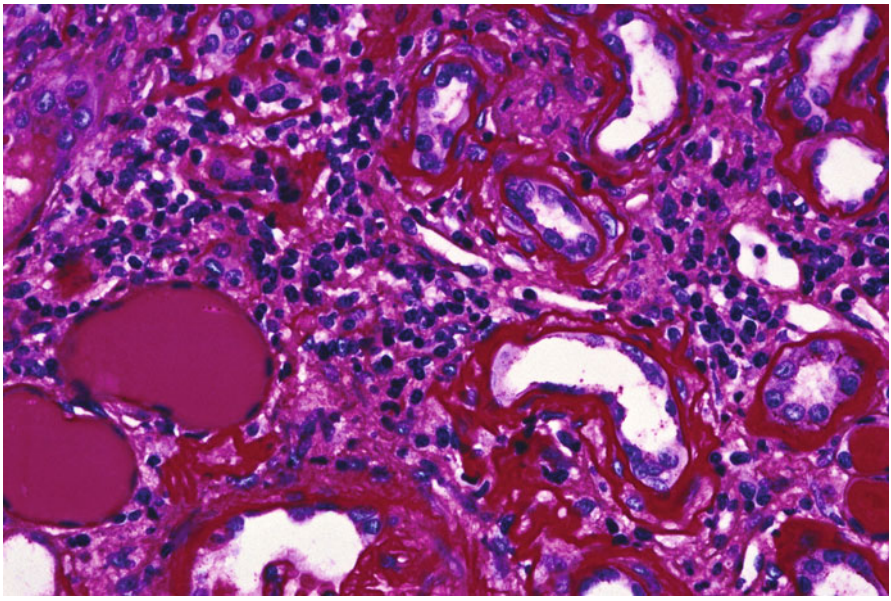

Fig. 14.2 Lymphocytes are in the fibrotic interstitium and in walls of some atrophied tubules (PAS stain)

protein in Bowman's space. In severe reflux nephropathy, there is hypertrophy of the glomeruli and tubules in the nonscarred parenchyma; there is sharp demarcation between the scarred and preserved parenchyma. Enlarged glomeruli may also be involved with focal and segmental glomerulosclerosis. Some investigators have reported that in nonscarred areas, glomeruli with elongated capillaries, adhesions, and podocyte detachment were associated with a poorer prognosis [4].

Etiology/Pathogenesis

Reflux nephropathy has been extensively studied in a pig experimental model; the pig has been used because it has compound papillae at the renal poles as humans do. Radiographic and pathologic studies have demonstrated that refluxing urine can gain access to the parenchyma in these locations. The compound papillae have large ducts of Bellini into which refluxed material can enter; the broad openings of these ducts do not prevent this process as the smaller more angulated duct openings of simple papillae do. The refluxing urine can induce tubular rupture with extravasation of the tubular contents or may cause forniceal tears with direct extension of urine into the parenchyma. This process of pyelotubular backflow is known as intrarenal reflux. There is local damage in response to the extravasated material, with scar formation occurring within 1–2 weeks in the pig model. While some investigators have proposed that the urinary contents alone are adequate to induce scar

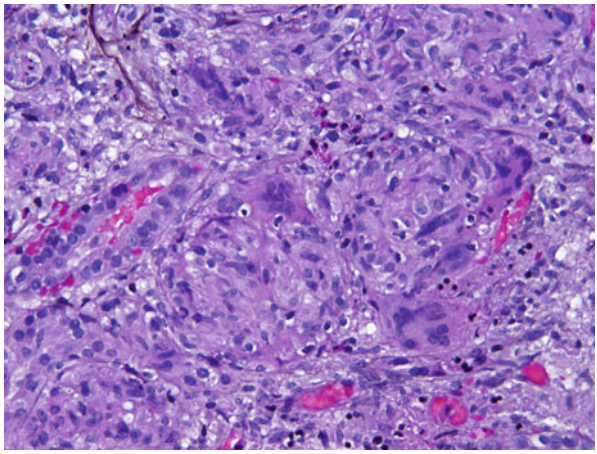

Fig. 14.3 Confluent nonnecrotizing granulomas, typical of renal involvement by sarcoidosis

formation, it is more widely believed that some element of infection is required to produce chronic interstitial nephritis. Refluxing urine, usually resulting from inadequate length or abnormal positioning of the ureterovesical junction orifice, is a common mechanism. Studies suggest that nitric oxide stimulated by macrophage colony-stimulating factor may be a major mediator of tissue damage in reflux nephropathy [7]. Children under the age of five have shorter ureters and more patent ducts of Bellini and therefore are more prone to develop reflux nephropathy. In fact, many polar scars occur prior to the age of 4 or 5 years and do not substantially worsen after that time as the intravesical ureter lengthens and reflux subsides. As the scarring occurs, a component of arterial intimal fibrosis often ensues, with additional damage resulting from ischemia.

Chronic pyelonephritis, usually resulting from chronic obstruction, is characterized by microscopic changes similar to those described above with few exceptions. There are more lymphocytes and plasma cells in scarred areas, but "thyroidization" is less well developed. Neutrophils are more plentiful in many locations. There are also specific forms of chronic pyelonephritis, with characteristic morphologies. Xanthogranulomatous pyelonephritis is typically associated with stones (usually staghorn calculi) and is almost always unilateral. The calyces are dilated and surrounded by large or small zones of yellow friable material, varying pus and necrotic tissue. Microscopic appearance of these areas is of accumulation of large numbers of xanthoma cells (foam cells) with macrophages, few multinucleated giant cells and, at the periphery, lymphocytes, plasma cells, neutrophils, eosinophils, and fibroblasts [8].

Numerous confluent nonnecrotizing granulomas are typical of sarcoidosis (Fig. 14.3).

Malakoplakia, an unusual morphologic response to infection more commonly affecting the bladder and calyces, may rarely involve renal parenchyma. It is the result of macrophage dysfunction, an inability to completely degrade ingested bacteria. The macrophages constituting the renal infiltrate contain small calcifications known as Michaelis-Gutmann bodies and represent the major diagnostic feature [9].

A similar disorder, megalocytic interstitial nephritis, is characterized by infiltration of the parenchyma by abundant macrophages. These cells are similar to those in malakoplakia, although without Michaelis-Gutmann bodies, suggesting these entities perhaps to be part of the same disease spectrum [10–12].

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Acute Tubular Necrosis

15

Introduction/Clinical Setting

Acute tubular necrosis (ATN) is a pathologic process that manifests clinically as acute renal failure. Although the term implies cellular death (necrosis), it should be appreciated that frank necrosis is not a constant finding; evidence of sublethal cellular injury is common. Thus, a more descriptive term "acute tubular injury" is in common use in many centers. Furthermore, there is often a lack of clinical-pathologic correlation, with severe acute kidney injury sometimes associated with trivial morphologic findings [1, 2]

Broadly speaking, ATN may be the result of one of two mechanisms: ischemia or toxin induced. The structural changes in each are reasonably distinctive, and pathogenic mechanisms are also considered different. Traditionally, ischemic ATN follows hypotension or hypovolemia or both [1, 3]. There may be many causes of this circulatory state; these include extensive trauma with rhabdomyolysis and myoglobinuria, incompatible blood transfusions, pancreatitis, septic shock in a variety of settings, extensive hemolysis as in malaria (blackwater fever), and shock following administration of barbiturates, morphine, and sedatives. Toxic ATN is a dose-dependent injury with tubular cell damage normally limited to proximal tubules and usually involving almost all nephrons. This is obviously in sharp contrast to ischemic tubular necrosis in which the changes are considerably more subtle and patchy. Many therapeutic and diagnostic agents, industrial chemicals, heavy metals, and plants may be responsible for this lesion.

Ischemic Acute Tubular Necrosis

Pathologic Findings

The pathologic changes in ischemic ATN are often subtle but are easily discernible with well-fixed tissue. Both proximal and distal tubules are affected. The proximal tubules are dilated and the lining cells flattened. Brush border staining is reduced

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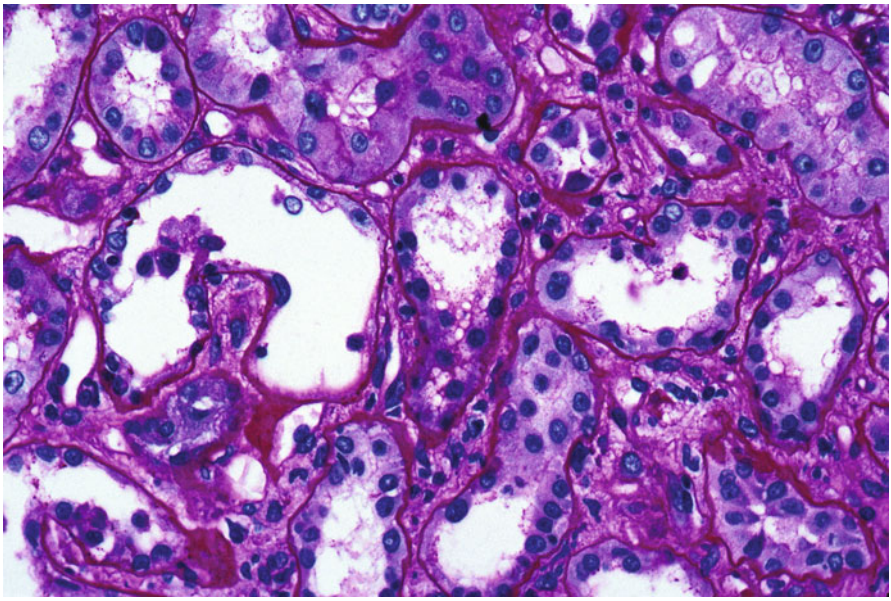

Fig. 15.1 Tubular cells are flattened and many proximal cells lack brush border staining; lumina are relatively dilated [periodic acid-Schiff (PAS) stain]

or absent (Fig. 15.1). This combination of changes causes proximal tubules to resemble distal tubules ("distalization") and is also known as simplification of tubules so that one nephron segment cannot easily be differentiated from another. Distal tubules, including the thick ascending limb of Henle, may be dilated and lined by flattened cells. Tamm-Horsfall protein-containing casts, sometimes incorporating granular material, are frequently present but are not specific for ATN. In addition, pigmented (tan-brown) granular casts are characteristic; many studies have concluded that heme pigment is responsible for this appearance. Oxalate crystals are commonly present and are located in the thick ascending limb, distal tubule, and collecting duct. It should be noted that the crystals are usually not numerous; marked accumulation of oxalate crystals is most commonly observed in ethylene glycol poisoning. Overt or extensive necrosis of tubular cells is neither common nor regularly observed. Instead, loss of individual cells, manifested by incomplete epithelial lining of tubules, is present. This change requires well-fixed tissue and a practiced eye to demonstrate. It is often referred to as the "nonreplacement" phenomenon. There are often desquamated cells or cellular debris in the lumina (Fig. 15.2).

Ischemic tubular necrosis is frequently associated with disruption of tubular walls (including cell loss and basement membrane disruption) with spillage of contents into the adjacent interstitium and rarely into peritubular capillaries and small veins. It also may be associated with localized inflammation, sometimes in the form of granulomata. However, inflammation is not constantly present. The interstitium

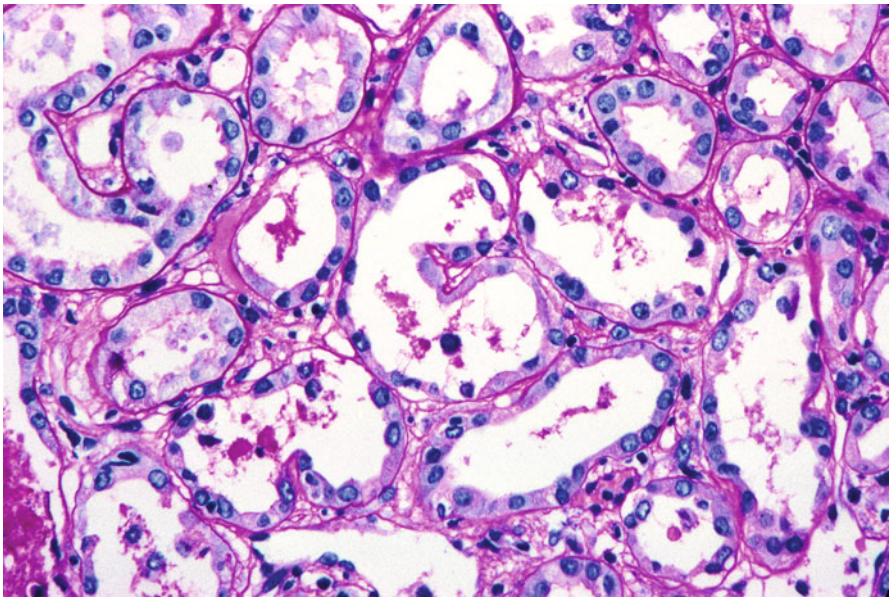

Fig. 15.2 One tubule contains cells and debris in lumen and is incompletely lined by epithelium (PAS stain)

is diffusely edematous and may be infiltrated by a small number of lymphocytes and monocytes. The outer medullary vasa recta often contain large numbers of nucleated circulating cells including lymphocytes and monocytes, both mature and immature forms, and granulocyte precursors.

These cells are in greater concentrations in the vasa recta than in other renal vascular beds. The glomerular capillary tufts are usually unaltered. However, there are several reasonably common abnormalities: there may be some degree of capillary collapse and dilatation of Bowman's space. Additionally, tubular metaplasia ("tubularization") of parietal epithelial cells may be evident in recovery. Solez and colleagues [4] assessed these morphologic changes as to their frequency in active renal failure, recovery phase, and normal controls. In their landmark study, they noted that the following were more common in biopsies from patients with renal failure: vasa recta leukocyte accumulation, tubular cell necrosis, regeneration (mitotic figures), dilatation of Bowman's spaces, loss of brush border staining, tubular casts, and interstitial edema and inflammation. However, only cellular necrosis and loss of brush border staining distinguished biopsies from patients with acute renal failure from those of patients in recovery from renal failure.

Ultrastructural observations indicate a reduction in brush border formation for most proximal tubules; this ranges from slight to almost complete loss of microvilli. There is also simplification of basolateral cell surfaces. Overt necrosis is also noted. Disintegration of cells, characterized by extreme lucency of cytoplasm together with disruption of plasma membrane, nuclear membrane, or organelles,

may affect single cells, with only minor abnormalities to neighboring cells. Apoptosis, characterized by condensation and increased density of cytoplasm and closely aggregated organelles, dilated vacuoles, cisternae and mitochondria, and folding of nuclear membrane with clumped chromatin, affects single cells and is increased compared to normal. The abovementioned nonreplacement phenomenon is identified as a defect in epithelial lining corresponding to loss of a single cell; the intact basement membrane may be covered by a thin projection of cytoplasm from an adjacent cell [1, 2, 5].

Pathogenesis

Mechanisms responsible for ischemic acute tubular necrosis are many and varied. The endothelial injury disrupts microvascular blood flow, contributing to decreased renal perfusion, renal hypoxia, and epithelial cell ischemia with resultant decrease in glomerular filtration rate. Furthermore, endothelial cell disruption may lead to impairment of vascular reactivity, increase in permeability, and leukocyte recruitment and activation. This results in upregulation of adhesion molecules and inflammation. Endothelial cell dysfunction alters the permeability barrier in peritubular capillaries leading to epithelial cell injury and dysformation. Reduction in renal cortical and glomerular blood flow is documented and is responsible for the gross autopsy findings of cortical pallor. Its mechanism may be related to vasoconstrictive humoral factors. Medullary blood flow reduction has also been documented, especially at the corticomedullary junction, affecting juxtamedullary nephrons. This regional hypoxia could explain the apparent susceptibility of the straight portion of the proximal tubule (S3) to ischemia; the medullary thick ascending limb may also be affected similarly. Tubuloglomerular feedback activation is implicated in some phases of acute renal failure, although its extent and the importance of vasoactive substances are not clarified [6, 7]. Rosen, Brezis, and coworkers [5, 8, 9], in a series of studies on experimentally induced acute renal failure, documented the regular occurrence of necrosis of cells of the thick ascending limb of Henle (TALH). The lesions affected only a few cells of this portion of the nephron and therefore are often difficult to detect in many biopsies unless sufficient medullary tissue is available. Because the cells of TALH are involved with feedback control of glomerular filtration and with production of Tamm-Horsfall protein as casts that may obstruct the nephron, injury to these cells may well be directly responsible for acute renal failure. These investigators have maintained that necrosis of thick ascending limb cells is the primary and, indeed, pathophysiologically important lesion in ATN with acute renal failure. The other changes of cells in different segments of the nephron are viewed, perhaps correctly so, as secondary lesions. The work of Brezis, Rosen, and colleagues points out the importance of reduced renal blood flow to the inner stripe of the medulla and the thick ascending limb of Henle in animals and suggests its applicability to human acute renal failure, including the lesion known as “lower nephron nephrosis.”

Toxic Acute Tubular Necrosis

Pathologic Findings

The basic morphologic findings in toxic ATN, rarely observed today, are best illustrated in mercuric chloride poisoning. At 3 days following exposure, there is extensive necrosis of cells of the proximal convoluted tubules; the necrotic cells are partially desquamated and the lumina are filled with cellular debris. At 7–9 days, most of the luminal contents are no longer present in the proximal tubules but are in more distal parts of the nephron. The proximal tubules are dilated and lined by flattened and basophilic cells with numerous mitotic figures. At 2 weeks, the proximal tubules are lined by cuboidal epithelium; tubular calcifications are not infrequent. In general, tubular basement membranes are intact, and interstitial edema with a variable mononuclear leukocytic infiltrate is evident. This sequence of events is reasonably constant for other agents, although the degree of overt necrosis rarely achieves that of mercuric chloride. There are some morphologic features that are reasonably characteristic of certain toxins; they may be observed by light or electron microscopy depending on the poison. For example, gentamicin may result in ultrastructurally defined myeloid bodies (lysosomes with phospholipid), lead is characterized by intranuclear inclusions (consisting of lead and lead-binding protein) as is bismuth, and gold accumulates in lysosomes in tubular cells as dense filamentous structures (aureosomes) [10].

Pathogenesis

Mechanisms of injury are varied depending on the drug or toxin [10]. Some agents are injurious in their native form, while metabolic by-products of others are responsible for damage. Some toxins alter renal hemodynamics leading to ischemic acute tubular injury. Some toxins interfere with mitochondrial function. Still other mechanisms include the development of thrombotic microangiopathy [1, 2]. Renal structural toxicity of some of the highly active antiretroviral agents is manifested by mitochondrial changes in proximal tubular cells in tenofovir toxicity and by crystal accumulation in tubular lumina and cells in indinavir toxicity [11–13].

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Part VII

Plasma Cell Dyscrasias and Associated Renal Diseases

Bence Jones Cast Nephropathy

16

Introduction/Clinical Setting

Renal involvement in multiple myeloma and other plasma cell dyscrasias is largely the result of the effects of the monoclonal protein, usually the light chain, and may be clinically manifested in multiple ways [1–3]. The major lesions include light-chain (Bence Jones or myeloma) cast nephropathy, monoclonal immunoglobulin deposition disease and amyloidosis, usually AL type. The pathologic features of all are distinct and will be discussed in individual chapters. Although each disorder appears to be the consequence of a distinct property of the monoclonal protein, usually the light chain and therefore affected patients theoretically may develop only one of these lesions (one light-chain disease per patient) in practice two or all three may be identified in renal biopsies.

Clinical Presentation

Patients with Bence Jones cast nephropathy usually present with acute kidney injury (less commonly with chronic kidney disease) and Bence Jones proteinuria. It has been known for many years that intravenous radiocontrast media, dehydration, infections, and the use of nonsteroidal antiinflammatory drugs may induce the precipitation of renal tubular light-chain casts and result in acute renal failure, which is reversible in only a small percent of affected patients. A less common manner of presentation is the acquired Fanconi syndrome. This is most often associated with intracellular crystals in plasma cells and tubular cells; the crystals represent the abnormal light chain [2, 4].

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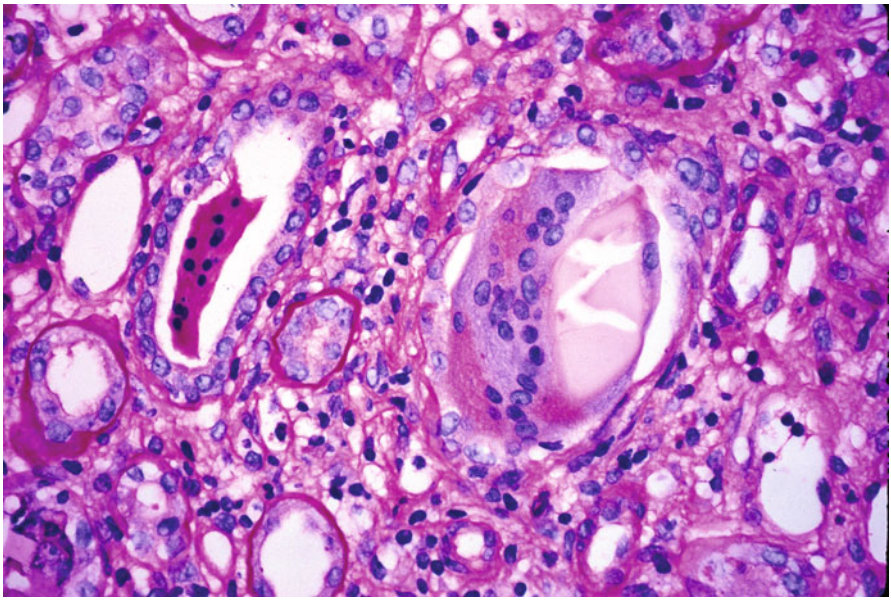

Fig. 16.1 Light-chain (Bence Jones) cast nephropathy with a tubule containing a pale-staining cast surrounded by a multinucleated giant cell. In contrast, casts composed primarily of Tamm-Horsfall protein are periodic acid-Schiff (PAS) positive (PAS stain)

Pathologic Findings

Light Microscopy

Light-chain (Bence Jones) cast nephropathy is characterized by prominent casts in renal tubules; the casts are usually large and "brittle," have fracture lines or are broken into many fragments often with geometric shapes, and are surrounded by tubular epithelium, neutrophils, and typically and diagnostically by multinucleated giant cells of foreign-body type (Fig. 16.1). While they are more common in distal tubules, the casts may be formed in any segment of the nephron, including Bowman's space. The casts have reasonably typical tinctorial properties: periodic acid-Schiff (PAS) negative, brightly eosinophilic (hematoxylin and eosin), fuchsinophilic with Masson's trichrome, and, infrequently, Congo red positive. The staining is not always uniform within the same cast or among all casts in the same kidney, but the above colors are most typical. The casts may be lamellated, contain crystals of a variety of shapes, and rarely at the periphery have a spicular appearance, which represents amyloid formation within the cast, not within renal parenchyma. There are reasonably constant abnormalities in tubular epithelium; proximal cells often contain numerous uniform cytoplasmic vacuoles.

Cells of all tubular segments may be necrotic and sloughed into lumina, where they may be adherent to the edges of the casts. Tubular basement membranes are

discontinuous, thereby allowing free communication between the interstitium and the tubular lumina; it is through these gaps that monocytes and other inflammatory cells migrate from the interstitium. The adjacent interstitium is edematous and often infiltrated by monocytes and lymphocytes [1–4]. This constellation of light microscopic abnormalities, especially the morphology and tinctorial properties of the casts and the surrounding giant cells, is sufficiently distinctive to be diagnostic of multiple myeloma in a patient who presents with acute kidney injury of seemingly unknown origin [7].

Immunohistochemistry and Electron Microscopy

The composition of the casts has been determined by immunohistochemistry. Most investigators have documented that they consist exclusively or primarily of the abnormal light chain [1, 2]. Depending on many factors, Tamm-Horsfall protein and the other light chain may also be part of the casts. Many other plasma proteins may also be present. When proteins are present, they are usually in a staining intensity less than the abnormal light chain. It is possible to detect Tamm-Horsfall protein in tubules with casts as well as in the glomerular urinary spaces, a finding that is indicative of obstruction (either intrarenal or extrarenal) of urine with retrograde flow in the nephron. The ultrastructural appearance of the casts is quite variable, although the basic structure is of a mass of deeply electron-dense material. The casts may be homogeneous, finely or coarsely granular, and may incorporate cytoplasmic debris [4] and crystals [2, 4].

Pathogenesis

Excess free monoclonal light chains lead to cast nephropathy likely for two key reasons. The free abnormal light chain is freely filtered by the glomerulus and is toxic to tubular epithelium (proximal and distal). Furthermore, in the distal nephron (thick ascending limb of Henle), Bence Jones protein coprecipitates with Tamm-Horsfall protein, thus forming casts, which are obstructing [5, 6]. It is likely that Bence Jones protein alone can also precipitate in tubules, thereby explaining the presence of the casts in the proximal nephron. It is also likely that a combination of direct damage to tubular cells (tubular necrosis), which is associated with tubular basement membrane breaks, and the physical effects of the geometrically shaped casts leads to tubular wall disruption and migration of monocytes into tubules to surround casts and form multinucleated giant cells. Because of the large size of the casts, they likely obstruct the nephron in which they are formed. Thus, it appears that renal impairment in Bence Jones cast nephropathy is the result of tubular necrosis, interstitial inflammation, and nephron obstruction [1, 7].

Investigators have sought to identify that which confers “nephrotoxicity” to light chains; in addition, as there are several light-chain-induced renal lesions, investigations to ascertain why a particular light chain will produce one lesion rather than

another are under way. It is likely that host factors are not of prime importance; the intrinsic physical or chemical properties of light chains are thought to be of greatest significance. However, despite initial evidence linking light-chain isoelectric point, molecular weight, degree of polymerization, and size, among others, to the development of this or the other light-chain-induced renal lesions, at the present time no property of monoclonal light chains has been identified to explain their nephrotoxic potential [2]. It is of interest to note, however, that monoclonal light chains from humans with specific light-chain-induced lesions (cast nephropathy, light-chain deposit disease, amyloid), when injected into mice, induced the same renal abnormality as in humans as elegantly documented by Solomon and colleagues [8] in 1991. However, still no definitive property has been identified; it is not well understood why, if there is a specific factor for each major lesion, some patients have two or three light-chain-induced lesions simultaneously [1, 9].

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Monoclonal Immunoglobulin Deposition Disease

17

Introduction/Clinical Setting

Patients with plasma cell dyscrasias may have other forms of renal disease than light-chain cast nephropathy. These include the closely related systemic disorders amyloidosis (AL type) and light-chain-deposit disease [1–7]. In the kidneys, although both of these conditions clinically and pathologically affect primarily glomeruli, there is important and often constant involvement of tubular basement membranes, interstitium, and arteries. On rare occasions, the intact monoclonal protein (light and heavy chains) or heavy chain alone may deposit in renal basement membranes and systemically. Consequently, these disorders, originally considered solely of abnormal light-chain pathogenesis and termed by some as light-chain-deposit diseases or nephropathies, are more correctly termed and thought of as monoclonal immunoglobulin deposition diseases [5]. Evaluation of immunoglobulin synthesis by bone marrow cells has determined that incomplete light-chain and/or heavy-chain fragments are produced [8].

Light-Chain-Deposition Disease/Heavy-Chain-Deposition Disease

Light-chain-deposit disease is characterized by the nonimmune deposition of a monoclonal light chain in all renal basement membranes as well as the glomerular mesangium. Renal involvement is part of a systemic disease, for virtually all other organs and tissues are also the sites of light-chain deposits. The kidneys are the most important organs involved in terms of clinical manifestations, although some patients can develop significant and fatal cardiac lesions [1–3, 5]. Approximately 80 % of affected patients have an abnormal kappa light chain [9].

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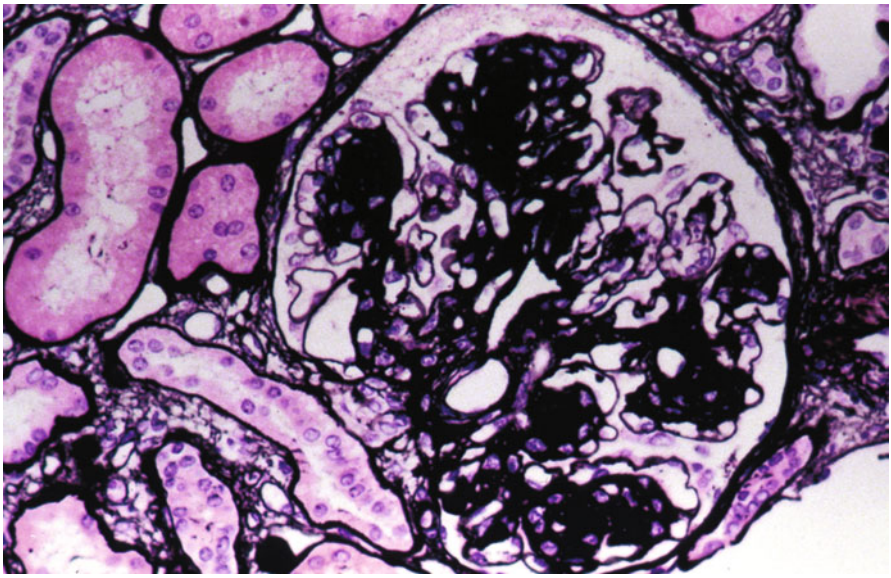

Fig. 17.1 Light-chain-deposition disease with glomerulus with nodular mesangium. This appearance is similar to diabetic nodular glomerulosclerosis (Jones silver stain)

Pathologic Findings

Light Microscopy

Light-chain-deposition disease can have many of the light microscopic morphologic features of diabetic nephropathy, especially because of the nodular glomerular lesions and capillary microaneurysms [2, 3, 10, 11].

The light microscopic appearance of glomeruli was initially emphasized as a nodular glomerulopathy with features virtually indistinguishable from nodular diabetic glomerulosclerosis (Fig. 17.1); however, it has become apparent that there is a large spectrum of glomerular morphologies including normal glomeruli, diffuse widening of mesangium, and crescents. The tubular basement membrane deposits often result in the light microscopic appreciation of thickened tubular basement membranes. Careful high-magnification examination of periodic acid-Schiff (PAS)-stained sections may indicate a slightly lighter staining band external to the normal basement membrane [1].

Heavy-chain-deposition disease is characterized by the nonimmunologic binding of an abnormal heavy chain, most commonly immunoglobulin G (IgG), to all basement membranes [8, 11]. The morphologic aspects differ from light-chain-deposit disease in that the glomerular structure is almost always nodular. However, glomerular hypercellularity mimicking membranoproliferative or other proliferative glomerulonephritis may be the dominant morphology [12, 13].

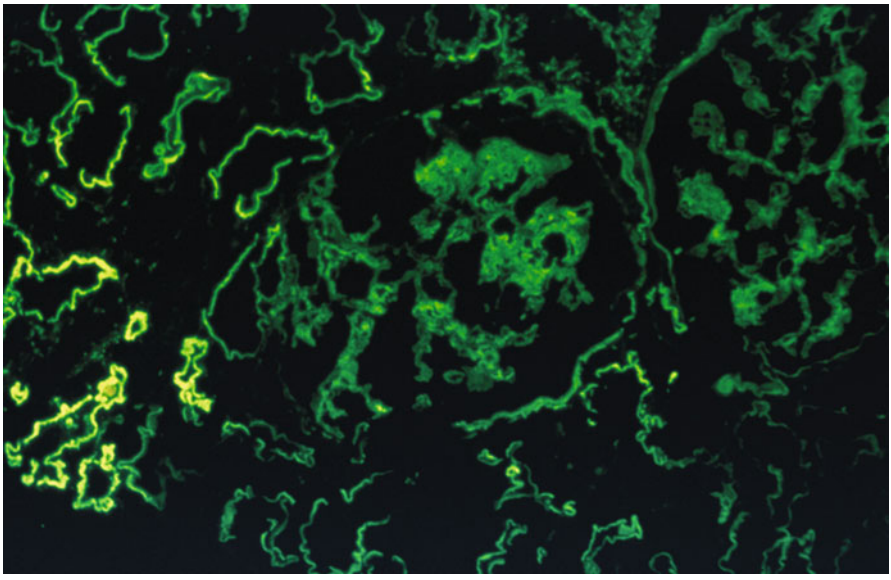

Fig. 17.2 Light-chain-deposition disease with linear staining of all renal basement membranes and mesangial regions of the glomeruli (kappa immunofluorescence)

Immunofluorescence Microscopy

These disorders require immunofluorescence evaluation of tissue sections, for the diagnosis rests on documenting a single light and/or heavy chain in the tissue basement membranes. Thus, the diagnosis of this deposition disease can be made only with the routine use of immunofluorescence; one cannot rely on the glomerular morphology to dictate when to evaluate the biopsy with antibodies to the light chains. Immunofluorescence shows monoclonal prominent staining along the tubular and glomerular basement membranes (Fig. 17.2). In addition, the paraprotein is also found in basement membranes of peritubular capillaries and vascular smooth muscle cells. In the absence of tissue for immunofluorescence, documentation of ultrastructurally defined deposits when present (see below) should serve as a strong indication of light chains. In heavy-chain-deposition disease, when IgG3 is the paraprotein, complement is also deposited with associated hypocomplementemia [11, 14].

Electron Microscopy

The ultrastructural manifestations of the light-chain deposits are of clustered punctate dense deposits external to tubular and within vascular basement membranes [2, 3]. Deposits in the glomerular basement membranes are similar (Fig. 17.3), whereas they are variably evident in the mesangium. However, there may be no electron microscopic counterpart of the immunofluorescence deposition [1].

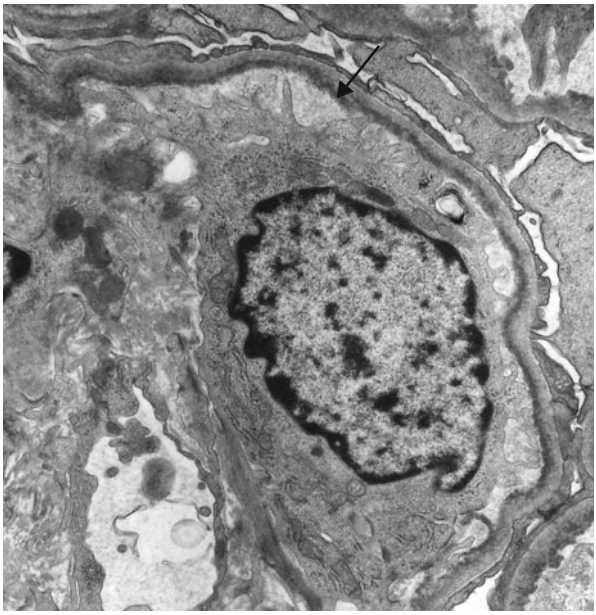

Fig. 17.3 Light-chain-deposition disease with continuous granular density in glomerular basement membrane (*arrow*) (electron microscopy)

Etiology/Pathogenesis

Clinically, this renal lesion presents with heavy proteinuria (both light-chain and larger plasma proteins), renal insufficiency, and sometimes hypertension. Approximately 50 % of the patients have overt multiple myeloma; the rest have either plasmacytosis or no evidence of increased plasma cells [1–3, 7]. In this last instance, there is increased immunoglobulin synthesis with excess light-chain production. Therapy may result in the disappearance of nodules and improvement of renal function [15].

Although properties of the abnormal light chains determine whether they deposit in tissue as multiple fibrils (amyloid) or without fibril formation (light-chain-deposit disease), the specific features of the paraprotein responsible are not known.

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Amyloidosis

18

Introduction/Clinical Setting

Amyloidosis (AL type) is conceptually similar to light chain deposit disease in many respects [1]. It represents the systemic deposition of a structurally altered light and/or heavy chain; it is more common than light chain deposit disease. Amyloid may also be due to deposition of proteins, other than immunoglobulin light or heavy chains, that form beta-pleated sheets. These include serum AA, apolipoprotein A-1, apolipoprotein A-IV, transthyretin, fibrinogen, beta-2 microglobulin, and leukocyte chemotactic factor 2, among many others [2]. Most patients with glomerular amyloid present with heavy proteinuria and approximately 50 % have concurrent renal insufficiency. Interstitial or vascular (nonglomerular) amyloid morphologically is similar to amyloid in other locations; in the absence of glomerular amyloid, its detection requires a reasonably high level of suspicion on the part of the pathologist. Isolated interstitial amyloid is usually manifested by some degree of renal insufficiency; "pure" vascular amyloid may be clinically silent or may be associated with renal functional impairment.

Pathologic Findings

Light Microscopy

Amyloid appears as amorphous acellular, pale eosinophilic material in the mesangium and extending out to glomerular capillary walls in some patients (Fig. 18.1). The capillary wall deposits may appear as silver positive fringe-like projections, longer than those seen in membranous glomerulopathy. Arterioles and arteries frequently show amyloid deposits as well. The renal pathologic features of other varieties of amyloid (e.g., AA, hereditary forms) are virtually identical in most respects to AL amyloid [1, 3]. Specific diagnosis is made by positive Congo red stain, with apple-green birefringence under polarized light (Figs. 18.2 and 18.3).

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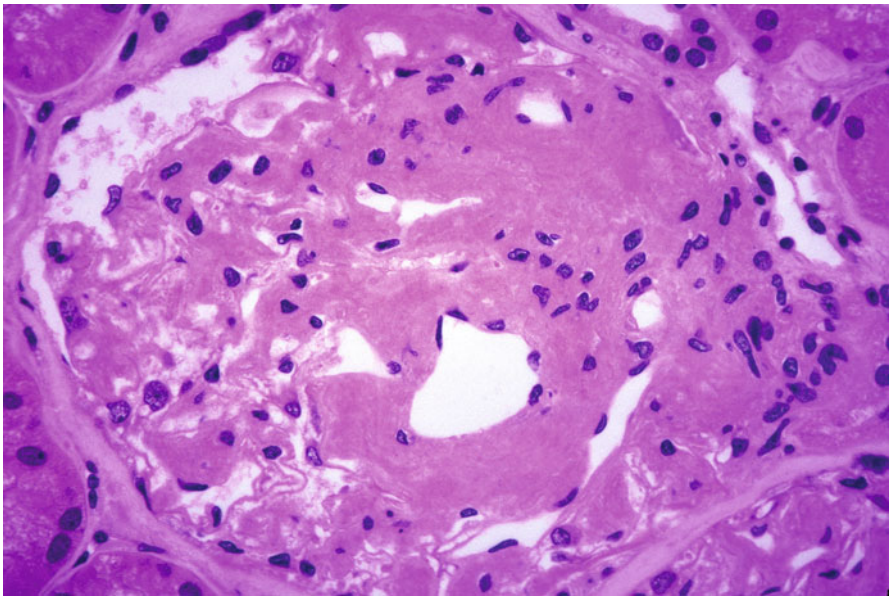

Fig. 18.1 Amyloid with glomerulus and arteriole infiltrated by homogeneous acellular material replacing normal structures [periodic acid-Schiff (PAS) stain]

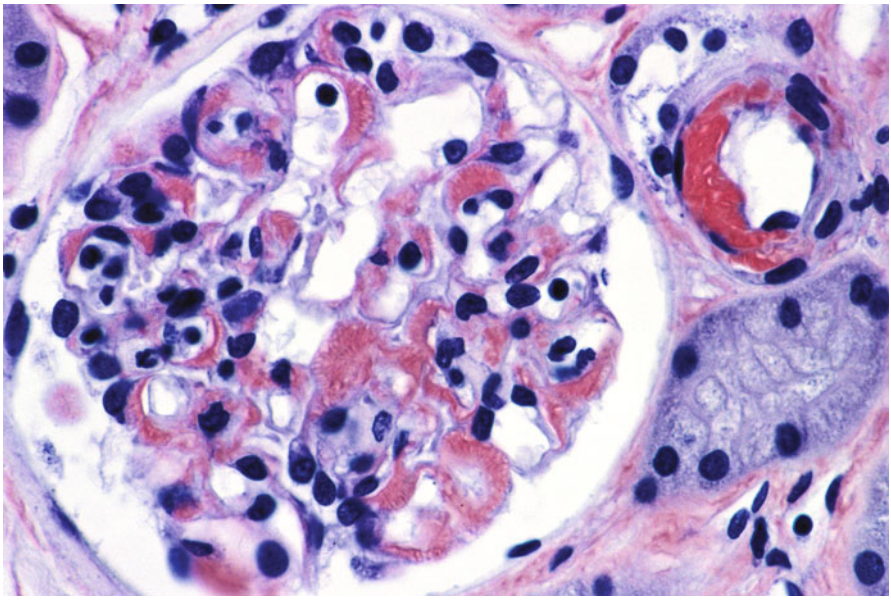

Fig. 18.2 Congo red stain disclosing the abnormal material to stain positively

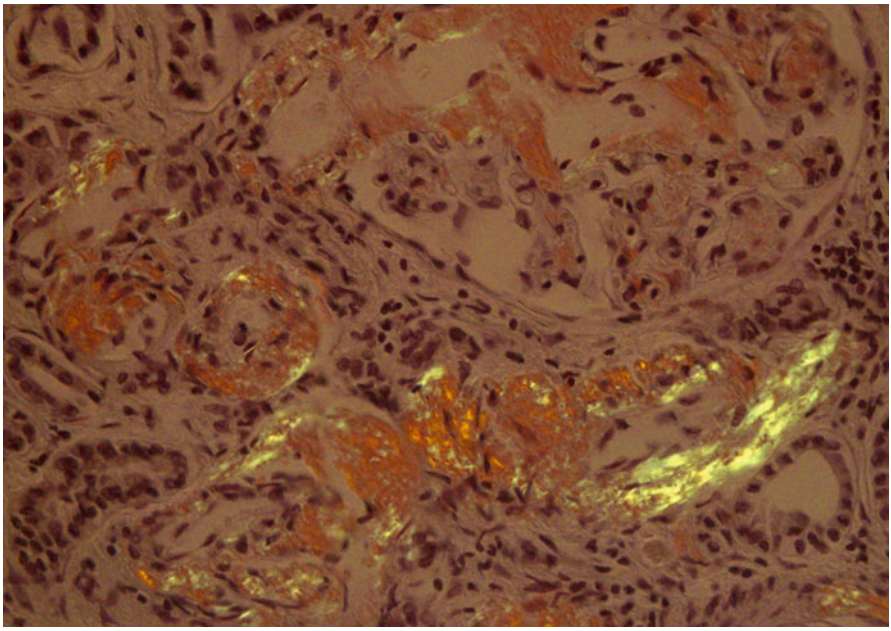

Fig. 18.3 The Congo red stain is greenish under polarized light, diagnostic of amyloid, involving artery, arteriole, and mesangium of the glomerulus

Immunofluorescence Microscopy

When amyloid is due to monoclonal AL, immunofluorescence may show smudgy positivity in affected areas for the responsible light chain. Light chain amyloid is more commonly due to lambda (75 %). Other types of amyloid do not stain for light chains by immunofluorescence, but may be detected by immunohistochemistry, with antibodies for specific amyloidogenic proteins such as AA.

Electron Microscopy

Randomly arranged non-branching fibrils, 10–12 nm, are present in extracellular sites in affected arterioles and arteries; in mesangial areas, often infiltrating GBMs; and occasionally in the interstitium (Fig. 18.4).

Etiology/Pathogenesis

Amyloid is composed of insoluble poorly degradable 10-nm fibrils that are commonly haphazardly arranged in basement membranes and walls of all types of vessels and in the interstitium around capillaries. In the kidneys, the glomeruli

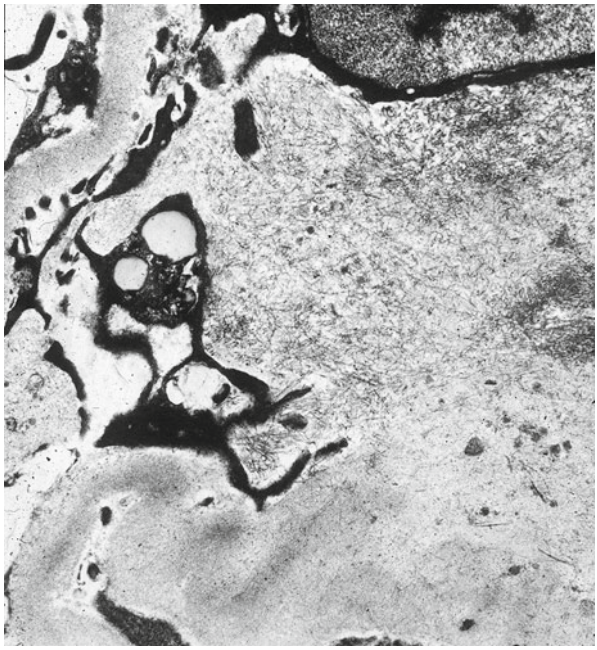

Fig. 18.4 The abnormal material in amyloid is composed of numerous fine fibrils seen on electron microscopy

are usually initially involved and almost always represent the most important component affected. In AL, the abnormal light chain (usually lambda VI subtype) is transformed into a beta-pleated sheet structure, which is responsible for the morphologic, optical, and tinctorial properties of amyloid. On rare occasions, amyloid may be composed solely of a monoclonal heavy chain [4–6]. Although some clinical and laboratory findings, including a negative family history, may appear to point to AL amyloid, a study documented amyloidogenic gene mutations indicating a hereditary form of amyloid in 10 % of such patients [7]. In addition, one study documented lack of sensitivity in using immunofluorescence as a means of identifying either light chain as the amyloid-producing protein [8]. This suggests that, in patients with amyloid in which AA is not documented and protein/light chain and bone marrow confirmation of AL amyloid is lacking, genetic causes of amyloid be considered. Work by the group of Herrera [9] concerning interaction between abnormal light chains and cultured mesangial cells indicates that the ability of the light chain to be internalized by the cell may be an important factor in the development of amyloid rather than light chain deposition disease. Further, cast-producing light chains had no effect on mesangial cells [9].

Similar to light chain deposit disease, patients with AL amyloid may have overt myeloma or only a slight plasmacytosis. Roughly 80 % do not have myeloma; conversely, amyloid occurs in approximately 7–10 % of patients with myeloma. Although light chain-induced renal lesions have been presented here as isolated entities, the coexistence of any two or even all three is well known [1, 3].

Determination of the type of amyloid in tissues is usually done with the use of immunoperoxidase staining or, in the case of renal biopsies, with routine

immunofluorescence using antibodies to the light (and heavy) chains. Unfortunately, commercially prepared antibodies to the different amyloid precursor proteins are not available for many. In addition, especially considering immunofluorescence, false-positive and false-negative results are not uncommon. A very effective and accurate but somewhat costly method using laser microdissection of the paraffin-embedded tissue subjected to mass spectrometry-based proteomics is available [2, 10].

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Other Diseases with Organized Deposits

19

Introduction

Other abnormal substances besides amyloid may infiltrate glomeruli and cause significant dysfunction. Certain glomerular diseases are defined by ultrastructural features of protein deposits. While typical immune complex electron dense deposits have a uniform appearance, some disorders are characterized by an organized substructure to infiltrating proteins. These include cryoglobulinemia and lupus nephritis among others. The two discussed below, fibrillary glomerulonephritis and immunotactoid glomerulopathy, were described within a few years of one another in the 1970–1980s and, for some time, were considered to be variants of the same disease.

Fibrillary Glomerulonephritis

Clinical Setting

Perhaps among the more important of these is the lesion known as fibrillary glomerulonephritis (Fig. 19.1) [1–3]. Presenting manifestations are similar to other glomerulopathies: proteinuria, frequently with nephrotic range, hematuria (70 %), renal insufficiency, and hypertension.

Pathologic Findings

The light microscopy of glomeruli indicates variable increase in mesangial cellularity and irregularly thickened capillary walls. Crescents may be present [1, 4]. Immunofluorescence is positive, with coarse linear/confluent granular immunoglobulin G (IgG), C3, and one or both light chains. This disorder is ultrastructurally defined and is characterized by the accumulation of fibrils that are roughly 18–20 nm in thickness and are throughout the mesangial matrix and basement membranes in a manner very similar to amyloid [1]. Indeed, the fibrils bear

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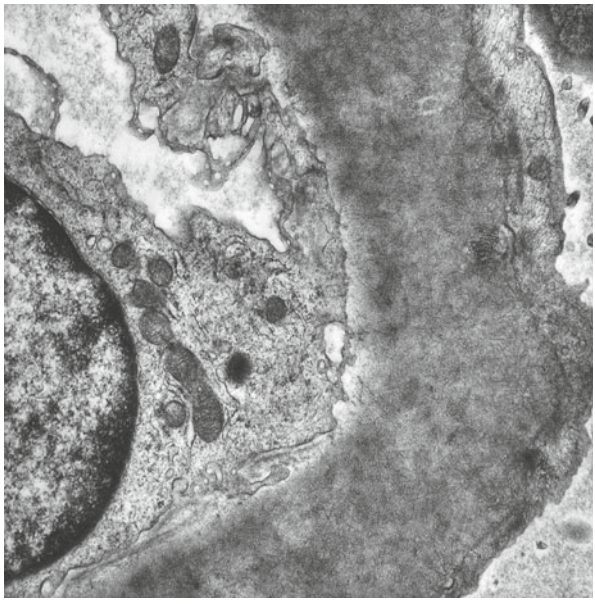

Fig. 19.1 Fibrillary glomerulonephritis; there are numerous randomly arranged fine fibrils permeating the basement membrane (electron microscopy)

Table 19.1 Features of amyloid and fibrillary glomerulonephritis (GN)

Amyloid	Fibrillary GN
Fibrils 10–12 nm	Fibrils 18–20 nm
Extraglomerular renal involvement—vessels, interstitium, etc.	Rare extraglomerular renal involvement
Extrarenal involvement common	Extrarenal involvement rare
Congo red positive	Congo red negative

striking similarity to amyloid. In contrast, however, the infiltrate is Congo red negative, unlike amyloid [5].

Extraglomerular and extrarenal involvement is rare [6, 7]. The typical clinical presentation is of heavy proteinuria with hematuria, hypertension, and some degree of renal insufficiency. Serologic studies are negative or noncontributory, although some patients may have a positive antinuclear antibody (ANA). Initially considered to be an idiopathic disorder, fibrillary glomerulonephritis is reported to be associated with carcinomas, dysproteinemia, or autoimmune disease in 23, 17, and 15 % of patients, respectively [8]. Thus, if not clinically evident, a biopsy diagnosis of fibrillary glomerulonephritis should stimulate a search for an associated disease. This disorder runs a chronic course with advanced renal insufficiency requiring renal replacement therapy in approximately 40 %. The nature of the fibrils is not known; one report described a circulating cryoprecipitated factor composed of immunoglobulins, light chains, and fibronectin [3]. The disease not infrequently recurs in the transplant [9, 10]. A comparison between amyloid and fibrillary glomerulonephritis is indicated in Table 19.1.

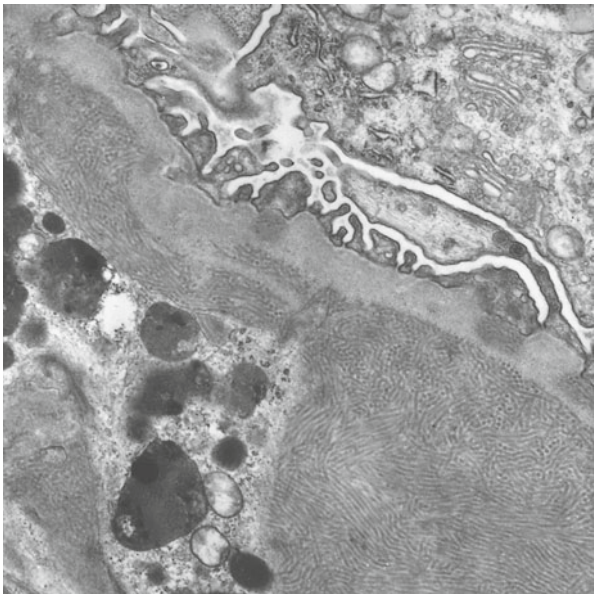

Fig. 19.2 Immunotactoid glomerulopathy; the large subendothelial deposit is composed of many hollow-cored tubular structures, some of which are in cross section (electron microscopy)

Immunotactoid Glomerulopathy

Another disorder with peculiar ultrastructural features is known as immunotactoid glomerulopathy (Fig. 19.2) [1, 4, 11]. Presenting manifestations are similar to fibrillary glomerulonephritis: proteinuria, hematuria, hypertension, and renal insufficiency. The light microscopic appearance of glomeruli is typically of a membranoproliferative glomerulonephritis pattern or membranous glomerulonephritis. Immunofluorescence microscopy discloses granular capillary wall deposits of IgG, complement, and one or both light chains. In this entity, glomerular immune (electron dense) deposits are composed of numerous coarse hollow-cored fibrils (immunotactoids) ranging in thickness from approximately 20–80 nm. Patients present with heavy proteinuria and hematuria; approximately 50 % have been found to have a concurrent or subsequently developing lymphoproliferative disease [1, 12].

Clinical Correlations

Until recently, a controversy existed concerning these two diseases [1, 2, 13, 14]. Some investigators consider them to be the same entity based on clinical presentation and course as well as ultrastructural features that are thought to represent structural manifestations of abnormal protein deposits. Other investigators, however, deem these disorders to be completely separate and distinct entities that happen to be diagnosed on the basis of ultrastructural abnormalities. Studies by Bridoux et al. [12] and Rosenstock et al. [4] have quite convincingly demonstrated that the distinct

pathologic features are associated with distinct clinical manifestations and significance. Most important is the tight link between immunotactoid glomerulopathy and lymphoproliferative disorders [12, 15, 16].

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Part VIII

Renal Transplant Pathology

Allograft Rejection

20

The renal transplant biopsy remains the gold standard for the diagnosis of episodes of graft dysfunction that occur in 10–30 % of patients after transplantation [1]. In a prospective trial, the biopsy diagnosis changed the patient management as based on the prebiopsy clinical diagnosis in 42 % of graft dysfunction episodes (39 % in the first month, 56 % in the first year, and 39 % after 1 year); in 19 % unnecessary immunosuppression was avoided [2]. Donor biopsies are used in many centers to get a baseline assessment of the status of the kidney. Protocol biopsies, once used only for research, have become part of the management of the high-risk patient and in some centers for all patients (surveillance biopsies).

The processing of the biopsy is the same as for native kidneys, with the addition of C4d staining for antibody-mediated rejection. In our center we routinely process two cores for histology, and portions of each are frozen and fixed for electron microscopy. Electron microscopy is valuable for the diagnosis of biopsies in which recurrent or de novo glomerular disease is in the differential and in chronic antibody-mediated rejection. An adequate sample includes two cores, because the sensitivity of detecting acute rejection on one core is about 90 %; with two cores the sensitivity is increased to 99 % [3]. We routinely make five levels, three stained with H&E and one each with PAS and trichrome. Immunohistochemistry is used for identification of microorganisms and cell types as indicated. Molecular tests are likely to be applied in the future to refine the diagnosis [1].

Renal allograft biopsies are a challenge for the pathologist, since they may have all the diseases of a native kidney, plus unique diseases seen only in allografts. The urgency for treatment often means a rapid diagnosis is sought, sometimes with only a frozen section, with its known limitations [4].

Furthermore, there are often multiple diseases present, and it is up to the pathologist and clinician to decide which is dominant. On the other hand, transplant biopsies provide a window on the early stages of native kidney diseases and can yield pathogenetic insights. The classification system we use for transplant biopsies is give in Table 20.1 [5].

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Table 20.1 Pathologic classification of renal allograft lesions

- I. Alloimmune
  - A. T-cell-mediated rejection
    - 1. Acute T-cell-mediated rejection (acute cellular rejection)
      - (a) Tubulointerstitial (Banff type I)
      - (b) Endarteritis/endothelialitis (Banff type II)
      - (c) Arterial transmural inflammation or fibrinoid necrosis (Banff type III)
      - (d) Transplant glomerulitis (no Banff type)
    - 2. Chronic T-cell-mediated rejection
      - (a) Tubulointerstitial (Banff type I + IF/TA)
      - (b) Transplant arteriopathy (Banff type II) + intimal fibrosis/foam cells
  - B. Antibody-mediated rejection
    - 1. Hyperacute rejection
    - 2. Acute antibody-mediated rejection (acute humoral rejection)
      - (a) Acute tubular injury (Banff type I)
      - (b) Capillary inflammation (Banff type II)
      - (c) Arterial fibrinoid necrosis (Banff type III)
    - 3. Chronic antibody-mediated rejection
      - (a) Transplant glomerulopathy and glomerulitis
      - (b) Peritubular capillary multilamination and capillaritis
      - (c) Transplant arteriopathy
  - C. Alloreactivity without pathologic evidence of rejection
    - 1. Accommodation (C4d and or DSA with active rejection)
    - 2. Treg-rich organized lymphoid structures (TOLS)
  - D. Autoantibody-/alloantibody-mediated renal diseases
    - 1. De novo membranous glomerulonephritis
    - 2. Anti-angiotensin type II receptor autoantibody syndrome
  - E. Recipient-specific alloantibody-mediated diseases
    - 1. Anti-glomerular basement membrane (GBM) disease (in Alport's syndrome)
    - 2. Anti-tubular basement membrane (TBM) disease
- II. Drug toxicity and hypersensitivity (partial list)
  - A. Calcineurin inhibitor nephrotoxicity: acute tubulopathy, chronic hyaline arteriolopathy, IFTA, FSGS, thrombotic microangiopathy (TMA)
  - B. mTOR inhibitor toxicity (acute tubular injury, FSGS, TMA)
  - C. Antiviral drug tubular toxicity
  - D. Allergic interstitial nephritis
- III. Infection (viral, bacterial, fungal)
  - A. Polyomavirus nephropathy
  - B. Adenovirus nephropathy
  - C. Posttransplant lymphoproliferative disease
- IV. Ischemia
  - A. Acute ischemic injury (ATN)
  - B. Perfusion injury
  - C. Major artery/vein thrombosis
  - D. Renal artery stenosis
- V. Obstruction

Table 20.1 (continued)

VI. Recurrent primary disease
A. Immunologic (e.g., IgA nephropathy, lupus nephritis, anti-GBM disease)
B. Metabolic (e.g., amyloidosis, diabetes, oxalosis)
C. Unknown etiology (e.g., dense deposit disease, focal segmental glomerulosclerosis)
VII. De novo glomerular disease (partial list)
A. Focal segmental glomerulosclerosis (hyperfiltration/collapsing FSGS)
B. Diabetic nephropathy

From reference [5]

The most widely used classification system is the Banff schema, as modified by the Collaborative Clinical Trials in Transplantation (CCTT) categories [3], and updated biannually [6–9]. The Banff system scores each element (infiltrate, tubulitis, arteritis, glomerulitis) on a 0–3 scale (1, mild; 2, moderate; 3, severe) as the basis for grading. The Banff system promoted standardization of definitions and has created a common language. However, there remain issues to be solved, such as the "borderline" category and glomerular lesions. The interobserver reproducibility for component grading of the Banff system is disappointing, with kappa values of <0.4 (in the poor range) [10]. The scoring for tubulitis and arteritis was improved by scoring photographs, indicating that finding the relevant lesion on the slide was a limiting factor; scoring of the percent infiltrate or glomerulitis was not improved by scoring a photograph, suggesting intrinsic problems in the definitions or methodology.

Acute Cellular Rejection (ACR)

Clinical

Acute cellular rejection (ACR) is the common form of rejection, mediated by T cells, that develops classically 1–6 weeks after transplantation but may erupt at any time. The typical clinical presentation is a rising creatinine over a few days, accompanied by weight gain and sometimes fever and graft tenderness. The frequency of clinical ACR has been reduced with modern therapy to about 10 %.

Pathologic Findings

Light Microscopy

Acute cellular rejection affects the interstitium, tubules, endothelium, and glomeruli, separately or in combination. The characteristic microscopic features of tubulointerstitial rejection (Banff type I) are pleomorphic interstitial infiltrates of activated lymphocytes and monocytes, accompanied by interstitial edema and tubular injury. The cells invade tubules ("tubulitis") and infiltrate the cortex (10–25 % in the Banff system is considered suspicious for rejection and >25 % is

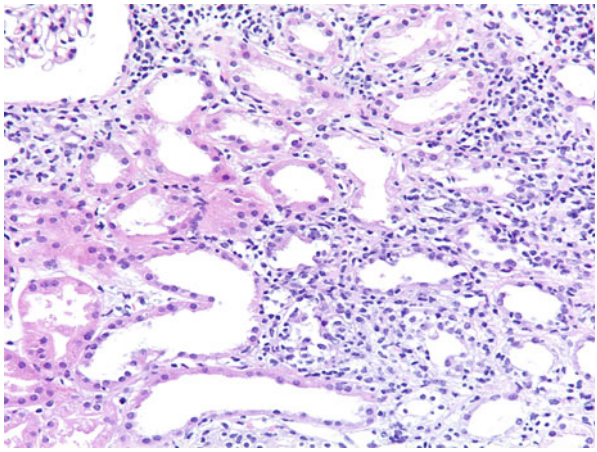

Fig. 20.1 Acute cellular rejection (type I). A diffuse mononuclear infiltrate is present with edema and tubulitis [periodic acid-Schiff (PAS) stain]

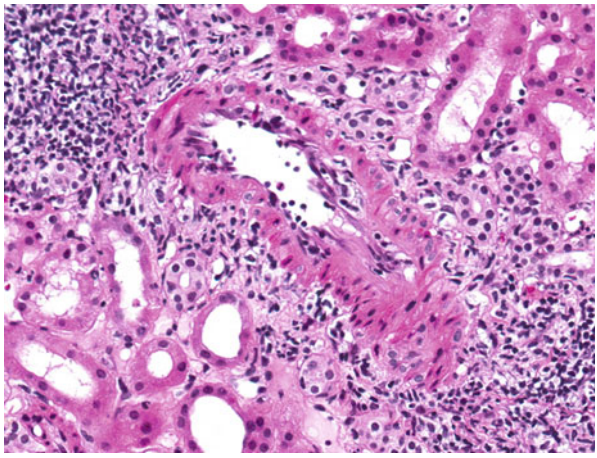

Fig. 20.2 Acute cellular rejection with endarteritis (type II). A small artery has subendothelial infiltration of mononuclear cells (H&E stain)

rejection) (Fig. 20.1). The infiltrating mononuclear cells typically include lymphoblasts, with cytoplasmic basophilia, nucleoli, and occasional mitotic figures, indicative of increased synthetic and proliferative activity. The infiltrate consists of T cells (CD4 and CD8), macrophages, and sometimes B cells. Foxp3+ cells (presumptive T regulatory cells) also accumulate in ACR [11] and may be correlated with a better prognosis in protocol biopsies [12]. TGF-β mRNA is associated with better outcome, perhaps related to promotion of Treg cells [13].

Infiltration of mononuclear cells under arterial and arteriolar endothelium is the pathognomic lesion of Banff type II ACR ("endarteritis" or "endothelialitis") (Fig. 20.2). When lymphocytes are only on the surface of the endothelium, their significance is less certain. Lymphocytes also commonly surround vessels, a nonspecific feature, unless the cells invade the media. Endarteritis has been reported in 20–50 % of the renal biopsies with acute cellular rejection [14]. Some do not find the lesion as often, which may possibly be ascribed to inadequate sampling, overdiagnosis of rejection, or timing of the biopsy with respect to antirejection therapy.

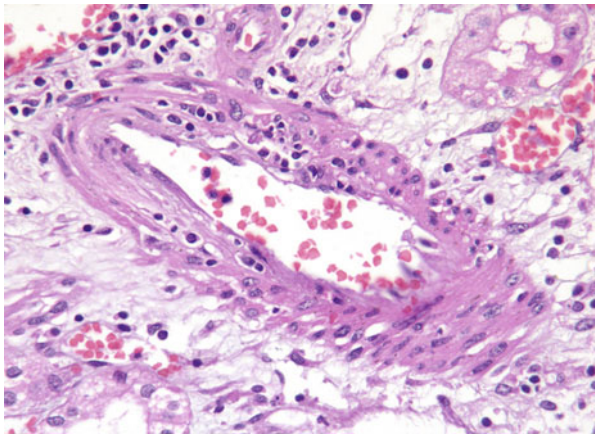

Fig. 20.3 Acute cellular rejection, type III. Transmural inflammation of an artery is shown. The C4d stain was negative

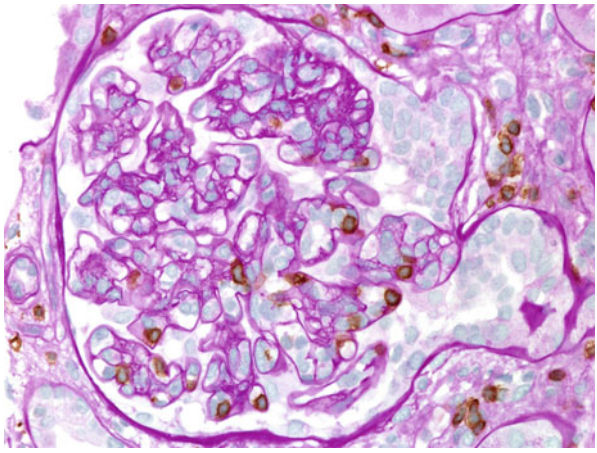

Fig. 20.4 Acute transplant glomerulitis. This pattern of glomerular injury can occur as a feature of cellular or humoral rejection; T cells predominate in cellular rejection, as in this case, which also has a tip lesion (PAS stain with anti-CD3) (Case courtesy of M. Pilichowska (Tufts))

These lesions are more frequent in the larger arteries [14]. In our experience, about 20 % of the arteries are involved so that levels of several arteries in the sample are essential for its detection [14]. Rarely, the lymphocytes invade through the media, so-called transmural endarteritis (Fig. 20.3).

In most cases of acute cellular rejection, the glomeruli are spared or show minor changes, typically a few scattered mononuclear cells (T cells and monocytes) and minimal segmental endothelial damage, termed "glomerulitis" [15]. Occasionally, a severe, diffuse form of glomerular injury is evident and dominates the histologic pattern (Fig. 20.4). In 1981 Richardson and his colleagues [16] drew attention to a distinctive, acute allograft glomerulopathy, characterized by hypercellularity, injury, and enlargement of endothelial cells, infiltration of glomeruli by mononuclear cells, and webs of periodic acid-Schiff (PAS)-positive material. This severe form of glomerulopathy is observed in ~4 % of biopsies taken for allograft dysfunction, typically 1–4 months after transplantation and is believed to be an unusual variant of cellular rejection, sometimes promoted by cytomegalovirus (CMV) infection [15]. T cells are regularly detected in glomeruli immunohistochemically and OKT3

can reverse the lesion [17]. For unknown reasons, rejection becomes focused on glomerular components; florid glomerulopathy may occur with little interstitial inflammation, although cellular endarteritis is common. Glomerulitis is also commonly seen in antibody-mediated rejection and is a sign of activity. Glomerulitis in AMR is predominately due to macrophages rather than T cells which dominate in ACR [18].

Interstitial mononuclear inflammation and tubulitis occur in a variety of diseases other than acute rejection, such as drug-induced allergic tubulointerstitial nephritis and obstruction, and therefore cannot be considered proof that rejection is present. The presence of systemic infection is another well-known cause of tubulointerstitial nephritis and tubulitis. Tubulitis is often present in atrophic tubules from any cause and does not indicate acute rejection. Posttreatment with anti-T-cell antibodies, the inflammation diminishes in most patients, and this is correlated with successful response to therapy. This type of rejection often responds to steroid pulses and rarely causes graft loss [3, 14, 19, 20].

In all large studies, endarteritis has a worse prognosis than tubulointerstitial rejection [3, 14, 19, 20, 21]. Cases with endarteritis are less responsive to steroid pulses, but do respond to OKT3 or antithymocyte globulin (ATGAM), and have a decreased 1-year survival [14]. Later development of intimal fibrosis is correlated prior type II rejection [19].

Endarteritis must not be confused with necrotizing arteritis, characteristic of humoral rejection (type III). Rarely, transmural cellular inflammation causes frank medial necrosis, but this complication of cellular arteritis can be distinguished from necrotizing arteritis by the heavy mononuclear infiltrate. Regrettably, many still do not distinguish these lesions, regarding all "vascular rejection" as predominately humoral. Endarteritis has a much better rate of reversal than necrotizing arteritis (75 % vs. <25 % 1-year graft survival), which alone justifies their separation [19].

Immunofluorescence Microscopy

Immunofluorescence microscopy shows little, if any, immunoglobulin deposition, but interstitial fibrin is typically present. Fibrin and scant immunoglobulin and C3 deposits may also be found in glomeruli. C4d in peritubular capillaries when present is indicative of a component of antibody-mediated rejection (see below).

Electron Microscopy

Electron microscopy is generally not used for the diagnosis of acute rejection. Studies have shown endothelial injury in peritubular and glomerular capillaries, invasion of lymphocytes into tubules. No immune deposits are detectable. Cases with acute allograft glomerulopathy show markedly reactive endothelial cells, with mononuclear cells in capillaries and often platelet/fibrin aggregates.

Pathogenesis

Type I and II cellular rejections are mediated primarily by T cells and their coconspirators, macrophages, and other cell types, rather than antibodies, since they both occur in the absence of circulating antibody or evidence of complement fixation in

the graft. In animals endarteritis occurs in the absence of humoral antibody (e.g., B-cell-deficient mice). In humans, rejection with vascular infiltrates can usually be reversed with antilymphocyte antibodies such as OKT3 or ATG [14, 22]. Both $CD8^+$ and $CD4^+$ cells invade the intima in early grafts, but later $CD8^+$ cells predominate [15, 23]. Arterial endothelium shows increased human leukocyte antigen DR (HLA-DR), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) in acute rejection [23], and the tubular epithelium shows increased HLA-DR [24]. Increased expression of major histocompatibility complex (MHC) antigen and adhesion molecules is believed to be a response to cytokines. Microarray and PCR studies have shown a marked increase in gene expression for a variety of molecules of the cytotoxic T cell, macrophages, and molecules induced by interferon gamma [25]. In contrast, mRNA for tubular cell transporter molecules is diminished, a marker of their injury. Practical application of these techniques is expected in the future once their added clinical value is demonstrated [1].

Acute Antibody-Mediated Rejection (Acute AMR) or Acute Humoral Rejection

Clinical

The clinical features of acute AMR consist of severe and acute (days) graft dysfunction that is not responsive to steroids or usually antilymphocyte antibodies and with a higher rate of graft loss than cellular rejection. It can arise anytime after transplant. The risk factors for acute AMR include elevated panel reactive antibody (PRA), prior transplant, and historically positive crossmatch, all associated with prior sensitization [26–29].

Pathologic Findings

Light Microscopy

Three forms of acute AMR have been recognized [6, 30]: (1) acute tubular injury with little inflammation, (2) peritubular and glomerular capillary inflammation with neutrophils, and (3) necrosis of arteries. Acute humoral rejection (AHR) can be missed in routine sections.

In one series, a component of AHR would not have been recognized in 25 % of cases without the C4d stain: 15 % showed only ACR and 10 % only acute tubular injury [30]. The 10 % acute tubular injury biopsies comprised of two donor-specific antibodies (DSA^+) in patients with widespread C4d staining of peritubular capillaries (PTCs) that showed predominantly acute tubular injury on initial biopsy. Later biopsies performed in one of these showed typical AHR with abundant neutrophils in PTCs and glomeruli as well as fibrinoid necrosis. Most cases have neutrophils in PTCs (Fig. 20.5). This feature is useful, but not highly sensitive or specific [30]. The histologic features in the Regele et al. series were similarly misleading: 32 % of those with C4d did not meet the Banff criteria for rejection, accounting for about 75 % of

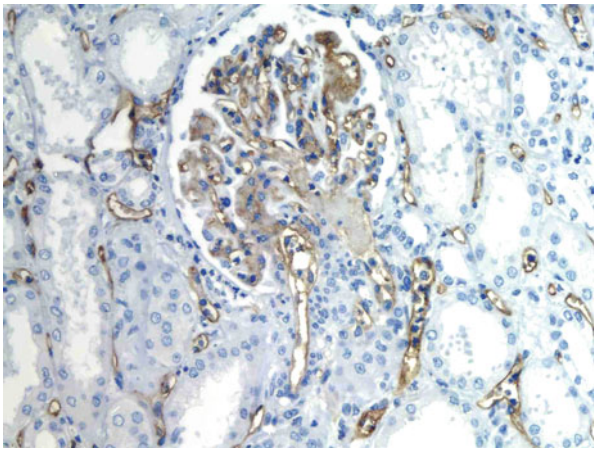

Fig. 20.5 Acute antibody-mediated rejection, type II. Neutrophils are in the peritubular capillaries (capillaritis) and in the glomeruli. The peritubular and glomerular capillaries stain strongly for C4d (immunohistochemistry, anti-C4d)

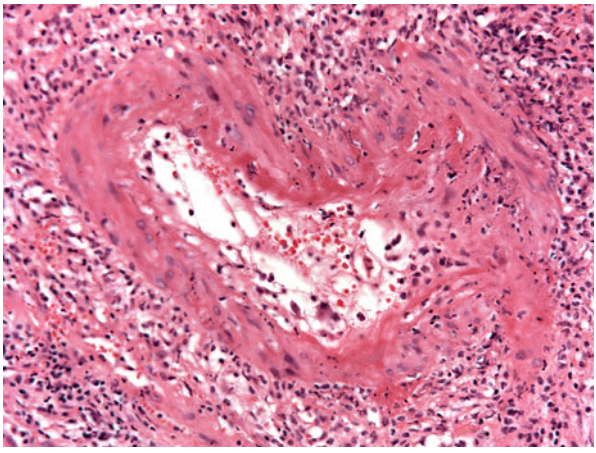

Fig. 20.6 Acute AMR with fibrinoid necrosis (type III). A small artery has fibrin, neutrophils, and necrosis in the media (H&E stain)

the patients with acute AMR [27]. In some cases arterial and arteriolar thrombosis and glomerular thrombosis and necrosis predominate similarly to thrombotic microangiopathy. These lesions must be distinguished from the hemolytic uremic syndrome of calcineurin inhibitor toxicity, which can also have thrombi in arterioles and glomeruli, but does not affect the peritubular capillaries (or have C4d). A minority of cases have fibrinoid necrosis, in which the arterial media shows myocyte necrosis, fragmentation of elastica, and accumulation of brightly eosinophilic material called "fibrinoid" and little mononuclear infiltrate in the intima or adventitia (Fig. 20.6). A scant infiltrate of neutrophils and eosinophils and thrombosis may be present.

Immunofluorescence Microscopy

Detection of C4d has proved to be useful in the detection of humoral rejection (Fig. 20.7). After antibody binds to antigen, C4 is proteolytically cleaved by activated C1 into C4a and C4b. The cleavage of C4 exposes the reactive and

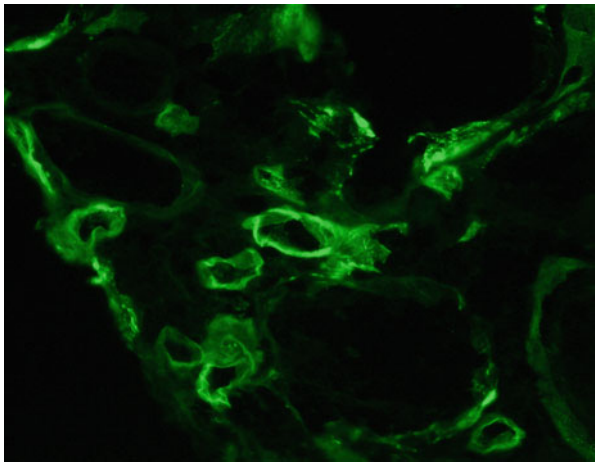

Fig. 20.7 Acute humoral rejection. C4d is present in peritubular capillaries (immunofluorescence on frozen section; monoclonal antibody to C4d)

Table 20.2 Criteria for acute antibody-mediated rejection

1. Widespread, linear C4d$^+$ staining of peritubular capillaries
2. Evidence for acute renal injury consisting of at least one of the following:
(a) Acute tubular injury
(b) Neutrophils in peritubular or glomerular capillaries
(c) Fibrinoid necrosis of arteries
3. Circulating anti-donor-specific antibodies

If only two of the three major criteria are established (e.g., when no human leukocyte antigen crossmatch is available or when C4d staining is not done), the diagnosis should be considered suspicious for acute AMR

short-lived thiol group in C4b that binds covalently to nearby molecules containing amino or hydroxyl groups, such as proteins and carbohydrates [31]. Bound C4b is proteolytically inactivated into C4d, a 44.5-kd peptide, which contains the thioester site and remains covalently bound at the same site. Thus, if C4d is bound to a structural protein, it is potentially a durable marker of local complement activation by the classical pathway. C4d can disappear as soon as 8 days [32] and after 60 days is usually negative (unless chronic humoral rejection develops) [30]. Cases with fibrinoid necrosis of arteries typically contain immunoglobulin (Ig, usually IgG and IgM), C3, and fibrin in the arterial walls. The criteria for acute humoral rejection proposed by Mauiyyedi et al. [30] and accepted with minor modification by the Banff conference are given in Table 20.2 [6].

Pathogenesis

Donor-specific anti-HLA antibodies are detected in 90 % of C4d$^+$ acute rejection cases compared with 2 % in C4d$^-$ acute rejection cases ($p < 0.001$) [30]. We have speculated that the DSA-negative cases are due to adsorption in the graft or to

non-HLA specificities. Circulating pretransplant and posttransplant DSA can be identified by T- and B-cell cytotoxicity assays or flow cytometry but best by solid-phase assay with single antigen beads.

Although most patients are having negative pretransplant for DSA, presensitization is sometimes missed due to lack of sensitivity of the assay [33]. Repeat testing with the most sensitive solid-phase techniques sometimes reveals an occult DSA [34]. The circulating antibodies are usually to donor HLA class I antigens [35], although a minority show only reactivity to class II MHC antigens, or to non-MHC molecules on endothelium [36]. C4d has been detected in cases of acute AMR due to non-HLA antibodies and therefore has potential value as an antigen-independent test for humoral rejection [37, 38]. A central role for complement fixation is supported by the ability of anti-C5 antibody to substantially inhibit acute AMR [39].

Clinicopathologic Correlations

A substantial fraction (about 25–50 %) of acute renal allograft rejection episodes have a component of AHR as judged by C4d deposition in PTC [20]. In one series 30 % of patients with biopsy-confirmed acute rejection had a humoral rejection component as judged by widespread C4d staining of the PTC, representing 9 % of renal transplant patients overall [26]. The overall graft loss at 1 year after AHR is considerably worse than after ACR. In a large, well-analyzed study, the presence of C4d strikingly and adversely impacted the outcome of either type 1 (tubulitis) or type 2 (endarteritis) acute rejection [20].

Hyperacute Rejection

Hyperacute rejection occurs when the recipient is presensitized to donor antigens expressed by the endothelium, usually HLA or ABO antigens. Graft dysfunction occurs within minutes to hours of reperfusion, and the grafts generally never function. The pathology is similar to that described for acute humoral rejection, including neutrophils in capillaries, thrombi, and hemorrhage (Fig. 20.8). C4d is generally demonstrable in peritubular capillaries. With ABO incompatibility, IgM is often detectable.

Late Graft Loss

Introduction/Clinical Setting

The rate of long-term graft loss changed little over the last decade, despite dramatic improvements in short-term graft survival [40]. The clinical features of late graft dysfunction are a slowly rising creatinine, often accompanied by severe proteinuria and hypertension. Graft function may be lost gradually over a period of months to

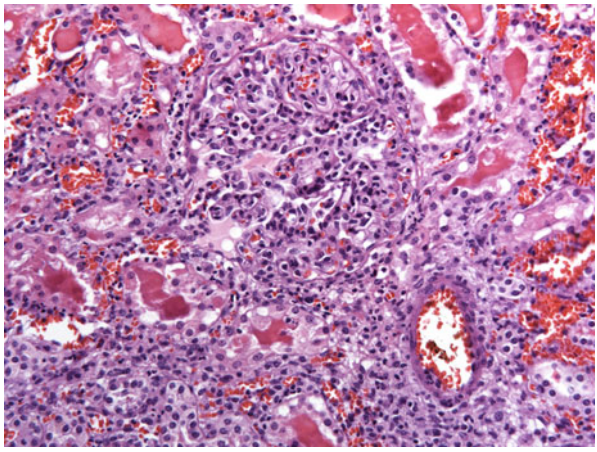

Fig. 20.8 Hyperacute rejection. The cortex shows hemorrhage and neutrophils in peritubular capillaries with prominent glomerular inflammation (H&E stain)

years, with or without episodes of acute rejection. The rate of graft loss is steady after the initial 3–6 months, with a half-life of 8.8 years for deceased donor grafts, 11.4 years for living donor grafts, and >20 years for grafts from HLA-identical siblings [40, 41].

Most late graft loss, other than patient death and recurrent disease, has been attributed to chronic allograft nephropathy (CAN). CAN entered prime time in 1993 as a category in the Banff working classification that was to include "at least four entities that at present cannot always be distinguished by biopsy (chronic rejection, chronic cyclosporine toxicity, hypertensive vascular disease, and chronic infection and/or reflux)" [8]. Chronic allograft nephropathy was *not* intended to replace specific diagnostic categories if these entities could be identified. Because CAN has been often misused as a generic term for chronic renal allograft dysfunction and fibrosis, or as a synonym for "chronic rejection," subsequent Banff classifications have replaced CAN with interstitial fibrosis/tubular atrophy, not otherwise specified (IF/TA, NOS) [42]. There is ample evidence that a majority of the cases of late graft loss are due to chronic antibody-mediated rejection (chronic AMR) and other discrete entities that can be recognized pathologically, such as recurrent disease and calcineurin inhibitor toxicity [43–46].

Chronic Antibody-Mediated Rejection (Chronic AMR) or Chronic Humoral Rejection

Clinical

Chronic AMR typically presents with a slowly progressive, insidious rise in Cr and proteinuria several years after transplantation. The majority of the patients do not have an episode of acute AMR. Patients who reduce immunosuppression late after transplant, either due to noncompliance or nonabsorption, account for a substantial

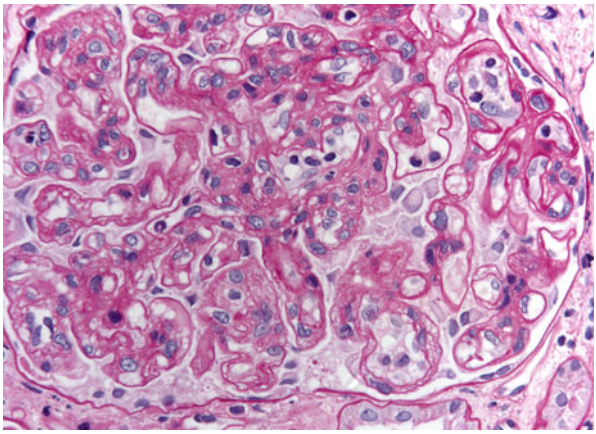

Fig. 20.9 Transplant glomerulopathy (TG). Mesangial hypercellularity and duplication of the glomerular basement membrane (GBM) are prominent, as well as endocapillary mononuclear cells (PAS stain)

fraction (~50 %) of patients with AMR. Once the diagnosis is made, outcome is poor, with about a 50 % 18-month graft survival [43]. The prevalence of humoral rejection may vary with the immunosuppressive protocol, but no current therapy prevents humoral rejection; cases have occurred with cyclosporine, azathioprine, mycophenolate, CAMPATH1, and tacrolimus. Among various series comprising >300 patients, about 50 % of those with TG/CAV had C4d deposition in PTC vs. <10 % of grafts without evidence of chronic rejection [47–51].

Pathologic Findings

Light Microscopy

The usual hallmark of chronic AMR is transplant glomerulopathy (TG), defined by prominent duplication of the GBM on PAS-stained sections, often accompanied by an increase in mesangial cells and matrix and various degrees of scarring and adhesions (Fig. 20.9). TG is not a specific lesion for chronic AMR, since it can occur in other settings (notably TMA, HCV infection, MPGN) [52]. However, about 30–60 % of patients with TG have C4d deposition [52]. Extensive crescents, diffuse granular or linear deposits of IgG, or subepithelial deposits are unusual and suggest recurrent or de novo glomerulonephritis. The glomerular capillaries often have accumulated mononuclear cells (glomerulitis). Similar intracapillary cells are evident in the peritubular capillaries (capillaritis, Fig. 20.10).

Arteries commonly show pronounced fibrous intimal thickening with myointimal cells, collagen fibrils, focal calcification, a variable infiltrate of T cells (often subendothelial), and lipid-filled, foamy macrophages disposed characteristically against the external elastica, which is duplicated and disrupted, a feature termed chronic allograft vasculopathy (CAV) (Fig. 20.11). The adventitia also often has an infiltrate of mononuclear cells, sometimes invading and destroying the outer media. Marked duplication of the internal elastica, a normal or thickened media, and relative sparing of the larger arteries (arcuate and larger) are more typical of

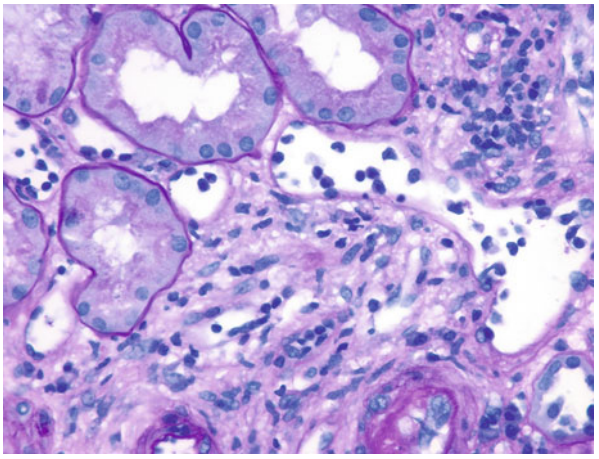

Fig. 20.10 Peritubular capillaritis. Numerous mononuclear cells are in dilated peritubular capillaries, a feature of chronic AMR that can be present in the absence of prominent C4d (PAS stain)

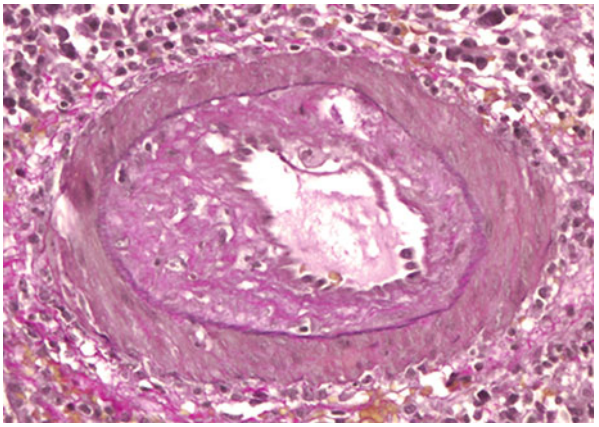

Fig. 20.11 Chronic allograft vasculopathy (CAV). Expansion of the intima with fibrous tissue and scattered infiltrating mononuclear cells, with little or no increase in elastin fibers is typical of CAV (elastin stain)

hypertension. The arterioles are relatively spared in chronic rejection, compared with chronic cyclosporin A (CsA) toxicity, thrombotic microangiopathy/hemolytic uremic syndrome, and systemic sclerosis. These processes do not cause a mononuclear infiltrate in the vessels. However, the healing phase of hemolytic uremic syndrome and systemic sclerosis may leave intimal fibrosis that resembles chronic rejection.

Immunofluorescence Microscopy

Immunofluorescence shows C4d deposition in the peritubular capillaries in the majority of cases. However, the extent of C4d can vary from >50 to 0 %. Glomerular C4d deposition is often detectable in paraffin sections. Numerous cases of chronic AMR with negative C4d have been reported (here AMR is defined by characteristic histology and DSA). PTC capillaritis and increased endothelial gene expression are also potential markers of chronic AMR in the absence of C4d. Glomeruli may also

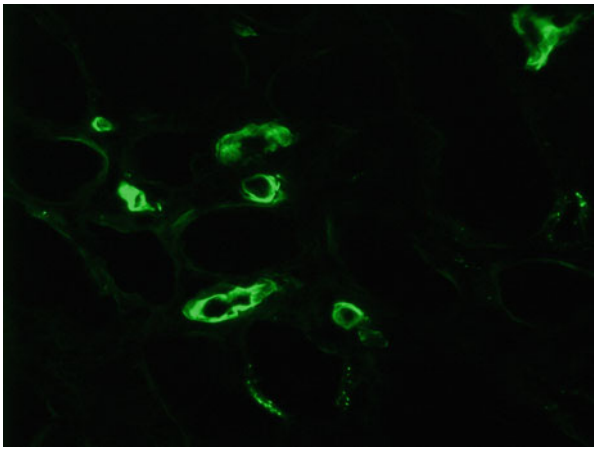

Fig. 20.12 Focal staining of peritubular capillaries (PTC). A minority of the peritubular capillaries stain for C4d, which is more common in chronic than acute AMR. PTCs may have no detectable C4d in cases with other signs of chronic AMR (e.g., transplant glomerulopathy and DSA)

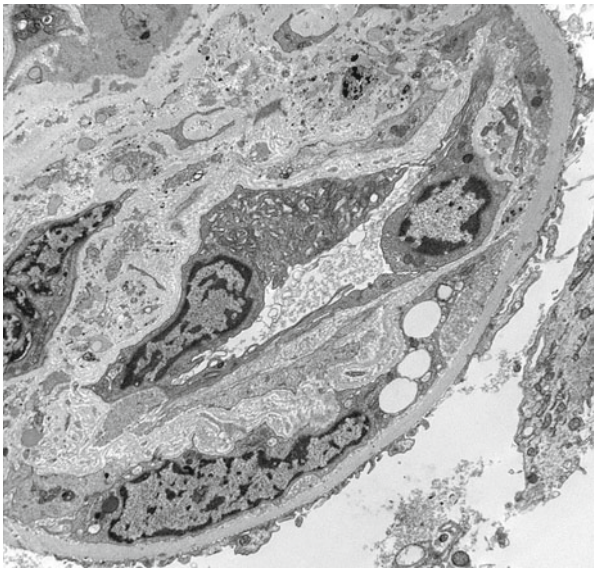

Fig. 20.13 Transplant glomerulopathy due to chronic AMR. The GBM is duplicated and cellular interposition is evident. The endothelial cells have lost their normal fenestrations and have increased cytoplasm, suggesting activation or dedifferentiation (electron microscopy)

show segmental or granular deposits of immunoglobulin (typically IgM and IgG, rarely IgA), C3, and sometimes fibrin in the capillary wall and in the mesangium (Fig. 20.12).

Electron Microscopy

Electron microscopy shows foot process effacement and focal mesangial cell interposition, and mesangiolysis may be present (Fig. 20.13). Endothelial cell "dedifferentiation" is often evident, as manifested by a loss of the normal fenestrations [53]. Loss of this normal differentiated structure of glomerular endothelial cells should markedly restrict bulk water flow through the capillary wall and decrease filtration. The other diseases with similar light and electron microscopic

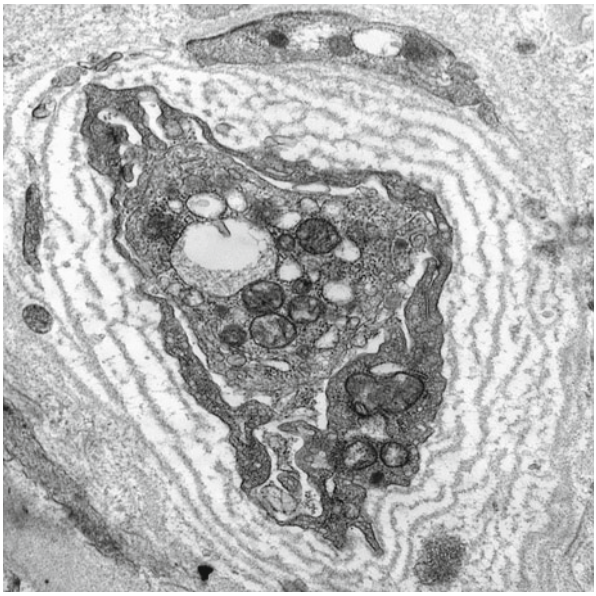

Fig. 20.14 Peritubular capillary basement membrane multilamination due to chronic AMR. Each new basement membrane layer is believed to be the residue of a past episode of endothelial injury. The greater the number, the more likely the lesion is due to chronic AMR [54] (electron microscopy)

glomerular features also are characterized by endothelial injury (thrombotic microangiopathy, scleroderma, and eclampsia) [52].

A chronic lesion in the peritubular capillaries has been observed consisting of splitting and multilayered duplication of the basement membrane, analogous to and correlated with the chronic glomerular changes. These changes can be seen by light microscopy, but EM is the gold standard [54] (Fig. 20.14). Thus, the common theme in chronic AMR is endothelial damage at the level of the arteries, glomeruli, and peritubular capillaries.

Pathogenesis

Previous studies with classic HLA techniques had reported that de novo antibodies to graft HLA class I and II antigens were risk factors for chronic transplant arteriopathy [55] and predicted graft loss [56, 57]. Now evidence has connected circulating DSA specifically with complement fixation and pathology in the graft. Biopsies in the majority of chronic rejection (TG or CAV) in humans have a detectable humoral component [47] as judged by C4d deposition and circulating DSA. This suggests that antibodies that fix complement at the level of the PTCs mediate a major subset of chronic rejection. Others have confirmed and extended these observations. Regele et al. [48] showed that 34 % of graft biopsies taken >12 months posttransplant had C4d in PTC. C4d was correlated with TG and lamination of the PTC basement membrane: 66 % of the cases with TG had C4d (similar to the 61 % in our study). Most importantly, C4d was found to *precede and predict* the later development of TG, arguing that it is related to the pathogenesis and not just an

incidental finding. A retrospective microarray analysis of gene expression in renal allograft biopsies suggested that that B-cell infiltrate predicts increased risk of graft loss due to rejection [58]. Subsequent studies showed the prevalence of B-cell/plasma cell transcripts increases with time posttransplant [59]. Plasma cells in the graft have been shown to produce DSA [60]. Whether complement fixation or other mechanisms participate in chronic AMR remains to be established. In mice DSA mediate chronic allograft vasculopathy via an NK cell-dependent pathway [61]. Certainly biopsies in patients with DSA can show little or no C4d and have capillaritis [62] or increased endothelial and NK gene expression [63, 64].

Differential Diagnosis

The glomerular features are not specific for chronic AMR but are typical [52]. The most distinctive features in my opinion are the loss of endothelial fenestrations and duplication of the GBM. The other diseases with similar light and electron microscopic glomerular features also are characterized by endothelial injury (thrombotic microangiopathy, scleroderma, eclampsia). If immune complex deposits are more than occasionally found, or if in a subepithelial location, recurrent or de novo glomerulonephritis should be suspected. The features that favor chronic AMR over chronic CsA toxicity are $C4d^+$ peritubular capillaries, capillaritis and glomerulitis, and marked intimal fibrosis of the small arteries. Atypical, monomorphic infiltrates particularly with necrosis are highly suspicious of posttransplant lymphoproliferative disease (PTLD). Peripheral hyalinosis replacing smooth muscle cells in the arterioles favors CsA toxicity.

A consensus meeting at the National Institutes of Health (NIH) established draft criteria for chronic AMR and four theoretical stages in its development [65]. According to this schema, the first evidence of humoral response is the new appearance of DSA (stage I). In some cases this rapidly progresses to AHR. In other cases, for unknown reasons, DSA does not elicit an immediate acute rejection. The next stage (II) shows evidence of antibody interacting with graft endothelium in the form of C4d deposition in PTC, but without graft damage, as judged by normal histology and function. The ensuing stages lead to pathologic injury (III) and finally clinical evidence of graft dysfunction (azotemia, proteinuria). This sequence has been observed in nonhuman primates [66]. Other possibilities can be considered. DSA may not be detectable in the circulation immediately, due to adsorption by the graft. C4d may appear in the graft before antibody "overflows" to the circulation. Regression may occur if antibody ceases to be produced or is intermittent. C4d may not necessarily lead to pathologic injury (e.g., accommodation), a feature typical of ABO incompatible grafts [67].

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Calcineurin Inhibitor Toxicity, Polyomavirus, and Recurrent Disease

21

Calcineurin Inhibitor Toxicity (CIT)

Introduction/Clinical Setting

Cyclosporin A (CsA) and tacrolimus have greatly improved graft survival since their introduction in the 1980 and 1990s, respectively. While the drugs are structurally unrelated, their mechanism of immunosuppression is remarkably similar. The dramatic immunosuppressive and nephrotoxic effects of CsA and tacrolimus are largely explained by their calcineurin inhibition. The pathology of CsA and tacrolimus toxicity is pathologically indistinguishable.

Pathologic Findings

There are three pathologic forms of toxicity: acute nephrotoxicity, chronic nephrotoxicity, and thrombotic microangiopathy (hemolytic-uremic syndrome). Each can also arise in native kidneys in patients on CsA or tacrolimus for other reasons.

Acute Tubulopathy

The biopsy features of acute toxicity range from no morphologic abnormality to acute tubular injury or marked tubular vacuolization and vascular smooth muscle apoptosis (Fig. 21.1). The proximal tubules show loss of brush borders and isometric clear vacuolization (defined as cells filled with uniformly sized vacuoles). The vacuoles, much smaller than the nucleus, contain clear aqueous fluid rather than lipid and are indistinguishable from those caused by osmotic diuretics. Immunofluorescence microscopy is negative. By electron microscopy, the vacuoles are dilated endoplasmic reticulum and appear empty [1]. These lesions are reversible with decreased dosage.

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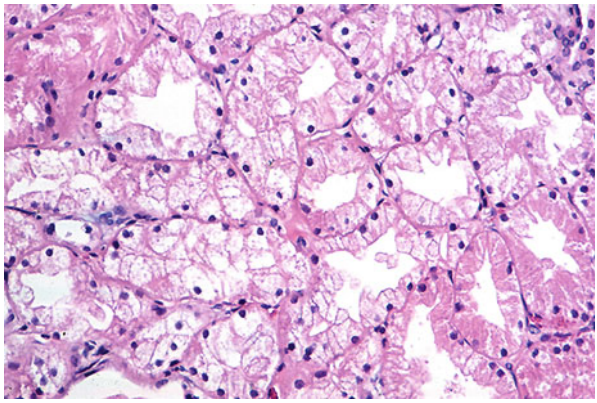

Fig. 21.1 Acute calcineurin inhibitor toxicity, showing isometric vacuolization of proximal tubules (H&E stain)

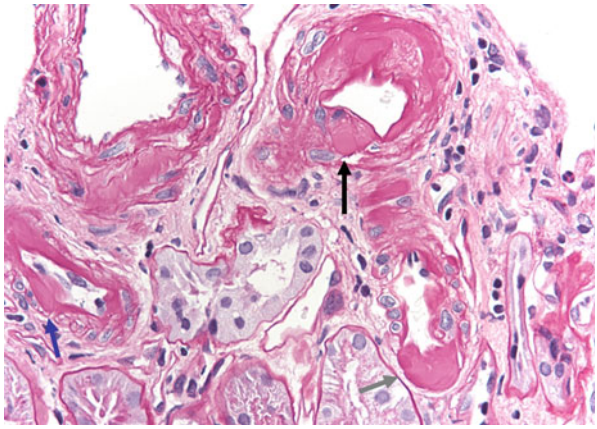

Fig. 21.2 Chronic calcineurin inhibitor toxicity. Peripheral nodules of hyaline are in an arteriole (*black arrow*). Conventional subendothelial hyaline is present (*blue arrow*), as well as advanced transmural hyaline deposits (*gray arrow*). PAS stain

Arteriolopathy

A spectrum of acute and chronic arteriolopathy has been described by Mihatsch, ranging from acute, focal myocyte necrosis and mucoid intimal thickening to indolent nodular hyaline deposits (Fig. 21.2) [2]. The characteristic features are individual smooth muscle cell degeneration, vacuolization, necrosis, and loss. The myocytes are replaced by hyaline deposits, which are classically in a beaded pattern in the media.

The usual hyaline deposits in hypertension or diabetes are subendothelial or transmural. The endothelial or smooth muscle cells may be vacuolated. Later biopsies show progressive scarring of arterioles, intimal fibrosis, and segmental glomerular obsolescence. Immunofluorescence of early lesions may show that the vessels have deposits of immunoglobulin M (IgM), C3, and fibrin. Electron microscopy shows apoptosis or necrosis of smooth muscle cells and replacement with hyaline material. Focal myocyte necrosis in the media of small arteries, in the absence of intimal changes, is regarded as a reliable indicator of CsA toxicity [3]. However,

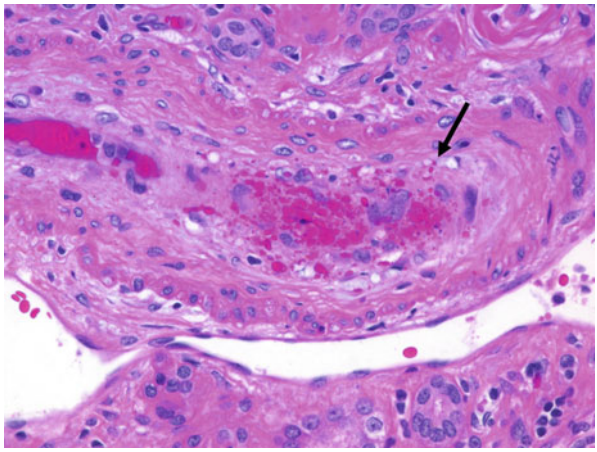

Fig. 21.3 Acute calcineurin inhibitor toxicity due to tacrolimus. Marked mucoid intimal thickening is present with a sparse mononuclear infiltrate and numerous trapped red cell fragments (*arrow*)

while nodular peripheral hyaline deposits are more prevalent in biopsies from patients on CNI, they also occur with some frequency in patients who have never received these drugs [4].

Thrombotic Microangiopathy

Although more prevalent with higher doses of CsA in the 1980s, thrombotic microangiopathy (Fig. 21.3) still occurs under current regimens, even with careful attention to blood CsA levels. By 1994, the prevalence of CsA-associated thrombotic microangiopathy had decreased to 0.9 %, accounting for 26 % of the cases of thrombotic microangiopathy after renal transplantation (acute rejection, probably humoral, accounted for 53 % and recurrent thrombotic microangiopathy 16 %) [5]. Patients typically present with acute renal failure, thrombocytopenia, microangiopathic hemolytic anemia, elevated lactic dehydrogenase, and hyperbilirubinemia. Despite these characteristic features, the clinical syndrome is not often recognized before biopsy. Those without systemic signs (thrombocytopenia, hemolysis) do considerably better [6].

The pathologic changes are the same as in thrombotic microangiopathy from other causes, although in the allograft the differential diagnosis with endarteritis can be challenging. Loose intimal thickening and trapped red cells are useful discriminators.

Differential Diagnosis

The criteria for the morphologic distinction of calcineurin inhibitor toxicity (CIT) and rejection have received much attention. Interstitial infiltrates are minimal in autologous kidneys with nephrotoxicity, but are common in early allografts, and have no differential value unless minimal. Patients with rejection typically have a

diffuse, interstitial mononuclear cell infiltrate, whereas patients with CIT and those with stable function have only focal mononuclear cell infiltrates [7]. Endarteritis is found rarely, if ever, in CIT (0–1 %) and is the most discriminating feature between acute rejection and CIT. Only the finding of endarteritis allowed the identification of rejection with any certainty [8]. This agrees with my experience and that of others [3]. Endothelial and medial smooth muscle cell vacuolization has been noted in CIT, best appreciated by electron microscopy. The frequency of vacuolization probably does not distinguish CIT from stable grafts [7].

Polyomavirus

Introduction/Clinical Setting

The BK polyomavirus was originally isolated from B. K., a Sudanese patient who had distal donor ureteral stenosis months after a living related transplant [9]. BK virus is related to JC virus (which also inhabits the human urinary tract) and to simian kidney virus SV-40. These viruses are members of the papovavirus group, which includes the papillomaviruses. The BK virus commonly infects urothelium but rarely causes morbidity in immunocompetent individuals. However, in renal transplant recipients three lesions have been attributed to BK virus: hemorrhagic cystitis, ureteral stenosis, and acute interstitial nephritis [10].

Pathologic Findings

Light Microscopy

The kidney shows interstitial nephritis, with mononuclear cells infiltrating the interstitium and tubules, often with a prominent component of plasma cells, which also may be occasionally found in tubules (Fig. 21.4) [11]. Polyoma infection is initially suggested by the occurrence of markedly enlarged tubular epithelial cells with nuclear atypia and chromatin basophilia. The recognition of viral nuclear inclusions is the key step in diagnosis. The affected nuclei are usually enlarged and tend to be grouped in tubules, particularly collecting ducts in the cortex and outer medulla, and can often be spotted at low power. The mononuclear interstitial infiltrate is associated with the infected cells. Routine urine cytology readily reveals characteristic viral inclusions (decoy cells). Discrimination between acute cellular rejection and polyomavirus infection can be difficult. Among the reliable indicators of a component of rejection are endarteritis and C4d deposition. If the inflammation is found primarily in areas of viral antigen, I believe this favors polyoma as the predominate disease.

Immunohistochemistry

Polyomavirus large T antigen can be demonstrated in tubular epithelial cells, typically in clusters, and especially in collecting ducts (Fig. 21.5). Monoclonal antibodies are

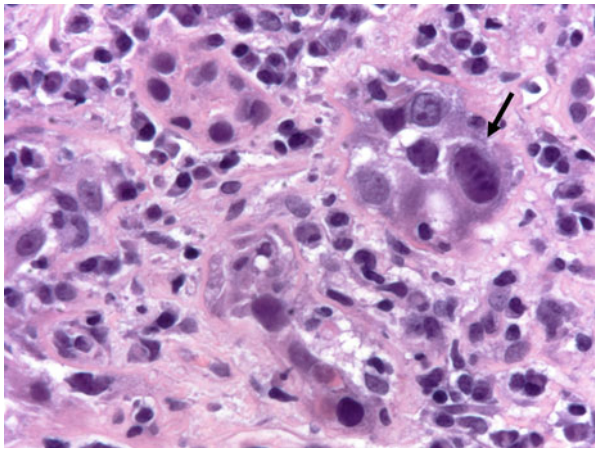

Fig. 21.4 Polyomavirus interstitial nephritis. Plasma cells are abundant and nuclear inclusions are evident (*arrow*) (H&E stain)

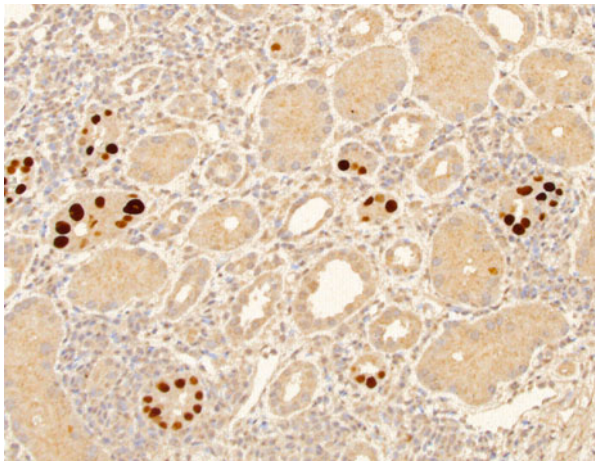

Fig. 21.5 Polyomavirus interstitial nephritis. Viral antigens are demonstrated by immunoperoxidase stains in tubular epithelial nuclei using a monoclonal antibody to SV-40 large T antigen

commercially available that react with BK specific determinants and with the large T antigen of several polyoma species. We have obtained good results with paraffin techniques. These techniques also work in urine cytology preparations. Immunofluorescence shows granular deposits of IgG and C3/C4d along the GBM in about half of the patients [12, 13]. The nature of the antigen (viral, autoantigen) is uncertain. Both BK and JC viruses can cause interstitial nephritis and are detected with the usual antibody to anti-large T antigen. However, JC alone rarely causes graft failure [14].

Electron Microscopy

Electron microscopy reveals the characteristic intranuclear viral particles of 30–40-nm diameter in tubular epithelium (Fig. 21.6). Aggregates of polyomavirus and matrix, termed "haufen," are evident in negatively stained urine sediment by electron microscopy [15].

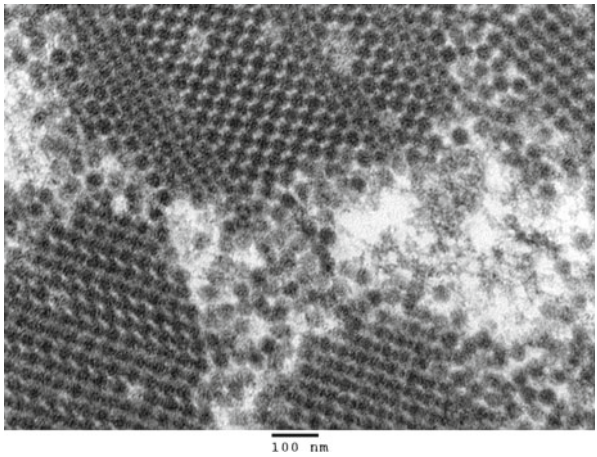

Fig. 21.6 Polyomavirus interstitial nephritis. Electron microscopy reveals the 30–40-nm viral particles in tubular nuclei (bar = 100 nm)

Pathogenesis

A promoting role for rejection appears likely, because polyomavirus interstitial nephritis is quite uncommon in recipients of heart, liver, or lung transplants. Alternatively, the allograft kidney may serve as a "sanctuary" for the virus, since T-cell killing of virally infected cells requires self-major histocompatibilitycomplex (MHC) antigens to be expressed on the target cells. Most recent cases have arisen in patients on tacrolimus or mycophenolate mofetil (MMF). Among centers using tacrolimus and MMF, the frequency of polyoma-associated interstitial nephritis (AIN) is 3–5 % [15–18]. Recovery, without reduction of immunosuppression, is not common (69 % graft loss). With reduction of immunosuppression, graft survival is likely (>95 %), but functional recovery is poor (38 % have residual Cr >3.0 mg/dL) [16, 17]. Protocol biopsies and monitoring of blood/urine for virus should permit earlier treatment and improved outcome. The use of polymerase chain reaction (PCR) to detect viral DNA in the circulation helps distinguish those with interstitial nephritis from noninvasive urothelial shedding of the virus [14, 18]. Antivirals, such as cidofovir, have had limited success.

Recurrent Renal Disease

The frequency and clinical significance of recurrence varies with the disease [19]. Recurrent disease is the third most common cause of graft loss in patients whose original disease was glomerulonephritis [20]. The diseases that recur commonly are dense deposit disease (>80 %), monoclonal immunoglobulin deposition disease (70–85 %), diabetes (>50 %), fibrillary glomerulonephritis (GN) (~50 %), IgA nephropathy (13–50 %), primary focal glomerular sclerosis (20–40 %), atypical hemolytic-uremic syndrome (>25 %), type I membranoproliferative GN (20–50 %), and lupus nephritis (>25 %). However, only 3 have a significant impact on graft

survival: MPGN, primary FSGS, and atypical HUS [21]. The diagnosis of recurrence requires accurate classification of the original disease and lesions that differ from chronic allograft glomerulopathy.

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