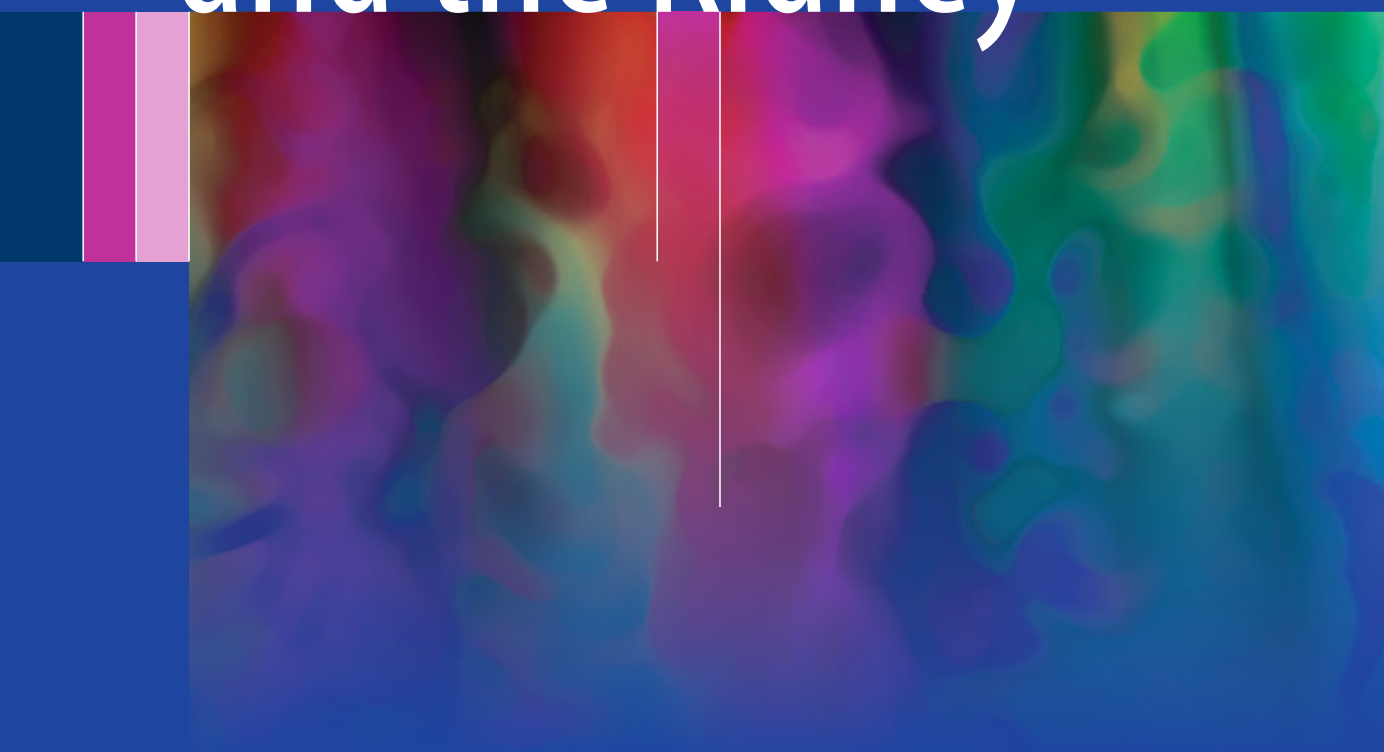
Anjali A. Satoskar
Tibor Nadasdy
Editors

Bacterial Infections and the Kidney



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To my devoted wife, Gyongyi and wonderful daughters Krisztina and Orsolya.

Tibor Nadasdy

To my parents, Nana and Lata for their unwavering support and husband Abhay for his never-ending enthusiasm.

Anjali A. Satoskar

Preface

There have been several important and interesting advances in renal parenchymal diseases during the last decade; however, perhaps the most clinically relevant is the paradigm shift in glomerulonephritis associated with infection. The frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is increasing both in hospital-associated and in community settings in the United States and worldwide. Infection due to *S. aureus* imposes a high and increasing burden on healthcare resources. A growing concern is the emergence of MRSA infections in patients with no apparent risk factors. Classic postinfectious/poststreptococcal glomerulonephritis is now rarely seen in Western countries, and most cases of infection-associated glomerulonephritis are secondary to *S. aureus* infections, affecting predominantly the elderly with underlying comorbidities, primarily diabetes but, with increasing frequency, also younger people with no predisposing factors. The differential diagnosis of infection-associated glomerulonephritis and immune-mediated glomerulonephritis not related to infection can be difficult. Infection-associated glomerulonephritis may mimic IgA nephropathy, Henoch–Schönlein purpura (IgA vasculitis), C3 glomerulonephritis, proliferative immune complex glomerulonephritis of autoimmune etiology or even pauci-immune crescentic glomerulonephritis. These forms of glomerulonephritis are treated with immunosuppressive medications. Immunosuppressing patients with active infection-associated glomerulonephritis can have serious consequences. In addition to glomerulonephritis, bacterial infections can cause a wide spectrum of kidney diseases involving the tubulointerstitium and vasculature. Pyelonephritis appears to be an easy diagnosis; however, it is not always so, particularly not in immunosuppressed renal allograft recipients. Bacterial infections can also lead to vascular diseases; the most well known of these are thrombotic microangiopathies, such as the hemolytic uremic syndrome associated with Shiga toxin-producing *E. coli* infection.

This textbook is designed to present a comprehensive and the state-of the-art but practical approach to the diagnosis and management of bacterial infection-associated renal disease. The chapters address the different types of glomerular tubulointerstitial and vascular diseases, associated with bacterial infections, describe diagnostic pitfalls, provide differential diagnosis and discuss treatment and management. Easy-to-follow diagnostic algorithms are included for practical usefulness. The chapters contain a large number of

color microphotographs, illustrations and each chapter refers to the most important up-to-date literature in the area. All chapters were written by experts in the field and include the most up-to-date clinical and scientific information at the time of the writing.

Infection-associated renal diseases are addressed in large textbooks on kidney diseases, frequently hidden in chapters discussing various forms of glomerulonephritis, interstitial nephritis or vascular disease. This book intends to be a comprehensive but user-friendly resource on renal complications of bacterial infection, which is becoming increasingly relevant now in the era of staphylococcus epidemic and emerging new resistant bacterial strains. We hope this textbook will be an important resource for nephrologists, general internists, infectious disease specialists, pathologists, and urologists. Transplant surgeons may find the chapter on transplant pyelonephritis useful.

We would like to thank our nephrologist colleagues for their input. Their dedicated interaction with us taught us more about infection-associated renal diseases than any pathology text we read. Several of them are authors of chapters in this book. Many infection-associated renal diseases, particularly interstitial diseases, such as pyelonephritis, can be diagnosed without involvement of the pathologist but the pathologist plays a crucial role in the correct diagnosis of infection-associated glomerular diseases. Still, we cannot emphasize enough that the pathologist alone is usually "lost" in the absence of close interaction with the nephrologist. Correct diagnosis of an infection-associated renal disease/glomerulonephritis (just like other forms of renal parenchymal diseases) is only possible if the pathologist and the nephrologist discuss the case in detail, considering every possible differential diagnosis, preferably above the microscope. We are particularly indebted to Drs. Lee Hebert and Brad Rovin, who for the last one and a half decades, since we have been at The Ohio State University, were our main mentors in nephrology issues. They were always available for advice in making clinicopathologic correlations in the interpretation of renal biopsies, even if they were not involved in the care of patients. Our renal biopsy reports frequently reflect their input.

Finally, we are grateful to Stephanie Laus, our administrative assistant and Dr. Gyongyi Nadasdy. Without Stephanie's expert secretarial help, this book would not have been possible. Gyongyi was instrumental in organizing the images and taking many of the images in the chapters we were involved in.

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Acute Poststreptococcal Glomerulonephritis

1

Sergey V. Brodsky and Tibor Nadasdy

Introduction

APSGN remains a significant clinical entity in spite of declining incidence rate in the pediatric population in well-developed countries. In developed countries APSGN became very rare but may still appear in adults with comorbidities, primarily diabetes mellitus and morbid obesity. APSGN is still prevalent in many parts of the world. In the past, it was the most common and the most studied form of acute postinfectious glomerulonephritis. These extensive studies provided us with invaluable information about the pathogenesis of acute glomerulonephritis, not only APSGN, but other forms of glomerulonephritides as well.

Acute glomerulonephritis has been known to follow certain infections a long time ago. Already, Hippocrates described the occurrence of back pain and gross hematuria leading to oliguria or anuria more than two millennia ago [1]. About two centuries ago, Wells noted bloody urine in patients with scarlet fever and postscarlatinal anasarca [2]. Later, Bright noted the association with scarlatina and described the finding of blood in the urine and swelling of the face in what were probably attacks of APSGN [3]. Therefore, acute glomerulonephritis was named after Bright (Bright's disease).

With the introduction of microscopic examination of the kidney, it became evident that main histologic findings are localized to the glomeruli, and Langhans [4] described a category of Bright's disease with glomerular inflammation. Schick [5] indicated similarity of the latent period in serum sickness to that of acute glomerulonephritis.

The first classification of Bright's disease was described by Drs. Volhard (the clinician) and Fahr (the pathologist) [6]. Longcope [7] recognized two general forms of glomerulonephritis: one associated with preceding bacterial infections and with quick recovery and a good prognosis (acute glomerulonephritis) and second group when the disease progressed to a chronic stage.

Majority of cases of APSGN are caused by group A streptococci, which are also associated with rheumatic fever. In areas with colder climates, acute glomerulonephritis usually occurs after upper respiratory tract infection, such as pharyngitis or tonsillitis. In warmer climates, many cases follow skin infections, [8]. Among streptococci that cause throat infection, types 12, 4, and 1 are more likely to cause acute glomerulonephritis than other types [9]. Type 12 is the most nephrogenic strain. The attack rate with certain nephritogenic strains ranges from 1 to 33% of patients [10].

Acute glomerulonephritis following skin streptococcal infection is not uncommon,

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especially in warm climates [4, 11–13]. Streptococcal M types 49, 42, 2, 57, and 60 seem to be predominant, and types 49, 42, and 2 are particularly potent to induce glomerulonephritis [13].

Streptococcus pyogenes (group A streptococcus, GAS) is the etiologic agent of a number of suppurative infections, including pharyngitis, cellulitis, necrotizing cellulitis, scarlet fever, erysipelas, pyoderma, puerperal sepsis, toxic shock-like syndrome, and impetigo. GAS produces virulence-enhancing extracellular products and toxins, including erythrogenic toxin, DNase, hyaluronidase, streptokinase, NADase, proteinases, and the hemolysins streptolysin-O (oxygen labile) and streptolysin-S (oxygen stable) [14].

APSGN is almost always secondary to strains of the serogroup A; however, several outbreaks have been caused by group C organisms in patients with septic arthritis, pneumonia, and septicemia [15] and by group G streptococci (skin infections) [16]. In addition, milk-borne *Streptococcus zooepidemicus* infection from unpasteurized milk and cheese has been reported with septicemia and clinical symptoms of APSGN [17].

Streptococcal M proteins are dimeric alpha helical-coiled molecules on the surface of the bacteria and they function as the major antiphagocytic factor [18]. Molecular typing of the M-protein has been used to investigate the molecular epidemiology of GAS, as well as group C and G streptococcal diseases [19]. The M-types (including 1, 4, 6, and 12) which are more common in the high-income countries are less common in Africa and the Pacific region.

The incidence of the suppurative and nonsuppurative complications of group A β-hemolytic streptococcal infections, such as glomerulonephritis and rheumatic fever, all but disappeared in the United States and developed countries between the 1940 and the 1980 [20, 21].

APSGN, however, continues to have a high incidence rate in other parts of the world [21], especially in areas with tropical climates, where skin infections are common, such as Africa [22], South America [3, 4, 23], the Caribbean [10], New Zealand [24], India, and in indigenous communities (Aborigines in Australia) [25]. Recent publications describe the global burden of APSGN/postinfectious glomerulonephritis worldwide [21]. Carapetis et al. [26] calculated an incidence of approximately 24.3 cases per 100,000 person-years in children and 2 cases per 100,000 person-years in adults in the developing world versus 6 and 0.3, respectively, in the developed world. There is significant global variation with the highest incidence of 239 per 100,000 in Australian Aborigines and the lowest incidence of 0.04 per 100,000 in Italy. Still, all these statistical calculations are likely to be underestimations, since they cannot account for the vast majority of subclinical disease, which is thought to be 4–19 times more common than symptomatic disease. The estimates are even higher in the reports by Rodriguez-Iturbe and coauthors [27, 28].

In the USA and other developed countries, the incidence of glomerular disease superimposed on diabetic nephropathy is on the rise. Because diabetic patients are susceptible for infections, they also develop infection-related renal disease, including poststreptococcal glomerulonephritis, more commonly. Nast et al. [29] studied 86 adult patients with postinfectious glomerulonephritis; 24 of those had nonstreptococcal glomerulonephritis, 25 (29%) of the 86 patients had diabetes, and 16 (18.6%) had diabetic nephropathy with diabetic glomerulosclerosis. The same authors later published data on 109 patients above the age of 65 years with postinfectious glomerulonephritis and found that 49% of them were diabetics [30]. Most patients had staphylococcus infection-associated glomerulonephritis, but the second most common glomerulonephritis was APSGN in 17 patients. Haas [31], at Johns Hopkins Hospital, found some ultrastructural evidence (such as subepithelial deposits in the glomerular mesangial notch region) of postinfectious glomerulonephritis in 23 (22%) of 104 kidney biopsies with the primary diagnosis of diabetic nephropathy. A large study by Mazzucco et al. [32] describes 393 renal biopsies from diabetic

patients, 37 (9.4%) of those with postinfectious glomerulonephritis. Twenty six of these biopsies were from patients who had evidence of diabetic nephropathy, and only 11 of them from patients who did not have histologic evidence of diabetic nephropathy [32]. Most of these cases were APSGN.

Clinical Presentation

APSGN most commonly affects children and young adults, although it can be seen in any age group. While the peak incidence is in the first decade of life, cases of APSGN in older patients have been reported, particularly in the diabetic population [8, 30, 33, 34]. Males are affected more commonly than females, the ratio often being 2:1 [35]. This ratio is different than in patients with rheumatic fever, which affects both sexes equally [36]. APSGN may appear in either sporadic or epidemic form; children are the group that is most often affected in the epidemic form.

For diagnosis of "acute postinfectious glomerulonephritis," clear evidence that an infection preceded the glomerulonephritis is required. A preceding infectious episode (such as pharyngitis, tonsillitis, mastoiditis, peritonsillar abscess, otitis media, or pyoderma) is the *sine qua non* for clinical diagnosis of APSGN [37, 38]. APSGN is most often associated with epidemics, particularly in humid warm climates. The offending organism is virtually always a GAS; types 12, 4, 1, and 49 appear to be the most typical nephritogenic types.

There is a delay, or latent period between the streptococcal infection and the onset of acute glomerulonephritis. This period is usually 1–4 weeks (average 10–11 days) before the onset of the acute nephritic syndrome (hematuria, edema, hypertension, acute renal dysfunction). In general, the latent period is 1–2 weeks after a throat infection but it may be longer (3–6 weeks) after a skin infection.

The onset of clinical symptoms of APSGN is typically abrupt. The urine becomes dark, smoky, or Coke- or coffee-colored. Puffiness of the face or eyelids as a manifestation of edema is sudden and common; in some cases, there also may be edema of the lower extremities and sacral region. Periorbital edema is characterized by prominence on awakening in the morning and a tendency to subside or decrease when the patient is up. Edema, as well as other features of circulatory congestion, such as dyspnea, cardiomegaly, and increased venous pressure, is the result of a disturbance in the water-salt homeostasis because of abnormalities in the renal excretion of sodium and water; although heart failure is also a contributing factor both in children and older patients [39]. The severity of edema in poststreptococcal glomerulonephritis is often disproportional to the degree of renal impairment.

Patients with severe proliferative glomerulonephritis may develop oliguria or even anuria. This is particularly common in elderly patients with APSGN. Oliguria may either be of a short duration or persistent; and it is possibly indicative of a severe form of glomerular disease (i.e., the crescentic form). Oliguria tends to be transient, with diuresis usually occurring within 1–2 weeks, whereas anuria is less common. During the onset of oliguria/anuria, proteinuria may actually diminish because of a decrease in the glomerular filtration rate (GFR) [40]. With the resolution of the glomerular inflammation, increasing proteinuria may indicate an increasing GFR.

Hypertension occurs in half of children with APSGN [40], but is more common in adults, especially in elderly patients [41]. Hypertension is usually transient with a rapid return to normal levels of blood pressure with normalization of the GFR, loss of edema, and normalization of the plasma volume. However, hypertension may persist, and when it does, it indicates either progression to a more chronic stage (the likelihood of this happening is discussed later) or that the disorder is not APSGN.

Hypertension may be complicated by hypertensive encephalopathy, which is noted in 5–10% of patients. Outcome usually is favorable, without any neurologic deficit. Despite sodium retention during the acute phase of APSGN, plasma levels of atrial natriuretic peptide may be increased [42].

Some patients may develop left ventricular dysfunction during the acute congestive and convalescent phases of APSGN. This cardiac dysfunction sometimes is not associated with hypertension or pericardial/pleural effusions [43]. APSGN may be seen in alcoholics with or without cirrhosis [44]. APSGN has often been reported to be superimposed on diabetic nephropathy. The symptoms of APSGN may be masked in diabetics, if they have diabetic glomerulosclerosis. In such cases, microscopic hematuria and proteinuria, as well as the worsening of renal function, may be erroneously attributed to diabetic nephropathy.

Laboratory Findings

Blood urea nitrogen (BUN) and serum creatinine levels are elevated, and this is often noted during the acute stages. Lack of normalization of these values within several weeks or a few months after the onset suggests that one may not be dealing with a true case of APSGN. Elderly patients have a higher rate of elevations of serum creatinine [41]. BUN and serum creatinine levels may remain elevated in patients with crescentic form of postinfectious glomerulonephritis [45, 46].

Proteinuria is in non-nephrotic range in most cases. Nephrotic syndrome presents in approximately 5–10% of patients [47]; however, some reports indicate nephrotic syndrome in as high as 20% of the patients [48] Proteinuria usually disappears within 6 months [49]. Proteinuria may persist for longer periods, but complete clinical recovery has been noted after proteinuria has been present for as long as 26 months [49]. Clinical symptoms, such as proteinuria, hypertension and renal insufficiency, are more severe in adults and, in particular, in the elderly with APSGN [19].

The urine of patients with APSGN has a high specific gravity. The urinary sediment has red blood cells (RBC), RBC casts, granular casts, and sometimes leukocyte casts. Microscopic hematuria often persists longer than proteinuria and may be present even after disappearance of clinical symptoms [49]. Hematuria may persist for as long as 18 months; but cases with microscopic hematuria with up to 11 years have been described [50].

Albuminuria and microhematuria can be detected in the period between infection and onset of nephritis in up to half the patients with streptococcal upper respiratory tract infections [35]. The serum albumin level is sometimes low because of severe proteinuria. The serum cholesterol level may be elevated in some children, as well as in adults.

Anemia is commonly noted in the early stages. This feature is thought to be primarily a dilutional phenomenon as a consequence of the expanded extracellular fluid, although cases with hemolytic anemia [51] and hemolytic uremic syndrome have been reported [52].

Serum complement (C3) levels are decreased during the acute episode in almost all patients with APSGN [52] and is considered as an evidence in favor of the diagnosis of APSGN and indicates an antigen–antibody reaction. Serum C3 levels usually return to normal within 6 weeks of the acute onset of the nephritis. In patients in whom the serum C3 levels are apparently normal, serial determinations will often show an increase during the recovery stage, suggesting that there was in fact a decrease in serum complement levels associated with the glomerulonephritis. Although there is activation of both the classic and the alternative pathways of the complement cascade, serum C4 levels are usually normal. Levy et al. [53] suggested that although both pathways are implicated in the early stages of the disease, continued C3 depression is probably via the alternative pathway.

Both intracellular and extracellular antigens of the streptococcus stimulate the production of antibodies in the infected host, which are of diagnostic significancy in clinical medicine, because the presence of such antibodies indicates a preceding streptococcal infection. These antibodies include antistreptolysin O (ASO), antistreptokinase (ASK), antihyaluronidase (AH), antideoxyribonuclease-B (anti-DNase-B), antidiphosphopyridine nucleotidase (anti-DNAse), and anti-nicotinamide adenine dinucleotidase

(anti-NADase). However, the specificity of these tests is questionable. More than 30 years ago, the "streptozyme" antibody test was introduced in a kit intended to simultaneously measure antibodies to five streptococcal extracellular antigens (exoenzymes), including streptolysin, streptokinase, hyaluronidase, DNase, and NADase [54]. However, approximately 20% of healthy children have elevated streptozyme titers. Also, there is data that the reliability of the streptozyme test is not as good as that of conventional methods for single-antibody determinations [55].

A rising ASO titer provides the best evidence of a streptococcal infection. The ASO titer begins to elevate within a few days of infection and reaches peak levels after several weeks, after then it usually declines. However, the ASO titer may not increase in all patients with streptococcal infections; thus, the absence of a high titer does not exclude the infection. This is especially true for patients with skin infections (pyoderma) [56]. The WHO suggests a rise of ≥ 0.2 $\log_{10}$ (1.59 times) between acute- and convalescent-phase sera assayed in parallel using the dilution method for neutralization tests. While there is variability between antigens and testing method, a rise of twofold or more is generally acceptable threshold in clinical practice [57].

The ASO titer can be modestly elevated in patients with nonstreptococcal diseases, and up to 30% of patients with other forms of nonstreptococcal glomerulonephritis may have mild elevations of ASO [57]. False-positive results may be induced by β-lipoprotein in liver disease, some other bacteria, and oxidation of streptolysin O. False-negative results may be seen after antibiotic treatment of the patient.

Kidney Biopsy Findings

Light Microscopy

Acute Phase Glomerulonephritis. Light microscopy shows endocapillary proliferative glomerulonephritis (Fig. 1.1). Although the glomerulonephritis is diffuse, there may be focal and segmental variability of the lesions among glomeruli, but this is uncommon. Many cell types can be identified in the glomeruli, including resident endothelial and mesangial cells and infiltrating inflammatory cells, among them polymorphonuclear leukocytes (PMN) and monocytes (Figs. 1.1 and 1.2). In most specimens with acute disease, PMN are the most easily identified cells and may be present in large

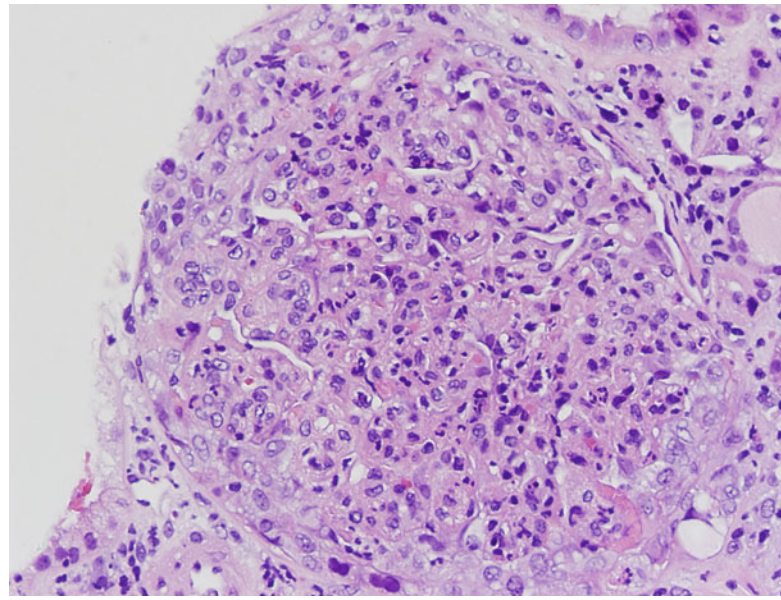

Fig. 1.1 An enlarged glomerulus shows diffuse endocapillary hypercellularity with numerous neutrophils and closure of all glomerular capillaries. The glomerulus is increased in size and cellularity, H&E, ×200

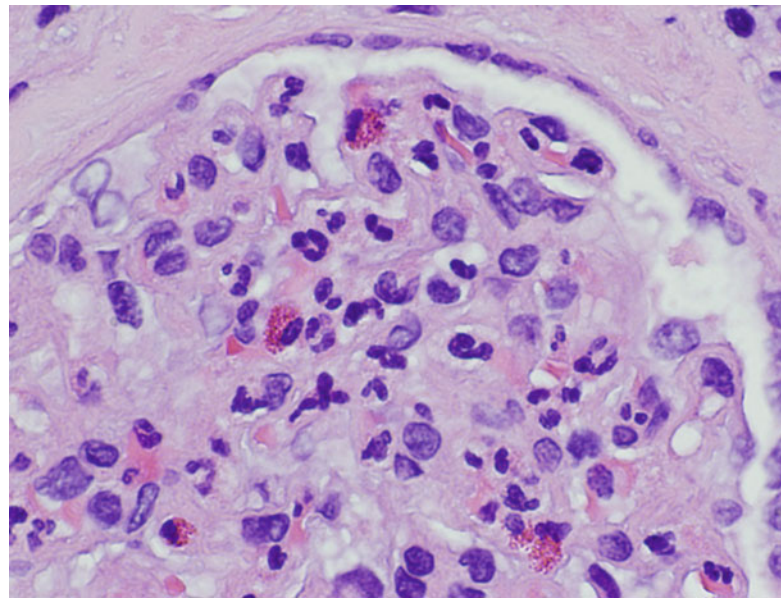

Fig. 1.2 Acute diffuse proliferative glomerulonephritis with considerable infiltration of the glomerulus not only by neutrophils but also by eosinophiles. H&E, ×400

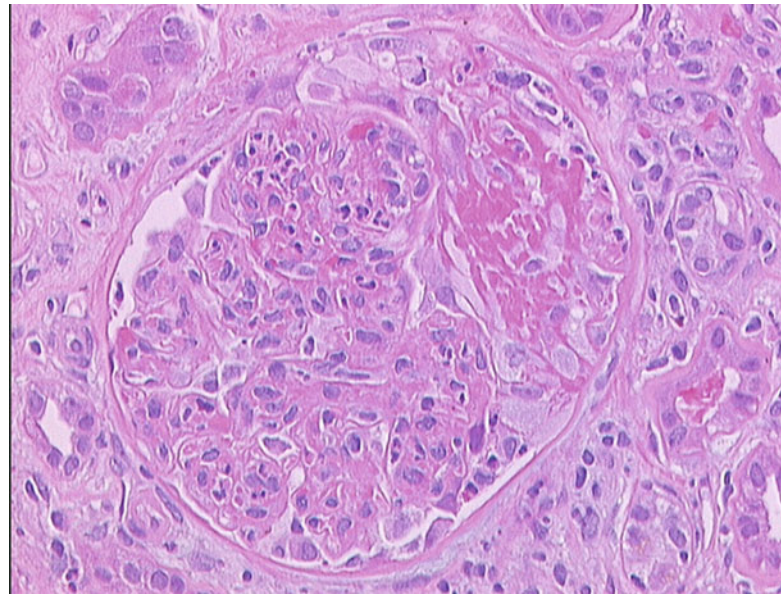

Fig. 1.3 Segmental glomerular necrosis with fibrin exudation into the Bowman's space. H&E, ×400

numbers; therefore, this lesion was called *exudative glomerulonephritis* by many investigators. However, sometimes the PMN are inconspicuous. It has been suggested by Jennings and Earle [49] that PMN may be more frequently found in biopsies performed shortly after the clinical onset of the disease. Occasionally, other inflammatory cells, such as eosinophils and lymphocytes, are noted, but this is unusual (Fig. 1.2) [12, 40]. Necrosis of the glomerular tuft is rare (Fig. 1.3).

The glomerular capillary walls are generally not thickened, although there may sometimes be mild thickening visible on light microscopy. The combination of expansion of the lobules, hypercellularity of the tuft, and localized thickening of

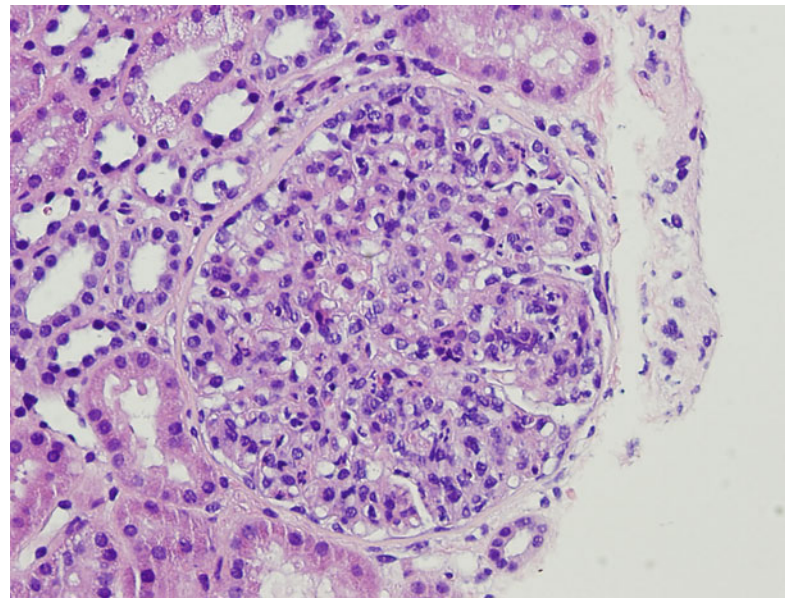

Fig. 1.4 A glomerulus with endocapillary hypercellularity. Because of the increased cellularity within each lobule, there is an accentuation of the lobularity. H&E, ×200

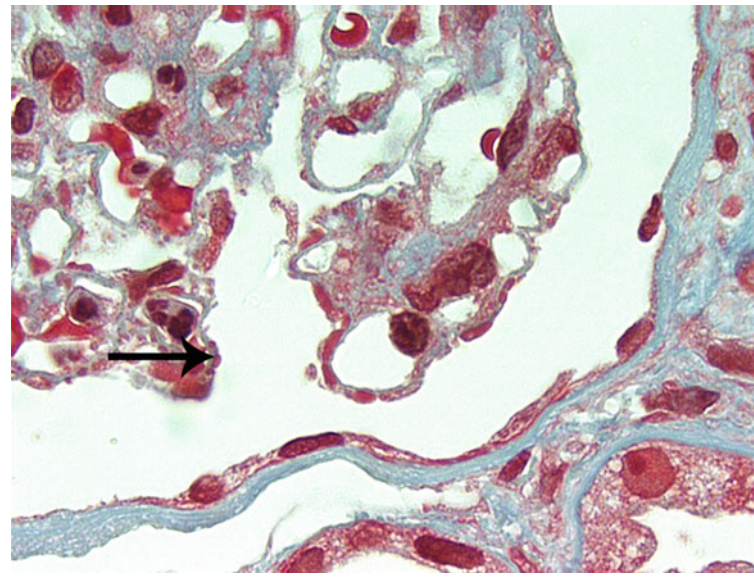

Fig. 1.5 The subepithelial humps may be seen as fuchsinophilic red dots (*arrow*) under high magnification, using Masson's trichrome stain, (×1000)

the glomerular capillary walls may produce a membranoproliferative pattern of glomerular injury (Fig. 1.4).

In some patients, at high magnification, particularly if using the oil-immersion lens, minuscule fuchsinophilic nodules on the epithelial side of the glomerular capillary wall can be detected. These minute structures correspond to the subepithelial deposits (humps) seen by electron microscopy (Fig. 1.5).

Glomerular crescents or small adhesions (synechiae) are usually rare (Fig. 1.6a–c). However, sometimes crescent formation may be so prominent that the term *crescentic glomerulonephritis* may be used, but usually only a small percentage of glomeruli are involved by crescents.

The diagnosis of APSGN superimposed on diabetic glomerulosclerosis may be difficult, because the underlying changes of diabetic glomerulosclerosis may alter the typical

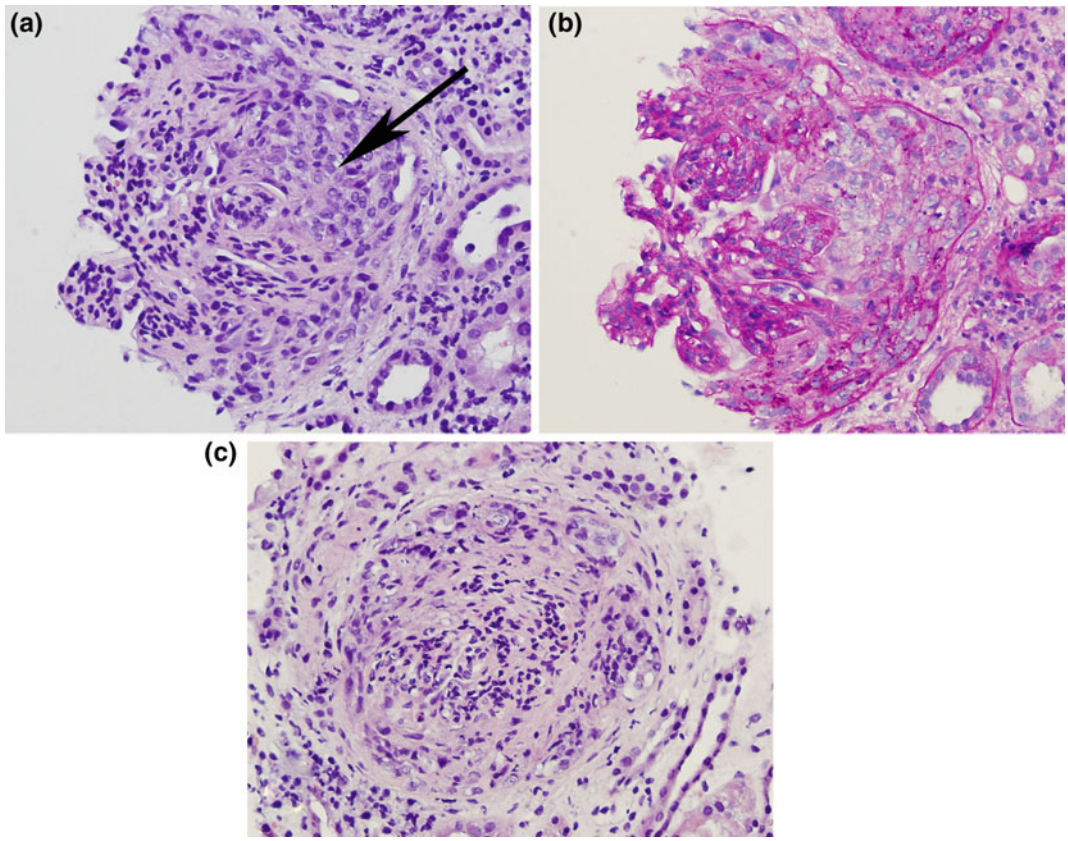

Fig. 1.6 Crescent formation in APSGN. **a** This cellular crescent (*arrow*) was noted in the renal biopsy of a 7-year-old girl with APSGN associated with acute kidney injury. Note that the compressed glomerular capillaries appear hypercellular. H&E, ×400. **b** The same glomerulus stained with PAS, ×400. **c** A large crescent completely obliterating the underlying glomerular capillaries in the biopsy of the same patient. H&E, ×400

histologic manifestations. Some degree of mesangial hypercellularity may occur in diabetic nephropathy. One has to look carefully for intracapillary accumulation of inflammatory cells, which is frequently not diffuse in APSGN superimposed on diabetic glomerulosclerosis (Fig. 1.7). Immunofluorescence shows various staining patterns in diabetic nephropathy, including linear staining for albumin and IgG along the glomerular and tubular basement membranes and smudgy or coarsely granular, frequently somewhat segmental, fluorescence for C3. One has to review carefully the electron micrographs in search for subepithelial humps as well as mesangial, intramembranous, and subendothelial deposits. Unfortunately, in many biopsies with diabetic glomerulosclerosis, electron-dense deposits, representing hyalin change, are abundant and these can be difficult to differentiate from true immune complex deposits.

The tubular changes are not as prominent as those involving the glomeruli. When proteinuria is present, there may be hyalin droplets (protein reabsorption droplets) or vacuoles (dissolved lipid droplets) in the proximal tubular epithelial cells. RBC casts may be seen in the lumen of the tubules (Fig. 1.8). PMN also can be present in the lumens, especially in the proximal regions of the proximal tubules. This feature is most commonly seen in patients with severe infiltration of PMN in the glomeruli. In patients with severe renal insufficiency, classic changes of ATN are usually evident (Fig. 1.9). In the most florid cases of APSGN with extensive crescent formation, there

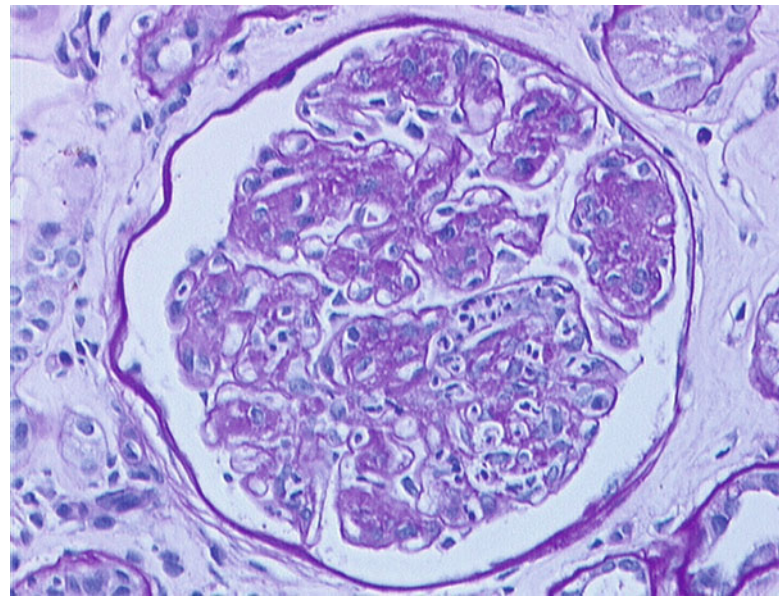

Fig. 1.7 APSGN in a patient with underlying diabetic glomerulosclerosis. The patient developed acute glomerulonephritis with very high ASO titers and low serum C3 levels after a "sore throat". *Note* the endocapillary hypercellularity superimposed on the preexisting mesangial expansion. PAS, ×400

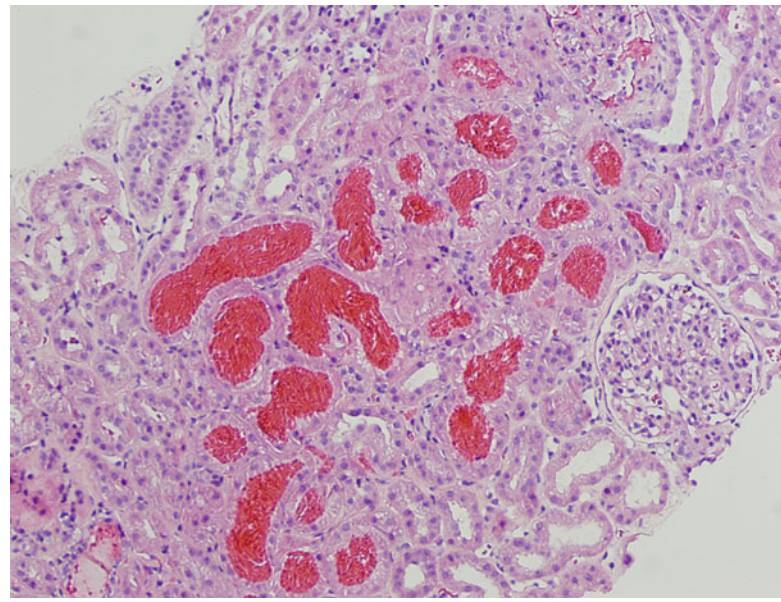

Fig. 1.8 Red blood cell casts persisting in a 45-year-old patient with resolving APSGN. The biopsy was done several weeks after the onset of proteinuria, hematuria and low serum C3 levels (the proteinuria improved from 3 to 0.5 g/24 h at the time of biopsy), H&E, ×100

may be tubulitis, which is characterized by inflammatory cells between the tubular basement membrane and the tubular epithelium or within the tubular epithelium. Progressive tubular injury with tubular atrophy and loss is rarely seen.

The degree of interstitial involvement in APSGN is variable. The interstitium may show edema with separation of the tubules. Scattered foci of inflammatory cell infiltrates, composed of mixtures of PMN, monocytes, and lymphocytes, are sometimes present (Figs. 1.9 and 1.10). Occasionally, severe interstitial mononuclear cell infiltration and scattered regions of interstitial fibrosis may be seen. However, usually, the interstitial changes are not remarkable. As noted earlier, interstitial changes may be found in relation to tubular changes [58].

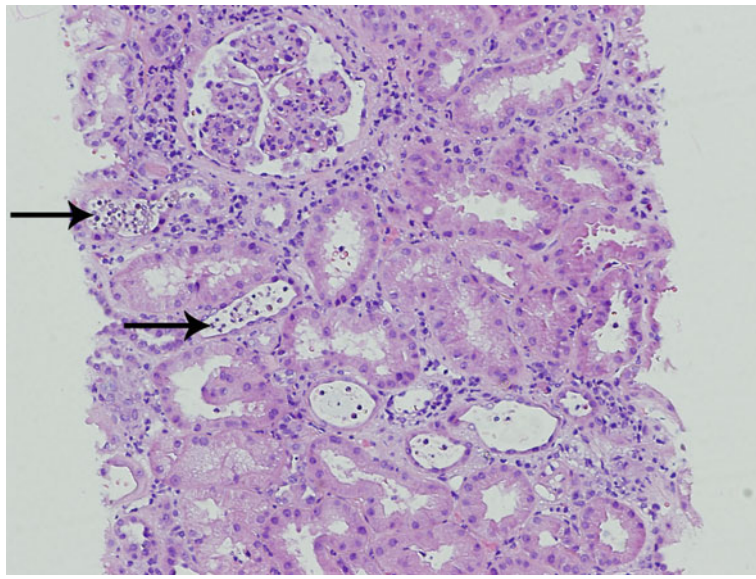

Fig. 1.9 Acute tubular necrosis in a 68-year-old nondiabetic male with APSGN. Note the several apoptotic tubular epithelial cells in dilated tubules (*arrows*). Such apoptotic cells should not be misinterpreted as neutrophil granulocytes, H&E, ×100

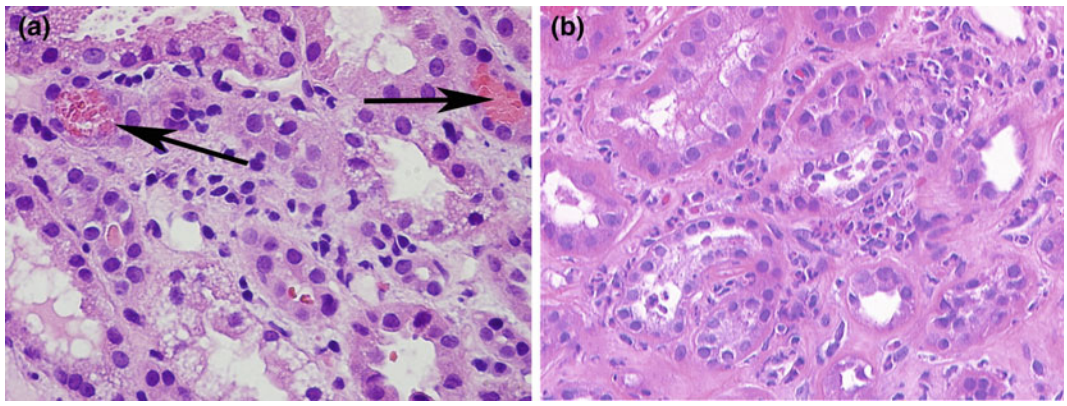

Fig. 1.10 Interstitial inflammation in APSGN. **a** ATN in a case of severe pediatric APSGN. *Note* the interstitial edema, inflammation and the tubular injury with epithelial irregularities, and vacuolization of the tubular epithelium. Few tubules contain red blood cells (*arrows*), H&E, ×400. **b** Mixed active interstitial inflammatory cell infiltrate with numerous polymorphonuclear leukocytes in an adult diabetic patients with APSGN and acute kidney injury, H&E, ×400

The arteries and arterioles generally do not show significant pathologic changes. In older patients, preexisting vascular abnormalities, such as arterial and arteriolar sclerosis, may be seen. Arteritis has been described in APSGN [59], but systemic necrotizing vasculitis must be excluded in those patients. There are other accounts of arteritis [60] as well, but they are rare. Fibrinoid necrosis of the arterioles may be associated with severe hypertension. In rare instances, morphologic changes of thrombotic microangiopathy may be seen [61, 62].

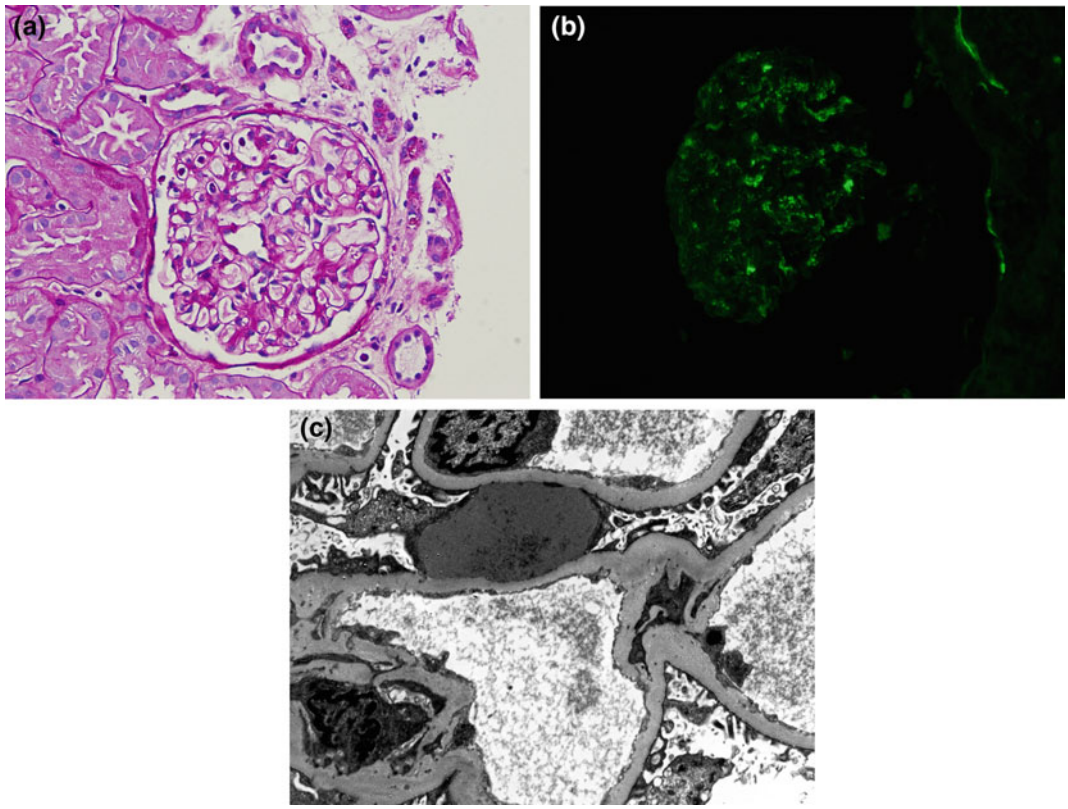

Fig. 1.11 **a** Normal appearing glomerulus in the biopsy of a hepatitis C virus positive patient who developed microscopic hematuria and mild proteinuria. Immunofluorescence and electron microscopy detected C3-positive subepithelial humps, PAS, ×200. **b** Granular C3 deposits. No immunoglobulins were detected, ×200. **c** Scattered subepithelial humps were evident by electron microscopy. Uranyl acetate–lead citrate, ×8000

Subclinical and Resolving Glomerulonephritis. Renal biopsies in patients with minimal urinary changes have been performed (usually in prospective studies) and show variable morphology. Sometimes there are no substantial abnormalities (Fig. 1.11). Increased cellularity of the glomeruli also has been noted, as well as morphologic changes similar to those in acute diffuse proliferative APSGN [63] In renal biopsies that are taken several weeks after the clinical onset of disease, there is usually diffuse mesangial hypercellularity; but the glomerular capillaries are patent (Fig. 1.12) [64]. Mesangial hypercellularity appears to persist for several months in patients, who eventually experience complete resolution of the glomerular lesion [65]. In the past, this phenomenon was termed as chronic *latent glomerulonephritis*. However, these findings should be interpreted with a caution, because an unusually thick paraffin section may give a false appearance of diffuse mesangial hypercellularity, and many cases termed *chronic latent glomerulonephritis* may not be resolving/resolved APSGN, but rather represent a nonspecific histologic pattern associated with various renal injuries that are unrelated to previous infections [66]. Buzio et al. [67] in a long-term follow-up study (more than 5 years) of 26 patients with APSGN, found diffuse mesangial hypercellularity in patients with persisting proteinuria.

Complete morphologic resolution occurs after APSGN, but follow-up biopsies in such patients usually are not performed. In fact, "incidental healed" postinfectious glomerulonephritis may be more common than anticipated. Haas [31]

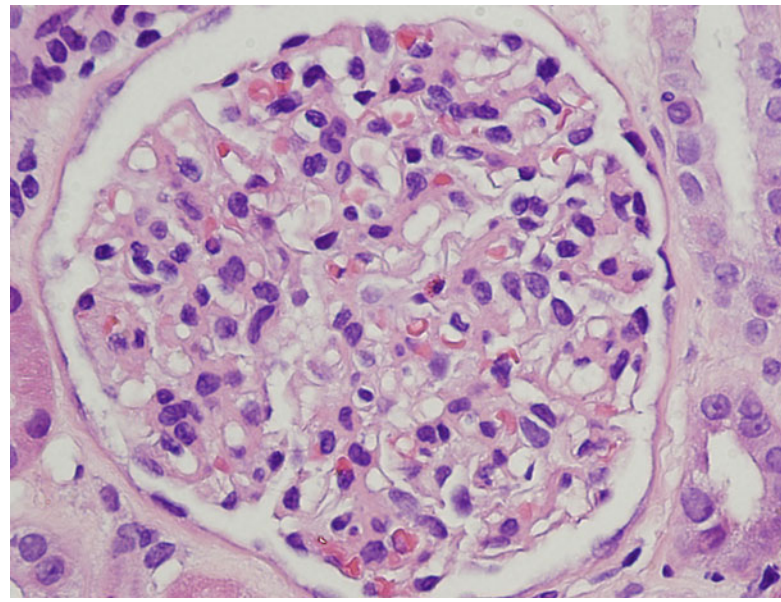

Fig. 1.12 Mesangial hypercellularity in a patient with resolving APSGN (same biopsy as Fig. 1.8), H&E, ×400

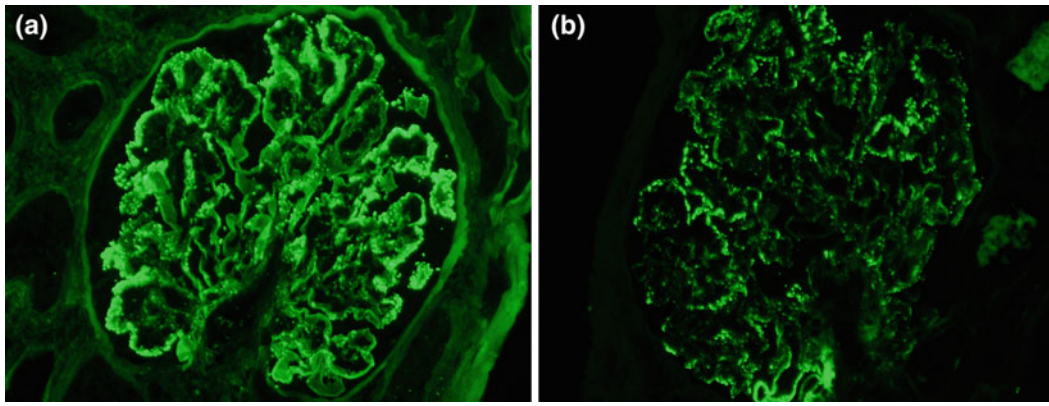

Fig. 1.13 Garland pattern of immunofluorescence staining. The coarsely granular staining along the glomerular capillary loops may be segmentally confluent. **a** IgG, **b** C3 staining from the same case, ×400

reviewed 1012 consecutive renal biopsy specimens and found 57 biopsies in which ultrastructural findings indicated resolving/healed APSGN. According to Haas, resolving or largely healed APSGN was present in 10.5% of renal biopsy specimens, excluding biopsies with a primary diagnosis of immune complex glomerulonephritis [31]. The conclusions were based on ultrastructural findings (subepithelial deposits in glomerular mesangial notch regions); therefore, this incidence may be somewhat overestimated because the specificity of subepithelial deposits in the mesangial notch region for resolving APSGN needs further confirmation. Interestingly, in Haas' study, 50% of the biopsies with incidental healing APSGN had evidence of mesangial hypercellularity [31].

Immunofluorescence Findings

Classically, in biopsies taken early in the clinical course of the disease (first 2 or 3 weeks), granular staining is noted along the glomerular capillary loops and also in the mesangium by immunofluorescence studies with anti-IgG and anti-C3 antibodies (Figs. 1.13, 1.14 and 1.15) [20, 65, 68–74]. The pattern is granular

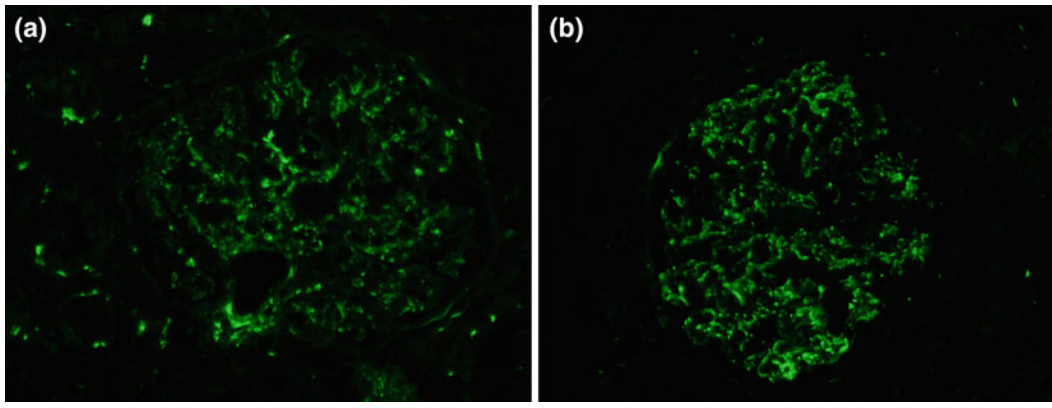

Fig. 1.14 The "starry sky pattern" of immunofluorescence. **a** The finely to coarsely granular deposits are randomly distributes across the glomerulus. Direct immunofluorescence with an antibody to C3, ×400. **b** More widespread mesangial and segmental C3 positive glomerular capillary deposits, ×400

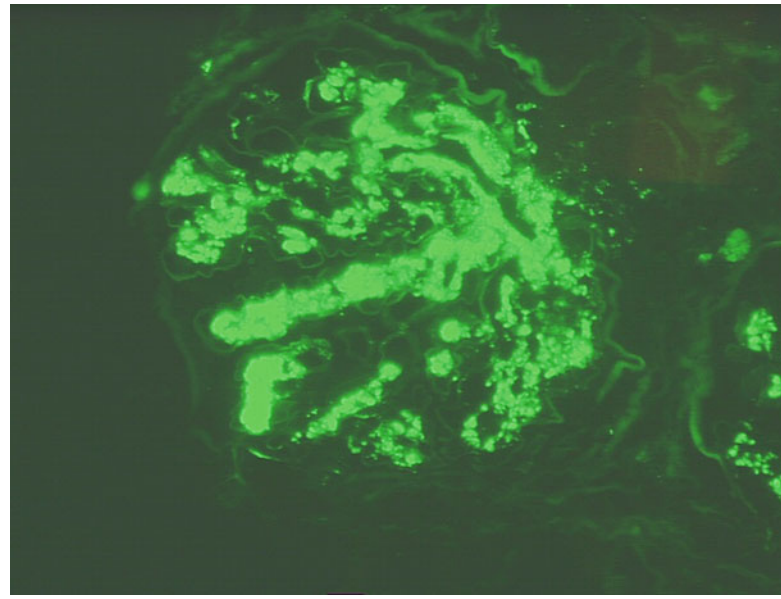

Fig. 1.15 Mesangial pattern of immunofluorescence in APSGN with granular C3 staining in the mesangium, ×400

("lumpy-bumpy") and usually more coarse than in patients with idiopathic membranous glomerulonephritis. This staining may assume a ribbon-like (garland) pattern in some capillaries, because of the confluence of subepithelial deposits. The granular deposits correspond to the glomerular subepithelial deposits (humps), evident on electron microscopy.

Sorger et al. [69–71] described different categories of immunofluorescence patterns. They noted three main arrangements, named the garland pattern (Fig. 1.13a, b), the starry sky pattern (Fig. 1.14), and the mesangial pattern (Fig. 1.15). The *garland pattern* is manifested by a discrete, more densely packed, and sometimes confluent heavy disposition of IgG and C3, corresponding to numerous humps noted on the subepithelial side of the glomerular capillary wall [64, 66]. This pattern resembles the immunofluorescence-staining pattern in membranous glomerulonephritis, and is most often seen in patients with acute glomerulonephritis

who have severe proteinuria (often with the nephrotic syndrome) (Fig. 1.13a, b). The *starry sky pattern* has a more irregular granular pattern, with the deposits being smaller and often situated on the GBM overlying the mesangial regions. This arrangement was most commonly seen in early cases of APSGN (Fig. 1.14a, b). Only a few large, typical humps were noted in these cases. This picture may turn into the *mesangial pattern*, characterized by a granular deposition of IgG and C3 (usually with predominance of C3). It seems to be most closely related to a resolving pattern (Fig. 1.15). The deposits are generally noted in the mesangium and are accompanied by mesangial hypercellularity.

There is no evidence that different etiologic factors are responsible for these three subtypes [70]. The individual immune response of the host and the stage of the disease are likely to play a role in the development of these different patterns. A diffuse granular pattern for IgG and, usually, C3 is also found in patients with subclinical glomerulonephritis [72, 75].

There is usually more intense and more constant staining with anti-C3 than with anti-IgG antibodies [68, 72, 73, 75]. Indeed, it is common to see granular glomerular C3 staining without relevant IgG staining. Some authors have noted the combination of granular and patchy interrupted linear staining along the glomerular capillary loops and in the mesangial regions [12, 34]. Sometimes, there seems to be an exclusively patchy interrupted linear pattern for C3 along GBMs close to the mesangium as well as in the mesangium, with no staining for IgG [76]. This interrupted linear pattern has been found most commonly in renal biopsies from patients at a late stage of APSGN [77]. C3 staining with negative IgG staining has been reported in the mesangial areas with no capillary wall deposits [71]. This mesangial pattern also tends to be seen in patients who undergo kidney biopsy later than usual (i.e., several weeks after the clinical onset of disease).

IgM staining is frequently present and was recorded in more than 50% of cases in one study [65]. Other authors [57] have not found significant IgM staining in biopsies from patients with APSGN. IgA staining is usually absent [12, 68, 75], but it has been noted from time to time [65, 72, 73]. If IgA immunofluorescence is strong, the possibility of an underlying staphylococcus infection has to be considered, irrespective of the presence or absence of diabetes mellitus. Staining for fibrin/fibrinogen-related antigen also can be seen in the mesangium (as well as in the Bowman's space in the crescentic form) [12, 65, 75].

Deposits of immunoglobulins and, especially, complement components may be detected in the glomeruli for months to years after apparent clinical resolution of APSGN [31]. The intensity of the immunofluorescence staining usually correlates with the severity of the glomerular lesion, although severe diffuse glomerulonephritis may be accompanied by unimpressive or negligible immunofluorescence.

Electron Microscopic Findings

The most consistent classic diagnostic feature is the presence of glomerular subepithelial electron-dense deposits, often referred to as "humps" (Fig. 1.16) [12, 31, 71, 78–80]. A "hump" is a non-scientific term used in renal pathology to describe dome-shaped subepithelial electron dense immune-type deposits that bulge outward toward the Bowman's capsule beyond the boundary of the GBM (unlike the subepithelial deposits seen in membranous glomerulonephritis). They are usually large in size. They are especially abundant in the first few weeks of APSGN, and they decline in number afterward. They are usually less than 1 μm wide and long, but they sometimes are up to 3 μm wide and 6 μm long. The electron density of the deposits is variable [81]. Although there is no direct correlation between the fine ultrastructural appearance of the deposit and the clinical or non-ultrastructural morphologic findings, Tornroth [80] has suggested that electron-lucent areas in the deposit may represent regions of resolution (Fig. 1.17).

The deposits are usually abundant and discrete and are most commonly found on that part of the GBM that overlies the mesangial regions. West and McAdams [82] reported that there may be no

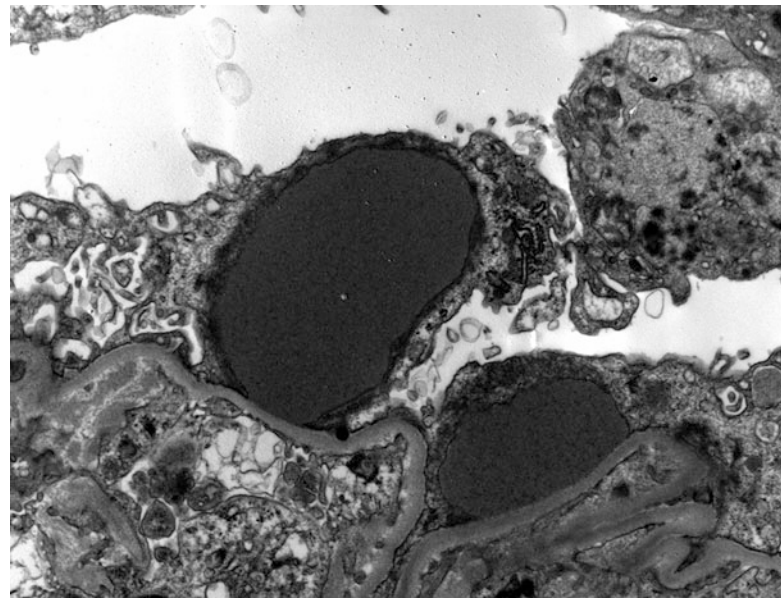

Fig. 1.16 Large dome-shaped subepithelial deposits (humps) are the hallmark ultrastructural finding in APSGN. Uranyl acetate–lead citrate, ×10,000

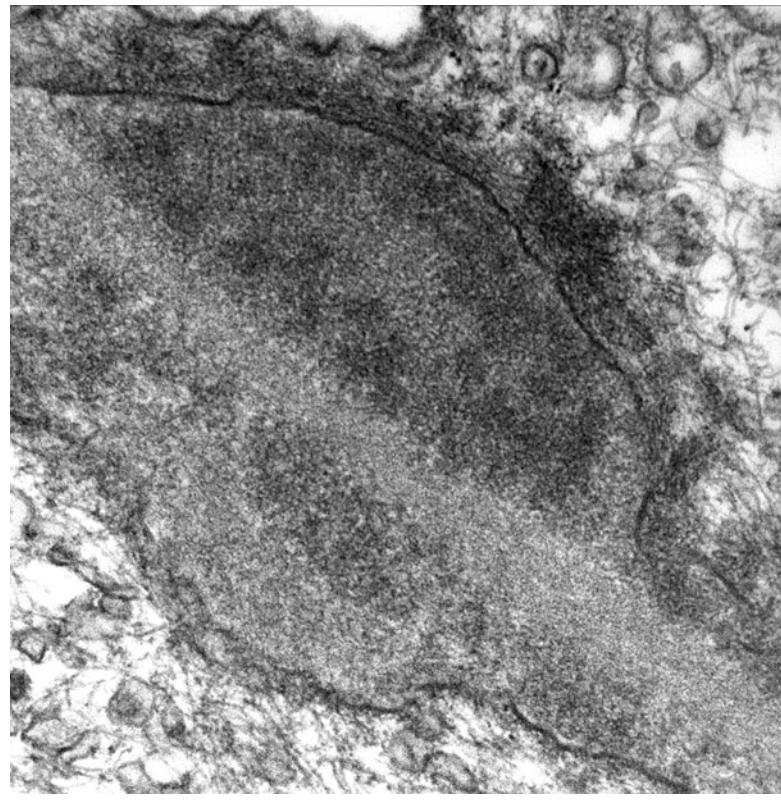

Fig. 1.17 A subepithelial hump with decreased and variegated electron density. This finding is thought to represent resolving immune complex deposits. Uranyl acetate–lead citrate, ×80,000

or only very few subepithelial deposits along the GBM covering the mesangium in some pediatric patients with APSGN in spite of prominent hypoalbuminemia and edema. On occasion, the subepithelial deposits may be numerous and along stretches of the GBM, particularly in cases

with the garland pattern of immunofluorescence (Fig. 1.18). Discrete electron-dense immune-type deposits may be seen in the lamina densa and the subendothelial regions [12, 71, 79, 80, 83] (Figs. 1.18 and 1.19). Various numbers of mesangial electron dense deposits are usually

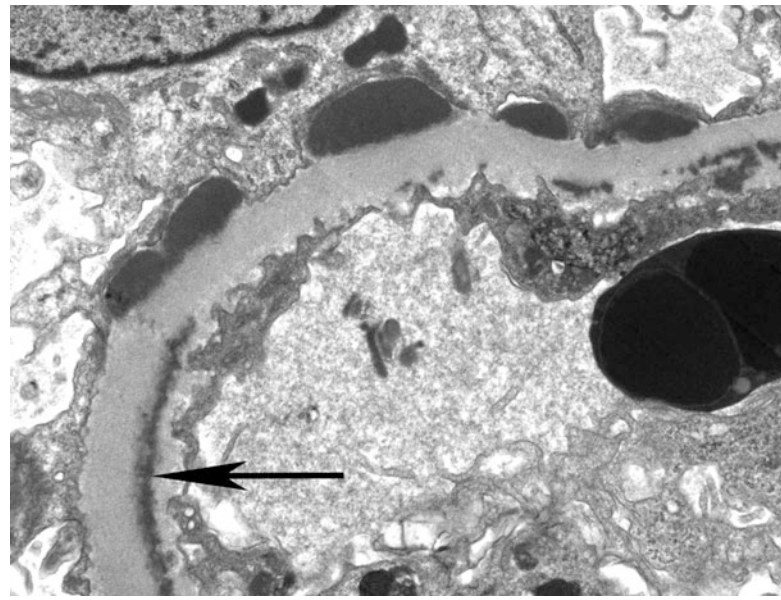

Fig. 1.18 Numerous subepithelial humps of various sizes along the GBM. This is frequently seen in biopsies with the garland pattern of immunofluorescence. Note that there are subendothelial deposits as well (*arrow*). Uranyl acetate–lead citrate, ×1100

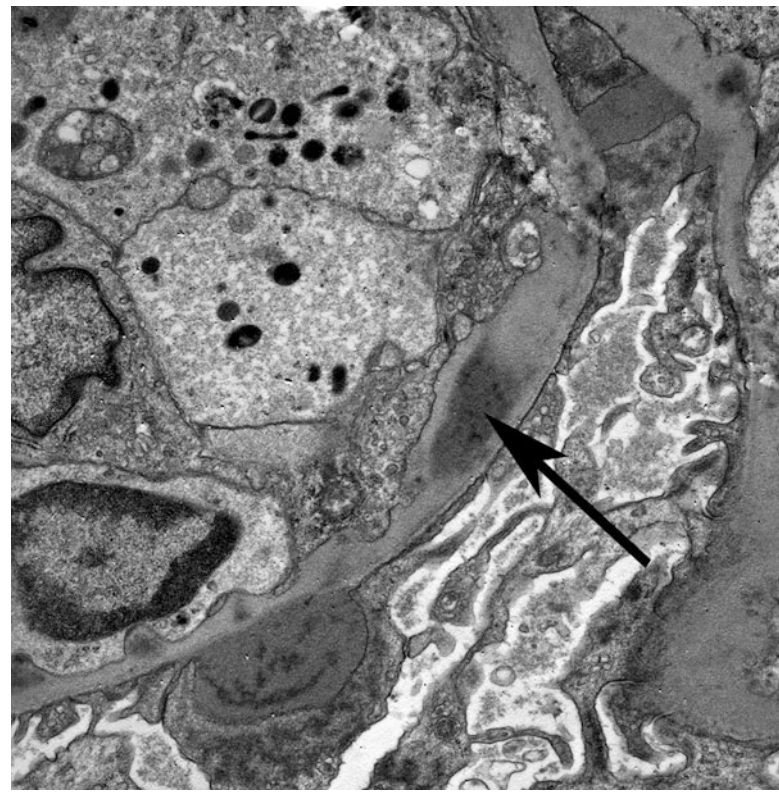

Fig. 1.19 In addition to subepithelial deposits, intramembranous deposits (*arrow*) are also common. Uranyl acetate–lead citrate, ×15,000

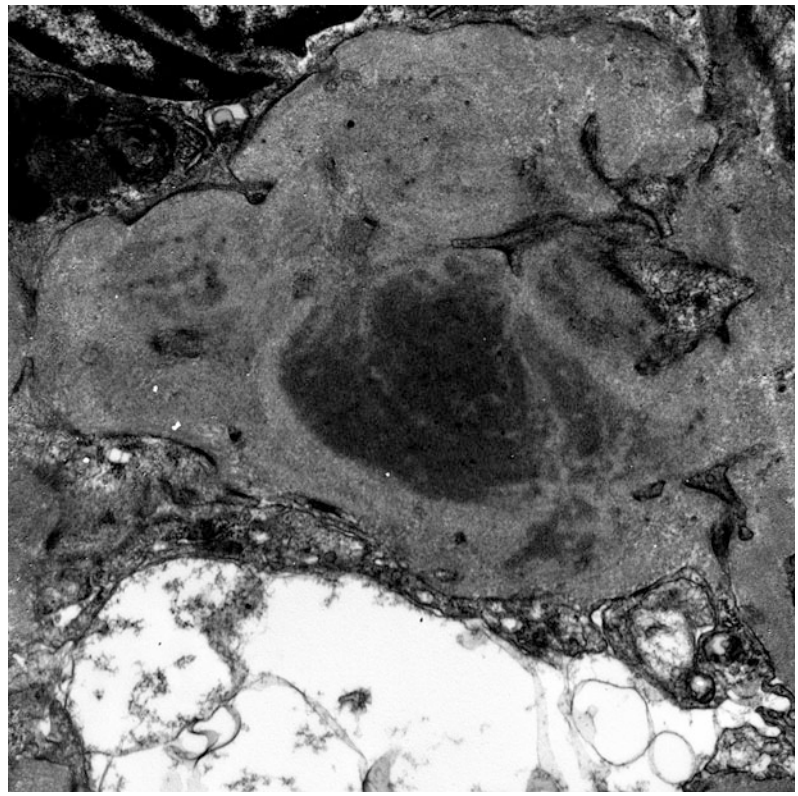

Fig. 1.20 Mesangial electron dense deposit in a case of APSGN. Uranyl acetate–lead citrate, ×20,000

present (Fig. 1.20). Although the glomerular subepithelial hump is the most characteristic lesion by electron microscopy, similar subepithelial deposits may be seen in other disorders, such as staphylococcus-associated glomerulonephritis, membranous glomerulonephritis, membranoproliferative glomerulonephritis C3 glomerulopathy, lupus nephritis, and Henoch–Schönlein purpura.

Data from patients undergoing serial biopsies indicated that during the recovery phase, the glomerular subepithelial humps tend to rapidly disappear (usually within 6 weeks of the clinical onset of disease) [78]. Sometimes, they may be present for a longer period of time [79], but the clinical course in such cases is unclear. The fate of the glomerular subepithelial deposits has been studied by Tornroth [80], who has demonstrated that the electron density (osmiophilia) of the deposits diminishes with time, so that translucent or electron-lucent regions are formed. Glomerular intramembranous electron-lucent regions have been seen in later biopsies (after 1 month), and, in some cases, these regions protruded toward the epithelium and were covered on that side by a thick layer of basement membrane-like material.

Sometimes electron dense deposits were found deeper in the lamina densa, giving it a somewhat mottled appearance [80]. Kobayashi et al. [79] showed that the deposits became buried in the GBM and also acquired a fine granularity with an electron density less than that of the original humps. Glomerular subendothelial deposits, that were present early, disappear with time [79, 80]. Increased cellularity may persist in the mesangial regions for several months, even in those patients in whom the clinical picture and urinary sediment have returned to normal. An increase in mesangial matrix is often found in patients who have chronic proteinuria. It appears that there are more subepithelial humps in those

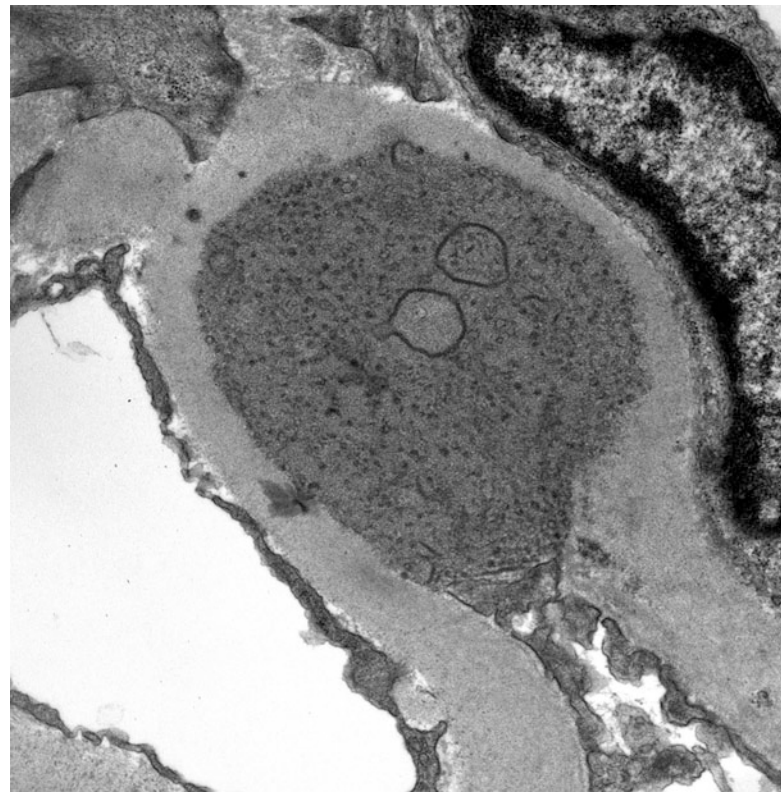

Fig. 1.21 A large subepithelial deposit in a mesangial groove (notch) region. In our experience, such deposits, particularly if they have microspheres and membrane-like inclusions in them, usually represent a nonspecific degenerative change. Uranyl acetate–lead citrate, ×25,000

patients with a severe, protracted clinical picture than in those with rapid clinical recovery [79]. The size of the deposits does not seem to correlate with clinical course or outcome [84].

Haas [31] emphasized the significance of scattered intramembranous and subepithelial remnant deposits in a renal biopsy in patients with possible history of APSGN. Using careful ultrastructural studies, Haas identified 57 renal biopsies with such deposits out of 543 biopsies that did not have a primary diagnosis of immune complex glomerulonephritis. Haas emphasizes the diagnostic significance of subepithelial deposits in the mesangial notch (or mesangial groove) region. The mesangial notch region represents a fold of the GBM overlying the mesangium. In our experience, isolated subepithelial deposits in the mesangial notch region usually represent a nonspecific finding and should not be interpreted as a specific lesion for remote postinfectious glomerulonephritis (Fig. 1.21).

Differential Diagnosis

Acute Postinfectious Glomerulonephritis of Nonstreptococcal Origin

The morphology of the various nonstreptococcal postinfectious or infection-related glomerular nephritides vary somewhat, according to the underlying pathogen. Thus, glomerular subepithelial humps are usually less prominent, and one can find more intramembranous or subendothelial and mesangial deposits in a postinfectious glomerulonephritis of nonstreptococcal origin, such as in staphylococcus infection-associated glomerulonephritis or secondary to other infections (Table 1.2) (see Chaps. 2 and 3).

It is important to note that many infection-associated glomerulonephritides are not truly postinfectious. In postinfectious glomerulonephritis, by the time the symptoms of

glomerulonephritis manifest, the infection has resolved; therefore, steroid/immunosuppressive treatment will usually not be harmful. In contrast, in infection-associated glomerulonephritides, the glomerulonephritis develops while the infection is still active, ongoing. Therefore, in infection-associated glomerulonephritis steroids or other immunosuppressive medications should be avoided [85].

In staphylococcus infection-associated glomerulonephritis, the glomerular deposits frequently contain IgA in addition to C3. Glomerular IgA deposits usually do not occur in APSGN. Making the distinction between APSGN and infection-associated glomerulonephritis is important from the perspective of history, pathogenesis, and clinical management. Unfortunately, steroid therapy in staphylococcus infection-associated glomerulonephritis can precipitate severe staphylococcal sepsis and even death and provides no observable benefits [85]. However, in some biopsies, based on morphologic examination alone, it is impossible to determine whether the etiologic agent is GAS or a nonstreptococcal pathogen. Only detailed clinical history and identification of the exact pathogen enables the definitive diagnosis. Rarely, both GAS and staphylococcal infections may be present in the same patient. Recently, we encountered a kidney biopsy from a patient with wound infection that had multiple microorganisms, including *S. pyogenes* and Methicillin-resistant Staphylococcus aureus (MRSA), in the exudate. Kidney biopsy showed immune complex-mediated proliferative glomerulonephritis with focal fibrocellular crescents. Immunofluorescence and electron microscopy indicated C3-, IgA, and IgG-containing immune complex deposits in the mesangium and along the glomerular capillary loops. The glomerular capillary loops deposits were subepithelial, intramembranous, and subendothelial. Although the morphology was not inconsistent with APSGN, because of the ongoing infection and the presence of IgA, we favored staphylococcus infection-associated glomerulonephritis.

C3 Glomerulopathy

The newly emerging entity of C3 glomerulopathy (particularly the hypercellular C3 glomerulonephritis) can be very difficult to differentiate from APSGN based on morphologic findings alone. C3 glomerulopathy is associated with congenital or acquired dysregulation of the alternate pathway complement activation with glomerular C3 deposits in the absence of immunoglobulin deposits [86]. It has been proposed that C3 glomerulopathy encompasses C3 glomerulonephritis (in which proliferative renal lesions are seen with C3 deposits but with no immunoglobulin deposits), dense deposit disease, familial membranoproliferative glomerulonephritis type III and familial complement factor H-related protein 5 abnormality nephropathy [86]. Differentiating APSGN from C3 glomerulonephritis can be a difficult task, because in both conditions glomerular endocapillary and mesangial hypercellularity and C3 containing mesangial and glomerular capillary deposits, including subepithelial humps, may be present [87]. If the biopsy in APSGN is performed in the resolving stage, the glomerular hypercellularity is mostly seen in the mesangium and the C3 deposits may also be mainly mesangial. Serum C3 levels are usually low both in APSGN and in C3 glomerulopathy/glomerulonephritis. However, there are two major differences between APSGN and C3 glomerulonephritis. APSGN is preceded by a streptococcal infection and is a self-limiting benign disease with recovery without intervention. In contrast, C3 glomerulopathy is usually not preceded by an infection and the disease is associated with persistent proteinuria/hematuria, persistently low serum C3 levels and usually slow disease progression. The differential diagnosis can be particularly complex if an infection (such as a streptococcal infection) evokes the alternate pathway complement regulatory abnormality, which can happen in patients who have otherwise subclinical mild form of dysregulation of the alternate complement pathway

activation [87, 88]. Differentiating dense deposits disease from APSGN is easy, because of the characteristic intramembranous dense deposits seen by electron microscopy. The other familial forms of C3 glomerulopathy can potentially cause a differential diagnostic problem, but the family history of renal disease and the persistent clinical symptoms should provide a clue.

Membranoproliferative Glomerulonephritis (MPGN)

The differentiation of MPGN (MPGN type I with C3 and IgG deposits) from APSGN is not a challenge for an experienced renal pathologist, if the case is typical. Unfortunately, in our experience, "typical" cases are becoming more and more an atypical occurrence in the renal biopsy material. Therefore, this differential diagnosis may be a challenge. In early stages of active MPGN type I, the glomerular hypercellularity can be quite striking and intracapillary polymorphonuclear leukocytes may be prominent. Immunofluorescence shows granular glomerular C3 deposition with IgG, which can be seen in both MPGN and APSGN, and occasionally, it is difficult to decide whether the immunofluorescence findings represent a garland pattern in APSGN or subendothelial deposits in MPGN. Ultrastructurally, MPGN is characterized by abundant subendothelial deposits, but the presence of subepithelial humps in MPGN is not unusual, and occasionally, quite a few humps can be seen. In APSGN, usually subepithelial humps predominate, but in many cases, subendothelial deposits are also seen. Mesangial deposits are present in both MPGN and APSGN. Based on these findings, it is evident that there are morphologic overlaps between APSGN and MPGN type I. The clinical presentation can also be quite similar because both diseases frequently present with nephritic syndrome and variable degrees of proteinuria and hypocomplementemia. Proteinuria occasionally can be quite prominent in APSGN. Serum complement levels (in particular, C3 levels) are low in both diseases. C3 nephritic factor is not always present in MPGN, and may occasionally be seen in APSGN. We have encountered a few renal biopsies in which we were unable to decide whether the biopsy represented an early active stage of MPGN type I or APSGN. In such cases, only careful follow-up will establish the diagnosis because the waste majority of APSGN cases will gradually improve and resolve, whereas MPGN type I, if untreated, usually progresses.

Cryoglobulinemic Glomerulonephritis

In a typical case, the differential diagnosis is easy because of the intracapillary hyalin thrombi, which represent cryoglobulin precipitates in the glomerular capillaries. However, particularly in a small biopsy specimen or in atypical cases, these hyalin thrombi may not be present and cryoglobulinemic glomerulonephritis shows the pattern of endocapillary proliferative glomerulonephritis. The predominant endocapillary cell in cryoglobulinemic glomerulonephritis is the monocyte, but it is not unusual to see many neutrophil granulocytes. The immunofluorescence pattern in cryoglobulinemic glomerulonephritis is distinctive (particularly in type I and type II cryoglobulinemia) if the cryoglobulin deposits are present. Unfortunately, as any glomerular disease, cryoglobulinemic glomerulonephritis also represents a disease spectrum and cases with little or no intraluminal cryoglobulin deposits in the glomerular capillaries occur. The distinctive IgG and IgM positive globules of type II cryoglobulinemia, which usually also stain for complement, may not be evident in such cases. Electron microscopy usually reveals the characteristic organized microtubular substructure in the cryoglobulin deposits, but this could be easily missed, particularly if not enough glomeruli are examined under the electron microscope. One important differential diagnostic hint is that in cryoglobulinemic glomerulonephritis humps are usually absent. Cryoglobulinemic glomerulonephritis in the differential diagnosis should be considered if there is an endocapillary proliferative glomerulonephritis with no or only few immune complex deposits and no subepithelial

humps. The clinical history may be quite helpful in differentiating APSGN from cryoglobulinemic glomerulonephritis. Similarly to APSGN, C3 levels may be low in cryoglobulinemic glomerulonephritis, but cryoglobulinemic glomerulonephritis is typically associated with normal or slightly low serum C3 levels and very low C4 levels. A positive cryoglobulin test may be helpful, but, unfortunately, this test is unreliable and cryoglobulins occur in some patients with APSGN. Another useful test in the differential diagnosis is rheumatoid factor, which is detectable in most patients with cryoglobulinemic glomerulonephritis. Rarely, even the clinical history may be misleading, because cryoglobulinemic glomerulonephritis may undergo spontaneous remission giving the impression of a resolving APSGN.

IgA Nephropathy

Exacerbation of IgA nephropathy is common after upper respiratory tract infection with the appearance of gross hematuria, or nephritic syndrome. However, this form of IgA nephropathy is a synpharyngitic glomerulonephritis, developing while the upper respiratory tract infection is still ongoing or is immediately following it. Unlike in APSGN, there is no latency between the infection and the glomerulonephritis. Renal biopsy findings are quite different in IgA nephropathy and APSGN, but if, in addition to glomerular IgA deposition there is also prominent C3 staining, acute kidney injury, heavy proteinuria and if the infection is other than a common upper respiratory tract infection, one should consider an underlying staphylococcus infection (see Chap. 2).

Membranous Glomerulonephritis

In our experience this is not a difficult differential diagnosis; however, Sotsiou et al. [89] described two patients with presumed postinfectious glomerulonephritis who had morphologic features of membranous glomerulonephritis, such as spike formation on methenamine silver stain, intracapillary hypercellularity with neutrophils, garland-type granular deposits of IgG and C3 along the glomerular capillaries, and elevated ASO titers. Unfortunately, no follow-up data are provided and it is difficult to exclude the possibility that these cases in fact represented atypical membranous glomerulonephritis rather than atypical postinfectious glomerulonephritis. A transformation of an acute proliferative and exudative glomerulonephritis into a membranous glomerulonephritis has been reported in 3 cases [90]. These cases are very unusual, and the pathogenesis is debatable. Wu et al. [91] described a patient who developed APSGN superimposed on membranous glomerulonephritis.

Recently, Larsen et al. [92] described an interesting form of glomerulonephritis in young adults: membranous-like glomerulopathy with masked IgG-kappa deposits. With routine immunofluorescence on frozen sections, the deposits stain predominantly for C3. Electron microscopy shows numerous subepithelial deposits, which are frequently large, hump-like. However, serum C3 is usually normal and the patients do not have evidence of prior or ongoing infection. Repeating immunofluorescence on paraffin sections after digesting them with pronase reveals that the subepithelial deposits contain IgG-kappa.

Diffuse Proliferative (Class IV) Lupus Nephritis

Diffuse proliferative lupus nephritis shows a diffuse endocapillary proliferative pattern, frequently with the presence of glomerular PMN. Therefore, if immunofluorescence and electron microscopy are not available, the differential diagnosis, based on light microscopy alone, may be difficult. One has to remember that in proliferative lupus nephritis large hump-like subepithelial deposits may be seen by electron microscopy. Still, because of the characteristic immunofluorescence and ultrastructural findings and the clinical history, the differential diagnosis is easy in most cases.

Etiology and Pathogenesis

The relationship between streptococcal infection and acute glomerulonephritis is well established, and a large amount of information is available about the mechanism of action by which the infection leads to the characteristic glomerular changes [93]. It has been known for a long time that the blood and urine are sterile in patients with APSGN [94], and the kidney parenchyma is also sterile. The renal changes in APSGN were noted to be different from those seen in patients with streptococcal septicemia, in which the major changes are interstitial nephritis and abscess formation. Although streptococcal toxins could play a role in APSGN, it is unlikely, because the renal injury would be expected to occur at the peak of the infection (whereas APSGN develops after the infection subsides). Moreover, acute proliferative glomerulonephritis is not the type of morphologic change usually noted in patients with various circulating toxins and it would be anticipated that the renal changes would be proportional to the severity of the infection, which is not the case.

It is now widely accepted that APSGN and other forms of postinfectious or infection-associated glomerulonephritis is an immunologic phenomenon. A long time ago, Schick [5] noted that there is the latent interval between clinical signs of infection and the onset of APSGN and likened it to the course of events in acute serum sickness and other allergic states. The latent interval after infection has been well documented and usually ranges between 7 and 21 days (in average, 10–11 days).

Unfortunately, there is no perfect animal model for APSGN. Many attempts have been made to create an animal model of APSGN by the injection of intact streptococci [95, 96], crude culture supernatants [38], or specific components of the streptococci [97, 98]. Although some of these experimental models produced histologic lesions somewhat similar to the disease pattern in humans, they do not precisely mimic the gradual release of streptococcal products that probably occurs at the site of infection in the clinical condition in humans [97]. Also, many of the experimental studies were performed at a time when electron and immunofluorescence microscopy and other biochemical determinations were not available, making it difficult to carry out an adequate comparison [97].

Several streptococcal fractions have been studied in search of the trigger for the glomerulonephritis (Table 1.1). One streptococcal fraction, endostreptosin, has been extensively studied [99–106]. This antigen is demonstrable in the glomerulus only during the initial phase of APSGN and reacts with antibodies present in the convalescent sera of patients with acute phase of APSGN. In the late phases of the disease, the antigen can no longer be detected, presumably because antigenic sites have been covered by the specific antibody. Seligson et al. [105] have suggested that acute elevations of endostreptosin titers are generally diagnostic of APSGN. Although low titers of antibody have been found in as many as 70% of normal individuals, significantly higher titers of antibodies are found in patients with APSGN [105]. Most patients with acute rheumatic fever do not have high levels of

Table 1.1 Streptococcal antigens potentially involved in the pathogenesis of poststreptococcal acute glomerulonephritis

Streptococcal antigen	References
Endostreptosin or preabsorbing antigen	[99–109]
Nephritis strain–associated protein (NSAP) (or streptococcal cationic protease exotoxin B [SPEB], exotoxin B, or nephritis plasmin-binding protein [NPBP])	[97, 98, 118–127, 176]
Nephritis-associated plasmin receptor (NAPlr) (or streptococcal glyceraldehyde-3-phosphate dehydrogenase [GADPH])	[124, 125, 128–133]
Streptococcal M protein and its fractions	[110–114]
Streptokinase	[115–117]

this antibody titer. Lange et al. [103] also believed that elevated levels of antibody to endostreptosin are diagnostic of APSGN and correlate well with the course of the disease process. Endostreptosin is similar to the preabsorbing antigen described by Yoshizawa et al. [106–108] and Holm et al. [109].

Yoshizawa et al. [108] isolated a 43-kDa protein from nephritogenic streptococci ("preabsorbing antigen") and noted identical precipitation lines by immunodiffusion between rabbit antisera against preabsorbing antigen and the sera of patients with APSGN. These authors developed a rabbit glomerulonephritis model by administering preabsorbing antigen for 8 days [107]. Histologically, kidneys obtained from these animals showed proliferative glomerulonephritis, immunofluorescence showed glomerular capillary and mesangial C3 deposits, and electron microscopy revealed occasional subepithelial "hump"-like deposits. Interestingly, IgG and preabsorbing antigen in the glomerular or deposits were not detected [107].

Streptococcal M protein is a strong candidate for the important antigenic bacterial fraction [110]. M-protein fractions can form complexes with fibrinogen and localize in glomeruli [111], and glomerulonephritis can be induced with injection of M-protein–M-protein/fibrinogen complexes. M-protein may be antigenically cross-reactive with the GBM [112]. However, Treser et al. [113] have proposed that the nephritogenic fraction is different from the M-protein. Immunoglobulins from patients that are recovering from APSGN, when labeled, could identify free antigenic sites in renal biopsy specimens showing APSGN; the fact that this serum had these antibodies independent of the M type of the original infection suggested that a non-M antigen was present in the glomerulus [113]. On the contrary, Mori et al. [114] found that IgG titers against the C region of the M-protein of group A streptococci are elevated in patients with APSGN, as compared to patients with other uncomplicated streptococcal infections, such as pharyngitis, chronic glomerulonephritis, as well as in and healthy controls. IgG titers against the A and B regions of streptococcal M-protein were not different between these groups.

Some researchers have suggested that streptokinase is the most important bacterial antigen leading to APSGN [115–117]. Holm et al. [115] showed loss of nephritogenic potential of a nephritogenic type 49 streptococcus strain by deletion of a streptokinase gene by using a molecular construct prepared by electrotransformation.

An extracellular protein unique to nephritogenic streptococcus strains from cultures of type 12 organisms was identified by Villarreal et al. [118]. This fraction (called *nephritis strain-associated protein, NSAP*) was noted in 56% of renal biopsies with morphologic features of APSGN; it was not found in biopsies from patients with other forms of nonstreptococcal glomerulonephritis or rheumatic fever. The vast majority of patients with glomerulonephritis had serum antibodies to NSAP [119]. NSAP (also called streptococcal cationic protease exotoxin B [SPEB] or nephritis plasmin-binding protein [NPBP]) can directly induce tissue destruction by cleaving extracellular matrix proteins (such as fibronectin and vitronectin), and might aggravate inflammation via superantigenic effects on the immune system, similar to staphylococcal enterotoxins A and C. SPEB can directly bind to Class II MHC molecules on antigen-presenting cells and specific *Vβ* chain of T cell receptors, inducing proliferation and massive activation of T cells. Antibodies to streptococcal glyceraldehyde-3-phosphate dehydrogenase (GADPH) and SPEB (NSAP) have been found in patients with APSGN [120]. More recent studies by using double immunofluorescence staining methods for NSAP and collagen type IV demonstrate that NSAP is localized to the inner side of the GBM [121, 122].

A 46 kDa subunit of NSAP has antigenic, biochemical, and structural similarities to streptokinase from group C streptococcal organisms, and it binds to plasmin and is a plasminogen activator that has been isolated and purified [98]. This protein is not related to group A streptokinase or to a recently described streptococcal dehydrogenase protein [123, 124]. Amino acid sequence analysis and immunologic reactivity

studies indicate that this protein is the streptococcal pyrogenic exotoxin B (SPEB) precursor (previously termed *zymogen-streptococcal proteinase precursor*) [124].

Vogt et al. [125] isolated and identified a number of different cationic proteins from nephritogenic streptococci. Studies from the group at the Rockefeller University indicate that the cationic protein described by Vogt et al. is structurally identical to SPEB [126]. This group and other investigators suggest an important role of SPEB in APSGN [126, 127]. Cu et al. [126] found that SPEB antibodies were present in the sera of patients with APSGN in significantly higher titers than in patients with acute renal failure, scarlet fever, and normal sera.

Another potential candidate to play a role in the pathogenesis of APSGN is nephritis-associated plasmin receptor (NAPlr) [124, 125, 128]. NAPlr is proved to be homologous with streptococcal GAPDH. Yoshizawa et al. [129] demonstrated that 92% of patients with early APSGN had anti-NAPlr in their serum and up to 80% of the renal biopsies of early cases of APSGN showed deposition of NAPlr. In a subsequent study, the authors showed that the distribution of glomerular plasmin-like activity and glomerular NAPlr is identical and postulated that NAPlr traps and maintains plasmin in the active form in the glomeruli, which, in turn, induces glomerular damage [130]. The authors propose that NAPlr will be released into the circulation following an infection with a nephritogenic strain of group A streptococci, which can bind to the glomerular mesangium and the GBM. This bound NAPlr traps plasmin and maintains its activity. Activated plasmin may degrade the GBM by itself or through activation of matrix metalloproteinases [130]. Activated plasmin may also attract neutrophils and macrophages to the site of inflammation. The circulating immune complexes, therefore, can easily pass the damaged GBM and accumulate along the subepithelial surface as large subepithelial deposits [130]. Transient immunostaining for NAP1r antigen has been demonstrated in the glomeruli during the early stages of APSGN and the staining diminishes within several months. This antigen is reported to be localized in mesangial cells, endothelial cells, and neutrophils, similar to the localization of SpeB antigen [130, 131]. However, glomerular NAP1r deposition has also been found in other glomerular diseases, such as Henoch–Schönlein purpura, lupus nephritis, and dense deposit disease [132, 133]. Therefore, the specificity of this nephritogenic antigen for APSGN is somewhat questionable.

The search for the antigens responsible for the development of APSGN still continues. A large number of streptococcal proteins have been proposed to be important in the pathogenesis of APSGN through their binding to plasmin, release of matrix metalloproteinases, destruction of glomerular capillary basement membranes and recruitment of inflammatory cells (Table 1.1). Lack of specificity of these proteins to APSGN alone is what plagues the findings. Another important obstacle is the fact that not only Streptococcus but a large number of other infectious agents can cause immune-mediated glomerulonephritis, suggesting that not one, but a large spectrum of bacterial proteins may be capable of binding to glomerular matrix and basement membranes and inducing tissue injury, complement activation and recruitment of inflammatory cells to the site.

Most patients with APSGN have elevated serum levels of IgG, IgM, and circulating immune complexes [106, 134, 135]. Circulating immune complexes were found in the serum of two-thirds of patients in the first week of the disease. After 4 weeks, the immune complexes were evident only in approximately 20% of patients [135]. It has been hypothesized that circulating immune complexes correlate with the severity of renal disease and with the detection of renal immune deposits [136].

Cryoglobulins (usually type III) are frequently found in patients with APSGN [65, 68, 137]. Most of these studies have found that the cryoglobulins contain combinations of IgG, C3, and/or IgM. IgA is less commonly found in precipitates. Streptococcal antigens are not generally detectable in the cryoprecipitates.

Low levels of serum complement (C3) in patients with APSGN have been described by

many investigators [40, 104, 138–140]. Serum C3 levels are almost always low in the acute stages of APSGN. Serum C3 levels increase after several weeks and almost always return to normal levels within 6 weeks.

It has been suggested that the persistence of low serum C3 levels is associated with a poor prognosis [140]. In such patients, renal biopsy must be performed to exclude other glomerular diseases, such as membranoproliferative glomerulonephritis or C3 glomerulopathy. Most authors have not found a correlation between serum C3 levels and the degree of proteinuria [139], confirming that complement was not diminished because of loss in the urine. Because the serum C3 level rises soon after the acute phase of the disease, it is generally not accepted that there is a generalized disorder in the synthesis of complement [139]. However, some authors [141] did show that children with APSGN had depressed synthesis of C3 relative to normal subjects. Serum C3 levels can be low even in patients with subclinical glomerulonephritis [138].

C3 glomerulonephritis is a recently described entity associated with abnormalities in the alternate pathway complement activation [142–144]. Both C3 glomerulonephritis and APSGN have low serum C3 levels associated with alternate complement pathway activation. IgG deposits are not seen in the glomeruli in C3 glomerulonephritis, but they are also frequently absent in biopsies from patients with APSGN. Therefore, one has to consider the possibility that APSGN may represent a transient acute form of C3 glomerulonephritis induced by streptococcal infection. Streptococcal antigen can activate the alternate complement pathway, and it is theoretically possible that in patients who have mild underlying complement regulatory deficiency, streptococcal infection could evoke an acute glomerulonephritis [87, 88].

In addition to the classic concept that streptococcal organisms produce a protein that is immunogenic and causes an antibody response, there is also a theory that the streptococcal organism may trigger an autoimmune disease by inducing antigenic modification of normal autologous proteins [61, 145, 146]. Some authors proposed that in APSGN autologous IgG is modified by a number of streptococcal enzymes or products of the bacterial organism released during infection (e.g., neuraminidase). Then, IgG becomes autoimmunogenic and stimulates the production of anti-IgG antibodies [119, 145, 146].

A number of autoantibodies against glomerular proteins were identified, but their pathogenic role in APSGN has not been proven. Most the autoimmune diseases are progressive without immunosuppressive medications. In contrast, APSGN resolves without immunosuppression; therefore, even if transient glomerular autoantibody formation occurs, these autoantibodies probably represent an epiphenomenon and do not have a relevant pathogenetic role.

Cell-mediated mechanisms have traditionally not been considered as an important factor in the initiation of acute glomerular injury. However, they increasingly have been studied and are now considered to play an ancillary role in the progression of acute glomerulonephritis to a chronic stage [147, 148]. These mechanisms also may be important in those patients with severe APSGN who have few immune deposits. Zabriskie et al. [147, 148] have suggested that proteins from nephritogenic streptococci may deposit in the glomerulus and release a glycopeptidase that is capable of altering the composition of the GBM and exposing new antigens. Progression of the disease may be related to antibodies on sensitized lymphocytes directed against the “new” GBM antigens.

Coagulation in patients with APSGN has been extensively studied. It has been demonstrated that during the acute phase, there was fibrin formation as evidenced by an increase in plasma high-molecular weight fibrinogen complexes and the development of either hypofibrinogenemia or hyperfibrinogenemia, and an elevation in fibrin degradation (split) products in the urine [149]. With resolution of APSGN, these abnormalities diminish. There was no correlation between the complement levels in the serum (such as C3) and serum fibrinogen degradation products [150]. Platelets may play a significant role in the

pathogenesis of various forms of glomerulonephritis [151], including APSGN [152].

Thrombotic microangiopathy (TMA), including hemolytic uremic syndrome, has been reported in patients with APSGN [61, 62]. Kakajiwala A et al. [153] reported that treatment with eculizumab showed significant clinical improvement in a such patient and the patient remained in remission after stopping eculizumab. The morphologic features in the 1-year follow-up kidney biopsy were indistinguishable from the expected findings in an individual with healed APSGN without associated HUS [153].

Interestingly, most patients with TMA and concomitant APSGN recover from both TMA and APSGN. It is possible that the TMA in these patients is secondary to endothelial injury that is caused by circulating antibodies that cross-react with endothelial cells and result in subsequent complement activation. One of the hypotheses is that removal of sialic acid from the cell membranes of endothelial cells, red blood cells, platelets, and inflammatory cells by streptococcal neuraminidase results in the exposure of the Thomsen–Friedenreich antigen. The exposed Thomsen–Friedenreich antigen reacts with an anti-T IgM antibody in the plasma, which, in turn causes endothelial injury and subsequent activation of the coagulation cascade [154]. If this hypothesis is true, it is puzzling why only so few patients with APSGN develop TMA.

Clinicopathologic Correlations and Outcome

Several studies have been performed to correlate various clinical and pathologic aspects of APSGN. There is no correlation between the presence of hematuria or proteinuria and the severity of the glomerular lesion. These findings are not surprising, because histologic evidence of glomerulonephritis has been noted in patients with minimal or absent hematuria and proteinuria [98]; also, considerable hematuria can be present with no changes or only mild changes in the glomeruli.

Several investigators have suggested that initial and/or persistent nephrotic syndrome is an indication of a poor renal outcome [155, 156]. Patients with low creatinine clearance, microscopic hematuria, and proteinuria usually show moderate to advanced glomerulosclerosis, mesangial hypercellularity, and strong immunofluorescent staining for IgG and C3 on renal biopsies [11]. The studies by Sorger et al. [69, 71] and others [74] indicate that the garland pattern of immunofluorescence is associated with more severe proteinuria. West and McAdams [82] demonstrated that children with APSGN and hypoalbuminemia had no subepithelial deposits (humps) on the paramesangial portion of the GBM. In contrast, children with subepithelial deposits along the paramesangial basement membrane had significantly higher serum albumin levels. Unfortunately, quantification of the proteinuria was not performed in this retrospective study and the clinical significancy of this association is unclear [82].

Some studies indicate that elderly patients (older than 60 years) tend to have a worse renal prognosis than younger adults [33]. As many as 50% of adult patients with oliguria/anuria and crescent formation progress to end-stage kidney disease [155, 157]. Of note, the prognosis for adult patients with oliguria/anuria may be related to the availability of dialysis and other medical support and these data are taken from the older literature. Also, many elderly patients have several comorbidities, such as hypertension and diabetes, with associated chronic kidney disease.

The most controversial aspect of APSGN is its long-term outcome. This is a question on which there are both strong opinions and incomplete data. The difficulty in connection between the glomerulonephritis in the individual patient and the streptococcal infection has made it difficult to interpret follow-up studies. Information about the correlation of morphologic changes with clinical outcome was sparse before the days of renal biopsy, although it was known that some patients pursued a variable clinical course ending with death secondary to renal failure within a few months. Most of these are APSGN cases in

which crescent formation is abundant. The presence of a large number of crescents is a sinister sign. However, it is quite common to see cases of APSGN with a few crescents where complete recovery is generally the rule [40]. Clinical recovery has been noted in half of patients with less than 40% crescents [40] as well as in some patients with a greater percentage of crescents [158].

Crescentic glomerulonephritis as a severe manifestation of a APSGN has been noted by many researchers [34, 45, 47, 83, 91, 155, 158, 159]. The significance of crescentic glomerulonephritis in children with APSGN remains the subject of controversy [45, 46, 159]. APSGN is usually fully reversible, even in crescentic forms. Still, long-term follow-up studies indicate that some patients who had a history of APSGN may develop renal failure or even end-stage renal disease after many years or decades of APSGN [27, 89, 160–163]. Unfortunately, most of these studies do not specify whether the cases that have poor long-term outcome had glomerular crescents or not.

Several cases of APSGN associated with diffuse alveolar damage in the lungs were reported [164–166]. ANCA was negative in one case [164]; information about ANCA is not provided for the remaining patients [165, 166].

Several authors have attempted to use morphologic markers, other than crescents, as prognostic indicators in APSGN. Some suggest that the overall degree of glomerular tuft hypercellularity is related to either the degree of persistent proteinuria [167] or clinical outcome [168], but other authors have stated that there is no good correlation between excessive glomerular hypercellularity and outcome [40]. Lesser degrees of glomerular hypercellularity also have been found to be associated with irreversible renal injury [168]. However, there are so many exceptions to the suggested correlations that a rule of thumb probably does not exist. It is likely that several of these morphologic features taken together may be of greater prognostic value than any single finding, but this type of study has not been performed yet. Some investigators have ascertained that glomerular necroses, adhesions, glomerular capillary thromboses, crescent formation, and interstitial nephritis have been found more commonly in patients with progressive disease [168]. Vascular changes, such as arteriolar sclerosis and arterial sclerosis, have been suggested to be a harbinger of a poor prognosis [48].

Large and confluent glomerular subepithelial electron-dense deposits have been thought to be associated with a poor prognosis [167]. Persistence of immunofluorescent staining for immunoglobulins and complement, primarily in the glomerular mesangium, has been considered to be evidence of continuing immunologic involvement and injury and this finding was noted in patients who progressed to a chronic stage [101]. However, some authors have noted the persistence of immunofluorescent staining for immunoglobulins and complement as long as 5 years after the initial acute attack; therefore, the presence of this finding beyond the acute stage of disease cannot be universally regarded as a definitive sign of a poor prognosis [169].

Linear immunofluorescence for IgG was noted in some patients who progressed to chronic renal failure [168]. These patients did not have anti-GBM antibodies in the serum. Baldwin et al. [48] reported similar linear immunofluorescence in subsequent renal biopsies with a significant number of globally sclerotic glomeruli, but renal failure had not yet developed in these patients. Whether these changes are truly specific and portend a poor prognosis is unclear; mild linear glomerular capillary staining for IgG is a common nonspecific immunofluorescence finding, particularly in diabetic patients.

The clinical outcomes of patients with APSGN are shown in (Table 1.2). In many of the series quoted, renal biopsies were not performed; thus, histologic evidence of APSGN is lacking. Without pathologic categorization of nephritis, the outcome might be altered by diseases erroneously diagnosed clinically as postinfectious glomerulonephritis, such as IgA nephropathy with onset or exacerbation initiated by streptococcal pharyngitis. The criteria used for making the diagnosis of APSGN were clinical and variable. Lengths of follow-up vary among the series,

Table 1.2 Clinical outcome in patients with poststreptococcal acute glomerulonephritis stratified by patient population

Patient population	Follow-up period (years), references	Number of patients	Mortality in acute stage (%)	Transformation to chronic or latent stage (%)	No follow-up (%)	Recovery (%)
Adults	Less than 4 [49, 58, 160]	134	0.8	39.6	0	59.6
	More than 4 [163, 177, 178]	468	5.1	19.1	13.7	62.1
Adults + children	1–18 [7, 28, 37, 48, 50, 94, 157, 171, 179–183]	2625	4	17[a]	5[a]	71[a]
Children	Less than 4 [76, 168, 172, 174, 184–186]	966	1	6	0	93
	More than 4 [161, 162, 170, 173, 187–190]	765	2	7	1[a]	89[a]

[a]Data is not available for all studies

but they were often short. The outcome criteria are also different; some authors used the presence of mild proteinuria and microscopic hematuria, whereas others relied on BUN and serum creatinine levels and the presence of hypertension.

Short-term follow-up data can give a wrong impression, because the disease resolves more slowly in some patients than in others, with the net result that the number of patients in the latent stage is exaggerated. Studies with short-term follow-up provide fewer opportunities for some patients with asymptomatic proteinuria to progress to the chronic stage, or for other patients to recover completely.

It is important to note that selection or entry bias plays a major role in the interpretation of many series. Patients in a hospital setting represent a highly selective population, and it is likely that most mild cases are not hospitalized or undergo kidney biopsy. Hospitalized patients are likely to have the most severe clinical course. Renal biopsy is usually reserved for those with an atypical or severe clinical picture of acute postinfectious glomerulonephritis. Despite these reservations, most investigators believe that the prognosis in children is good in both the epidemic and sporadic cases of APSGN. The mortality rate for children in the acute stage is generally low, although some researchers have noted higher death rates than others [170]. These high mortality rates are usually the result of other comorbidities, such as severe infection, cardiac failure, or hypertensive encephalopathy, not the nephritic process itself.

The patients with epidemic forms of APSGN have almost uniformly shown excellent clinical outcomes, and only a few have persisting renal injury, as determined by clinical and laboratory examinations (hematuria/proteinuria) [11, 37, 171–173].

Some reports [156, 157] suggest that children do not do as well as generally believed and that a high proportion have clinical or laboratory evidence of kidney function abnormalities at follow-up. It is also believed that patients who once had APSGN in childhood have an increased propensity or susceptibility to chronic glomerulonephritis as adults [49, 168, 174]. The following features maybe associated with an unfavorable clinical outcome: underlying chronic kidney disease, persisting proteinuria with or without the nephrotic syndrome, acute kidney injury, particularly if associated with oliguria/anuria, extensive crescent formation, and the garland pattern on immunofluorescence [45, 71, 89, 156, 157].

The prognosis for adults is even more controversial, and many authors consider that it is not as favorable as for children [30, 33, 48, 134]. This is not surprising, considering the fact that

many adults with APSGN have coexisting comorbidities such as diabetes, hypertension and obesity with underlying chronic kidney disease. The complete recovery rate ranges from 53 to 76%, and death in the acute stage reaches up to 9% of adults [175].

The prognosis of APSGN in patients with underlying diabetic nephropathy appears to be much worse than that of APSGN without any underlying kidney disease. In the study by Nasr et al. [30] on adult postinfectious glomerulonephritis, 9 (81.8%) of the 11 patients with underlying diabetic glomerulosclerosis progressed to end-stage kidney disease. Their extended study on a larger number of elderly patients [33] showed similarly dismal outcome: 55% of patients with diabetic glomerulosclerosis progressed to end-stage kidney disease during the short follow-up period in contrast to the 19% progression rate in patients without diabetic glomerulosclerosis. It is not uncommon that an otherwise relatively mild APSGN may represent the last "hit" to the kidney with underlying diabetic nephropathy. Because of the prominent microvascular disease, frequent hypertension, cardiac disease and other complications, renal function in these patients may never recover.

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Staphylococcus Infection-Associated Glomerulonephritis

2

Jessica A. Hemminger and Anjali A. Satoskar

Introduction

Historically, glomerulonephritis due to underlying Staphylococcus infection was mostly seen in the setting of endocarditis, deep-seated visceral abscess, or infection associated with ventriculoatrial shunt. In fact, prior to the 1990s, only a few small studies had reported glomerulonephritis associated with an acute Staphylococcus infection involving other sites [1–7]. However, in more recent years, a number of publications have drawn attention to glomerulonephritis related to Staphylococcus infections involving a variety of sites, including cellulitis, osteomyelitis, and pneumonia, among others [8–24]. The earliest reports came from Japan and were subsequently followed by reports from the United States [8–26]. Most of the Staphylococcus infections were due to coagulase positive *Staphylococcus aureus*. Much less frequently, strains of coagulase negative *Staphylococcus epidermidis* have been implicated. Both methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) strains have been reported. Pathogenetic mechanisms are still poorly understood, but Staphylococcal enterotoxins acting as superantigens are thought to play an important role by causing activation of large populations of T lymphocytes and massive cytokine release that results in immune complex glomerulonephritis occasionally accompanied by leukocytoclastic vasculitis [8, 9]. IgA and C3 immune complex deposition is frequently present.

Recent literature has used a variety of terms for glomerulonephritis associated with Staphylococcus infection, including IgA-dominant postinfectious glomerulonephritis or post-staphylococcal glomerulonephritis [19, 20, 22, 23], staphylococcal infection-associated glomerulonephritis mimicking IgA nephropathy [21], or staphylococcal superantigen-associated glomerulonephritis [8, 9]. It is probably best to not use the prefix 'post' so as to avoid confusion with post-streptococcal infection-associated glomerulonephritis (PSAGN), which is a distinct disease entity with defined epidemiology, treatment, and prognosis that differs from glomerulonephritis associated with Staphylococcus infections. We prefer the term Staphylococcus infection-associated glomerulonephritis (SAGN).

Over the recent years, SAGN has gained a lot of interest among both nephrologists as well as nephropathologists. The main reasons are as follows:

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1. In developed countries, SAGN is becoming more common. The rise in SAGN is likely primarily due to (i) the emergence of virulent, drug-resistant staphylococcal strains in both nosocomial and community-acquired settings [27, 28] and (ii) the increasing population of elderly patients (above 60 years old) with underlying comorbidities such as diabetes mellitus, malignancy, and postoperative status, which is the primary population at risk for SAGN [26, 29–31].
2. In SAGN, the infection is frequently ongoing at the time the glomerulonephritis develops; thus, timely detection and treatment of the infection is most important since these infections are not self-limiting [32, 33]. In fact, typically the infection is persistent and difficult to treat, such as infected foot ulcers in diabetic patients, endocarditis, and osteomyelitis. Effective treatment usually requires early diagnosis and treatment with appropriate antibiotics possibly for a prolonged period of time.
3. Clinical presentation is variable, and in some cases the clinical picture is confounded by lack of obvious signs of an active infection. In such cases, patients may present with nonspecific signs and symptoms such as worsening hypertension, lower extremity edema, fatigue, and renal dysfunction, and the possibility of an occult infection is only raised after review of a kidney biopsy that shows features suspicious for SAGN [32].
4. By kidney biopsy findings alone, SAGN can be difficult to differentiate from IgA nephropathy and Henoch–Schönlein purpura (HSP) [11, 34–38]. However, distinction is critical because of treatment implications since treating SAGN with immunosuppressive therapy, including corticosteroids, is considered contraindicated in most instances due to the risk of sepsis [14, 34].

Epidemiology: Incidence and Demographics

The exact incidence of SAGN is difficult to estimate. At The Ohio State University Wexner Medical Center, we identified 78 cases of culture-proven SAGN out of a total of 9500 native kidney biopsies from January 2004 to April 2016 [39]. Thus, our data show that SAGN is infrequent (0.8% of native kidney biopsies); however, the true incidence is probably higher for a variety of reasons. One reason is that microbiological culture results are often delayed and unavailable at the time of the kidney biopsy. In fact, we found at least 30 additional kidney biopsies in our records with histologic and clinical findings highly suspicious for SAGN, but the cases were not included in our cohort since definitive culture results were not available. Additionally, incidence is difficult to define since many of the patients are treated early and empirically with antibiotics, which can result in subsequent negative cultures. Lastly, in many cases, the patient has an "occult" infection that is not clinically apparent; thus, evaluation for an underlying infection is delayed.

Similarly, other studies have reported an overall relatively low incidence of infection-associated glomerulonephritis in adults. Nasr et al. [20] identified five cases of IgA-dominant SAGN out of 4600 biopsy samples (0.1%) between 2000 and 2002. In a subsequent study, Nasr et al. [26] identified 93 cases (out of 10,080 biopsies; 0.9%) of "postinfectious" glomerulonephritis in elderly patients (great than or equal to 65 years) over a period of eleven years from 2000 to 2010. In this study, staphylococcal (50/109) as well as non-staphylococcal, including Streptococcus, Pneumococcus, Pseudomonas, and Enterococcus, infections were included. In 34% of the patients the infectious agent was unknown. In a

report by Haas et al. [22], of the 6334 renal biopsies examined over a period of 4 years (2004–2007), 13 (0.2%) showed IgA-dominant infection-associated glomerulonephritis. Documented staphylococcal infection was present in 6 of 13 cases. Worawichawong et al. [23] reported an incidence of 0.8% (7 of 905) for IgA-dominant infection-associated glomerulonephritis, of which 4 of 7 had a proven underlying staphylococcal infection.

The majority of the patients with SAGN are older with a mean age of 55 ± 12 years; however, young adults with intravenous drug abuse are also a significant at risk group [39]. The age range in our cohort of 78 patients was 21–91 years. In our experience, men were affected more commonly than females (M:F ratio 3.5:1), and 95% of the patients were Caucasian with the remaining being African American or Asian. Rare case reports of SAGN in children also exist [40, 41].

Clinical Presentation and Laboratory Findings

Clinical and laboratory findings in our cohort of 78 patients with SAGN are listed in Table 2.1. SAGN is frequently seen in older patients with comorbidities such as long-standing diabetes mellitus, malignancy, severe trauma, recent surgery, indwelling catheter, chronic infections (including hepatitis C virus), and/or severe coronary artery disease requiring catheterization, bypass arterial grafting or stent placements. Intravenous drug abuse is also an important risk factor. In our study of 78 patients with SAGN, 32 (41%) had diabetes mellitus and 22 (28%) had hepatitis C virus infection. The association with hepatitis C virus infection may reflect the subset of patients that were intravenous drug abusers [39]. Although most patients with SAGN present with signs and symptoms indicative of an underlying infection, it is important to recognize that in some cases overt signs of infection may not be present. Patients may present with nonspecific symptoms such as worsening hypertension, increased swelling in lower extremities, fatigue, and/or poor appetite. Or perhaps the signs of an active infection are masked by other comorbidities such as congestive heart failure or diabetic complications. Sometimes the infection comes to attention only after the renal biopsy is performed for renal dysfunction [32]. According to the largest series from Japan, the average duration from detection of the infection to the glomerulonephritis is 5.4 weeks [10]. However, in patients with chronic open wounds such as cutaneous ulcers in diabetic patients or in surgical patients with open wounds, it can be difficult to determine when the infection started.

A variety of underlying infections have been described in patients with SAGN, including osteomyelitis [23], septic arthritis [3], discitis [15], pneumonia [6, 20], infected leg ulcers [17], skin infection, rectal abscess, other deep-seated abscesses, peritonitis, and pancreatitis [3, 7, 21] as well as unknown primary site of infection with positive blood cultures [7–9]. In our study of 78 patients with SAGN, 18 had endocarditis, 10 had bacteremia with unclear primary site of infection, 17 had osteomyelitis, one had septic arthritis, six had pneumonia, and 17 had an infected skin ulcer, most of which were diabetic patients [39]. The remaining ten patients had various other infections: post-surgical site infection, urinary tract infection, abdominal mesh infection, indwelling tunnel catheter infection, infected wounds related to motor vehicle accident, and deep-seated abscess (epidural abscess, scrotal abscess, and hip abscess). Five of the patients had multiple sites of infection at the same time, for example, endocarditis, pneumonia, and paraspinal abscess or pneumonia and abdominal abscess. In our experience, in diabetic patients with cutaneous ulcers, amputation, and/or gangrene, osteomyelitis can be an overlooked complication.

MRSA is the most frequently encountered infective organism in SAGN [3, 7–12]. In our study of 78 cases of SAGN, 42 patients had MRSA infection; 17 patients had MSSA infection; 3 patients had methicillin-resistant *Staphylococcus epidermidis* (MRSE); and 2 patients had methicillin-sensitive *Staphylococcus epidermidis* (MSSE) [39]. In the remaining patients, the exact speciation was not available (7 patients) or it was a mixed bacterial infection including

Table 2.1 Clinicopathologic characteristics of the 78 cases of culture positive Staphylococcal infection-associated glomerulonephritis from 2004 to 2016 at the Ohio State University Medical Center

Clinicopathologic features	*n*	%
Age (years)	55 ± 12.1 (21–91)	
Ethnicity		
Caucasian	74	95
African American	3	3.8
Asian	1	1.2
Gender		
Males	61	78
Females	17	22
Diabetes mellitus	32	41
ANCA positive	9/41	22
Hepatitis C positive	22	28
Staphylococcal strain		
MRSA	42	59
MSSA	17	27
MRSE	3	1.20
MSSE	2	1.20
Staph strain unknown	7	11
Mixed bacterial infection	7	9
Blood culture positive	39	50
Local wound culture positive	43	55
Both cultures positive	4	5
Low C3	19 of 64	30
Low C4	9 of 64	14
Both C3 and C4 low	9 of 64	14
Purpuric lower extremity skin rash	16	20.5
Nephrotic range proteinuria	35 of 73	48
Type and site of infection		
Endocarditis	18	21
Bacteremia	10	14
Osteomyelitis, septic arthritis	17	22
Leg ulcers, cellulitis	17	22
Pneumonia	6	8
Others	10	13
Infected abdominal mesh	1	1
Post-surgical site infection	1	1
Visceral abscess	6	8
Urinary tract infection	2	3

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Staphylococcus (7 patients). Positive blood cultures are commonly found with staphylococcal endocarditis infection. However, in other sites of infection, blood cultures are often negative. Culture studies from the actual site of infection tend to be more useful. Out of the 78 cases in our study, 38 (49%) had positive blood cultures, 43 (55%) had positive wound cultures, and 4 patients had both blood and wound cultures positive.

On physical exam, the patient's blood pressure is typically moderately increased. Additionally, a subset of patients with SAGN present with a purpuric skin rash mimicking HSP, also termed IgA vasculitis [11, 34–38]. In our study of 78 patients, 16 (21%) patients with SAGN had a purpuric lower extremity skin rash [39]. Of note, skin biopsies show a leukocytoclastic vasculitis with mild IgA deposits [34]. Given the similarities to HSP, this presentation is a potential diagnostic pitfall (see differential diagnosis section).

Regarding laboratory findings, the most common presentation is acute renal failure with increased serum creatinine, microscopic hematuria, and proteinuria. Proteinuria can be nephrotic range with reports of greater than 10 g/day. Eight of the ten patients described by Koyama et al. [8] had nephrotic range proteinuria at one point during their disease course. Nasr et al. [26] reported proteinuria in the majority of their cohort of elderly patients with postinfectious glomerulonephritis, which was commonly nephrotic range (43%) with full nephrotic syndrome in 26% of patients. Patients usually have an active urine sediment with numerous red blood cells. Gross hematuria is not very common but can occur. Rarely, SAGN can be associated with a positive cryoglobulin test. We previously reported a case of SAGN with IgA/IgG-containing cryoglobulin-like deposits with circulating cryoglobulins, raising the possibility of IgA/IgG mixed cryoglobulin deposits [21]. Serum complement levels (especially C3) may be decreased, but can be normal. Among our 78 patients, complement data was available for 64 patients, and of those low C3 levels were seen in 19 patients (30%) and low C4 levels were seen in 9 patients (14%) [39]. Nasr et al. [26] reported hypocomplementemia in up to 72% of the patients in their series. Low C3 is more common than low C4. Lastly, ANCA serologies can be positive in SAGN [39, 42–49]. SAGN with ANCA positivity are typically cases with underlying endocarditis; however, cases with other sites of infection have been identified [39]. Boils et al. [42] reported ANCA positivity in 28% (8 out of 29 patients tested) of patients with endocarditis-associated glomerulonephritis. ANCA specificities can be pANCA (myeloperoxidase), cANCA (proteinase-3), dual specificity with both pANCA and cANCA, or atypical ANCA without known specificity. In our cases of SAGN, 22% (9 of 41) of the patients tested for ANCA had positive serology [39].

Kidney Biopsy Findings

Light Microscopy

Glomerular lesions in SAGN are those of an immune complex-mediated glomerulonephritis, but histomorphology can be variable and nonspecific. The light microscopic findings are usually that of mesangioproliferative (mesangial hypercellularity without closure of the capillary loops) and/or endocapillary proliferative immune complex glomerulonephritis with or without crescents as shown in Fig. 2.1. In our series of 78 patients, mesangial proliferation was the most commonly seen glomerular lesion with or without segmental endocapillary proliferation [39]. The glomerular mesangial hypercellularity can vary from mild and segmental to prominent and diffuse [5–7]. Of note, the mesangial hypercellularity may in some cases be masked by nodular mesangial matrix expansion secondary to underlying diabetic glomerulosclerosis (Fig. 2.1c). Based on the literature review and our experience, the light microscopic appearance of the glomeruli, including the degree of glomerular hypercellularity, and the clinical activity do not show a good correlation.

Endocapillary hypercellularity was seen in 47/78 (60%) SAGN biopsies in our cohort

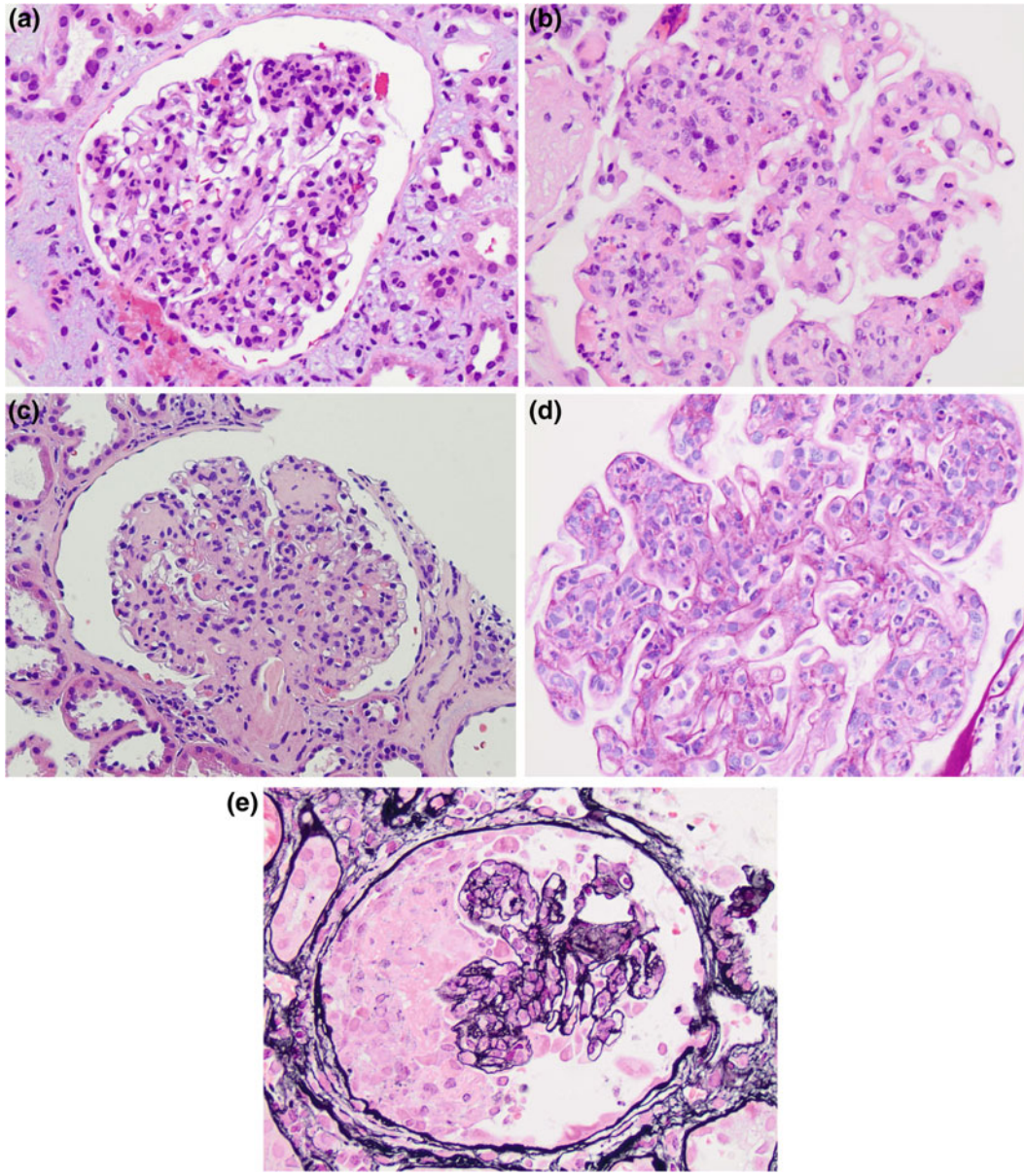

Fig. 2.1 Spectrum of light microscopic morphology of glomerular lesions in SAGN. **a** Mesangial hypercellularity (H&E 400×). **b** Mesangial and segmental endocapillary hypercellularity (H&E 400×). **c** Underlying nodular diabetic glomerulosclerosis with superimposed mesangial hypercellularity (H&E 200×). **d** Intracapillary hypercellularity with predominance of neutrophils "exudative lesion" (Periodic Acid Schiff 40×). **e** Crescent formation (Jones methenamine silver 400×)

(Table 2.2) [39]. Out of these 47 biopsies, 26 had diffuse endocapillary hypercellularity with polymorphonuclear leukocytes (exudative lesions) resembling PSAGN (Fig. 2.1d). Some biopsies can show a membranoproliferative glomerulonephritis (MPGN)-type pattern of injury with thickening and duplication of capillary loops [20–23, 26, 29]. Crescent formation can occur, and approximately one-third of the SAGN cases in our study had crescents, ranging

Table 2.2 Histologic features in biopsies with Staphylococcus infection-associated glomerulonephritis (n = 78)

Biopsy features	SAGN (n = 78)							Primary IgAN (n = 100) (%)	SAGN vs IgAN P value (Chi-square)
	Endocarditis n = 18	Bacteremia of unknown source n = 10	Osteomyelitis, septic arthritis n = 17	Infected skin ulcers n = 17	Pneumonia n = 6	Others n = 10	Total		
Biopsies with endocapillary hypercellularity	12	6	10	11	4	4	47 (60%); (Diffuse in 26/47)	10	<0.001
Biopsies with focal crescents/necrotizing lesions	7	2	7	2	4	5	27 (35%)	20	0.03
Biopsies with focal segmental glomerular sclerosis (FSGS)	0	0	0	1	1	0	2 (2.5%)	49	<0.001
Biopsies with subepithelial humps	4	3	4	7	2	4	24 (31%)	0	<0.001
Patients with diabetes mellitus	3 (17%)	2 (20%)	10 (59%)	13 (76%)	1 (17%)	3 (30%)	32 (41%)	8	<0.001
Biopsies with nodular diabetic glomerulosclerosis (nodular mesangial expansion)	0	2	5	6	1	2	16 (21%)	1	<0.001

Corresponding features in 100 biopsies of primary IgAN with p-values are shown for comparison. Number of patients with diabetes mellitus, and diabetic glomerulosclerosis are also shown

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from small subtle segmental necrotizing lesions to large cellular crescents [21–23, 26, 29, 39], Fig. 2.1e. In the study of infection-associated glomerulonephritis by Nasr et al., 37% (40/109) of the biopsies had crescents with the majority of cases showing focal crescent formation [26].

Admixed fibrocellular crescents may also be seen, but they are much less common given the acute nature of the disease. Typically in SAGN with crescents, the glomeruli without crescents will be hypercellular. However, we identified a few cases characterized by crescents and/or necrotizing glomerular lesions in which the uninvolved glomeruli were not hypercellular [39]. Additionally, these cases had only mild immune complex deposition, overall reminiscent of ANCA-associated glomerulonephritis, which is a potential diagnostic pitfall (see differential diagnosis section). We have not seen vasculitis or fibrinoid necrosis in arteries in SAGN even in the presence of glomerular necrotizing lesions. Rarely, there can be extensive endocapillary hypercellularity with glomerular "hyalin thrombi", reminiscent of cryoglobulinemia; however, the deposits in such cases lack microtubular substructure on ultrastructural examination.

Acute tubular necrosis (ATN) is seen in almost all cases, and red blood cell casts are frequently seen. Interstitial inflammation, although active-appearing, tends to be mild to moderate. Interstitial fibrosis and tubular atrophy depend on the underlying condition of the kidney. The tubulointerstitial findings do not always correlate with glomerular lesions. For example, there may be only mild mesangial hypercellularity without conspicuous endocapillary hypercellularity or crescents with numerous red blood cell casts and ATN. Vacular changes, if present, are secondary to underlying comorbidities (hypertension and diabetes mellitus).

Immunofluorescence Microscopy

SAGN characteristically contains IgA-dominant or codominant immune complex deposits [5–7, 11, 16, 17, 20–23, 29, 30, 32]. There is typically concurrent C3 staining and occasionally IgG (Fig. 2.2). This staining pattern is also seen in IgA nephropathy (Berger's disease) and HSP (IgA vasculitis), creating a potential diagnostic pitfall (see differential diagnosis section). The IgA immunofluorescence staining in SAGN is granular in appearance, but the intensity and extent can vary. The staining intensity can range from trace (less than 1+) to strong. The majority of biopsies in our cohort showed mild to moderate (1 to 2+) IgA and moderate to strong (2 to 3 +) C3 staining (Fig. 2.3) [39]. Of note, in a subset of cases of SAGN, the IgA staining is trace or negative (25% of SAGN biopsies in our

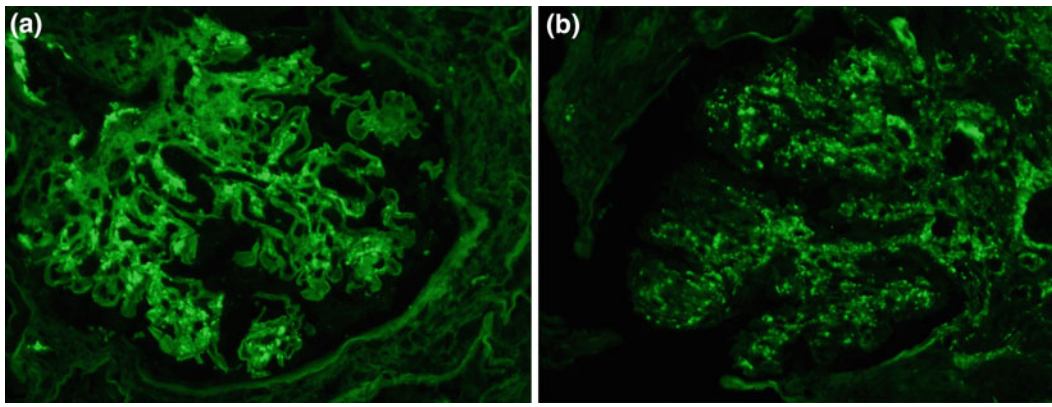

Fig. 2.2 50 year old male with diabetic foot ulcers and osteomyelitis requiring multiple debridements and amputations. He had multibacterial infection with MRSA, Pseudomonas and Enterococcus. Biopsy showed strong mesangial granular IgA staining (**a**) and strong granular C3 staining on IF (**b**) (400×)

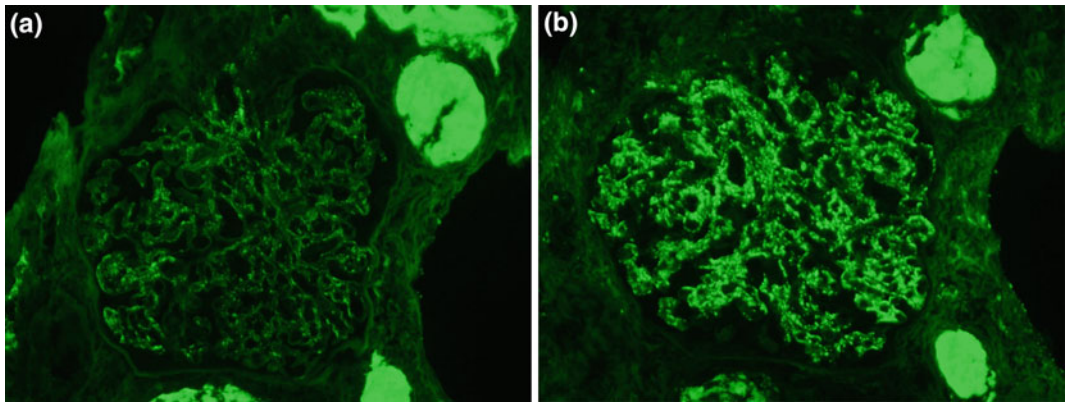

Fig. 2.3 27 year old female with intravenous heroin abuse and MRSA tricuspid endocarditis. Biopsy showed mild to moderate IgA (**a**) and strong C3 on IF (**b**) staining (400×). This is the most commonly seen IF pattern of staining in SAGN biopsies

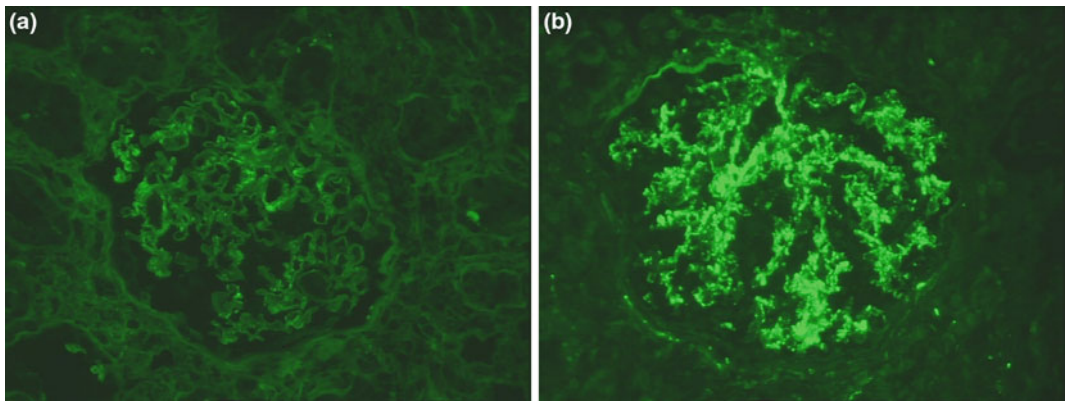

Fig. 2.4 63 year old male with MSSA scepticemia and endocarditis. Biopsy showed mild, segmental IgA (**a**) and strong C3 staining on IF (**b**); 400×

study) (Figs. 2.5 and 2.6). IgA staining is seen predominantly in the mesangium but can also be seen segmentally along the glomerular capillary loops. IgA staining can also vary from one glomerulus to another within the same biopsy. Thus, in the presence of appropriate clinical history and morphologic findings, trace or even absent IgA staining does not exclude the possibility of SAGN. Fortunately, C3 staining is almost always present even when IgA staining is weak. C3 staining alone was seen in 11/78 (14%) of the biopsies in our series [39]. C3 staining tends to be strong, coarsely granular, and abundant, similar to that seen in PSAGN (Figs. 2.2, 2.3 and 2.4); however, there are cases of SAGN with mild to absent C3 staining (14% of cases in our study) as depicted in Figs. 2.5 and 2.6. Early components of the complement cascade, such as C1q and C4, are usually not seen. Particularly in diabetic patients, IgA and C3 staining can be strong, but by electron microscopy the deposits appear scant and/or are seen only along peripheral capillary loops around the expanded nodular mesangium.

Codominant granular IgG staining is seen in 40% of the SAGN biopsies in our study [39]. In diabetic patients, there is frequently smudgy IgG staining in the mesangium or linear staining along the glomerular capillary loops, which is a nonspecific staining pattern seen in diabetic glomerulosclerosis. Mesangial granular fluorescence for lambda light chain tends to be stronger

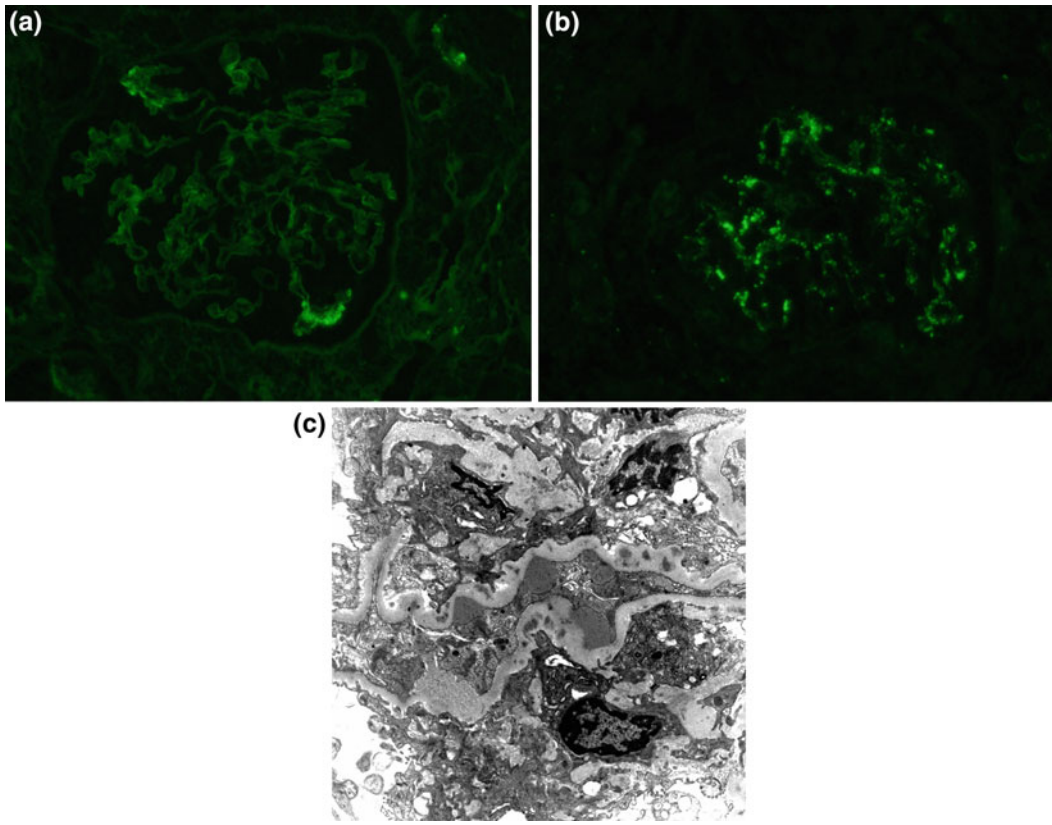

Fig. 2.5 38 year old female with MRSA endocarditis and bilateral pneumonia. Biopsy showed trace IgA staining (**a**); mild C3 staining on IF (**b**) (40×), and subepithelial humps on ultrastructural examination (**c**) (Uranyl acetate and lead citrate fixation, 10,000×)

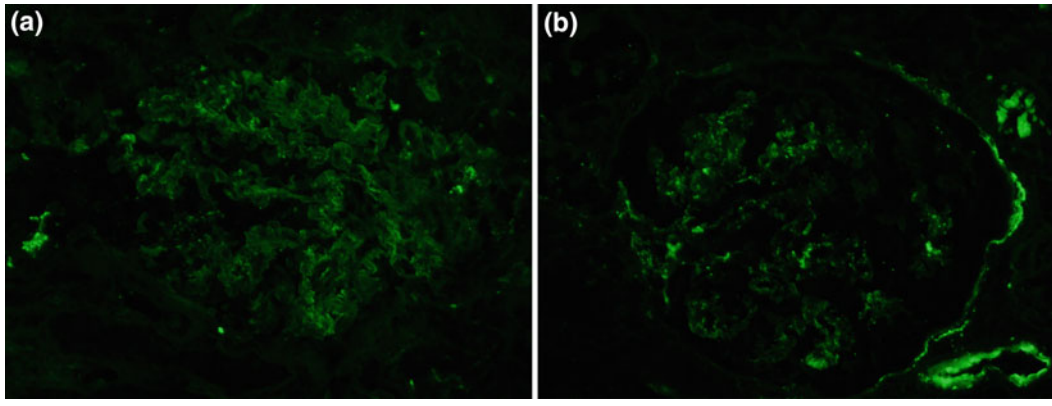

Fig. 2.6 83 year old diabetic female with left knee MSSA abscess. Biopsy showed trace IgA (**a**) and trace C3 staining on IF (**b**) (400×)

than for kappa light chain in most cases, which is similar to IgA nephropathy. Staining for IgM tends to be quite inconspicuous. Strong fibrinogen staining can help identify focal segmental necrotizing lesions or crescents. Rarely, there is concomitant weak staining for all three immunoreactants (IgG, IgA and C3), which we label as "pauci-immune pattern" (13% in our study) [39].

We encountered three biopsies containing globular cryoglobulin-like glomerular capillary hyaline thrombi that lacked microtubular substructure on electron microscopy. In two of these biopsies the deposits showed strong staining for IgA and C3 with no IgG, and in the third biopsy there was strong IgG and C3 staining with no IgA.

Electron Microscopy

The degree of electron-dense immune complex deposition is variable. Most commonly, there are electron-dense deposits in the mesangium (Fig. 2.7a); however, subepithelial and occasional subendothelial deposits can also occur (Fig. 2.7b) [13, 17, 21, 26, 29, 30]. Mesangial electron-dense deposits can vary from a few scattered deposits to several easily identified deposits. These may be accompanied by small scattered intramembranous and/or subendothelial deposits. Rarely, large intraluminal and/or subendothelial electron-dense deposits are present, resembling cryoglobulin; however, these deposits lack microtubular substructure [21]. "Humps", defined as large subepithelial deposits bulging outward beyond the boundary of the glomerular capillary basement membrane toward the Bowman's space, are characteristic of PSAGN but are also seen in SAGN (Fig. 2.5c) [29]. Some studies have suggested that the presence of "humps" be a requirement for the diagnosis of SAGN; however, in our 78 cases of SAGN, "humps" were detected in only 31% of the biopsies [39]. Thus, we feel that "humps" are not required for a diagnosis of SAGN, and that the absence of "humps" does not exclude the possibility of SAGN. Of note, "humps" are not specific to infection-associated glomerulonephritides since they can be seen in other glomerular diseases such as C3 glomerulopathy, proliferative glomerulonephritis with monoclonal

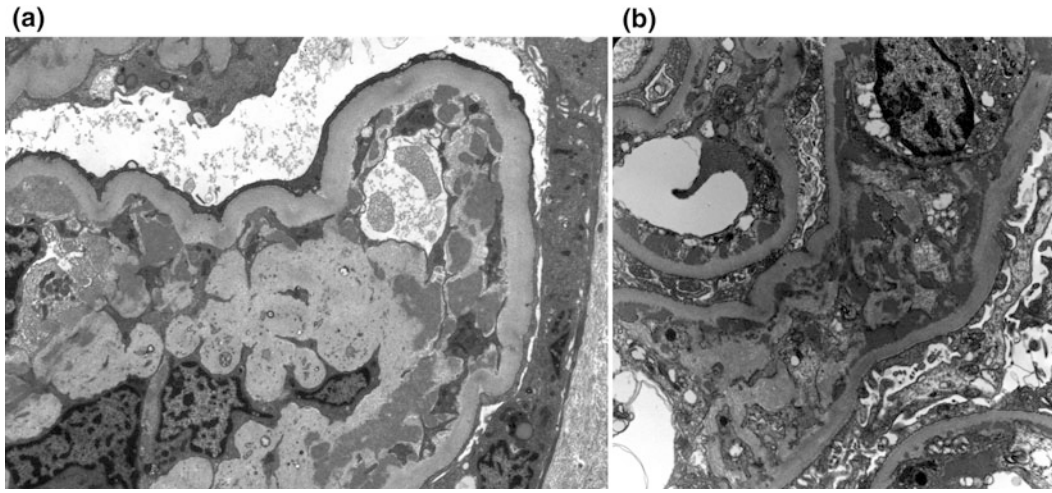

Fig. 2.7 **a** 56 year old male with diabetes mellitus and infected leg ulcer and osteomyelitis. Biopsy showed numerous mesangial electron-dense immune-type deposits on ultrastructural examination (uranyl acetate and lead citrate fixation, 20,000×). **b** 47 year old male with MRSA and Pseudomonas infection and motor vehicle accident and multiple wounds. Biopsy showed mesangial and subendothelial electron-dense immune-type deposits on ultrastructural examination (uranyl acetate and lead citrate fixation, 5000×)

IgG deposition disease and, rarely, in lupus nephritis. Also, subepithelial "humps" may be seen in infection-associated glomerulonephritis caused by other pathogens as well, such as Gram negative bacteria and non-bacterial pathogens [29].

Etiology and Pathogenesis

In the 1970s Sato et al. [7] detected *Staphylococcus aureus* antigens within mesangial immune complex deposits in a small number of cases of diffuse proliferative glomerulonephritis. These patients also had antibodies against staphylococcal antigens (antistaphylolysin antibodies) in the sera, prompting the proposal that *S. aureus* has a pathogenic role in a small subset of diffuse proliferative glomerulonephritides. One hypothesis is that staphylococcal enterotoxins, typically enterotoxin C, A, or toxic shock syndrome toxin-1, act as superantigens that stimulate proliferation of resting T cells, resulting in exuberant T cell activation and ultimately B cell activation and immune complex formation [5, 7, 9, 12, 50]. Superantigens activate T cells by binding directly to the MHC class II molecules on antigen-presenting cells and then binding to the T cell receptor (TCR) Vβ region of T cells irrespective of TCR antigen specificity. As a result of this nonspecific binding, there is activation of large subsets of polyclonal T cells leading to a "cytokine storm". Activated T cells then stimulate B cell proliferation and antibody production. In fact, in SAGN, polyclonal elevation of serum IgA and IgG, as well as circulating immune complexes, are frequently detected [5, 7, 11]. Hirayama et al. [36] studied six patients with "staphylococcus infection-induced HSP-like (IgA vasculitis) clinical syndrome with acute glomerulonephritis", which can be considered cases of SAGN. These six patients with SAGN demonstrated skewed TCR Vβ chain usage (Vβ 5.2, 5.3 and 8) compared to normal controls and to patients whose *S. aureus* infection had improved. Additionally, they reported increased serum levels of cytokines (interleukins 1β, 2, 6, 8, and tumor necrosis factor-alpha) in patients with SAGN compared to normal individuals, and the cytokine levels normalized with resolution of the staphylococcal infection.

Staphylococcal enterotoxins acting as superantigens are also implicated in other diseases such as staphylococcal toxic shock syndrome. Of note, staphylococcal antigens may also play a role in IgA nephropathy. Koyama et al. [15] found the *S. aureus* cell envelope antigen in 68% of renal biopsy specimens from patients with IgA nephropathy and proposed that this antigen is a pathogenetic factor in the development of IgA nephropathy. The same group from Japan developed an experimental model of IgA nephropathy in mice following biweekly immunization of the animals with antigens derived from *S. aureus* mixed with Freund's adjuvants [51]. Lastly, the comorbidities commonly present in patients with SAGN are likely contributing factors to pathogenesis by compromising the host immune response, which enables persistent infections/bacteremia and antigenemia that increases the likelihood of developing large antigen-antibody complexes that then accumulate in the glomerulus [26, 29, 30, 32].

Differential Diagnosis

Detailed clinical data are essential for a diagnosis of SAGN, and the main differential diagnostic considerations are:

1. IgA nephropathy.
2. Henoch–Schönlein purpura (HSP) or IgA vasculitis.
3. Post-streptococcal glomerulonephritis (PSAGN).
4. ANCA vasculitis.
5. Other immune complex glomerulonephritides including C3 glomerulopathy, lupus nephritis, cryoglobulinemic glomerulonephritis.
6. Warfarin-related nephropathy.

This is also shown in Table 2.3. Distinguishing between SAGN and idiopathic IgA nephropathy can be quite difficult using kidney biopsy findings alone since both entities

Table 2.3 Brief summary of renal biopsy findings in SAGN and differential diagnostic entities

Disease	Light microscopy	Direct immunofluorescence	Electron microscopy
Staphylococcus infection-associated glomerulonephritis (SAGN)	Endocapillary hypercellularity and crescents are more common than in IgAN. Crescents are less common than in ANCA. FSGS pattern is not seen	Variable intensity of IgA, but usually mild to moderate IgA and strong C3. Sometimes weak to negative IgA, IgG, and C3 ("pauci-immune")	Mesangial deposits most common. Few small subendothelial deposits can be seen. 31% of the cases show variable number of subepithelial humps
IgA nephropathy	Endocapillary hypercellularity and crescents are less frequent than in SAGN. FSGS pattern is more common than in SAGN	Strong IgA and mild to moderate C3	Mesangial deposits most common. No subepithelial humps and capillary loop deposits are uncommon
Henoch-Schönlein purpura (HSP) nephritis (rarely seen in adults)	Mesangial and segmental endocapillary hypercellularity with occasional crescents	Strong IgA and mild to moderate C3	Mesangial deposits most common. Few small subendothelial deposits can be seen
ANCA vasculitis	Crescents are defining lesions. Co-existence of fibrous, fibrocellular, and active crescents is common. No endocapillary hypercellularity. Necrotizing arterial lesions may be present (not seen in SAGN)	"Pauci-immune"	Few to absent immune complex deposits
Incidental mild IgA deposits (often in chronic liver disease)	Unremarkable glomeruli	Mild IgA without C3	No or few mesangial deposits
Post-streptococcal glomerulonephritis	Endocapillary hypercellularity (global, diffuse). Crescents are uncommon	Strong C3 with lumpy-bumpy coarse staining. IgA negative. IgG can be present	Subepithelial humps (numerous)
C3 glomerulonephritis (excluding dense-deposit disease)	Mesangial and endocapillary hypercellularity is common. Crescents are uncommon	Strong C3 and weak to absent IgG. Staining can be global or segmental involving mesangium and capillary loops. Lumpy-bumpy staining due to large C3 deposits may be seen. IgA is absent	Mesangial and capillary loop deposits. Humps may be seen
Cryoglobulinemic glomerulonephritis	Mesangioproliferative pattern common. Intracapillary inflammatory cells are monocytes, not PMNs. Hyaline thrombi may be present	Wide spectrum depending on the type of cryoglobulins, usually mixed IgG and IgM. IgA staining minimal if any	Microtubular substructure is frequently seen in type II. Type I commonly has crystalline/paracrystalline substructure with fibrils or microtubules. Deposits are randomly scattered and can be intracapillary, subendothelial, and/or mesangial

Reproduced with permission of Satoskar et al. [39]

frequently show mesangial hypercellularity with IgA and C3 dominant/codominant immune complex deposits. However, the clinical findings can be very helpful. A history of a staphylococcal infection with positive cultures or clinical features suspicious for an infection accompanied by acute renal failure, recent onset nephrotic range proteinuria, and/or hematuria with active urine sediment should raise the possibility of SAGN. IgA nephropathy is rarely associated with acute renal failure, unless it is crescentic IgA nephropathy or an advanced-stage IgA nephropathy with superimposed acute kidney injury due to other causes. In typical cases of progressive IgA nephropathy, the patients have a protracted, slowly progressive clinical course with long-standing microscopic hematuria, hypertension, and gradually worsening proteinuria. The "synpharyngitic" presentation of IgA nephropathy is characterized by episodic gross hematuria following upper respiratory tract infections (typically viral) and most of these patients lack acute kidney injury and nephrotic range proteinuria. If the kidney biopsy shows chronic glomerular lesions, such as segmental or global glomerular sclerosis, adhesions, or old fibrous crescents, IgA nephropathy can be favored since such chronic lesions are unusual in SAGN with the exception being when the chronic lesions are unrelated to SAGN (for example, glomerular changes of diabetic glomerulosclerosis). Endocapillary hypercellularity can be seen in both SAGN and IgA nephropathy, however, it is significantly more common in SAGN. In our study [39], it was present in 60% of the SAGN biopsies and 10% of the IgA nephropathy biopsies (Table 2.2). Focal segmental glomerular sclerosis (FSGS) lesions on the other hand are more frequently seen in IgA nephropathy (49% of the biopsies) as compared to SAGN (2.5% biopsies). Also, the intensity of IgA and C3 staining is different between SAGN and IgAN. Although there is a spectrum of staining in SAGN as mentioned previously, the IgA staining intensity tends to be mild to moderate (1+ to 2+) and C3 tends to be moderate to strong (2+ to 3+) in SAGN while in IgAN staining for IgA is more frequently moderate to strong (2+ to 3+) and C3 staining is mild to moderate (1+ to 2+) [39].

Since a subset of patients with SAGN develop a purpuric rash with leukocytoclastic vasculitis, it can be difficult to distinguish SAGN from HSP (IgA vasculitis) [18, 34–38]. Similar to IgA nephropathy, the kidney biopsy findings can be indistinguishable between the two entities. Again a detailed clinical history, particularly the presence of an underlying staphylococcal infection, is imperative. Also, since HSP is a rare disease in adults, in our experience, it is more common to see SAGN with purpuric skin lesions rather than HSP. Therefore, if an adult patient presents with symptoms of HSP vasculitis and a renal biopsy shows IgA-dominant glomerulonephritis, an underlying Staphylococcus infection should be excluded prior to initiation of immunosuppressive therapy since such treatment in the setting of an active infection can result in sepsis [11, 34–38].

It is important to recognize the differences between SAGN and PSAGN. In developed countries, the incidence of PSAGN has declined due to successful treatment of acute streptococcal infections with antibiotics; however, SAGN is becoming more common. One of the major differences in SAGN and PSAGN, other than the causative bacterial organism, is that in SAGN the infection is frequently ongoing at the time the glomerulonephritis develops. Conversely, in PSAGN the glomerulonephritis develops after the streptococcal infection has completely resolved, either spontaneously or after antibiotic treatment [32, 33]. Although the light microscopic and ultrastructural findings can be similar in SAGN and PSAGN, especially in cases of SAGN with "humps", the presence of IgA in the immune deposits would be unusual in PSAGN. The overall frequency of "humps" is much less in SAGN (only 31% in our cohort) compared to PSAGN, where such lesions are characteristic [39]. Lastly, there is general agreement that the renal prognosis in cases of "glomerulonephritis with active infection" is guarded in sharp contrast to the good prognosis associated with PSAGN in children [13, 21–23, 26, 29, 30].

SAGN can have crescents and/or segmental necrotizing glomerular lesions sometimes with very minimal immune complex deposition; thus,

pauci-immune or ANCA-associated crescentic and necrotizing glomerulonephritis can be included in the differential diagnosis [39, 52]. Furthermore, SAGN can be associated with positive ANCA serologies, particularly in cases with underlying endocarditis [39, 42–49]. Boils et al. [42] recently studied endocarditis-associated glomerulonephritis of which 53% were associated with *S. aureus* (23% Streptococcus species, 9% culture negative, and the remaining were associated with *Bartonella henselae*, *Coxiella burnetti*, *Cardiobacterium hominis*, or Gemella species). Crescents and/or segmental necrotizing lesions were seen in 53% of the kidney biopsies. Additionally, 28% of patients had a positive ANCA serology. In our case series of SAGN, 35% (27/78) of the biopsies had focal crescents and/or segmental necrotizing lesions [39]. Six of these 27 also showed a pauci-immune pattern by immunofluorescence and electron microscopic examination. One biopsy showed both crescents and a pauci-immune pattern accompanied by positive ANCA serology, thus closely mimicking ANCA-associated glomerulonephritis.

There have been similar reports of pauci-immune crescentic and necrotizing glomerulonephritis associated with staphylococcal infections [10, 15]. In fact, the possibility that *S. aureus* may play a role in the pathogenesis of ANCA-associated granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) has been proposed [24]. An additional confounding factor relevant to this differential diagnosis is that in 2–3% of kidney biopsies there is incidental, non-pathologic IgA staining; thus, it is possible, albeit infrequent, to have mild IgA staining in pauci-immune ANCA-associated crescentic and necrotizing glomerulonephritis. Of note, the definition of "pauci-immune" can differ slightly between pathologists. Our definition is weak to absent immunofluorescence staining for immunoglobulins (mainly IgG and IgA) and complement C3 in combination with scant to absent electron-dense immune-type deposits on ultrastructural examination. Although some may consider C3 staining alone in the absence of immunoglobulins as "pauci-immune" (described in the endocarditis chapter), we do not label such staining as "pauci-immune". In fact, 11 of our 78 cases of SAGN contained C3 staining alone. Additionally, rarely, there is discordance between the degree of immunofluorescence staining and deposition of immune-type deposits assessed by ultrastructural examination. In such cases, it is possible that the electron-dense deposits do not stain because of hidden epitopes.

Distinguishing between SAGN and ANCA-associated glomerulonephritis is crucial since immunosuppressive therapy used to treat ANCA-associated glomerulonephritis is contraindicated in the setting of an active *S. aureus* infection. After the infection is cleared, if renal dysfunction persists and there are active crescents seen in the biopsy, a cautious trial of corticosteroids is recommended by some, but this remains a controversial issue [53, 54]. It is therefore important to interpret the biopsy in light of a detailed clinical history. Also, if the biopsy shows distinct vasculitis and/or fibrinoid necrosis of the arteries, then ANCA vasculitis is favored even if there is mild IgA staining or a few immune-type deposits present. Also, the uninvolved glomeruli tend to be hypercellular in SAGN but not so in ANCA-associated glomerulonephritis.

Since SAGN can have a membranoproliferative glomerulonephritis (MPGN)-type pattern of glomerular injury with immune complex deposition, other immune complex glomerulonephritides with MPGN-type morphology can enter the differential diagnosis, including C3 glomerulopathy, lupus nephritis, and cryoglobulinemic glomerulonephritis. C3 glomerulopathy is characterized by C3 deposits with absent immunoglobulin components, thus, may be confused with cases of SAGN with absent or weak IgA and strong C3 staining. Lupus nephritis typically has a "full house" staining pattern with more IgG, IgM, and C1q staining compared to SAGN. Lastly, hyaline thrombi resembling cryoglobulin deposits can rarely be seen in association with bacterial infections, and the patients may have mixed type III cryoglobulinemia. We identified three biopsies in our

series of 78 cases of SAGN that contained large cryoglobulin-like immune complex deposits [21]. These however did not show microtubular substructure as typically seen in cryoglobulinemic glomerulonephritis. Fortunately, in most instances SAGN can be differentiated from other MPGN-type immune complex glomerulonephritides using a combination of kidney biopsy findings, a detailed clinical history (presence of infection, systemic lupus erythematosus, Hepatitis C virus infection, etc.), and thorough laboratory work-up (autoimmune serologies, cryoglobulin testing, rheumatoid factor level, C3 and C4 complement levels, culture results, etc.).

SAGN can be associated with prominent intratubular red blood cells and red blood cell casts; thus, in patients on anticoagulation therapy, warfarin-related nephropathy can be included within the differential diagnosis. If a biopsy from an anticoagulated patient shows prominent ATN and numerous red blood cell casts, but only mild mesangial hypercellularity and a few immune-type deposits, a diagnosis of warfarin-related nephropathy may be rendered when SAGN is the true cause of the renal dysfunction. SAGN with concurrent warfarin-related nephropathy can be difficult to definitively diagnose. Of note, the risk of warfarin-related nephropathy is greater in the presence of a glomerular disease. In such cases, the possibility of concomitant warfarin-related nephropathy should be discussed with the nephrologist and the coagulation parameters should be closely monitored.

Clinical Course and Outcome

The prognosis in adults with SAGN is guarded since a significant proportion of adults does not recover and have persistent renal dysfunction or progress to end-stage renal disease. Persistent renal dysfunction develops in 8–54% of patients and progression to end-stage renal disease in 4–33% of patients as described in several case series [21, 26, 29, 30, 55, 56]. Poor prognostic indicators in adults include older age, higher serum creatinine at biopsy, tubulointerstitial scarring, and presence of underlying debilitating conditions [21–23, 26, 29]. The goal of treatment should be eradication of the underlying *S. aureus* infection and management of comorbidities that may be present, such as diabetes, hypertension, congestive heart failure, and surgical complications [29, 56, 57]. Regarding treatment of the infection, appropriate antibiotics are crucial and surgical debridement of the infected wound or abscess drainage may also be necessary [14, 58]. In severe cases of diabetes, amputation of the infected lower extremity may be required to bring the infection under control. Of note, some antibiotics commonly used to treat staphylococcal infections, such as vancomycin, can be nephrotoxic, causing acute tubular injury with or without interstitial nephritis. In such instances, it can be difficult to determine the cause of persistent renal dysfunction. Therapeutic monitoring of drug levels, particularly vancomycin levels, may be helpful in the evaluation for drug-induced renal dysfunction.

The role of immunosuppressive therapy, including corticosteroids, in adult patients with ongoing SAGN is highly controversial and considered contraindicated in most instances. There are no randomized prospective clinical trials on the role of corticosteroids in this condition. The available data are based on retrospective studies. Corticosteroid use has been reported in patients with an accompanying leukocytoclastic vasculitic skin rash mimicking HSP (IgA vasculitis) with some reports of resolution of the rash following steroid therapy [34–37]. Also, there are a few case reports that describe good results with the use of corticosteroids in the treatment of infection-associated glomerulonephritis in adults [53, 54]. However, there are also studies that show no improvement or worsening renal function as well as the development of sepsis in patients with SAGN treated with corticosteroids [34]. None of the case series with statistical analyses have found a significant benefit on outcome with the administration of corticosteroids [21, 26, 29, 30, 34, 55, 56]. Thus, based on the absence of any proven benefit and the

potential risk of sepsis, immunosuppressive therapy, including corticosteroids, is generally not recommended in adults with SAGN. Treatment of SAGN and other infection–associated glomerulonephritides is discussed in detail in Chap. 5.

Staphylococcus Species—Microbiological and Immunological Aspects

Although there are more than 30 species in the genus Staphylococcus, *S. aureus* and *S. epidermidis* are responsible for the majority of staphylococcal infections in man [59]. *S. epidermidis* is a commensal organism of the skin and has emerged as a potential pathogen primarily due to the use of implantable and indwelling medical devices such as central venous catheters. *S. aureus*, the more pathogenic of the two species, is a commensal organism colonizing the moist squamous epithelium of the anterior nares as well as the nasopharynx, groin, and perineum [60, 61]. Permanent and transient colonization of *S. aureus* is noted in approximately 20% and 60% of the population, respectively [60]. *S. aureus* is exposed to innate and induced immune responses when it colonizes the nasal mucosa, and the immune status as well as other host factors play an important role in nasal colonization [59]. For example, polymorphisms in the glucocorticoid receptor, C-reactive protein, mannose binding lectin, complement factor H, and interleukin 4 gene promoter (which influences mucin secretion) have all been associated with increased or decreased carriage rates [59]. It is thought that *S. aureus* has intrinsic pathogenic potential due to the acquisition of virulence factors and immune avoidance mechanisms necessary to overcome the innate and induced immune responses present in the nasal-associated lymphoid tissue of the nares [59]. *S. aureus* can cause mild to severe superficial skin and soft tissue infections such as abscesses or impetigo as well as serious invasive infections, including endocarditis, bacteremia, pneumonia, osteomyelitis, septic arthritis, among others [27, 28]. Colonization by *S. aureus* is a risk factor for invasive disease both in the hospital and the community [62–64]. Particularly in hospitalized patients, indwelling medical devices, compromised immune system, and/or postoperative status increases risk of infection [28, 65]. In the community setting, poor personal hygiene and a compromised skin barrier likely play important roles in developing *S. aureus* infections. Transmission of *S. aureus* from an infected to an uninfected person can occur through direct skin-to-skin contact or through contaminated fomites in public and household settings [66].

Staphylococcus aureus has been implicated in human infections since prehistoric times [67]. Penicillin, introduced in the 1940s, was the first antimicrobial drug effective against staphylococcal infections; however, *S. aureus* developed penicillin resistance within a few months via a plasmid-encoded beta-lactamase gene capable of cleaving the beta-lactam ring of penicillin [68–71]. Methicillin, a derivative of penicillin resistant to cleavage by beta-lactamase, was introduced in 1959; however, within 2 years, methicillin-resistant strains (MRSA) were identified [28]. Methicillin-resistant strains acquired the mobile genetic element, staphylococcal chromosome cassette mec [SCCmec], which harbors the *mecA* gene that encodes a penicillin-binding protein with reduced affinity toward methicillin [72–74]. Thus, there is less efficient binding of methicillin to the bacterium, ultimately resulting in reduced capacity to inhibit bacterial cell-wall synthesis. Of note, according to the Centers for Disease Control and Prevention, the definition of methicillin-resistance includes resistance of *S. aureus* not only to methicillin but also other related and more commonly used antibiotics such as oxacillin and amoxicillin [28]. Furthermore, the *mecA* gene provides resistance to many beta-lactam antibiotics, including penicillin, and SCCmec elements may also contain genes enabling resistance to a variety of non-beta-lactam antibiotics. Beta-lactams are the typical first line antibiotic in the treatment of staphylococcal infections. However, given the acquisition of resistance to these drugs, treatment of *S. aureus* infection relies increasingly on non-beta-lactam-based

antibiotics [75]. Although vancomycin is most commonly used in the treatment of MRSA infection, other drugs, namely linezolid, daptomycin, and tigecycline, are also effective against MRSA infections [76, 77]. Unfortunately, strains of *S. aureus* resistant to these drugs have been reported [78–81].

MRSA is the most prominent cause of nosocomial infections caused by a single bacterial pathogen in the USA, and it is estimated that MRSA causes approximately 44% of all hospital-associated infections [28, 82]. MRSA infections were largely health-care associated (HA-MRSA) until the late 1990s, when otherwise healthy individuals in the community began to develop MRSA infections reaching epidemic proportions (community-acquired MRSA [CA-MRSA]) [83]. HA-MRSA infection is defined by the onset of infection occurring after 48 hours of hospital admission while the onset of CA-MRSA infections is within 48 hours of admission to the hospital with no previous history of hospitalization in the past year [84]. While specific strains are typically associated with either HA-MRSA or CA-MRSA infections, the CA-/HA-MRSA definition is clinical, not microbiological, since strains have successfully transferred between the two settings. For example, the highly pathogenic CA-MRSA strain USA300 was first isolated in the year 2000 as a community-associated strain, but has since spread across the globe and represents a major threat in hospital and long-term care facilities as well as the community setting [85–89].

The marked virulence of *S. aureus* is largely due to:

- Resistance to a wide spectrum of antimicrobial agents
- Ability to evade host immunity.

Antimicrobial Resistance

The main determinants of resistance include the plasmid-encoded beta-lactamase gene and the *mecA* gene encoded on the mobile genetic element SCCmec, as discussed previously. Other molecular determinants of resistance and well as virulence are encoded on other mobile genetic elements; thus, the presence of these factors is highly strain-dependent [28].

Immune Evasion

This is an extensive topic discussed in detail in several review articles [65, 90]. It is beyond the scope of this book to describe the immune evasive mechanism of Staphylococcus in detail, but the important points will be highlighted.

1. Efficient adhesion and colonization

Staphylococcus aureus expresses surface proteins that promote adhesion to damaged tissue and to the surface squamous epithelium [91]. Several surface proteins have been found that promote adhesion of *S. aureus* to squamous cells in vitro. Critical surface proteins include clumping factor B (ClfB) and iron-regulated surface determinant (Isd) [59]. ClfB can bind to fibrinogen as well as to cytokeratin 10, which is exposed on the surface of squamous cells [92]. Isd is involved in iron acquisition and promotes survival in the iron-deficient environment of the nasal mucosa and skin as well as promotes adhesion to squamous epithelium [59, 93].

There are a few features of certain staphylococcal species that promote survival on the skin. One is the presence of the arginine catabolic mobile element (ACME) that contains a cluster of genes encoding enzymes that produce ammonia that is thought to aid pH homeostasis in the acid environment of the skin [94]. ACME is present in certain strains of *S. epidermidis* and *S. aureus*. Additionally, *S. aureus* produces Isd that essentially protects the bacteria from bactericidal fatty acids present in the sebum of the skin [95].

Staphylococcus epidermidis is normally a harmless commensal of the human skin, however, can be pathogenic due to its ability to colonize implanted medical devices and form biofilms [59]. Biofilms are multilayered, high-density structures that protect bacteria from

antibiotics and the human immune system. Initially, *S. epidermidis* adheres to the biomaterial by surface-associated proteins such as major autolysis AtlE or fibrinogen-binding proteins Fbe/SdrG. *S. aureus* can also form biofilms via binding to the biomaterial by surface-associated proteins such as clumping factor A (ClfA) and fibronectin-binding proteins. Multilayered biofilms are typically help together by the charged polymer polysaccharide intercellular adhesion (PIA) [96].

Staphylococcus aureus can bind to resting platelets and activate them resulting in platelet aggregation [97]. The bacteria can then grow in platelet-fibrin thrombi where they evade detection by neutrophils. Fibronectin-binding proteins and ClfA are bacterial proteins involved. This process is thought to be an important factor in endovascular infections/infective endocarditis.

2. Inhibition of neutrophil migration and resistance to phagocytosis

Staphylococcus aureus has developed mechanisms that compromise innate, humoral and cell-mediated immunity [65]. *S. aureus* can secrete several small proteins that interfere with different stages of neutrophil recruitment: staphylococcal superantigen-like (SLL) 5 and SSL11 inhibit neutrophil rolling on activated endothelial cells; MHC class II analog protein (Map) inhibits neutrophil transmigration through endothelial cells (diapedesis); and chemotaxis inhibitory protein of staphylococci (CHIPS) and formyl peptide receptor like-1 inhibitory protein (FLIPr) inhibit chemotactic migration of neutrophils to the site of infection [59]. Efficient phagocytosis of bacteria by neutrophils and macrophages requires recognition of bound complement and antibody. *S. aureus* can interfere with the complement pathways and antibody deposition, ultimately preventing opsonization and phagocytosis [59]. Staphylococcus complement inhibitor (SCIN) essentially inhibits complement activation and subsequent phagocytosis by preventing production of the C3a chemoattractant peptide and opsonin C3b peptide [98]. *S. aureus* can also reduce phagocytosis by cleaving/inactivating complement factor C3b as well as IgG molecules that are bound to the surface of opsonized bacterial cells by secreting staphylokinase, a plasminogen activator protein [99]. Additionally, *S. aureus* can activate factor I, which is a natural downregulator of complement fixation [100]. Other *S. aureus* proteins, such as Protein A, clumping factor A, and extracellular fibrinogen-binding protein (Efb), also have antiphagocytic effects via various mechanisms [59, 65, 101]. Lastly, the capsule of certain staphylococcal species appears to have anti-opsonic properties, possibly related to the particular capsular polysaccharide as well as PIA.

3. Survival inside the host immune cell

Staphylococcus aureus has multiple mechanisms that enable it to survive in phagosomes [59]. The organism can modify its cell wall teichoic acid and membrane lipids, reducing the surface negative charge and ultimately diminishing the effectiveness of cationic antimicrobial defensin peptides that are secreted into the phagosomes. Secreted factors such as staphylokinase and metalloprotease aureolysin as well as PIA also likely contribute to the neutralization of antimicrobial peptides [102–104]. Furthermore, within the phagosome, *S. aureus* can neutralize reactive oxygen intermediates formed during the respiratory burst as well as nitric oxide radicals [59]. The bacterial cell wall peptidoglycan is also resistant to lysozyme, a bactericidal protein important in the innate immune response [105]. Not only can *S. aureus* survive in neutrophils and macrophages, there is evidence that it can invade and survive within nonprofessional phagocytes such as endothelial and epithelial cells, allowing escape from host immunity [59].

4. Toxins produced by *S. aureus*

Several cytolytic toxins are produced by *S. aureus* that target and damage the cytoplasmic membranes of host cells [59]. Some of the well-known toxins include α-toxin, γ-toxin (γ-hemolysin), Panton–Valentine leukocidin

(PVL), and leukocidin E/D. The γ-toxin can lyse both erythrocytes and leukocytes while PVL targets only leukocytes. *S. aureus* can secrete several cytolytic peptides that at high concentrations can cause neutrophil lysis. Furthermore, *S. aureus* can secrete extracellular enzymes, including various proteases, hyaluronidases, lipases and nucleases, which result in tissue destruction and host cell lysis as well as facilitate bacterial spread [65].

5. Immunomodulatory molecules, including superantigens

Staphylococcus aureus can secrete powerful T cell mitogens, termed superantigens, resulting in altered T cell function associated with exuberant T cell activation and proliferation as well as release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin (IL)-beta, and T cell mediators, such as IL-2 [59, 106]. Furthermore, superantigen expression can prevent the development of a normal immune response. Superantigens bind to the MHC Class II molecule on the surface of antigen-presenting cells outside of the peptide-binding groove region and then bind to the T cell receptor (TCR) of T helper cells via the variable region of the TCR β-chain [106]. Binding occurs without the need for the MHC Class II molecule to present an antigenic peptide to a suitable T cell. Each superantigen recognizes a specific subset of TCR Vβ chains and therefore has a characteristic Vβ signature. Up to 30% of T cells can become activated in extreme cases leading to very high levels of cytokines causing toxic shock syndrome [59, 107]. Superantigens prevent normal immune response since in the presence of superantigens antigen-specific T cells fail to proliferate in response to antigens that are presented normally by MHC Class II [107, 108]. This superantigen-induced anergy likely contributes to the diminished targeted antibody response and compromised immunological memory associated with *S. aureus* infections [59, 65]. Of note, protein A, which has antiphagocytic effects, also has immunomodulatory properties by promoting depletion of antibody secreting B cells in the spleen and bone marrow [109].

In summary, staphylococcal organisms, particularly *S. aureus*, can evade human immune responses through a variety of mechanisms directed toward both innate and acquired immune defenses. Some of them are summarized below.

1. Efficient colonization of skin and mucosal surfaces and formation of biofilms that promote bacterial survival.
2. Binding to and activating platelets to form platelet-fibrin thrombi with subsequent neutrophil evasion, particularly important in the pathogenesis of endocarditis.
3. Interfere with neutrophil recruitment.
4. Resist phagocytosis through surface and secreted anti-opsonic proteins in addition to the polysaccharide capsule.
5. Intracellular survival in the phagosome by neutralizing antimicrobial peptides and reactive oxygen species.
6. Secretion of cytolytic toxins that damage cytoplasmic membranes of immune cells.
7. Immunomodulatory molecules can result in altered T and B cell functions, ultimately preventing the development of normal cell-mediated and humoral immune responses to infection.

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Glomerulonephritis Associated with Other Bacterial Infections

3

Neeraja Kambham and Megan Troxell

Introduction

Although *Streptococcus* and *Staphylococcus* are the most common pathogens associated with glomerulonephritis, several other bacteria (also viruses and parasites) can trigger similar immune-mediated kidney injury. It is estimated that approximately a quarter of infection-associated glomerulonephritis in adults is due to *Streptococcus* and another quarter due to *Staphylococcus* [1]. Other responsible bacterial infections include *Pneumococcus*, gram-negative rods, gram-positive rods, *Mycobacterium,* etc., although most are documented in either isolated case reports or small case series. Nonstreptococcal glomerulonephritis, especially in developed countries, is a disease of the elderly with comorbidities such as alcoholism, diabetes mellitus, malignancy, intravenous drug use, and HIV infection [1–3]. If often affects males, typically in the fifth decade of life. Caucasians and Asians appear to be more commonly affected in the nonpediatric age group, although all ethnic groups are at risk [4].

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Clinical Presentation

A clinical history of infection can be elicited in most patients, but more than a third lack evidence of infection [1, 2, 5]. The common sites of infections include upper respiratory tract infections, lung, skin, and heart valves with less-frequent reports of associated osteomyelitis, urinary tract infections, deep-seated abscesses, infected vascular Dacron prosthesis, and infected ventriculoperitoneal shunts [6, 7]. In typical cases, the acute infectious process usually comes to immediate clinical attention and the onset of renal manifestations range from 2 to 4 weeks. However, "postinfectious" glomerulonephritis may be unsuspected in the setting of insidious chronic infections with symptoms that range from none to mild and nonspecific. Quite often, the infection in an elderly person comes to light at the time of renal biopsy or only *after* a biopsy diagnosis of "postinfectious" glomerulonephritis prompts exhaustive investigation [7–9]. In this context, infection-associated GN appears to be a better terminology than postinfectious glomerulonephritis [4].

The usual clinical presentation of infection-associated glomerulonephritis involves mild proteinuria and hematuria, associated with new onset hypertension and sometimes oliguria [1, 2, 5, 7]. Although this acute nephritic syndrome presentation is more common, some patients have nephrotic range proteinuria or nephrotic syndrome. Low serum complement levels are seen in 35–80% of adults and 90% of

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children with postinfectious glomerulonephritis [1, 2, 5, 7]. Low C3 levels are more frequently encountered than low C4. However, normal complement levels should not deter a clinical or a pathological diagnosis of infection-associated glomerulonephritis. Circulating immune complexes have been detected in many infections. Their disappearance in the blood correlates with treatment of the corresponding infection, but these are not routinely investigated for clinical management. On occasion, rheumatoid factor is positive and serum cryoglobulins may be detected, especially in infective endocarditis and shunt nephritis [2, 7].

Light Microscopy

The renal biopsy findings are typically those of proliferative glomerulonephritis [1, 7] (Fig. 3.1). Diffuse proliferative glomerulonephritis is the most common pattern of glomerular injury with endocapillary proliferation and inflammatory cells occluding the capillary lumens (Table 3.1). The glomerular inflammatory infiltrate can be rich in neutrophils, leading to "exudative" glomerulonephritis [2, 10, 11] (Fig. 3.1a). Monocytes and macrophages may predominate in later phases, and are particularly prominent in infection-related cryoglobulinemic glomerulonephritis (type II or III) [12]. Scattered hump-shaped deposits can occasionally be seen on silver and trichrome stains. Depending on the severity of infection and the time internal between onset of symptoms and the kidney biopsy, milder glomerular changes such as focal proliferation and mesangioproliferative changes are encountered [2, 10, 11] (Fig. 3.1d). Crescents, when found, are often small and focal [1, 7]. However, rare cases of crescentic glomerulonephritis have also been reported. Chronic infections such as shunt nephritis result in membranoproliferative glomerulonephritis with lobular accentuation, mesangial proliferation, and basement membrane double contours [13–15] (Fig. 3.1g). Membranoproliferative glomerulonephritis has also been reported with pneumonia, deep-seated infections, and osteomyelitis. Visualization of deposits by light microscopy is usually a feature of cryoglobulinemic glomerulonephritis with large subendothelial deposits, intraluminal deposits, and intracellular deposits within macrophages [16, 17]. Variable degrees of focal segmental and global glomerulosclerosis are seen as a consequence of chronic glomerulonephritis (Fig. 3.1h), but in an elderly patient, chronic changes also represent underlying renal disease. The interstitial inflammation is predominantly localized to areas of tubular atrophy and interstitial fibrosis, but can be related to chronic infection or other causes. There are no specific infection-associated vascular changes, but underlying hypertensive arteriosclerosis may be evident. Transmural vasculitis and necrosis may be present in cryoglobulinemic glomerulonephritis [16, 17].

Immunofluorescence Microscopy

As with streptococcal infections, C3-dominant deposits are the defining feature of all postinfectious glomerulonephritis (Fig. 3.1b). Immunofluorescence with IgG is also positive in infection-associated glomerulonephritis and isolated C3 is seen in less than a third of the patients, especially in the resolving phase [7, 18]. In most cases, IgM and IgA staining is minimal or absent; however, in the cases of cryoglobulinemic glomerulonephritis and IgA-dominant postinfectious glomerulonephritis, respectively, these immunoglobulins are abundant. Underlying diabetic nephropathy manifests as linear glomerular and tubular basement membrane staining with IgG and albumin. Staining for kappa and lambda light chains is usually absent in infection-associated glomerulonephritis. A renal biopsy performed early in the course of disease has a "starry sky" pattern with C3 and IgG capillary wall deposits, while a late biopsy in an acute self-limited infection with resolving glomerulonephritis reveals mesangial deposits with mostly C3 staining (Fig. 3.1e). Bulky capillary wall deposits manifest as "garland" pattern on immunofluorescence [2, 11].

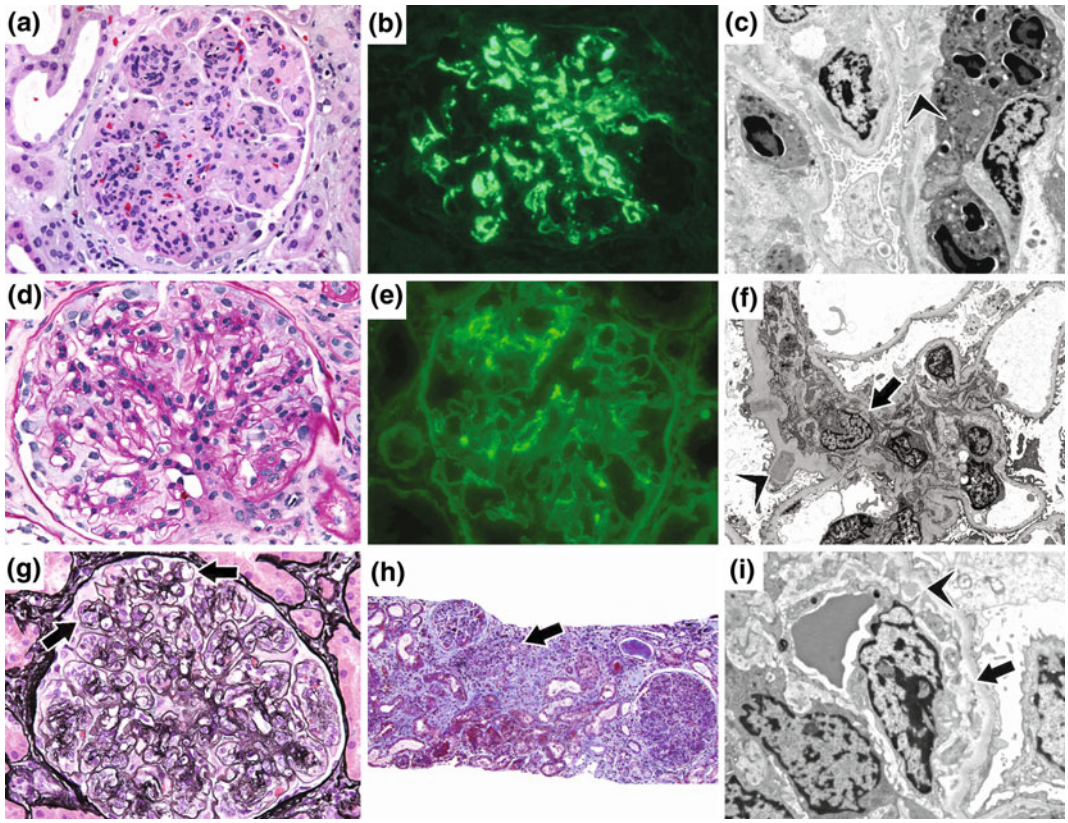

Fig. 3.1 Histological spectrum in infection-associated glomerulonephritis. **a–c** Infection-associated exudative glomerulonephritis with numerous infiltrating neutrophils is usually associated with acute presentation of nephritic syndrome (**a** H&E, ×400). The glomerular deposits are C3-dominant and are often bulky, involving the mesangium and capillary walls (**b** C3, ×400). Ultrastructural examination confirms the presence of small subepithelial deposits (*arrow head*) in addition to mesangial and subendothelial deposits (**c** ×7500). **d–f** Resolving phase of postinfectious glomerulonephritis is often associated with mild clinical disease and histological changes. Segmental mesangial hypercellularity is seen (**d** PAS, ×400) and the C3 deposits are weak and segmental (**e** C3, ×400). Electron microscopy shows mesangial deposits (*arrow*) along with occasional subepithelial humps (*arrow head*) (**f** ×3000). **g–i** Membranoproliferative glomerulonephritis is often a feature of chronic infection-associated immunological injury to the kidney. Lobular accentuation of glomeruli is present along with basement membrane double contours (*arrow*) (**g** JMS, ×400). The renal cortical tissue shows patchy tubular atrophy and interstitial fibrosis (*arrow*) in a young patient without preexisting disease, reflective of chronic injury (**h** trichrome, ×100). Electron microscopy confirms the presence of basement membrane reduplication (*arrow*) along with subendothelial deposits (*arrow head*) (**i** ×5000).

Electron Microscopy

Ultrastructural examination characteristically shows large subepithelial deposits that are fewer per capillary loop than membranous nephropathy and have a special predilection for mesangial "notch" (glomerular basement membrane reflection over the mesangium) (Fig. 3.1c, f). These "humps" or "bell shaped" deposits also lack associated glomerular basement membrane remodeling and are overlaid by podocyte basement membrane. Mesangial and subendothelial deposits are typically small and few [1, 2, 5, 7, 18] (Fig. 3.1c, f). However, mesangial deposits may predominate in chronic infections and

Table 3.1 Nonstreptococcal and nonstaphyloccocal infection-associated glomerulonephritis: histological patterns

	Diffuse proliferative GN	Focal proliferative GN	Mesangioproliferative GN	Membranoproliferative GN	Cryoglobulinemic GN	Membranous nephropathy
Common renal presentation	Acute nephritic syndrome	Mild hematuria and proteinuria	Mild hematuria and proteinuria	Nephrotic range proteinuria, nephrotic syndrome, hematuria	Nephrotic range proteinuria, nephrotic syndrome, hematuria, skin purpura	Nephrotic range proteinuria or nephrotic syndrome
Clinicopathological correlation	Acute infections	Early or resolving infection	Early or resolving infection	Chronic infections	Acute or chronic infections	Acute or chronic infections
Laboratory investigations	Low C3 ±	Low C3 ±	Low C3 ±	Low C3 ±	Low C3, normal C4, cryoglobulins +, rheumatoid factor +	Normal C3, C4
Light microscopy	variable neutrophils (if ≫ exudative GN); visible subepithelial deposits	Focal and segmental endocapillary proliferation	Mesangial proliferation	Mesangial proliferation, lobular accentuation, GBM double contours	> monocyte/macrophage infiltration, bulky subendothelial and intraluminal deposits	Thick GBMs, mesangial proliferation ±
Immunofluorescence microscopy	C3 dominant, IgG +; starry sky or garland pattern	C3 dominant, IgG (starry sky pattern)	C3, IgG ± (mesangial pattern)	C3 dominant, IgM or IgG +	C3 dominant, IgM or IgG +	C3, IgG ±
Electron microscopy: deposits	Subepithelial humps, mesangial, subendothelial ±	Subepithelial humps, mesangial, subendothelial ±	Mesangial, subepithelial and intramembranous ±	Mesangial, subendothelial, subepithelial/intramembranous ±	Mesangial, subendothelial, intraluminal deposits	Subepithelial deposits, mesangial ±

(continued)

Table 3.1 (continued)

	Diffuse proliferative GN	Focal proliferative GN	Mesangioproliferative GN	Membranoproliferative GN	Cryoglobulinemic GN	Membranous nephropathy
Common associated infections	*S. epidermidis, Pseudomonas aeruginosa, Hemophilus influenzae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Enterobacter cloacae, Mycobacterium leprae, Mycoplasma pneumoniae, Treponema pallidum, Bartonella henselae, Coxiella burnetii, Rickettsia rickettsii, Borrelia burgdorferi, Chlamydia pneumoniae*			*S. epidermidis* (*shunt nephritis*), *Mycoplasma pneumoniae, Mycobacterium leprae, Propionibacterium acnes, Neisseria meningitidis, Borrelia burgdorferi, Nocardia, Coxiella burnetii*	*S. epidermidis* (*Shunt Nephritis*)	*Yersinia enterocolitica, Treponema pallidum*
Comments				ANA frequently + in shunt nephritis		

glomerular basement membrane duplication with mesangial cell interposition is often present (Fig. 3.1i).

Pathophysiology

Infection-associated glomerulonephritis is an immune complex-mediated process, triggered by the host response to an extrarenal infection [19]. Circulating immune complexes have been detected in several infections and microbial antigens have been detected within glomerular immune deposits [20–22]. The physiochemical properties of antigen and/or antibody such as size and charge play a role in localization of the deposits. A cationic antigen traverses the anionic glomerular basement membrane resulting in subepithelial localization with subsequent binding of circulating antibody, while bulkier immune complexes are entrapped in the subendothelium [19, 23]. Activation of innate and adaptive immune system, coagulation, and complement pathways triggers the cascade of tissue injury [24, 25]. Classical, alternative, and lectin-binding complement pathways are likely involved in a variety of infections. In addition, the host factors such as underlying diseases causing immunodeficiency and possibly defective alternative complement pathway are likely needed for development of clinically recognized glomerulonephritis [25]. These mechanisms are well characterized in streptococcal infections [9], but data suggests that similar pathogenic mechanisms could account for other infection-related glomerulonephritis.

Treatment and Prognosis

Treatment of underlying infection is the mainstay of therapy in infection-associated glomerulonephritis. It includes surgical drainage of abscesses and antibiotic therapy. Successful therapy leads to resolution of GN and the serum complements normalize within a few weeks [5]. There may be a role for immunosuppressive therapy in unresponsive severe proliferative or crescentic glomerulonephritis once the infection is cleared. In general, the renal survival of infection-associated glomerulonephritis in elderly individuals is significantly worse than in pediatric poststreptococcal glomerulonephritis. The underlying comorbidities influence the outcome adversely. Despite successful therapy, a third to two-thirds of patients have either persistent renal dysfunction or progress to end-stage renal disease [1, 4, 7].

Related Diagnoses

C3 Glomerulopathy: Postinfectious glomerulonephritis and C3 glomerulopathy fall within a spectrum of glomerulonephritis with overlapping clinical and pathological features [26]. C3 glomerulopathy is related to dysregulation of alternative complement pathway and is characterized by isolated/predominant C3 stain, intramembranous or transmembranous deposits and less-frequent subepithelial hump-like deposits [27]. Patients with C3 glomerulopathy have progressive renal disease despite milder disease at presentation [26]. Persistent low C3 levels and proteinuria in the setting of treated infection should suggest a diagnosis of C3 glomerulopathy. Such atypical postinfectious glomerulonephritis patients have an underlying defect in alternative pathway of complement [28]. To further complicate the diagnostic challenges, infections can precipitate C3 glomerulopathy in a predisposed individual [29, 30].

Autoimmunity, ANCA, and Pauci-immune Glomerulonephritis: Many chronic infections are known to trigger autoantibodies such as cryoglobulins (IgM antibodies directed against IgG), rheumatoid factors, antinuclear antibodies, and antineutrophil cytoplasmic antibodies (ANCA) [12, 25, 31]. The mechanisms by which pathogens can trigger autoimmunity include dysregulated host immune system, molecular mimicry, epitope conformational change, epitope spreading, and anti-idiotypic antibodies [25]. Polymorphisms of various genes involved in immunological processes can modulate the regulator T cell function and predispose an

individual to develop infection-triggered autoimmunity. Some bacterial antigens share amino-acid sequences with self-antigens and the antibodies that develop in the host can target the self [32]. It has been shown that such molecular mimicry by clostridial antigens of glomerular basement membrane can result in anti-GBM disease [33]. Similarly, *Staphylococcus aureus* has sequences similar to complementary proteinase 3 (PR3) peptide resulting in anti-idiotype antibodies (ANCA) directed against PR3 antigen [34]. ANCA serology has been documented with suppurative lung disease, gram-negative bacterial infections (*Pseudomonas, Klebiella, Escherichia coli*), and subacute bacterial endocarditis [35, 36]. Antibodies to lysosomal membrane protein-2 (LAMP-2) were identified in some, but not all, patients with pauci-immune glomerulonephritis [37, 38]. Their pathogenic role has been demonstrated by some investigators [37, 38]. LAMP-2 antigen is expressed on the surface of neutrophils and endothelial cells and has homology to fimbrial adhesin of *E. coli* and *Klebsiella.* The antibody response to fimbrial adhesin in urosepsis can trigger anti-LAMP-2 antibodies and precipitate pauci-immune glomerulonephritis [37, 39].

Positive ANCA serology has been documented in association with subacute bacterial endocarditis due to *Streptococcus, Staphylococcus, Enterococcus, Bartonella, and Brucella* [40, 41]. A recent study indicated that up to 28% of patients with endocarditis have serum pANCA or cANCA with most having either positive MPO or PR3 or both [35]. In such a clinical setting, renal biopsy findings are critical in distinguishing between immune-mediated endocarditis-associated glomerulonephritis and pauci-immune ANCA-mediated glomerulonephritis as both are associated with prominent glomerular crescents [35] (Fig. 3.2). The dominant C3 ± immunoglobulin staining with electron-dense deposits favor endocarditis-associated glomerulonephritis, while paucity of staining and lack of deposits on electron microscopy suggests ANCA-mediated glomerulonephritis. The possibility of pauci-immune glomerulonephritis superimposed on endocarditis-associated GN adds to the diagnostic challenge [41]. Treatment of infection is critical in both and the role/effectiveness of immunosuppression is not well established due to limited data [35].

Specific Bacterial Infections

Pneumococcal Infections

Streptococcus pneumoniae can trigger a postinfectious glomerulonephritis similar to *S. pyogenes*. It typically causes pneumonia and bacteremia and the data related to acute nephritis is limited to a few case reports [21, 42–44]). The renal manifestations are hematuria, proteinuria, edema, and renal insufficiency, which typically develop 2–3 weeks after pneumococcal infection. The immune mechanisms triggered by pneumococcal antigen result in acute proliferative glomerulonephritis or pure mesangial proliferative glomerulonephritis. The serum complement C3 levels can be either reduced or normal depending on the stage of the disease at the time of testing [20]. Antistreptolysin (ASO) titers are often elevated and cryoglobulinemia has also been reported. In addition to dominant C3 staining in the mesangium and capillary walls, IgG, C1q, and properdin have also been found, compatible with activation of both classical and alternative complement pathways [20, 21]. The pathogenic mechanism involves glomerular deposition of pneumococcal polysaccharide capsular antigen that triggers the complement activation. The pneumococcal antigen has been detected by immunofluorescence in glomeruli as well as alveoli [20, 21]. Ultrastructural evidence of subepithelial humps helps render a diagnosis of postinfectious glomerulonephritis. Treatment of the infection with antibiotics and supportive therapy result in complete resolution of glomerulonephritis.

Meningococcal Infections

Caused by *Neisseria meningitidis*, meningococcal infections can result in immune complex-mediated glomerulonephritis [45]. Clinically overt renal disease is rare, but biopsy triggered by laboratory

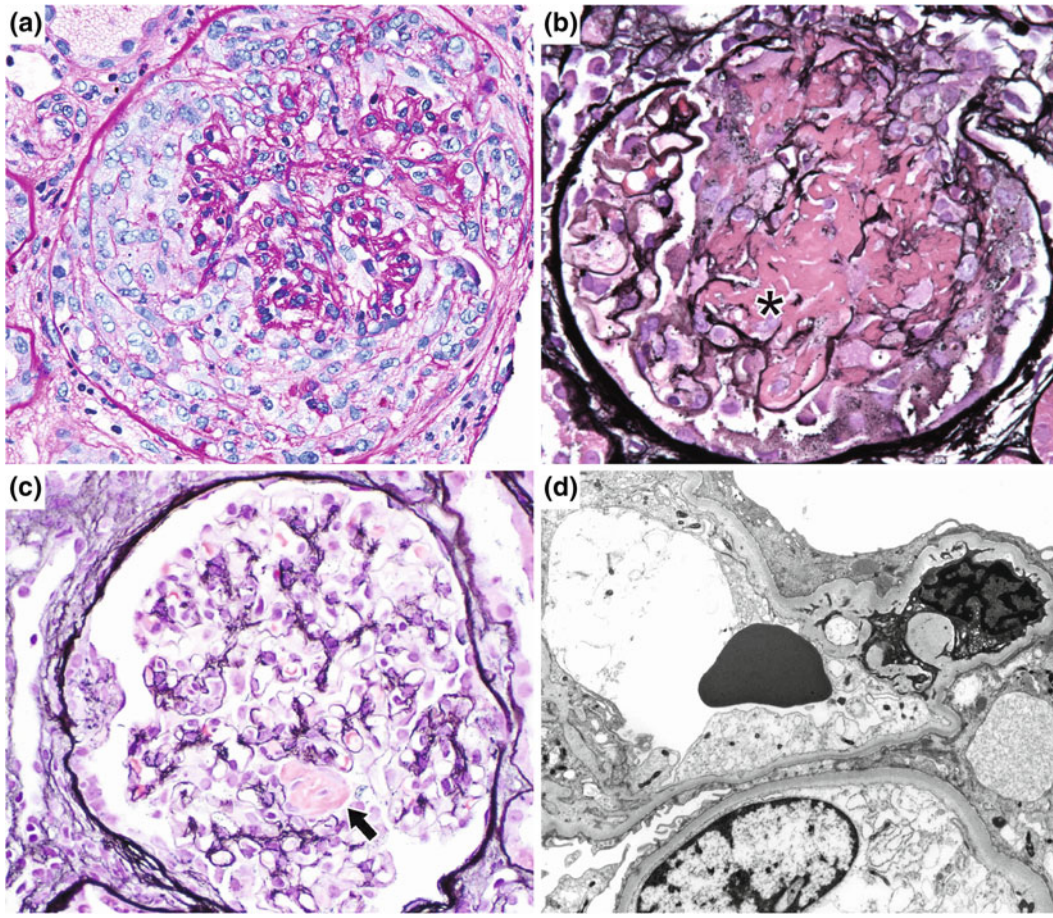

Fig. 3.2 Infection-related pauci-immune glomerulonephritis. **a** Glomerular crescents in a patient with subacute bacterial endocarditis and positive ANCA serology. Immunofluorescence staining for immunoglobulins and complements was negative (PAS, ×400). **b** Glomerular basement membrane rupture and extensive fibrin extravasation (*) (JMS, ×400). **c** Relatively preserved glomerulus with focal necrosis (*arrow*). Lack of prominent mesangial or endocapillary proliferation should suggest pauci-immune glomerulonephritis (JMS, ×400). **d** Ultrastructural examination confirms the lack of electron-dense deposits. Mild endothelial swelling and podocyte foot process effacement is seen (×6000).

evidence of circulating immune complexes showed acute proliferative glomerulonephritis. Membranoproliferative glomerulonephritis has also been reported with meningococcal infection. The immunofluorescence and electron microscopy shows features similar to poststreptococcal glomerulonephritis [45].

Syphilis

Syphilis is a sexually transmitted disease caused by a spirochete *Treponema pallidum* whose only natural hosts are humans [46]. Renal involvement is rare [47] and is due to direct tissue invasion by the spirochete or is precipitated by immune-mediated mechanisms. The overall seroprevalence is extremely low [48], but syphilis is undergoing resurgence over the last 2 decades in the developed world and the diagnosis can be missed if not suspected clinically [46]. The clinical presentation of syphilis varies widely and depends on the stage of disease. Primary syphilis presents as a painless ulcerated skin lesion (chancre) 2–6 weeks after infection. If untreated, 25% of patients progress to secondary syphilis in weeks to

months. It is represented by non-itchy generalized rash, lymphadenopathy, fever, and malaise due to disseminated spirochetal infection. Approximately, 20–40% of untreated secondary syphilis cases progress to tertiary syphilis over 1–30 years after the primary infection. Tertiary syphilis primarily affects the cardiovascular system and brain, and the formation of gumma, i.e., granulomatous locally destructive lesion, is common. Glomerulonephritis related to syphilis occurs during (a) secondary or tertiary syphilis stage, (b) congenital syphilis infection, or rarely (c) after initiation of anti-syphilis therapy [49–52] (Table 3.2). Congenital syphilis due to transmission of organisms from mother to baby during pregnancy or at birth is relatively rare in the Western countries, but membranous nephropathy in an infant should prompt a search for treponemal infection [53].

Proteinuria is the most common renal manifestation and occurs in up to 8% of secondary syphilis patients [49]. It can range from mild proteinuria to nephrotic syndrome in the setting of membranous nephropathy. Mild hematuria, acute nephritis syndrome, renal insufficiency, or rapidly progressive renal failure can all occur depending on the type of glomerulonephritis [54]. Hypocomplementemia is reported with proliferative glomerulonephritis. The most common glomerulonephritis associated with syphilis is membranous nephropathy with variable mesangial hypercellularity. Other patterns reported include proliferative glomerulonephritis (ranging from mild to diffuse ± neutrophils), crescentic glomerulonephritis, and minimal change disease [49, 54]. The immune-mediated glomerulonephritis has immunofluorescence evidence of immunoglobulin and complement

Table 3.2 Glomerulonephritis associated with treponemal infections

	Secondary/tertiary syphilis	Congenital syphilis	Therapy-related GN
Renal presentation	Nephrotic syndrome, less common nephritic syndrome	Nephrotic syndrome, nephritic syndrome or hematuria	Extremely rare: nephrotic syndrome, nephritic syndrome
Histology	Membranous nephropathy, Diffuse proliferative GN ± crescents, minimal change disease	Membranous nephropathy ± mesangial hypercellularity	Membranous nephropathy (rare)
	Membranous nephropathy ± mesangial hypercellularity most common		
	Tubulointerstitial nephritis with plasma cells, gumma formation; spirochetes on Warthin–Starry stain	Tubulointerstitial nephritis with plasma cells; spirochetes on Warthin–Starry stain	
Immunofluorescence microscopy	IgG and C3 granular deposits in mesangium and capillary wall	IgG and C3 granular deposits in mesangium and capillary wall	Treponemal antigen detected in immune complexes
	Treponemal antigen detected in immune complexes		
	Membranous nephropathy is PLA2R negative		
Electron microscopy	Subepithelial deposits ± spikes ± mesangial deposits in membranous nephropathy	Subepithelial deposits ± spikes ± mesangial deposits in membranous nephropathy	Subepithelial deposits ± spikes ± mesangial deposits in membranous nephropathy
	Subepithelial "humps" ± mesangial/subendothelial deposits in proliferative GN		

deposits. Tubulointerstitial inflammation is often present and tends to be plasma-cell rich. Demonstration of tissue spirochetes indicates direct tissue invasion. Although not specific, positive rapid plasma regain (RPR) or VRDL should raise concern for syphilis. Once suspected, a diagnosis of syphilis can be confirmed by treponemal antibody tests (*T. pallidum* hemagglutination assay and fluorescent treponemal absorption test). The organisms can also be detected in the tissue by Warthin–Starry silver stain, dark field microscopy, immunofluorescence microscopy, or polymerase chain reaction.

The glomerulonephritis is likely due to the glomerular deposition of treponemal antigen with subsequent binding of the circulating antitreponemal IgG antibody or deposition of circulating immune complexes. Antibodies have been eluted from the kidney biopsy and the treponemal antigen has been demonstrated in the immune deposits in both acquired and congenital syphilis-associated glomerulonephritis [22, 55, 56]. Treponemal antigen–antibody complexes deposited in the glomeruli activate the classical and alternate complement pathway.

Syphilis is treated with penicillin or ceftriaxone and requires 3–6 weeks of therapy. The resolution of glomerulonephritis can take 1–6 months after therapy. The consequent treponemal death triggers a massive release of bacterial antigens and endotoxins causing a systemic reaction referred to as Jarisch–Herxheimer reaction. It usually last only a few hours during which the patient develops fever, chills, tachycardia, flushing, and myalgias. Prominent skin rash can also occur and is thought to be due to immune complex formation and deposition. Rare case reports of renal involvement with transient nephrotic syndrome are also reported [52].

Lyme Disease

Lyme disease is the most common tick-borne infection in USA, seen especially in the Northeastern regions and Wisconsin [57]. It is a multisystem disorder caused by a spirochete *Borrelia burgdorferi* and transmitted by ticks of genus *Ixodes*. Renal involvement is rare and the diagnosis requires high index of clinical suspicion [57, 58]. The early symptoms of fever, fatigue, and the characteristic skin rash of erythema migrans might be forgotten by the patient at presentation. If left untreated, Lyme disease has frequent relapses and remissions manifested by arthritis, cardiac, and neurological symptoms. The diagnosis rests on serological confirmation including ELISA detection of IgM and IgG antibodies specific to *B. burgdorfer*i, western blot, and polymerase chain reaction detection of *B. burgdorferi* DNA in body fluids [59–61]. Unfortunately, all these tests are prone to false-positive and false-negative results, further complicating the diagnosis.

The renal symptoms are microscopic hematuria and proteinuria, but nephrotic syndrome is not uncommon and rare cases present with acute renal failure [58, 62, 63]. Although hypocomplementemia is helpful when present, C3 levels are often normal. Membranoproliferative glomerulonephritis is the most common histology on renal biopsy, but mesangioproliferative glomerulonephritis, membranous nephropathy, and IgA nephropathy have also been described [58, 61, 62] (Fig. 3.3). Mild interstitial inflammation accompanies the glomerular changes and the extent of chronic tubulointerstitial damage is variable. Interstitial foam cells have been described with chronic nephrotic range proteinuria. IgG and dominant C3 staining in the mesangium and capillary walls is typical and on rare occasion IgA staining has been described in mesangioproliferative glomerulonephritis [58, 62]. The electron-dense deposits are mostly in the mesangium and subendothelium with rare subepithelial deposits.

Lyme disease associated with glomerulonephritis is caused by chronic antigenemia, robust host response with antibody production, and immune complex formation. The circulating immune complexes deposit in the glomeruli and initiate tissue injury [57]. There may be a role for autoimmunity as *B. burgdorferi* antigens mimic self-antigens at the molecular level [64]. The treatment of Lyme disease includes oral doxycycline for 14–28 days or even longer in chronic infection [65]. The renal disease of membranous glomerulonephritis may respond to steroids,

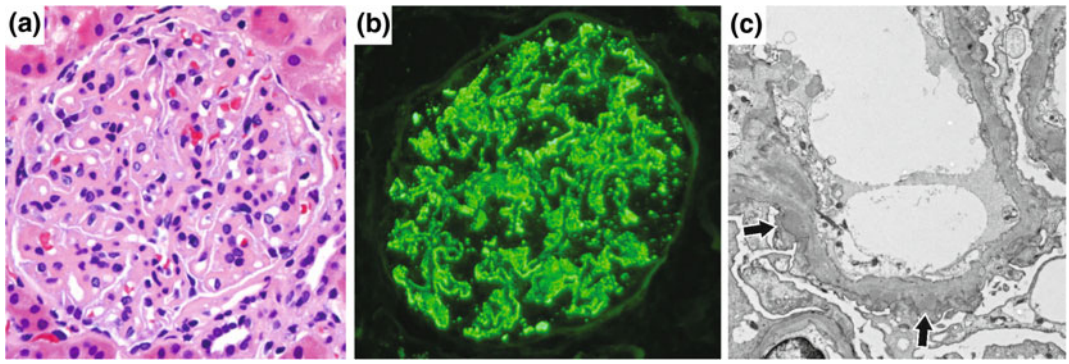

Fig. 3.3 Infection-associated membranous nephropathy. **a–c** Membranous nephropathy is less commonly seen in association with nonstreptococcal and nonstaphylococcal bacterial infections. This patient with Lyme disease presented with nephrotic syndrome. Diffuse thickening of the glomerular basement membranes is seen with mild segmental mesangial proliferation (**a** H&E, ×400). The glomerular capillary walls have diffuse granular capillary wall deposits that stain for IgG, C3, κ and λ (**b** IgG, ×400). Electron microscopy shows numerous small subepithelial deposits (*arrow*) in the capillary loops, confirming the diagnosis of membranous nephropathy (**c** ×9000).

intravenous immunoglobulin, and on occasion, plasmapheresis [61]. Although not universal, complete resolution of membranoproliferative glomerulonephritis has been described in the literature [61].

Bartonella "Cat-Scratch Disease"

Bartonella species are fastidious gram-negative organisms; *B. henselae* and *B. quintana* are associated with human disease. *B. Henselae* is the culprit in 'cat scratch' disease; organisms are carried by fleas, transmitted to cats, and then to humans through broken skin, most typically via scratch from a kitten [66]. In immunocompetent individuals, there is a self-limited regional lymphadenitis, but in immunosuppressed patients more widespread granulomatous inflammation can involve spleen, liver, central nervous system, and bone, and in severely immunocompromised patients angiomatosis (bacillary angiomatosis of the skin or peliosis of the liver–spleen) occurs [66, 67]. Patients with cardiac or valvular defects are at risk for *Bartonella* endocarditis, with *Bartonella* comprising up to 17% of endocarditis, and 28% of 'culture negative' endocarditis [66, 67]. Since *Bartonella* endocarditis is often blood 'culture negative,' it requires a high index of suspicion in conjunction with serologic or PCR studies for confirmation [68]. However, *Bartonella* serologic testing is not particularly specific, though very high titers have increased specificity (>1:800) [67, 68]. Cases of *Bartonella*-associated glomerulonephritis have been reported; one series cited "kidney failure" in 45% of patients with *Bartonella* endocarditis [68]. Importantly, in some cases the renal biopsy findings have prompted the rigorous search for an infectious process [68, 69].

As with other types of infection-associated glomerulonephritis, histopathologic findings in *Bartonella*-related glomerulonephritis have been variable. Light microscopy generally shows a proliferative and/or focal necrotizing-crescentic glomerulonephritis [66–72]. Immunofluorescence results are also variable, and have most commonly been reported as IgM-dominant or pauci-immune, but cases of 'full house' deposition, C3-dominant, or IgA-dominant staining have been documented [66–72]. Ultrastructural studies tend to show mesangial electron-dense deposits, most often without the classic subepithelial 'hump' deposits [66–72]. Thus, infection should be considered in glomerulonephritis with an IgM-dominant immunofluorescence pattern. Further, a *Bartonella* and other endocarditis-associated glomerulonephritides often are associated with positive ANCA serologies. Thus, an infectious

process should remain on the differential in cases of ANCA-positive necrotizing and crescentic glomerulonephritis [66, 71, 73] (Fig. 3.2).

Brucella

Brucellosis is a zoonotic infection caused by gram-negative coccobacilli *Brucella* sp., and is endemic in Middle East and Mediterranean countries. Close contact with infected animals, consumption of unpasteurized dairy products, and inhalation of aerosols leads to human infection [74]. All organ systems are affected and clinical picture can be varied. Although *Brucella* organisms can be isolated in 4–5% of infected patients, renal involvement is rare [75]. The renal histology in *Brucella* infection can be in the form of acute interstitial nephritis (due to direct invasion of bacterium), chronic granulomatous inflammation, renal abscess, and occasionally glomerulonephritis.

Derived from the limited literature related to *Brucella* glomerulonephritis, most patients present with hematuria, proteinuria (can be nephrotic range), and sometimes renal insufficiency. Low C3 levels can be seen, especially with membranoproliferative glomerulonephritis. The site of infection can vary, but glomerulonephritis has been reported with endocarditis, mycotic aneurysm, and others [74, 76]. Although the data is limited, the most common *Brucella* organism isolated is *B. melitensis*. The renal biopsy findings reported are membranoproliferative glomerulonephritis, mesangioproliferative glomerulonephritis, cryoglobulinemic glomerulonephritis, diffuse proliferative v, IgA nephropathy, and membranous nephropathy [76–81]. Definitive diagnosis rests on serological confirmation (serum agglutination test, ELISA) or isolating brucellae from blood or infected tissues. Polymearase chain reaction results in rapid confirmation of the infectious organism and is preferred over cultures [82]. Circulating immune complexes with glomerular deposition is the main mechanism involved, likely initiated by chronic antigenemia [83]. On occasion, proliferative and crescentic glomerulonephritis or renal vasculitis occurs in the absence of immune complexes [76]. It has been suggested that endotoxemia triggers a cellular inflammatory response within the glomerulus with subsequent injury in the absence of immune complexes as in ANCA-mediated injury [76]. Treatment of *Brucella* infection-related glomerulonephritis includes doxycycline in combination with rifampin, gentamicin, streptomycin, or trimethoprim/sulfamethoxazole. Additional steroid therapy may be helpful in the setting of crescentic glomerulonephritis and vasculitis [76].

Mycobacterium

Mycobacterium tuberculosis complex: The mycobacterial infections in humans include tuberculosis caused by members of *Mycobacterium tuberculosis* complex, mainly *M. tuberculosis* and rarely by a bovine tubercle bacillus, *M. bovis* [84]. Both are obligate pathogens while most other species within the genus mycobacterium are environmental saprophytes typically not associated with human disease in an immunocompetent state. On occasion, an environmental mycobacterium such as *M. avium* causes disseminated disease in an immunocompromised human host [85]. The kidney is mainly involved by *M. tuberculosis* in the form of genitourinary tuberculosis, while *M. avium* can infect the kidney as part of disseminated disease. Another mycobacterium, *M. leprae,* is known to affect the kidney in endemic areas [86].

Tuberculosis is caused by either reactivated latent *M. tuberculosis* infection in an immunosuppressed host or by dissemination of active pulmonary infection. Renal involvement in the form of genitourinary tuberculosis accounts for 14–41% of extrapulmonary tuberculosis in developed countries [84, 87]. The infected pelvic calyces and medulla undergo ulceration and destruction with accumulation of cheesy caseous material [84, 88]. Chronic tubulointerstitial nephritis with necrotizing caseating granulomas is not uncommon.

On rare occasion, *M. tuberculosis* infection can result in glomerulonephritis, especially in endemic areas [89]. The clinical manifestations of patients with tuberculosis-related glomerulonephritis include hematuria and proteinuria. The systemic symptoms related to tuberculosis

infection such as fatigue, mild fever, night sweats, weight loss, and hypertension are more common than local genitourinary symptoms such as urinary frequency, urgency, and flank pain. Accurate diagnosis depends on confirmation of active tuberculosis infection by demonstration of acid-fast bacilli (sputum), cultures (sputum, urine), polymerase chain reaction (renal biopsy tissue), or more recently Quantiferon test [84, 89, 90]. In one study, more than 70% of patients with tuberculosis-related glomerulonephritis had pulmonary or extrapulmonary tuberculosis [89]. Most patients with glomerulonephritis are over 40 years of age, likely reflective of prolonged tuberculosis infection predisposing to the development of glomerular disease. Over 72% of patients with tuberculosis-related glomerulonephritis had IgA nephropathy, but other glomerulonephritides have also been reported. These include mesangioproliferative glomerulonephritis, crescentic glomerulonephritis, collapsing glomerulopathy, membranous nephropathy, and membranoproliferative glomerulonephritis [91–96].

While the immune responses in *M. tuberculosis* are primarily cell-mediated, there is a humoral component as well [97–99]. High levels of immune complexes have been detected in patients with disseminated tuberculosis [100]. T cell suppressed environment with negative Mantoux skin test while not a requisite may predispose to development of circulating immune complexes [91, 99]. It appears that IgA antibodies directed against A-60 mycobacterial antigen play a role in the frequent association between tuberculosis infection and IgA nephropathy. These antibodies have been detected in the serum of patients with active tuberculosis as well as the immune complexes of IgA antibodies and mycobacterial antigens [97].

The diagnosis of tuberculosis-related glomerulonephritis is difficult due to nonspecific symptoms and insidious nature of the disease. High index of suspicion is needed. Treatment is mainly antituberculosis therapy and care should be taken to address multidrug-resistant tuberculosis [84]. Resolution of hematuria and proteinuria with treatment also supports the diagnosis of tuberculous glomerulonephritis [89, 99]. Interestingly, rifampin antituberculous therapy in turn can precipitate crescentic glomerulonephritis [101].

Mycobacterium leprae is a weak intracellular acid-fast bacillus that causes either tuberculoid leprosy or lepromatous leprosy base on robustness of the host response. The bacillus has a predilection for Schwann cells and skin. Leprosy is endemic in several developing countries. Although highly infectious with prolonged exposure, clinical disease is less common as *M. leprae* is slow growing with an incubation period of 2–12 years.

Tuberculoid leprosy is characterized by granulomatous inflammation and paucity of bacilli due to effective cell-mediated immunity. On the other hand, lepromatous leprosy is more common with multibacillary forms associated with weak host defenses. The renal lesions described include glomerulonephritis, granulomatous interstitial nephritis, AA amyloidosis, and pyelonephritis [102].

Glomerulonephritis represents the most frequent type of renal involvement in leprosy, found in approximately 30% of patients [103]. Lepromatous leprosy patients with abundant bacilli are particularly vulnerable. These bacilli trigger a robust humoral response, but these antibodies are not protective against the lepra bacilli. Immune complexes form in this high antibody milieu and glomerulonephritis may ensue. Antigens from other co-infections may also play a role. Skin erythema nodosum has similar pathogenesis and according to one study, there is a strong correlation between erythema nodosum and development of glomerulonephritis [104]. The potential mechanisms for glomerulonephritis and erythema nodosum include either deposition of circulating immune complexes or in situ deposition of lepra antigens. Circulating cryoglobulins have also been documented in leprosy [105]. Lepra bacilli antigens are released in massive amounts after the antibiotic therapy, and immune complexes can be formed in this setting as well [104].

Renal presentation of mild hematuria and proteinuria is common with leprosy-associated glomerulonephritis, but nephrotic syndrome also can occur, depending upon the type of tissue

injury [86, 103, 106]. A few patients also have functional tubular defects of acidification or urinary concentration. Histologically, the glomerular changes reported include membranous nephropathy, IgA nephropathy, mesangioproliferative, endocapillary proliferative, or membranoproliferative glomerulonephritis [102, 103, 107]. Crescents are rare and can result in acute renal failure [108]. The tubulointerstitium may show granulomatous inflammation with acid-fast bacilli demonstrated on Fite stain. Immunofluorescence reveals granular C3 and IgG deposits in the mesangium and along the capillary walls. The corresponding electron-dense deposits are in the mesangium and subendothelium. Antibiotic treatment of *M. leprae* with dapsone, rifampin, and clofazimine is main course of treatment. But steroids and nonsteroidal anti-inflammatory drugs might be of help in the setting of glomerulonephritis related to acute immunological episodes.

Others: There are many other bacterial infections reported in association with glomerulonephritis [44]. Patients with *Klebsiella* and *Mycoplasma* pneumonia develop proliferative glomerulonephritis [109, 110]. The renal presentation includes hematuria, proteinuria, or renal insufficiency, but glomerulonephritis may also be clinically occult. *Klebsiella* polysaccharide antigen has been demonstrated in the mesangial and glomerular capillary wall deposits and the eluate of the glomerulus-bound IgG antibody was specific to *Klebsiella* [109]. Similar evidence of mycoplasma antigen was found in a patient with *Mycoplasma* infection-associated diffuse proliferative glomerulonephritis [111]. The serum complement levels are reportedly low in *Mycoplasma*-associated proliferative glomerulonephritis and the immune deposits are predominantly in the mesangium [110, 111]. Recent reports of *Mycoplasma*-related crescentic glomerulonephritis and vasculitis have also been documented [112–114]. Following an infection with *Mycoplasma*, a patient developed MPO-ANCA with subsequent pulmonary-renal syndrome and glomerular crescents [114].

Renal involvement in *Salmonella* infections is reported to occur in 2–3% of patients, and it includes cystitis, pyelitis, pyelonephritis, and rarely glomerulonephritis [115]. However, it has been postulated that subclinical glomerulonephritis is not uncommon and kidney biopsies performed in three typhoid fever patients with no evidence of renal dysfunction did demonstrate immune complex glomerulonephritis [116]. Reported histological findings in typhoid glomerulonephritis include diffuse proliferation and IgA nephropathy, in addition to thrombotic microangiopathy [117–119]. Deposition of immunoglobulin and C3 is seen along with subepithelial humps on electron microscopy. *Salmonella* Vi antigen has been demonstrated in the glomerular capillary wall confirming the pathogenic role of *Salmonella typhi* [116].

Infection-Associated Amyloid

Amyloidosis as a complication of chronic inflammatory conditions including infection and autoimmune disease has been recognized for nearly a century [120]. Serum amyloid A (SAA), an acute phase reactant synthesized in the liver in response to IL-1, IL-6, and tumor necrosis factor [121], is the amyloid fibril constituent in this setting, as well as in Familial Mediterranean fever. In the developed world, the incidence of infection-associated SAA amyloid has decreased with reduction in chronic tuberculosis, leprosy, osteomyelitis, chronic decubitus ulcers in paraplegics, and infections in burn patients, hidradenitis suppurativa, dermatoses, and cystic fibrosis [120, 122–124]. However, some of these conditions remain prevalent in less-developed areas of the world [122]. Further, there was an 'epidemic' of SAA amyloid amongst illicit drug users with skin infections in the 1970s–1980s, and such cases have been seen continually since then, although infrequently reported [121–123, 125–133].

Menchel et al. and then Neugarten et al. characterized SAA amyloid amongst drug users in New York City. In a group of 150 drug addicts at autopsy, amyloid was identified in 6 of 44 (14%) subcutaneous drug users but in only 1 of 105 (1%) intravenous drug users. Of 23 drug addicts with skin infections, 6 had amyloid (26%) [131, 133]. In a subsequent study

incorporating these autopsy cases as well as larger group of biopsy cases, *Neugarten* et al. identified cutaneous suppurative lesions in 17/20 drug addicts with amyloid [131, 133]. The authors estimated that 25–50% of drug addicts biopsied for proteinuria had SAA amyloid in this era [126, 133]. Other glomerular findings in heroin addicts include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, or infection-related proliferative glomerulonephritis (endocarditis, skin infection, other) [126, 128].

Patients with infection-associated SAA amyloid present with heavy proteinuria (range 1.5–29 gm/day) [126, 133]. They may have the full nephrotic syndrome, and generally also have elevated serum creatinine, with several reporting polyuria and polydipsia [126, 133]. Patients inevitably had a long history of intravenous drug use, and a more recent history (2–3 years) of cutaneous drug use, so-called 'skin-popping,' after veins are longer useable for injection [126, 133, 134]. In a series of renal biopsies from 35 heroin addicts, Dubrow et al. reported older age, longer duration of addiction, lower serum albumin, and lower blood pressure in those with renal amyloid as compared to those with focal segmental glomerulosclerosis [126]. In a contemporary study, skin infections in drug users were frequently polymicrobial, including both methicillin-sensitive and methicillin-resistant *Staph.* species, *Strep*. species, and a mixture of anaerobic organisms [135].

Histopathologically, features of SAA amyloid in the kidney are similar to other forms of

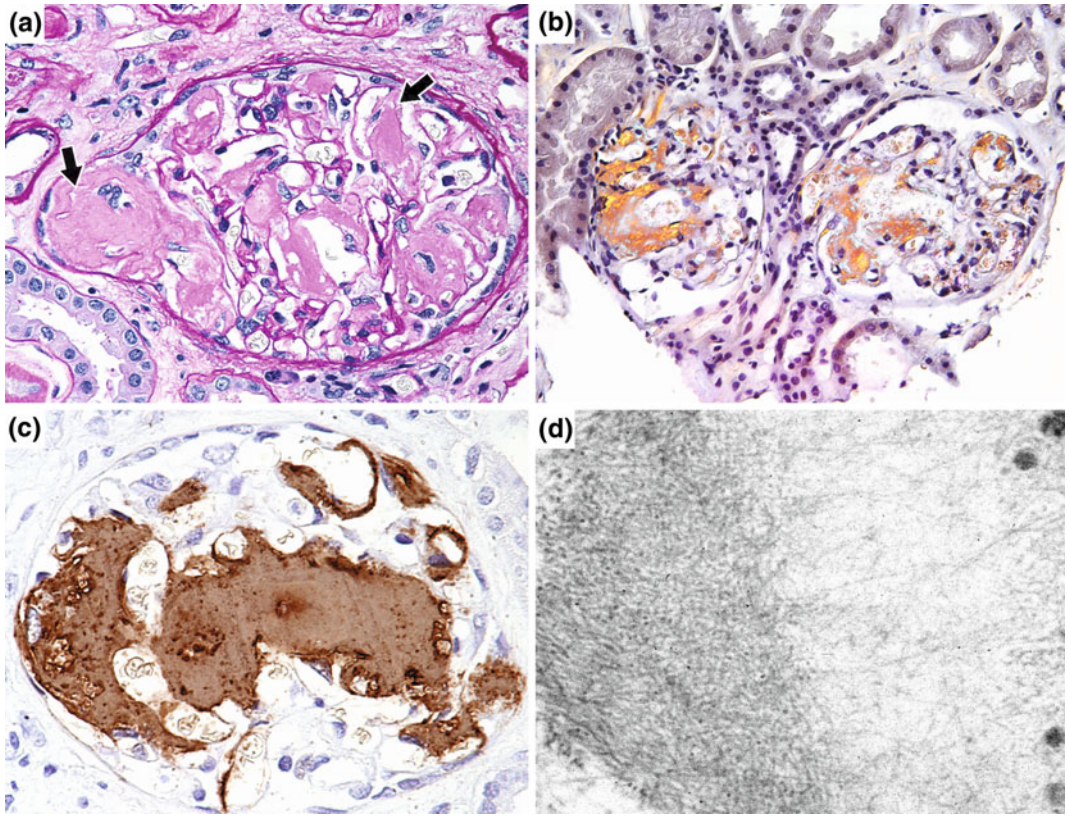

Fig. 3.4 Amyloid A deposition in chronic infections. **a** Pale amorphous deposits of amyloid (*arrow*) in the mesangium, capillary walls, and vascular pole in a patient with history of IV drug abuse who presented with nephrotic syndrome (PAS, ×400). **b** The Congo red stain under polarized light highlights the glomerular amyloid with patchy apple *green* birefringence (Congo Red, 200). **c** The amyloid subtype associated with chronic infections is AA type, as confirmed on immunohistochemical stain (Serum amyloid A stain, ×400).

amyloid. Amyloid deposits in glomeruli are seen in the mesangium and, with extensive deposition, involve and efface much of the glomerular tuft [136] (Fig. 3.4a). Unfortunately, skin infection-associated SAA is often biopsied at this late phase with extensive renal damage. Amyloid deposits are lightly eosinophilic and 'waxy' on H&E, pale on PAS, metachromatic (blue-purple) on trichrome, and silver negative [136]. Amyloid 'spicules' by light microscopy may be aligned perpendicular to the glomerular basement membrane. SAA amyloid frequently involves the interstitium as well as arteries and arterioles. Congo red staining is positive in amyloid with green birefringence on polarization (Fig. 3.4b). Fluorescent light may also be used to evaluate Congo red or thioflavin stains [136, 137]. By immunofluorescence microscopy, the amyloid deposits are essentially negative for immunoglobulin, light chain, and complement staining, but there is often nonspecific background in the amyloid. Serum amyloid A staining will be positive by immunofluorescence or immunohistochemical methods (Fig. 3.4c); alternatively, mass spectroscopy or other proteomic methods can be used to type the amyloid [138]. Electron microscopy shows deposits with the characteristic randomly oriented fibrils of 8–12 nm diameter [136] (Fig. 3.4d).

A few case reports demonstrate improvement of the proteinuria and partial histologic remission in the rare patient successfully cleared of infection and inflammation, with cessation of drug abuse [121, 123, 129]; however, renal disease is progressive in most [132–134]. Serum amyloid A protein levels may be monitored in the serum [122].

Special Circumstances

Deep-Seated Visceral Abscess

Initially described by Whitworth et al. and Beaufils et al. [139, 140], glomerulonephritis can occur in association with visceral abscesses in the absence of infective endocarditis. These deep-seated suppurative infections are caused by gram-positive or gram-negative organisms. *Staphylococcus* osteomyelitis in a diabetic patient is one of the more frequent associations, but others include lung abscesses, wound infections, subphrenic abscess, abdominal abscess, mediastinitis, and infected vascular Dacron prostheses caused by a variety of bacterial organisms [141, 142]. Case reports of associated nocardial cerebral abscesses are also known [143]. The duration of the abscess ranges from a few weeks to a few years. The blood cultures are usually negative and the serum complement levels are normal. Fever, hypertension, and oliguria are often present and glomerulonephritis is suspected in the presence of hematuria (gross or microscopic) and proteinuria. In the presence of circulating cryoglobulins, patients can have extrarenal manifestations of arthralgias and purpura.

The morphological spectrum of biopsy changes can range from mesangial hypercellularity in early disease when the infection is <2 months duration to diffuse proliferative/crescentic glomerulonephritis to membranoproliferative glomerulonephritis in long standing infections [140, 141]. One study demonstrated increased glomerular monocytic infiltration in visceral infection-associated glomerulonephritis even in the absence of cryoglobulinemia [144]. Immunofluorescence shows granular deposits in mesangium and glomerular capillary walls with C3 and less frequently IgG. Staphylococcal infections can show predominant or codominant IgA staining along with C3 (described in chap. 2). Electron-dense deposits are located in mesangium and subepithelium. Small subendothelial or intramembranous deposits can also occur. Immune complex deposition and activation of alternative complement pathway are the likely pathogenic mechanisms.

Eradication of infection with surgical approaches and antibiotics is the main course of treatment. Renal recovery occurs with successful antimicrobial treatment and the follow-up renal biopsies would show resolution of morphological changes with only mild residual mesangial hypercellularity, capillary wall thickening, and global glomerulosclerosis [140]. Failure to completely clear the infection results in persistence of glomerulonephritis with progression to an end-stage kidney disease.

Shunt Nephritis

Chronic glomerulonephritis associated with infection of ventriculoatrial shunts is referred to as shunt nephritis. These shunts are inserted for treatment of hydrocephalus and are prone to bacterial colonization. *Staphylococcus epidermidis* is the offending organism in over 75% of shunt infections. It is either inadvertently introduced from a skin source during the surgery or gets deposited during transient bacteremia. *Staphylococcus* also can form a biofilm around the catheter tips in vivo thus escaping the effects of antibiotics and colonizing the shunt. Other organisms associated with shunt infections include *Listeria monocytogenes, Peptococcus, Corynebacterium bovis, Bacillus subtilis, Mycobacterium gordonae, Micrococcus, diphtheroid species, and gram-positive anaerobic* rods such as *Propionibacterium acnes* [14, 15, 145, 146].

The incidence of ventriculoatrial shunt infection can be as high as 27%, but in most instances, this chronic infection is asymptomatic for several years [13, 147]. Blood and cerebrospinal fluid cultures are usually sterile possibly due to prior antibiotic therapy and the shunt infection can be demonstrated only on removal and culture of the shunt. Only a small proportion (4–5%) of patients with infected shunts actually develop glomerulonephritis and the time frame can be as early as 4 weeks or as late as 21 years after the shunt operation [13, 14, 145, 147]. Most shunt infections are in pediatric population, but are also seen in adults. The risk of developing shunt infections is much lower with ventriculoperitoneal shunts and they have largely replaced the ventriculoatrial shunts in hydrocephalus treatment [14].

The clinical features of shunt nephritis such as fever, malaise, and nausea are nonspecific and are likely due to bacteremia. On occasion, renal manifestations are the presenting symptoms. These include hematuria and mild proteinuria, although nephrotic syndrome can also occur. Oliguric acute renal failure has been reported. The systemic symptoms accompanied by renal dysfunction can lead to an erroneous diagnosis of urinary tract infection [14]. Patients may also develop hypertension, arthralgias, lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, and anemia. Serum C3 levels are low in up to 90% and C4 is low in 50% of patients with shunt nephritis. Hypocomplementemia in shunt infection typically indicates renal involvement. Some patients may have positive ANCA titers (anti-proteinase 3) and infection-related ANCA disease is a consideration [148]. Other laboratory investigations that are helpful in diagnosis of infection are elevated ESR, cryoglobulins, rheumatoid factor, and positive blood

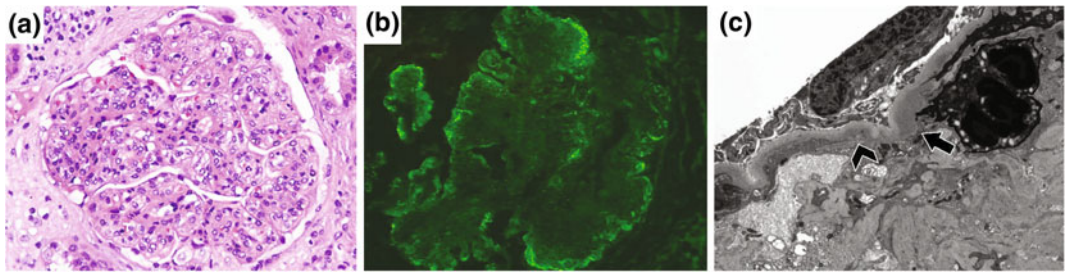

Fig. 3.5 Renal biopsy findings in shunt nephritis. **a** The glomeruli demonstrate lobular accentuation with mesangial and endocapillary proliferation and basement membrane double contours. The biopsy is from a 36-year-old male with ventriculoperitoneal shunt in place for more than 3 decades. The patient presented with increased serum creatinine, nephrotic proteinuria, hematuria, and hypertension. The serum complement levels were normal and the shunt was subsequently found to be infected with *Propionibacterium acne* (H&E, ×400). **b** Immunofluorescence microscopy revealed peripheral capillary wall and segmental mesangial deposits that were predominantly positive for C3 and to a lesser extent IgG (C3, ×400). **c** On ultrastructural examination, scant, weakly electron-dense deposits were seen in the paramesangium (*arrow*), subendothelium (*arrow head*) and occasional intramembranous locations (×6000). Figure courtesy of Tibor Nadasdy, with permission

cultures [13, 14]. Positive antinuclear antibody has also been noted in association with shunt nephritis.

The histological spectrum seen in shunt nephritis is similar to that seen with other infection-associated glomerulonephritis. Approximately, one-half of patients show membranoproliferative glomerulonephritis (Fig. 3.5a) and one-third show diffuse proliferative glomerulonephritis with mesangioproliferative glomerulonephritis in the remainder. On occasion, focal proliferative glomerulonephritis and crescentic glomerulonephritis have been reported [13]. A few neutrophils can be seen in glomeruli, but florid exudative glomerulonephritis is uncommon. Immunofluorescence microscopy typically has mesangial and capillary wall deposits that stain for C3 (Fig. 3.5b) and IgG; IgM can sometimes be the predominant immunoglobulin. C1q and C4 may be present, suggestive of classical complement pathway activation. The electron-dense deposits are in the mesangium and subendothelium (Fig. 3.5c) with occasional intramembranous and subepithelial deposits.

Immune complex deposition is the likely pathogenic mechanism, followed by classical and to a lesser extent alternative complement pathway activation [149]. Bacterial antigens have been demonstrated in the glomerular deposits [149]. Serum cryoglobulins can develop in shunt infections and can also activate classical pathway of complement.

Treatment of shunt nephritis is antibiotic therapy and removal of infected shunt. The renal function usually recovers completely within a few weeks of successful therapy. The hypocomplementemia and cryoglobulinemia, if present, resolves too [14, 145]. The glomerulonephritis improves and the residual changes may be mild mesangial hypercellularity [150]. The immune deposits and electron-dense deposits also disappear. Approximately, a third of the patients have persistent mild proteinuria, microhematuria, hypertension, and renal insufficiency. Depending on the extent of prior glomerular damage, global glomerulosclerosis and chronic tubulointerstitial damage may be significant, eventually leading to an end-stage kidney.

Shunt nephritis is increasingly a rare diagnosis. More recently, we encounter glomerulonephritis associated with infected central vein catheters, and other devices such as LVAD (left ventricular assist device) which has similar clinical and histological features as shunt nephritis [151, 152]. The most common pathogen in central venous catheter infections is also *S. epidermidis* (Tables 3.1 and 3.2).

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Endocarditis-Associated Glomerulonephritis

4

Christie L. Boils

Abbreviations

IC	Immune complex
MPGN	Membranoproliferative glomerulonephritis
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
C3	Complement component 3
C4	Complement component 4
GN	Glomerulonephritis
Ig	Immunoglobulin
MPO	Myeloperoxidase
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
PR3	Proteinase-3

Introduction Overview

Renal biopsy interpretation demands clinicopathologic correlation, which is particularly challenging in cases of endocarditis-associated glomerulonephritis. Not only can the clinical diagnosis of endocarditis be challenging, the morphologic spectrum of endocarditis-associated glomerulonephritis is unique among infection-associated glomerulonephritides in that it can mimic other diseases, and importantly, those that require a vastly different therapy. Though much of the available literature pertaining to endocarditis-associated glomerulonephritis originated from autopsy specimens obtained during the pre-antibiotic era, it is critical for the clinician and pathologist alike to be familiar with the current era of endocarditis-associated glomerulonephritis literature described in recent renal biopsy and autopsy series and as well as case reports, and to maintain a high index of suspicion.

Infective Endocarditis Terminology

Historically, infection of the heart valves has been classified as either acute or subacute

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bacterial endocarditis on the basis of clinical grounds. This division not only reflected severity of disease and clinical course but also was influenced by virulence of the infecting microorganism and presence of underlying cardiac disease. Acute bacterial endocarditis usually involves a virulent bacterial organism infecting a previously normal heart. The classic example of this is *Staphylococcus aureus* infection in intravenous drug abusers. In subacute bacterial endocarditis, a bacterial organism of low virulence infects a previously damaged heart, such as the case in a rheumatic heart infected by *Streptococcus viridans*. The virulent microorganisms of acute bacterial endocarditis can lead to necrotizing valvular infections that are difficult to cure with antibiotics and may require surgery, whereas the lower virulence microorganisms in subacute bacterial endocarditis cause less destructive disease and a protracted clinical course typically with a better outcome. Other causative bacteria include coagulase negative Staphylococci (*Staphylococcus epidermidis*), known to infect prosthetic valves, enterococci, and the HACEK group of oral cavity commensals (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella) [1]. There have also been reports of Gonococcus and gram-negative bacteria such as *Coxiella burnetii, Bartonella henselae*, and Brucella [2–5]. Although bacteria are the most common cause of endocarditis, infections are also caused by viruses, fungi, rickettsiae, and chlamydiae [6]. Given the numerous potential organisms underlying this disease, the preferred term today is infective endocarditis.

Furthermore, the glomerulonephritis due to infective endocarditis is not a postinfectious glomerulonephritis in that there is no latent period between eradication of the infection and onset of the glomerulonephritis, but is rather the result of an ongoing infection. Hence, the term endocarditis-associated or -related glomerulonephritis is preferred. In some patients with infective endocarditis, identification of the glomerulonephritis coincides with the first clinical recognition of infection [7].

Renal Disease Due to Infective Endocarditis

Renal disease due to infective endocarditis is well established with the earliest reports published over 100 years ago [8, 9]. The earliest literature on endocarditis-associated glomerulonephritis originated from autopsy specimens during the pre-antibiotic era. Though renal infarction and abscess formation were the most common findings, Löhlein in 1910, Baehr in 1912, and then in the 1930s Bell each described glomerular lesions associated with endocarditis [8–10]. All emphasized the presence of "embolic lesions." These lesions were thought to be caused by small infected emboli from the infected cardiac valve that lodged within glomerular capillaries. Given that septic emboli leading to micro- and macro-abscess formation was a very common finding in these autopsy studies, this was a seemingly sensible explanation for microscopic focal proliferative glomerular lesions with mild exudation. However, after prolonged searching only Baehr was able to demonstrate bacteria within these glomerular lesions in rare cases [9]. Building upon the work of others, Bell characterized two forms of glomerulitis found in association with endocarditis. The diffuse form he described as an increase in number and size of the endothelial cells with thickening of the capillary basement membranes. The embolic or focal form included the presence of two lesions, "fresh and fibrotic." The "fresh hyaline" lesion he described as thrombosis and necrosis of capillary loops and the "fibrous lesion" was described as a segmental or global fibrous obliteration of glomeruli. Analysis of his data reveals what appears to be the first description of epithelial crescents in the context of infective endocarditis [10]. Although not a point of emphasis, epithelial crescents were found in 31% of cases studied with subacute bacterial endocarditis. Even his well-known description of the "hyaline lesion," thought to be the result of the 'lodgement' of bacteria into glomerular capillaries, appears to be a segmental necrotizing lesion in the photomicrographs [10]. Illustrations of crescents

appeared in publications as early as the 1870s–1880s by Langhans and Purdy [11, 12]. Recognition that glomerular crescents correlated with poor outcome began to occur in the early 1900s by investigators including Volhard and Fahr and others [8, 13, 14]. However, perhaps Bell's lack of emphasis on the presence of crescents and failure to recognize the necrotizing lesions was due to the fact that this was written in an era before the full significance of these findings were well recognized. One should also keep in mind that these earlier studies were on autopsy specimens and that they all occurred during the pre-antibiotic era.

Historical Evolution of Glomerular Injury Pattern in Endocarditis-Associated Glomerulonephritis

Based on these early studies and the many reports that followed, it was thought that the most common form of glomerulonephritis associated with infective endocarditis is a focal, segmental, or diffuse proliferative glomerulonephritis consisting of the presence of endocapillary proliferation with occasional infiltrating leukocytes [15–17]. This is the endocarditis-associated glomerulonephritis previously discussed in the major renal medicine [18, 19] and renal pathology [20–23] textbooks and was said to be the major pattern seen in more than 80% of cases of infective endocarditis with a glomerulonephritis. However, the literature supporting this view in these reference works was largely derived from autopsy studies from the pre- and post-antibiotic era or early renal biopsy studies from the 1970s. Renal involvement related to infective endocarditis previously described in the literature was also in part based on clinical observations that lacked histologic confirmation.

The advent of antibiotics has drastically altered the clinical course and prognosis of infective endocarditis. Data by Spain and King [24] proved the decreased incidence of renal complications of infective endocarditis with the use of antibiotic therapy. In time, several observations argued against the embolic nature of renal injury in infective endocarditis, and a circulating immune complex mechanism was proposed [25–28]. The use of immunofluorescent microscopy for the evaluation of glomerular immunoglobulin and complement deposition has been pivotal in shifting this paradigm. Supporting the concept of circulating immune complex injury, the finding of granular glomerular basement membrane and mesangial deposition of immunoglobulins and complement was documented [25]. In contrast, support for activation of the alternate complement pathway has been shown in cases of *S. aureus* infective endocarditis [29]. There have also been reports of endocarditis-associated glomerulonephritis that show no immunoglobulin or complement positivity by immunofluorescence, and a single report of "full house" immunostaining [30–32].

However, though insight into the mechanism of infective endocarditis-associated glomerulonephritis is better understood, the most common histologic pattern related to infective endocarditis was until recently still thought to be the classic description of infection-associated glomerulonephritis: a focal, segmental, or diffuse global proliferative glomerulonephritis consisting of endocapillary hypercellularity with the conspicuous presence of inflammatory cells by light microscopic examination, and immunofluorescence showing granular immune complex deposition positive for C3 and IgG [15–17]. In these cases, large subepithelial "hump-like" deposits are typically seen by electron microscopy. These findings are prototypical of post-Streptococcal glomerulonephritis and were the pattern most commonly seen in a recent large series of post-infectious glomerulonephritis in the elderly in which Staphylococcus was the most common infectious agent [33].

Fernandez Guerrero et al. [16] published a large case series of infective endocarditis in 2012. It was derived entirely from autopsy study of 68 patients from 1970 through 2008 with emphasis on cardiac and brain pathology but they did also examine for glomerulonephritis. Although renal infarcts and abscess formation were the most often described renal

manifestations (in 30–36 and 18–19% of cases, respectively), still, glomerulonephritis was noted in 15% of cases between 1970 and 1985 and in 7% of cases between 1986 and 2008, with the most common pattern focal proliferative glomerulonephritis, with only one case of diffuse proliferative glomerulonephritis mentioned and no other patterns described. Interestingly, in another autopsy study of 82 cases with infective endocarditis from 1972 through 1986, Toth et al. noted 8 cases (10%) of crescentic glomerulonephritis [34]. Of interest, dating back to 1995, Montseny et al. studied 76 patients with infection-associated glomerulonephritis, of which 10 were related to endocarditis. Of these patients with endocarditis-associated glomerulonephritis, 3 had an endocapillary proliferative pattern and the majority, 7 patients, were crescentic. In comparison, glomerulonephritis related to all other sites of infection (including upper respiratory track, lung/pleura, skin, and teeth) showed an endocapillary proliferative pattern in the majority of cases, and in only a minority of cases a crescentic pattern [35]. Additionally, over the last twenty years, there have been case reports and mostly small case series describing the less familiar association of infective endocarditis with crescentic glomerulonephritis rather than focal or diffuse endocapillary proliferative glomerulonephritis [7, 17, 36–47].

One such series from the modern era was published in 2000 by Majumdar et al., with the majority of cases studied from post-mortem samples. They found that two-thirds of patients with endocarditis-associated glomerulonephritis showed a pauci-immune crescentic pattern of glomerular injury [48]. This long history of endocarditis-associated glomerulonephritis was built on by our study of 49 patients in 2015, which was the largest cohort of endocarditis-associated glomerulonephritis in the current era (2001–11) from nonautopsy cases studied exclusively by renal biopsy [49]. In this book chapter, this cohort has been further built on since that publication to now include 62 patients with endocarditis-associated glomerulonephritis. Of these 62 patients that fulfilled the modified Duke criteria [50] for diagnoses of infective

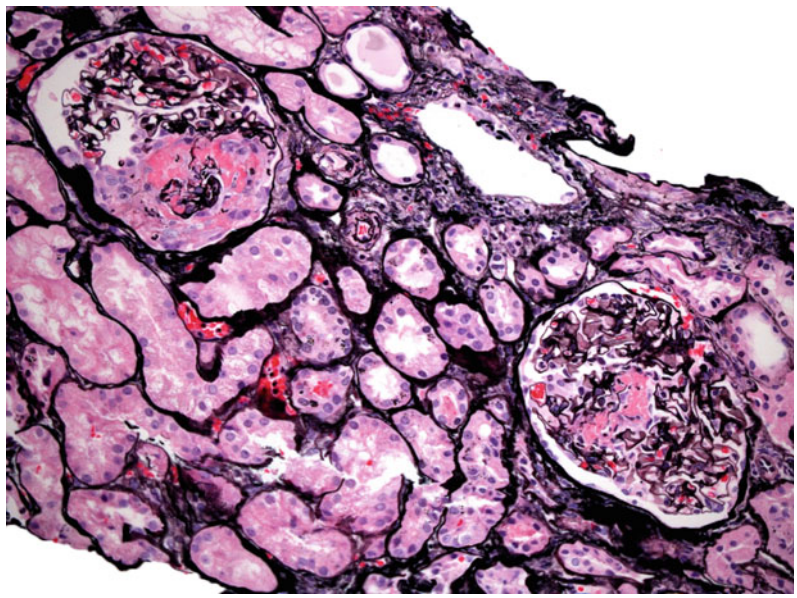

Fig. 4.1 Two glomeruli with segmental necrosis and one with a cellular crescent (glomerulus on the *left*) in a 62-year-old male with crescentic glomerulonephritis associated with mitral valve *Streptococcus viridans* infective endocarditis. The uninvolved portions of the glomerular tufts appear normal, with no mesangial expansion or endocapillary hypercellularity (Jones methenamine silver; ×200)

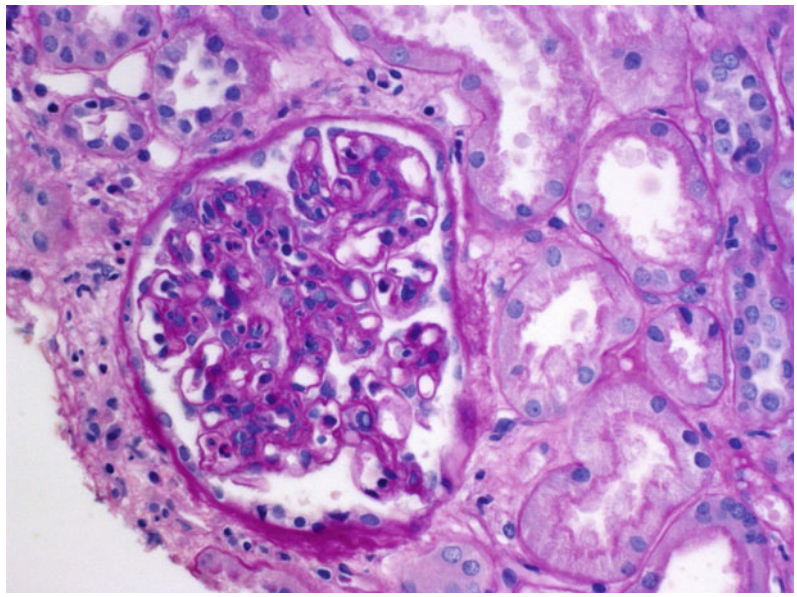

Fig. 4.2 Endocapillary hypercellularity in a patient with focal proliferative glomerulonephritis associated with aortic valve methicillin-sensitive *Staphylococcus aureus* infective endocarditis (periodic acid-Schiff; ×400)

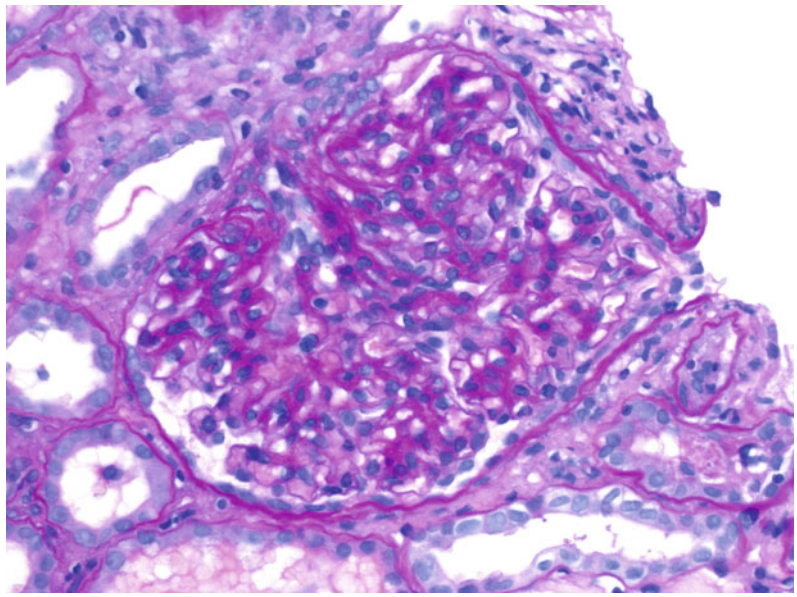

Fig. 4.3 Mild mesangial hypercellularity in a patient with infective endocarditis (periodic acid-Schiff; ×400)

endocarditis and underwent renal biopsies during the active phase of their illnesses, crescentic glomerulonephritis was the most common pattern of glomerular injury (47%) (Fig. 4.1), followed by focal or diffuse endocapillary proliferative glomerulonephritis (43%) (Fig. 4.2), and mesangial proliferative glomerulonephritis (10%) (Fig. 4.3). Of the endocarditis-associated crescentic glomerulonephritis cases, 41% were pauci-immune.

Therefore, endocarditis-associated glomerulonephritis is unique among infection-associated glomerulonephritides in that more recent studies demonstrate an evolution in awareness to a pauci-immune necrotizing and crescentic glomerulonephritis as the most commonly manifested pattern [49, 51]. Cases with immune complex deposition still occur, and various patterns are noted by light microscopy including the more familiar pattern of endocapillary proliferative glomerulonephritis. Mesangial proliferative glomerulonephritis also occurs, though least commonly and consequently receives little attention in the literature. Thus, the pattern of glomerular injury related to infective endocarditis is a spectrum, both in terms of light and immunofluorescence microscopy findings. The true incidence of glomerulonephritis associated with infective endocarditis is unknown, with autopsy studies reporting up to 22–26% [17, 48].

Clinical Presentation and Laboratory Data

Clinical Evolution of Endocarditis-Associated Glomerulonephritis

Just as the morphologic spectrum of endocarditis-associated glomerulonephritis has evolved, our own findings in infective endocarditis [49] confirm and extend observations emphasized in recent reviews documenting the evolution in clinical findings in bacterial infection-related GN in adults over the past three decades [51–53]. This evolution occurring in recent decades includes the change in demographics from younger to older patients, the frequency of comorbidities such as diabetes and HIV, and the change in predominance of infectious agents from primarily Streptococcal to a broader array of organisms with predominance of Staphylococci [33, 51, 54, 55].

Infective endocarditis carries a mortality rate of 40–50% [56]. Over the past decades, infective endocarditis outcomes have not improved, and infection rates are steadily increasing [56]. Recent case series and reviews of infective endocarditis have compared findings from current and previous eras, confirmed similar changes in the demographics of the disease and updated the clinical and pathologic features in both adults and children [16, 57]. However, few of these recent reports have focused primarily on infective endocarditis-related renal lesions, and much of the data currently available still includes predominately autopsy-derived information [16, 48].

Clinical Presentation

In keeping with the overall trends in infection-related glomerulonephritis, findings in infective endocarditis in the current era involve predominately adult males with a 2.6:1 male predominance, older mean age at biopsy (mean age 47 years) with 25% elderly patients, and increased prevalence of Staphylococcal rather than Streptococcal infection (Tables 4.1 and 4.2) [49]. In general, postinfectious and infection-associated glomerulonephritis typically present with the acute nephritic syndrome and hypocomplementemia [23]. The most common presentation of infective endocarditis-associated glomerulonephritis is acute renal failure in which there was doubling of the serum creatinine (82%) (Table 4.1) [49]. This observation that the most common presentation is acute renal failure rather than acute nephritic syndrome differs from overall findings in infection-related glomerulonephritis [23, 51] and may be unique to this patient population with compromised cardiac function. In our material, only 8% presented with the typical acute nephritic syndrome of hematuria, hypertension, and renal failure and only about sixty percent with low serum complement levels. Other clinical syndromes at presentation include rapidly progressive glomerulonephritis (5%), and nephrotic syndrome with nephrotic range proteinuria (>3.5 g/day), hypoalbuminemia (serum albumin <3 g/dL), and peripheral edema (5%) (Table 4.1). The unique manifestations of endocarditis-associated glomerulonephritis are possibly related to the fact that these infections are

Table 4.1 Demographics, predisposing factors for infection, and clinical characteristics of 62 patients with endocarditis-associated glomerulonephritis

	No. of patients (%)
Male: female	45:17 (73:27)
Age, mean years (range)	47 (3–84)
<19	2 (3)
19–29	7 (11)
30–39	14 (23)
40–49	14 (23)
50–59	9 (15)
60 or older	16 (25)
Predisposing factors for infection	
Intravenous drug abuse	23 (37)
Prosthetic cardiac valve	10 (16)
Cardiac valve disease/shunt	7 (11)
Hepatitis C	15 (24)
Diabetes mellitus	11 (18)
Clinical presenting syndrome of 60 patients	
Acute renal failure	49 (82)
Acute nephritic syndrome	5 (8)
Rapidly progressive glomerulonephritis	3 (5)
Nephrotic syndrome	3 (5)
Laboratory data and serologies	
Mean serum creatinine at biopsy (mg/dL) (range)	3.8 (1.0–12.0)
Mean Proteinuria (grams per day) (range)	2.1 (0.5–15)
Hematuria, n = 47	46 (98)
Positive ANA, n = 28 patients tested	4 (14)
Positive ANCA, n = 32 patents tested	8 (25)
C3/C4, n = 40	–
Normal C3 and C4	16 (40)
Low C3, Normal C4	14 (35)
Low C4, Normal C3	1 (2)
Low C3 and C4	9 (23)

often persistent and ongoing at the time of the kidney biopsy rather than being a classic postinfectious phenomenon [51]. Furthermore, the diagnosis of glomerulonephritis could prompt investigations that lead to a diagnosis of infective endocarditis. Indeed, cases of rapidly progressive ANCA-positive glomerulonephritis have been reported as the presenting feature of infective endocarditis [58, 59].

Predisposing States or Coexisting Conditions

Conditions favoring endocarditis are noted in a majority (64%) of our patients, including intravenous drug use (37%), prosthetic valves (16%), and prior valvular disease (11%), yet this leaves over 50% of patients with no known prior cardiac disease (Table 4.1) [49]. A minority of patients

Table 4.2 Culture data and cardiac characteristics of endocarditis from 62 patients with endocarditis-associated glomerulonephritis

	No. of patients (%)				
Culture results					
Positive	57 (92)				
Negative[a]	4 (6)				
Unknown	1 (2)				
Valve/location[b]	–				
Tricuspid	24 (44)				
Mitral	21 (38)				
Aortic	13 (24)				
Pulmonic	2 (4)				
Chordae tendinae	1 (2)				
Bacterial agent					
Staphylococcus	36 (58)				
Methicillin-resistant *Staphylococcus aureus*	16				
Methicillin-sensitive *Staphylococcus aureus*	17				
Staphylococcus not further specified	3				
Streptococcus	13 (21)				
Streptococcus viridans	4				
Streptococcus agalactiae	1				
Streptococcus mitis	1				
Streptococcus sanguinis	1				
Enterococcus faecalis	3				
Streptococcus not further specified	3				
Bartonella henselae	4 (6)				
Coxiella burnetii	2 (3)				
Cardiobacterium hominis	1 (2)				
Gemella	1 (2)				
Location					
–	Tricuspid	Mitral	Aortic	Pulmonic	Chordae
Agent	(%)	(%)	(%)	(%)	(%)
Staphylococcus	84	48	46	50	0
Streptococcus	8	38	23	0	0
Other or culture-negative	8	14	31	50	100

[a]One of the four patients with Bartonella infection was identified by serologies not blood culture
[b]Two patients had involvement of both the aortic and mitral valves, three with involvement of both tricuspid and mitral valves, and one with involvement of tricuspid and pulmonic valves

had associated comorbid conditions, with the most common being hepatitis C infection (24%) and diabetes mellitus (18%) (Fig. 4.4). Less common predisposing states or coexisting conditions included coronary artery disease, chronic obstructive pulmonary disease, congestive heart failure, autoimmune disease, recent surgery, and malignancy [49].

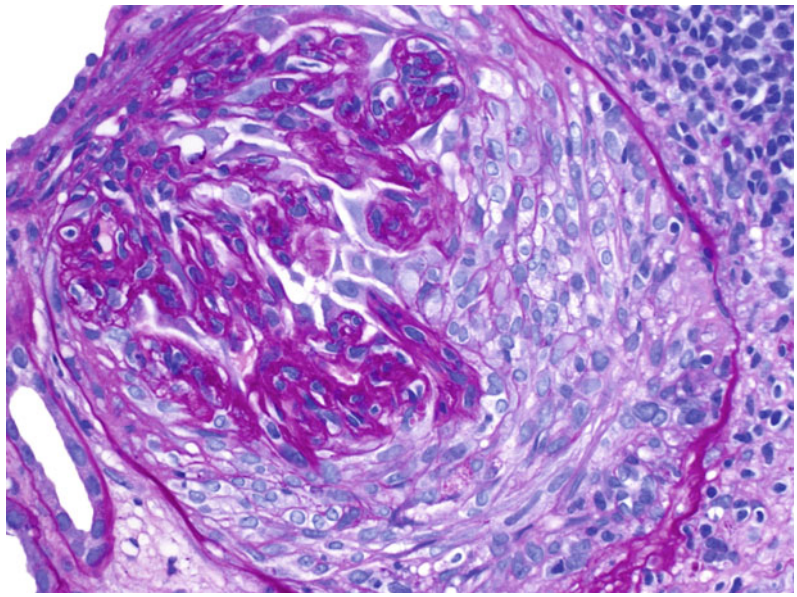

Fig. 4.4 Cellular crescent in a 54-year-old diabetic male with *Streptococcus agalactiae* tricuspid valve endocarditis who presented with nephrotic syndrome (periodic acid-Schiff; ×400)

Laboratory Data and Serologic Studies

In general, bacterial infections can trigger the production of various autoantibodies, such as antinuclear antibodies (ANA), anticardiolipin antibodies, cryoglobulins, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies (ANCA) [37, 60]. In our renal biopsy study of endocarditis-associated glomerulonephritis [49], the average serum creatinine was 3.8 mg/dL (range 1.0–12.0) (Table 4.1). Hematuria was present in almost all cases. Daily proteinuria averaged 2.1 g (range 0.5–15). Twenty-eight patients had an ANA test, 86% of which were negative. ANCA testing was carried out in over half of patients and was positive in 25%. ANCA specificities included both pANCA and cANCA, as well as cases with dual positivity (Table 4.1) (Fig. 4.5) [49]. In general, ANCA specificity associated with endocarditis was initially thought to be anti-PR3, but cases with dual ANCA positivity and MPO-ANCA positivity have also now been reported in association with endocarditis [37, 49, 61–63]. Testing for cryoglobulins have varied reports of positivity from 17 to 95% positive, though many of these studies have limited renal histologic correlation [60] and the cryoglobulin test is frequently false negative. Similarly, large amounts of serum immunoglobulins and circulating immune complexes may be formed as a result of bacteremia, but this does not necessarily imply deposition within the kidney by immunofluorescence [47]. Just over half of patients (60%) had hypocomplementemia in our renal biopsy series, which was most commonly (35%) low C3 (complement component 3) with normal C4 (complement component 4); since only a few patients had reduction in C4 this suggests most had activation of the alternative complement pathway.

Cardiac Involvement

Infective endocarditis can involve any one of the four cardiac valves. In our current expanded study of 62 patients, endocarditis leading to glomerulonephritis most commonly involved the tricuspid valve (44%), followed by the mitral (38%), aortic (24%), and pulmonic (4%) valves

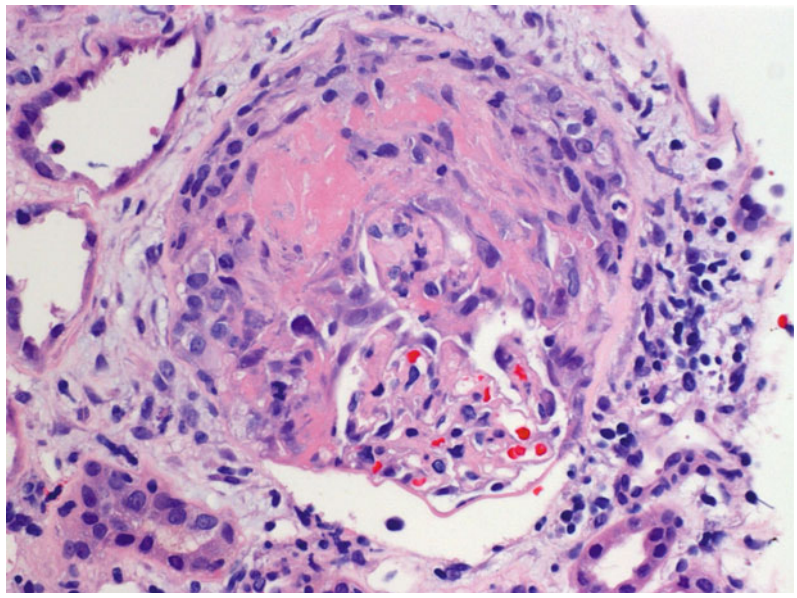

Fig. 4.5 Necrosis in a glomerulus from a patient with a prosthetic pulmonic valve and Bartonella pulmonic valve infective endocarditis in which the immunofluorescence showed 2+ IgG, 2–3+ IgM, and 2–3+ C3. ANCA serologies were positive for both MPO and PR3. The patient was treated with antibiotics and steroids, then after surgical treatment with pulmonic valve replacement, the ANCA titers decreased. (hematoxylin and eosin; ×400)

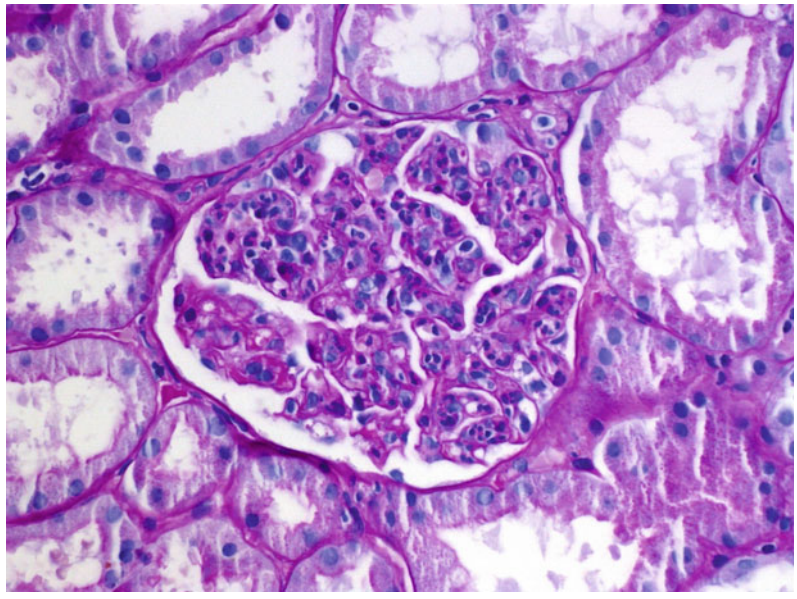

Fig. 4.6 Global endocapillary hypercellularity in a 47-year-old female intravenous drug user with diffuse proliferative glomerulonephritis associated with tricuspid and pulmonic valve methicillin-sensitive *Staphylococcus aureus* infective endocarditis. Immunofluorescence microscopy showed trace IgG, negative IgA, negative IgM, and 2–3+ C3 in a granular mesangial and capillary wall pattern. The patient had recurrent infective endocarditis two years following the initial biopsy. (PAS; ×400)

(Table 4.2); infection of more than one valve was seen in 10% of patients (Fig. 4.6). In our study, 84% represented patients with community-acquired infective endocarditis in native valves, 94% of which had positive blood cultures compared to 90% positive blood cultures in the patients with prosthetic valve endocarditis [49]. One of the major Duke's criteria to the diagnosis of infective endocarditis is vegetations noted by echocardiogram; these were noted in greater than two-thirds of patients in our renal biopsy study [49]. Of note, because transthoracic echocardiogram may not be able to detect small vegetations, transesophageal echocardiogram may be needed [64]. The most commonly noted sign of cardiac involvement in patients without vegetations on echocardiogram was new valvular regurgitation/murmur; the most common other criteria for diagnosis of infective endocarditis in these patients included fever, septic pulmonary emboli, and predisposing heart condition or injection drug use. For the entire cohort, the most common vascular phenomena was septic pulmonary infarcts, with only a minority of patients with the finding of intracranial hemorrhage, and rare patients with findings including conjunctival hemorrhages, nail splinter hemorrhages, or evidence of mycotic aneurysm [49].

Infectious Agents

Several studies note a similar rate of culture-negative endocarditis at about 8–9% [49, 65, 66]. Over half of patients with culture positive endocarditis are classified as having acute rather than subacute endocarditis. In our experience, the agent found on culture in the acute group is most often *S. aureus* (58%), with methicillin resistance in almost half (44%); the second most common pathogens found are Streptococcus species (21%) (Table 4.2) [49]. Less common causes of endocarditis noted include Gemella species, Gonococcus, and gram-negative bacteria such as *C. burnetii, B. henselae*, and Brucella [2–5, 49], as well as the HACEK group of oral cavity commensals (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella) [1]. The most common cause of endocarditis in patients with history of IV drug abuse is Staphylococcal infection (86%), affecting the tricuspid valve or tricuspid and pulmonic valves in 74%, followed by mitral or aortic valves in 26% [49].

Pathologic Findings and Clinicopathologic Correlation

Light Microscopy

Glomerular Findings

The patterns of glomerular injury described associated with infective endocarditis predominately include focal or diffuse necrotizing and crescentic glomerulonephritis, focal or diffuse endocapillary proliferative glomerulonephritis, and mesangial proliferative glomerulonephritis. Rare reports of endocarditis-associated glomerulonephritis with cryoglobulinemia with an MPGN pattern have also been described [59]. Designation as focal versus diffuse is made by applying the typical cut-off value of 50%, with focal meaning <50% of nonsclerotic glomeruli are involved and diffuse meaning $\geq$50% of nonsclerotic glomeruli are involved [67, 68]. Glomerular endocapillary proliferation in biopsies with focal or diffuse proliferative patterns is defined as endocapillary hypercellularity and occlusion of capillary lumens by endothelial cells, mesangial cells, and/or white blood cells from the peripheral circulation. In our study, cases of endocarditis-associated glomerulonephritis with a crescentic pattern do not show proliferative changes in portions of the glomerular tufts uninvolved by necrosis or crescent formation. Glomeruli with an increase in mesangial matrix and cells without closure of capillary lumens are included in the mesangial proliferative group. Proliferation in biopsies with the mesangial proliferative pattern of glomerular injury is defined as $\geq$4 cells per mesangial region in more than 50% of glomeruli without occlusion of capillary loops [69].

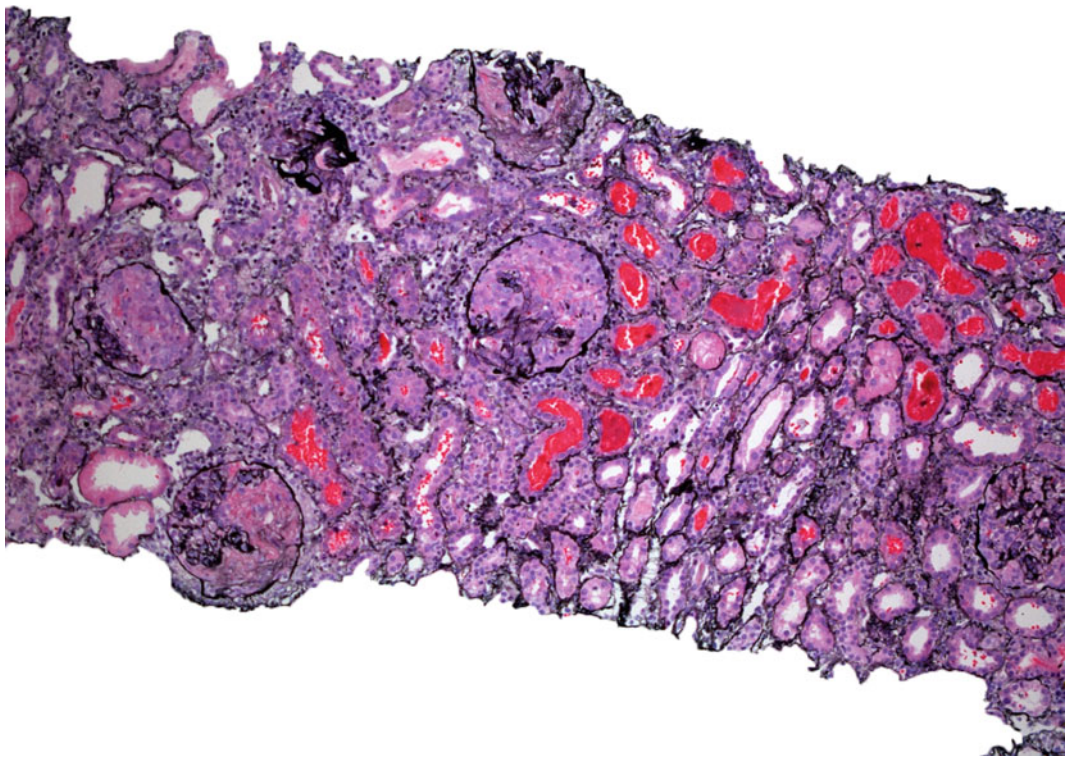

Fig. 4.7 Diffuse necrotizing and crescentic glomerulonephritis with numerous red blood cell casts in a 31-year-old male with culture-negative aortic valve endocarditis involving 88% of glomeruli. ANCA serology was negative. The patient was treated with antibiotics, steroids, and cytoxan, and had persistent renal dysfunction at 23 months follow-up (Jones methenamine silver; ×100)

The most common pattern of glomerulonephritis associated with infection in general is typically that of endocapillary proliferation. However, infective endocarditis-associated glomerulonephritis is unique in that the most common pattern recently recognized is a crescentic glomerulonephritis (in 47% of patients) (Fig. 4.7); in a majority of patients these glomerular inflammatory changes are diffuse (59%) and necrotizing lesions are frequent (79%) (Table 4.3) [49]. Diffuse endocapillary proliferative glomerulonephritis is the second most common pattern (37%) (Fig. 4.8). Of the patients with proliferative glomerulonephritis, some also had focal crescent formation. Only two cases in our renal biopsy study of 49 patients published in 2015 had the previously classically described pattern of focal proliferative glomerulonephritis without crescents or necrosis (4%) [49]. Over 20 years prior, case reports and small case series have also documented the association of infective endocarditis with crescentic glomerulonephritis rather than focal or diffuse proliferative glomerulonephritis [7, 17, 34, 36–47]. In 2000, Majumdar et al. [48] found that two-thirds of patients with endocarditis-associated glomerulonephritis showed a pauci-immune crescentic pattern of glomerular injury.

Mild mesangial hypercellularity is the third major finding after crescentic and endocapillary proliferative glomerulonephritis and account for 10% of cases [49]. All of these cases showed only mild and often segmental mesangial hypercellularity without endocapillary proliferation or crescent formation.

In our study of 62 patients with endocarditis-associated glomerulonephritis, glomerulonephritis with membranoproliferative pattern or

Table 4.3 Renal biopsy findings from 62 patients with endocarditis-associated glomerulonephritis

	No. of patients (%)			
Glomerular pattern of injury by light microscopy				
Crescentic	29 (47)			
Focal	12 (19)			
Diffuse	17 (28)			
Necrotizing foci	23 of 29 (79)			
Proliferative	27 (43)			
Focal	4 (6)			
Diffuse	23 (37)			
Mesangial Proliferative	6 (10)			
Staining pattern by immunofluorescence microscopy				
Negative	3 (5)			
Granular mesangial only	24 (39)			
Granular capillary wall only	2 (3)			
Granular mesangial and capillary wall	33 (53)			
Location and quality of electron dense deposits by ultrastructural examination				
Mesangial electron dense deposits	54 (87)			
Subendothelial electron dense deposits	29 (47)			
Subepithelial electron dense deposits	21 (34)			
Subepithelial or hinge region hump-like deposits	11 (18)			
No deposits identified	5 (8)			
Immunoreactant profile				
	IgG	IgM	IgA	C3
Positive staining (%) (mean intensity)	34 (1.8)	34 (2.0)	29 (2.0)	95 (2.5)
C3 + single immunoglobulin or C3 only (%)	6	13	5	37
Combined immunoglobulins	IgG IgM	IgG IgA	IgM IgA	IgG IgM IgA
%	8	15	5	5

membranous glomerulopathy was not seen. Specifically, no cases of membranoproliferative glomerulonephritis with or without cryoglobulinemic features or cases of thrombotic microangiopathy were found. In our study, a mean of 10% of glomeruli were globally sclerotic (range, 0–53%) [49].

Tubulointerstitial and Vascular Findings

Acute tubular injury is present in the background in the majority of cases, typically manifested by thinning of the tubular epithelium (Fig. 4.9). In part, this may be the result of obstructed blood flow through glomeruli and thus impaired perfusion of the tubules by way of the peritubular capillaries. Red blood cell casts are noted histologically in more than half of the cases. Almost all cases have interstitial inflammation (Fig. 4.10), which is most often focal, but abundant interstitial neutrophils are present in a minority of cases. Large numbers of eosinophils are usually not seen.

Though infarcts and micro-abscesses are noted most commonly in autopsy studies, no micro-abscesses or cortical necrosis were present in our renal biopsy material of 62 cases. The degree of tubular atrophy and interstitial fibrosis

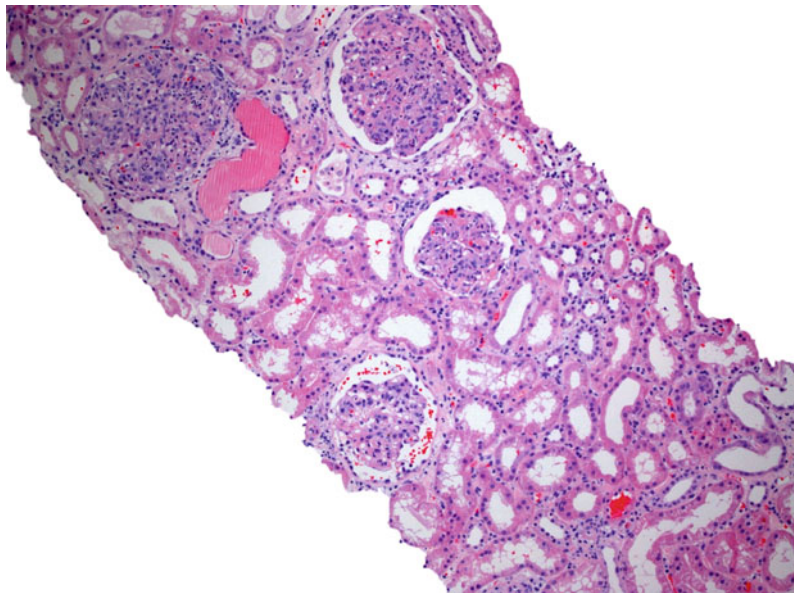

Fig. 4.8 Diffuse endocapillary proliferative glomerulonephritis in a patient with methicillin-resistant *Staphylococcus aureus* infective endocarditis (hematoxylin and eosin; ×100)

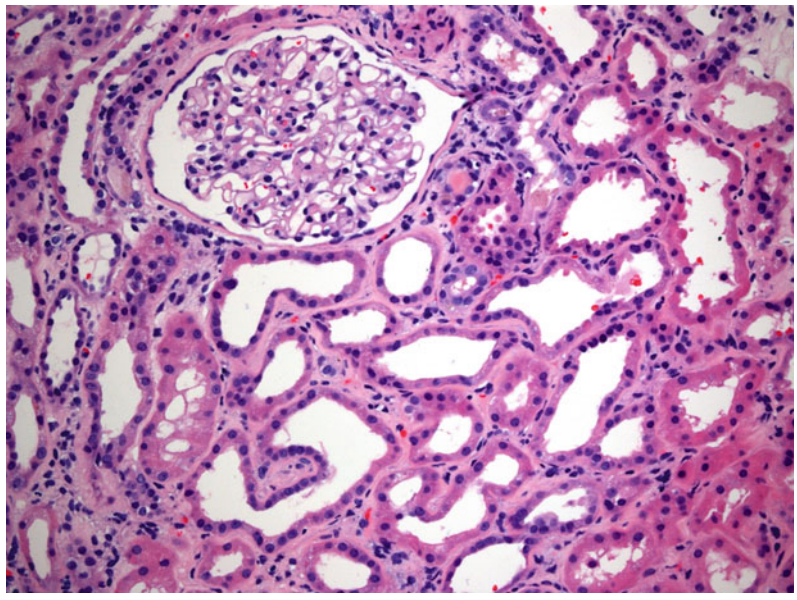

Fig. 4.9 Normal appearing glomerulus and surrounding tubular injury manifested by cytoplasmic thinning and mild luminal ectasia, from a 45-year-old male with history of rheumatic fever as a child and mitral valve insufficiency. He developed mitral valve *Coxiella burnetii* infective endocarditis with acute kidney injury and a renal biopsy showed focal crescentic glomerulonephritis (not shown) involving 15% of glomeruli. The patient was treated with antibiotics, and had persistent renal dysfunction at follow-up (hematoxylin and eosin; ×200)

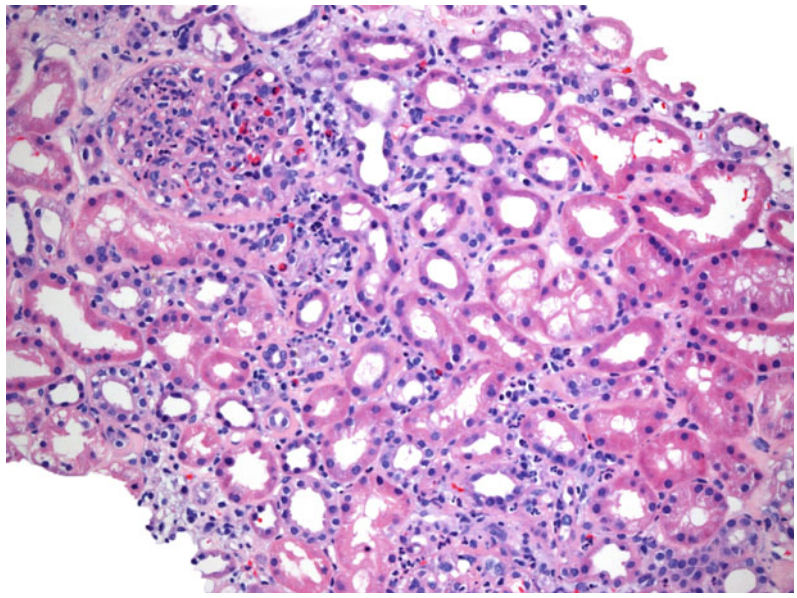

Fig. 4.10 Glomerulus with endocapillary proliferation including neutrophils, and surrounding mild interstitial inflammation in an 84-year-old male with infective endocarditis-associated diffuse proliferative glomerulonephritis (hematoxylin and eosin; ×200)

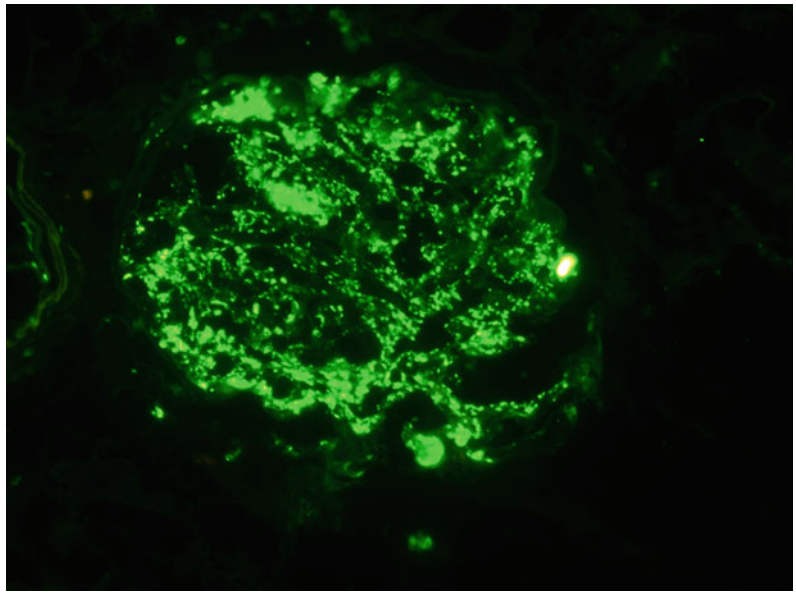

Fig. 4.11 Glomerulus with coarsely granular mesangial and capillary wall staining for C3 (direct immunofluorescence; ×400)

present was most often mild (<25% of estimated cortical involvement) (40%) or absent (42%). Similarly, arteriosclerosis and arteriolar hyalinosis were most often absent (33%) or mild (32%). Vasculitis in the form of necrotizing arteritis was not noted.

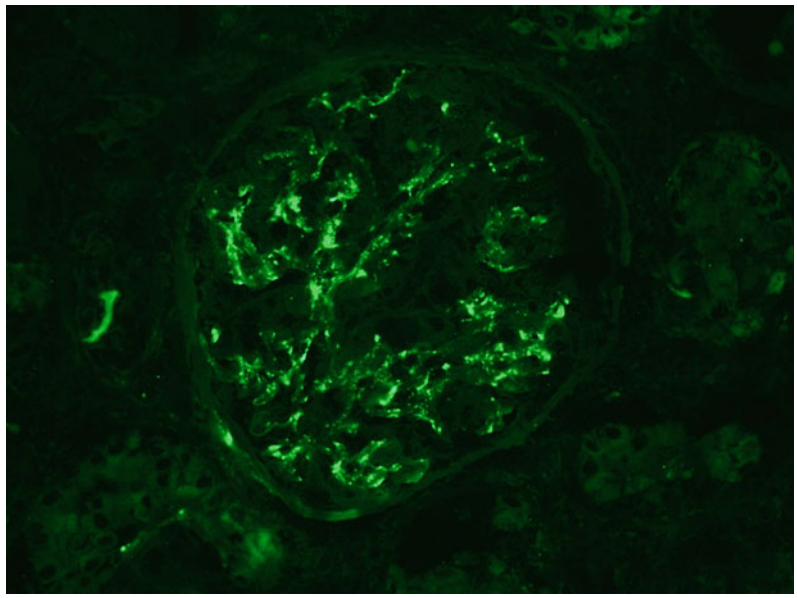

Fig. 4.12 Glomerulus with granular predominantly mesangial staining for C3 (direct immunofluorescence; ×400)

Table 4.4 Immunofluorescent findings related to light microscopy pattern of endocarditis-associated glomerulonephritis in 62 patients

	Crescentic, n = 29	Acute proliferative, n = 27	Mesangial proliferative, n = 6
Pauci-immune, n (%)	12 (41)	9 (33)	6 (100)
–	% Positive (mean intensity)	% Positive (mean intensity)	% Positive (mean intensity)
Immunoreactant			
IgG	21 (1.6)	56 (1.9)	0
IgM	55 (2.0)	19 (2.5)	0
IgA	17 (1.8)	52 (2.2)	0
C3	93 (2.5)	100 (2.7)	100 (2.8)

Immunofluorescence

One has to pay attention to and look for and evaluate glomeruli with no or small crescents to avoid over-interpreting nonspecific staining secondary to glomerular necrosis and crescent formation. Deposits by immunofluorescence appear granular, with the location most often either a combination of mesangial and capillary loop (53%) (Fig. 4.11) or within the mesangial region only (39%) (Fig. 4.12) (Table 4.3). Though completely negative staining by immunofluorescence for immunoglobulins and complement is rare (5% of biopsies), up to 44% of biopsies in our study of 62 patients met criteria for pauci-immune staining intensity of immunoglobulins. Almost half of these (12 patients) had crescentic glomerulonephritis by light microscopy (Table 4.4). Of these 12 patients, ANCA was positive in 3, negative in 5, and not done in 4. In 2000, Majumdar et al. [48] also found that two-thirds of patients with endocarditis-associated glomerulonephritis have a pauci-immune pattern. Pauci-immune was

defined as staining 0–2+ or less intensity for all immunoglobulins (IgG, IgM, and IgA) on a scale of 0–4+ [70]. Most pathologists using a 0–3 + scale, pauci-immune is usually defined as positivity of 1+ or less. Though the staining properties of C3 can be controversial and inconsistently interpreted as immune complex type or not, in our study of endocarditis-associated glomerulonephritis, the definition of pauci-immune disease is defined by immunoglobulin staining only, and does not account for the intensity of complement staining in glomeruli. This also seems prudent given that large case series have shown glomerular C3 deposition is not uncommon in pauci-immune, ANCA-associated glomerulonephritis [70, 71].

Immunofluorescence examination in cases of endocarditis-associated glomerulonephritis will most likely show C3 (95% of cases show positivity) (Table 4.3) [49]. C3 also has the highest mean intensity compared to other immunoreactants when positive (Tables 4.3 and 4.4). Cases with positivity for at least one subclass of immunoglobulin will typically also show complement staining. In our study of 62 patients, IgA was the least common immunoglobulin to be positive (29%), whereas IgG and IgM were both positive in 34% (Table 4.3) [49]. Interestingly, just over half of the cases with an endocapillary proliferative pattern by light microscopy had positive IgG (56%), and biopsies with a crescentic pattern had IgG in only 21% of cases. In this study, nine cases had IgA-dominant staining and an additional two were codominant for IgA and IgG (total 18%). A "full house" pattern with IgG, IgM, IgA, and complement positivity was seen in only 3% of cases. C3 only staining was present in 37% of cases (Table 4.3).

It is worth mentioning that the definition of pauci-immune necrotizing and crescentic glomerulonephritis is arbitrary. Mostly, "pauci-immune" is defined based on immunofluorescence findings, and some base this only on the presence or absence of immunoglobulins, disregarding complement (particularly C3). To some, immunofluorescence with C3 only staining better fits into the category "pauci-immune" because C3 only is not technically not part of an "immune complex" (meaning, complement together with immunoglobulin). However, strong C3 staining despite lack of immunoglobulin, especially together with well-defined electron dense deposits by ultrastructural examination, still suggests an immune-mediated process that should raise the possibility of an infection-related etiology; this is the case with many of the cases of endocarditis-associated glomerulonephritis described herein. The classic designations of immunofluorescent findings are primarily the subdivisions of "immune complex type" versus "pauci-immune." In reality, C3-predomiant staining could be a third and separate category in itself because when C3 only or predominant staining is detected, one must make the sometimes arduous decision as to which category to place these findings. For example, in that sense, many cases of poststreptococcal glomerulonephritis could in theory be classified as pauci-immune because there is only C3 deposition, even though there are plenty of subepithelial "humps" by electron microscopy. Many cases of infection-associated glomerulonephritis have C3 deposits only or C3-dominant deposits with only relatively weak immunoglobulin staining. The key is that pauci-immune is not synonymous with not being immune-mediated, it is just not associated with large clumps of immune complexes. For this reason, electron microscopy, if possible, should be performed in every case because, if there is a well-perfused glomerulus with open capillaries present for examination, and if there are no or very few electron dense immune-type deposits present, that finding is more consistent with a pauci-immune process such as that noted in the majority of ANCA-mediated disease.

Electron Microscopy

Consistent with immunofluorescence findings, electron dense deposits by ultrastructural examination are most commonly present within the mesangium (Fig. 4.13). In our renal biopsy series of 62 patients with endocarditis-associated

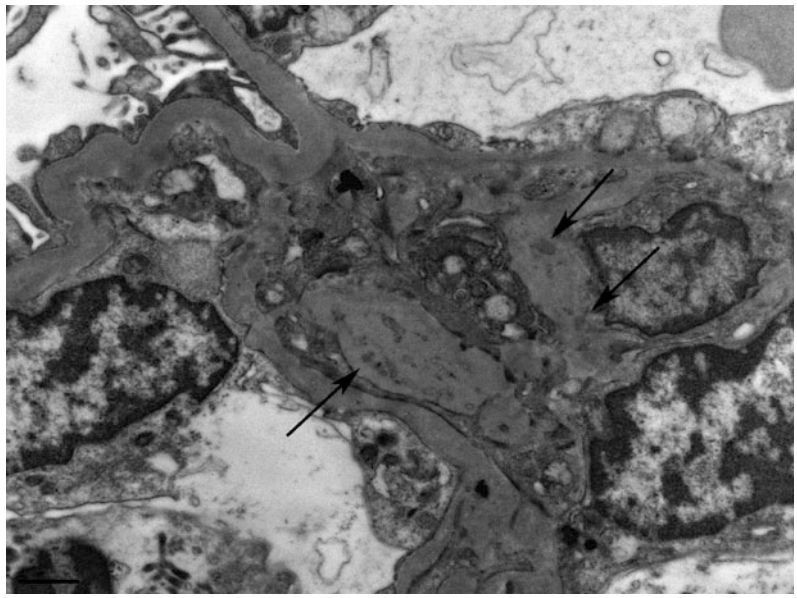

Fig. 4.13 Small electron dense deposits within the glomerular mesangium (*arrows*) (osmium tetroxide, ×12,000)

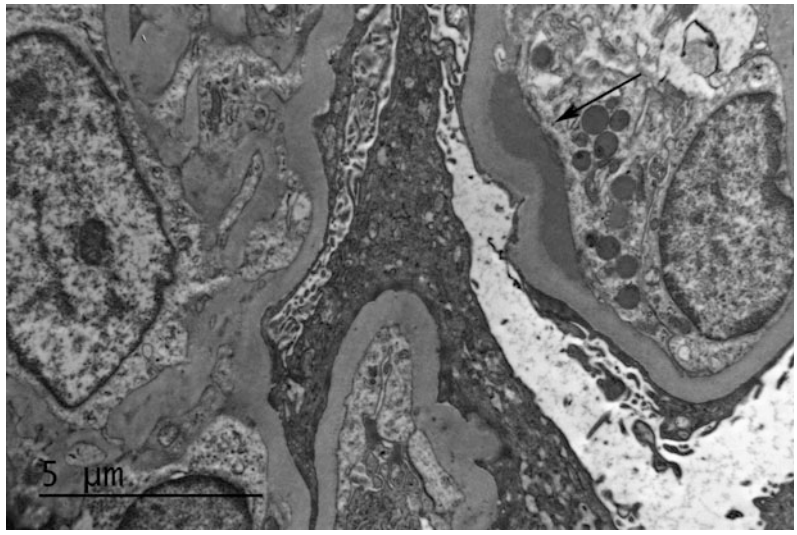

Fig. 4.14 Subendothelial electron dense deposit in a patient with diffuse proliferative glomerulonephritis associated with prosthetic aortic valve *Streptococcus viridans* infective endocarditis (osmium tetroxide, ×12,000)

glomerulonephritis, mesangial electron dense deposits were noted in 87% of cases, subendothelial electron dense deposits in 47% (Fig. 4.14), and subepithelial electron dense deposits in 34% of cases (Table 4.3); but only the minority of cases (18%) showed the classic infection-related large subepithelial humps [49]. Interestingly, in more than one series of IgA-dominant Staphylococcal infection-associated glomerulonephritis in the literature, large subepithelial humps were similarly rare or were not seen [72, 73]. In contrast, in

a study of 109 elderly patients with postinfectious glomerulonephritis from various etiologies combined, subepithelial electron dense deposits were seen in 92% of cases and in most cases exhibited a "hump-shaped" appearance [33]. Therefore, while it is helpful when large "hump-like" subepithelial or hinge region electron dense deposits are noted, their absence does not exclude an infectious etiology. The degree of foot process effacement in endocarditis-associated glomerulonephritis ranges from none to severe, with approximately equal proportions of none, mild, moderate, and severe [49].

Clinicopathologic Correlation

Infectious Agent and Biopsy Findings

Interestingly, although there was no statistical difference between the occurrences of staphylococcal or streptococcal species on blood cultures between pauci-immune cases and those with immune complex deposition in our series, all cases with Bartonella, Coxiella, or Cardiobacterium on culture had immunoglobulin and C3 deposition by immunofluorescence [49]. We did not find significant associations between the bacterial agent on culture and the various light microscopic patterns of glomerulonephritis except that most cases with Bartonella, Coxiella, Cardiobacterium, or Gemella had crescentic glomerulonephritis and 3/4 cases of culture-negative endocarditis patients had crescentic glomerulonephritis. Similarly, Bookman et al. [4] and Liapis (referenced in [23]) presented 4 cases of *B. henselae* endocarditis-associated necrotizing and crescentic glomerulonephritis which mimicked vasculitis by light microscopy, with C3 staining by immunofluorescence and mesangial and subendothelial deposits by electron microscopy [4, 23].

Immunopathology

The immunopathology of endocarditis-associated glomerulonephritis has not been well characterized previously beyond identification of IgG and C3 deposition in an immune complex pattern [25–28, 48]. Recent biopsy series suggest that more complex pathogenic mechanisms are involved. Although C3 staining was positive in virtually the entire cohort in our large renal biopsy series, staining for IgG was present in only 34% and in fewer than 21% of those with the most severe crescentic lesions [49]; in fact, IgM was equal to IgG as the most commonly noted immunoglobulin (34%), and showed higher mean staining intensity when positive (2.0) compared to IgG (1.8) (Fig. 4.15, Tables 4.3 and 4.4). A lack of immunoglobulin staining in crescentic endocarditis-associated glomerulonephritis has been noted in more than one study [48, 49]. The finding of prominent C3 staining and the presence of readily detectable immune deposits by EM are more consistent with the C3-dominant pattern of immune deposition commonly seen in infection-related GN in general [51]. Some C3 deposition can also be seen in ANCA-associated vasculitis in 33–85% of cases; however, electron microscopy usually shows no or only few deposits [70, 71, 74].

Furthermore, there is as much inconsistency in the literature as there is controversy regarding the classification of glomerulonephritis as immune complex-type versus pauci-immune. In theory, the term "immune complex" would refer to complexes of both immunoglobulins together with complement components identified by tissue immunofluorescence study. One must observe when the term "immune complex-type" is reported yet immunofluorescence reveals C3 only without immunoglobulin staining. Though large amounts of serum immunoglobulins and circulating immune complexes may be formed as a result of bacteremia, this does not necessarily imply deposition within the kidney by immunofluorescence.

Interestingly, despite the now known association of IgA-dominant infection-associated glomerulonephritis occurring with staphylococcal infections in both diabetic patients and non-diabetics [72, 73] and the fact that staphylococcal infections are now the most common causative agent for endocarditis-associated glomerulonephritis, IgA is present in less than one third of cases of endocarditis-associated glomerulonephritis by immunofluorescence.

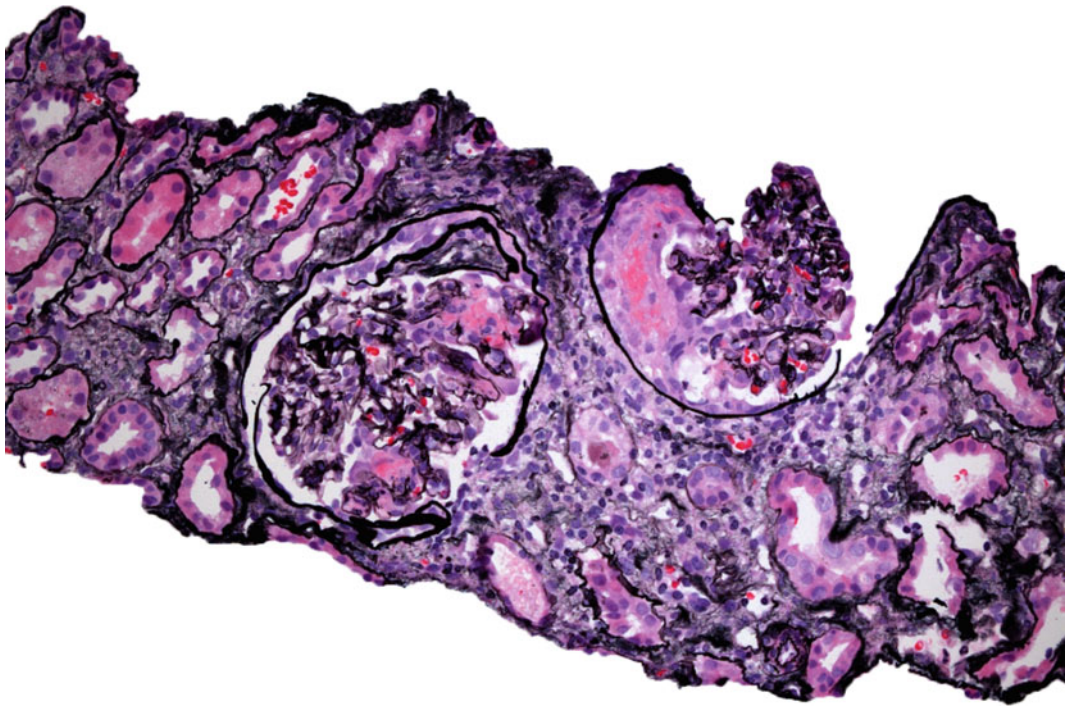

Fig. 4.15 Glomeruli with necrosis and cellular crescent formation from a biopsy with crescentic glomerulonephritis involving 75% of glomeruli, associated with tricuspid valve *Streptococcus mitis* infective endocarditis in a 43-year-old female intravenous drug user. ANCA serology was negative. Immunofluorescence microscopy showed 2–3+ IgM and C3 in a granular mesangial and capillary wall pattern. The patient was treated with antibiotics and had a full renal recovery at 6 months (Jones methenamine silver; ×200)

Crescentic Glomerulonephritis and Differential Diagnosis of Vasculitis

Initiating mechanisms that lead to crescent formation have been simplified to antibodies (including ANCA via activating neutrophils and anti-GBM) and immune complexes, however, more complex and heterogeneous mechanisms are likely triggers to glomerular injury. Today, when a pauci-immune crescentic glomerulonephritis is present, the emphasis is on ANCA-associated glomerulonephritis and it can be easily forgotten that glomerular injury of various etiologies can result in crescent formation. Indeed, crescentic glomerulonephritis has been recognized by others as a final and fatal pathway of several etiologically diverse glomerular disease processes [75]. The common initiating mechanism is rupture or compromise of glomerular capillary walls, allowing inflammatory mediators to enter Bowman's space and stimulate epithelial proliferation. The presence of fibrin is an indication that plasma constituents have entered as well. In time, the cells of the crescent are replaced by collagen as evidenced by the evolution of cellular crescents to fibrocellular and then fibrous crescents. Rather than being a specific disease, necrotizing and crescentic glomerulonephritis is the most severe form of glomerular inflammation observed histologically [76]. Today, we know the aggressive nature of this lesion and the importance of excluding ANCA-associated disease when a crescentic glomerulonephritis is present. After all, ANCA-associated disease is the most common cause of pauci-immune crescentic glomerulonephritis [74, 77].

However, endocarditis-associated glomerulonephritis is an important entity to consider in the differential diagnosis given the significant morphologic and clinical overlap (Fig. 4.16).

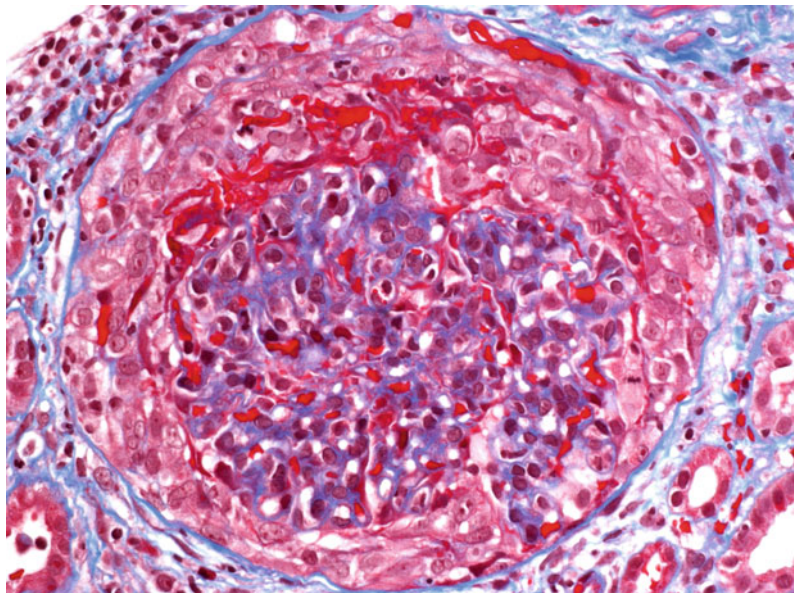

Fig. 4.16 Necrosis and circumferential cellular crescent in a 30-year-old male with ANCA-negative diffuse crescentic glomerulonephritis associated with methicillin-resistant *Staphylococcus aureus* infective endocarditis (Masson's trichrome stain; ×400)

Importantly, the presence of a positive ANCA serology does not exclude the possibility of endocarditis-associated glomerulonephritis, as 25% of patients tested for ANCA were positive in our series. In another study, 20% of cases with endocarditis-associated pauci-immune necrotizing and crescentic glomerulonephritis were ANCA positive [48]. There have also been several recent case reports detailing this pitfall as well [37, 61, 78–83]. Of note, the forms of small vessel vasculitis that can accompany glomerulonephritis or that can occur associated with ANCA disease in the kidney, including necrotizing arteritis, necrotizing arteriolitis, and leukocytoclastic medullary angiitis were not present in any of the 62 patients in our renal biopsy series with endocarditis-associated glomerulonephritis. However, the skin manifestations of endocarditis including Osler's nodes, Janeway lesions, and splinter hemorrhages can mimic cutaneous vasculitis associated with ANCA. In a study by Chirinos et al. of eight ANCA-positive patients with subacute bacterial endocarditis, seven had skin manifestations, most commonly purpura [78].

Given that infectious organisms have long been thought to play a significant role in both the development and the activation of ANCA, the finding of a significant number of patients with both infective endocarditis and pauci-immune crescentic glomerulonephritis should perhaps not be surprising [74, 84, 85]. Renal biopsies with pauci-immune crescentic glomerulonephritis associated with strong C3 staining should raise the possibility of endocarditis. However, even though C3 staining is very common in biopsies with a crescentic pattern (that is, it is sensitive), it is not specific in that renal biopsy case series from documented ANCA-associated glomerulonephritis show glomerular C3 staining in 33–85% of cases [70, 71, 74]. Of course, the best preserved glomeruli should be evaluated and interpreted by both immunofluorescence and electron microscopy, as C3 may be entrapped within areas of scarring, and even immunoglobulins can become entrapped within areas of fibrinoid necrosis. Therefore, it is important for the clinician and renal pathologist alike to always interpret biopsy findings in the context of clinicopathologic correlation and to maintain a high

index of suspicion for the changing face of infective endocarditis-associated glomerulonephritis, especially considering the potential adverse outcome if a patient with endocarditis was mistakenly treated for ANCA-associated glomerulonephritis with cytotoxic agents in lieu of antibiotics.

Diagnostic Challenges of Endocarditis and Endocarditis-Associated Glomerulonephritis

The clinical identification of infective endocarditis can be very difficult. In one report, infective endocarditis was unrecognized in almost 20% of cases at the time of nephrology consult [48]. Also, in the most recent large autopsy series, infective endocarditis was not diagnosed until autopsy in 38.2% of cases [16]. Though they also examined their cases pre- and post-echocardiography availability, the introduction of echocardiography did not reduce the undetected diagnosis rate in their autopsy series. These studies are in disagreement with current reliance on either the original or the modified Duke criteria for the diagnosis of endocarditis [50, 86, 87]. Fernandez Guerrero et al. [16] attribute this to the common absence of fever, cardiac murmurs, and other clinical features considered characteristic of infective endocarditis. Transthoracic echocardiogram is less sensitive than transesophageal. If transthoracic echocardiogram is negative and there is suspicion for endocarditis, transesophageal echocardiogram has to be performed [64, 88]. Additionally, the prevalence of negative blood cultures among patients with endocarditis ranges from 2.5 to 31% [65] and, in one report, 19% of patients with culture-negative endocarditis were afebrile [66]. Although knowledge of both the clinical and pathologic spectrum of glomerulonephritis in patients with infective endocarditis in the current era is expanding, including the frequency of acute kidney injury and of crescentic glomerulonephritis, these clinical diagnostic challenges suggest that the immunologic mechanisms that underlie endocarditis-associated glomerulonephritis are more complex than previously appreciated. Perhaps the spectrum of pathological findings is in part due to the spectrum of infectious agents and pathophysiology as well.

As previously mentioned, another challenge the pathologist and clinician alike encounter is the morphologic overlap between renal biopsy findings in ANCA-associated glomerulonephritis and infective endocarditis-associated glomerulonephritis, and the fact that 20–25% of patients with infective endocarditis-associated glomerulonephritis can have positive ANCA serology [48, 49]. Furthermore, noninfective ANCA-associated endocarditis is yet another complicating factor when considering the differential diagnosis of bacterial endocarditis [78].

Pathogenesis

Several questions regarding the pathogenesis of the glomerulonephritis in patients with infective endocarditis have been raised. Initially, the glomerulonephritis was believed to be embolic in nature. Subsequently for many years, an underlying immune complex pathogenesis was assumed based on immunofluorescence findings of granular IgG and C3 deposits in glomeruli [25–28]. However, our largest renal biopsy series to date supports a primary immune complex mechanism in only a minority of patients, a conclusion also reached by others [48]. Several possibilities may explain when glomerular immune complex (IC) formation does occur; these include passive trapping of ICs from the circulation, formation of ICs in situ following prior localization of exogenous cationic bacterial antigens, or reactivity of an IgG antibody with endogenous components of the glomerulus itself as occurs in membranous nephropathy or anti-glomerular basement membrane antibody disease [89]. In the latter case, molecular mimicry between glomerular and bacterial constituents would likely be involved, thus making the process autoimmune in nature [52]. In a

majority of cases, it is likely that formation of ICs in glomeruli is not the principal pathogenic event given the paucity of IgG deposition found in cases of severe glomerulonephritis and the probable alternate pathway mechanism of complement activation.

Several potential mechanisms could explain how glomerular tissue injury occurs in patients with infective endocarditis without IgG deposition. Bacterial antigens could localize in glomeruli independently of antibody and cause injury through initiation of activating the plasmin system or direct activation of the alternate complement pathway via mannose-binding lectin, thus producing a C3-dominant nephropathy. This is the case of the Streptococcal pyogenic exotoxin B antigen incriminated in post-Streptococcal glomerulonephritis [52, 90]. Staphylococcal super-antigens are also capable of causing direct tissue injury in the absence of immune deposits, especially to endothelial cells [91]. No studies of biologic activity or localization of bacterial antigenic proteins in infective endocarditis have yet to be performed.

Another possible mechanism that has been reported from several sources could be formation of the associated ANCA antibody in patients with infection [61, 78]. Bacterial infections that are well-known to lead to ANCA-positive serology include suppurative lung disease, and infections with Pseudomonas, Klebsiella, *Escherichia Coli,* and Ross River virus [74, 84, 85, 92]. High levels of cytokines secondary to the infection may prime neutrophils and monocytes to be activated by ANCA when present, therefore result in a synergistic inflammatory process [93]. This concept is supported by worsening glomerulonephritis and increased levels of circulating tumor necrosis factor-alpha in mice with anti-myeloperoxidase (MPO)-related glomerulonephritis after injection of bacterial lipopolysaccharide [94]. Induction of antibodies to complementary peptides of the target antigen (auto-antigen complementarity) leading to anti-idiotypic antibodies that react with self-proteins such as proteinase 3 (PR3) has been postulated for infectious agents such as Staphylococci, which then can produce autoimmune tissue injury without depositing in glomeruli [95]. If these ANCA antibodies are pathogenic in these patients rather than a secondary phenomenon, they are believed to damage glomeruli indirectly by activating neutrophils in the microvasculature. The activated neutrophils then release complement-activating factors which lead to alternative pathway activation involving the C5a receptor [84, 85, 96]. Another consideration is the consequence of coinfection by hepatitis C virus (HCV) in some of these patients. Chronic HCV infection can lead to prolonged antigen stimulation and severe autoimmune manifestations including induction of ANCA against MPO, PR3, and bactericidal permeability increasing protein and cathepsin G [83, 97, 98].

Lastly, the recent explosion of interest in glomerulopathies with a dominance of C3 deposition has clarified the role of both inherited and acquired abnormalities in complement-regulatory proteins, such as complement factor H (CFH), in contributing to unregulated activation of the alternative complement pathway and thus deposition of complement proteins in glomeruli [99]. Initiation of complement activation by infections in the presence of inherited or acquired abnormalities in complement regulation has been documented to lead to persistent, chronic C3 nephropathies, with similar pathologic appearances to many of the patients with documented infective endocarditis-associated glomerulonephritis [100]. Therefore, some of the lesions seen in endocarditis-associated glomerulonephritis could reflect an underlying complement-regulatory protein dysfunction.

Another unique feature of endocarditis-associated glomerulonephritis is that these occur during the course of infection rather than a latent reaction seen weeks after as in other etiologies of infection-associated glomerulonephritis. Perhaps this in part has to do with the protracted course that can occur in endocarditis or that when the glomerulonephritis is detected the infection had already been going on for some time.

Treatment and Outcome

Treatment

The presence of both a serious infection and a serious glomerulonephritis produces a challenging therapeutic dilemma. Certainly treatment of the infection is paramount, though no clear guidelines exist as to whether the addition of steroids with or without cytotoxic agents is helpful or harmful. There are case reports of successful use of plasmapheresis in endocarditis-associated glomerulonephritis [39, 101]. One report of an ANCA-negative *S. viridans* endocarditis-associated diffuse crescentic glomerulonephritis with C3 and C1q staining by immunofluorescence showed dramatic improvement with plasmapheresis [42]. Others have reported using plasmapheresis plus immunosuppression [44], while some report therapeutic success with antibiotics alone [45]. Also reported is a case of ANCA-positive *Streptococcus bovis* and *Neisseria subflava* infective endocarditis in a patient with vasculitic purpura showing resolution of skin lesions and renal recovery with antibiotic therapy alone [102].

Treatment data was obtained from 48 of 62 patients with endocarditis-associated glomerulonephritis in our study, and consisted of antibiotics in 71% of patients and antibiotics plus immunosuppressive therapy in 29%, with the latter comprised of combinations of prednisone, methylprednisone, and/or Cytoxan. Only one patient was treated with antibiotics plus prednisone and also received plasma exchange. Surgical treatment was performed in 21% of patients including seven with valve replacement and three with valve repair. More details of the treatment are provided in Chap. 5.

Follow-up and Outcome

Ultimately, the prognosis of a patient with endocarditis-associated glomerulonephritis most likely has more to do with the various extra renal manifestations, such as brain and lung involvement, than with the renal findings. In our renal biopsy study of 62 patients with endocarditis-associated glomerulonephritis, follow-up and outcome data were available in 45 patients with an average follow-up term of 21 months (range 0.5–84 months). For outcome analysis, end-stage renal disease was defined as requiring renal replacement therapy, persistent renal dysfunction was defined by elevation of serum creatinine 0.2 mg/dL above baseline levels or follow-up creatinine >1.2 mg/dL (for those in whom baseline levels were unavailable), and complete recovery was defined as normalization of serum creatinine to baseline levels or to creatinine $\leq$ 1.2 mg/dL (for those patients in whom baseline creatinine were unavailable). Of these 45 patients, eleven died (25%); 5 progressed to end-stage renal disease (11%), 15 had persistent renal dysfunction (33%) and 14 had complete renal recovery (31%) (Table 4.5).

Of the eleven patients that died, one was a three-year-old child and ten were adults (age range 31–79 years, mean 61); seven of these deaths occurred within two months of biopsy. The valve involved by endocarditis was the aortic valve in five patients, tricuspid valve in three, mitral valve in two, and combined tricuspid and mitral valves in one. Four patients had a prosthetic cardiac valve. Common clinical findings in all eleven patients that died include fever and vegetations by echocardiogram, as well as a combination of various other clinical findings. The organisms on culture included *C. burnetii*, Gemella species, Bartonella, and *S. viridans*, with the remainder Staphylococcal species. Over half were treated with antibiotics alone (60%) and less than half (40%) with antibiotics and immunosuppression. There were no clinicopathologic trends useful in differentiating the patients that died versus surviving patients (Figs. 4.17 and 4.18). Among surviving patients, those with higher percentages of globally sclerotic glomeruli, more interstitial fibrosis, and higher average serum creatinine at biopsy had worst outcomes.

While a second attack of infection-associated glomerulonephritis may be unusual as is the case with post-Streptococcal glomerulonephritis, in our study, two patients (3%) were found to have

Table 4.5 Outcome and associated clinical and pathologic features in 45 patients with endocarditis-associated glomerulonephritis

	Death	End-stage renal disease	Persistent renal dysfunction	Complete recovery
No. of patients (% out of 45 with follow-up)	11 (25)	5 (11)	15 (33)	14 (31)
Agent on culture, n (%)				
Staphylococcus	6 (55)	4 (80)	5 (33)	10 (72)
Streptococcus	1 (9)	1 (20)	5 (33)	2 (14)
Other or culture-negative	4 (36)	0	5 (33)	2 (14)
Light microscopy pattern				
Focal crescentic	3 (27)	0	3 (20)	3 (21)
Diffuse crescentic	5 (46)	1 (20)	5 (33)	3 (21)
Focal proliferative	1 (9)	0	0	0
Diffuse proliferative	1 (9)	3 (60)	5 (33)	8 (57)
Mesangial proliferative	1 (9)	1 (20)	2 (14)	0
Treatment, n(%)				
Antibiotics only	7 (64)	4 (80)	9 (60)	10 (71)
Antibiotics and immunosuppression	4 (36)	1 (20)	6 (40)	4 (29)
Valve replacement or surgical repair	1 (9)	1 (20)	4 (27)	3 (21)

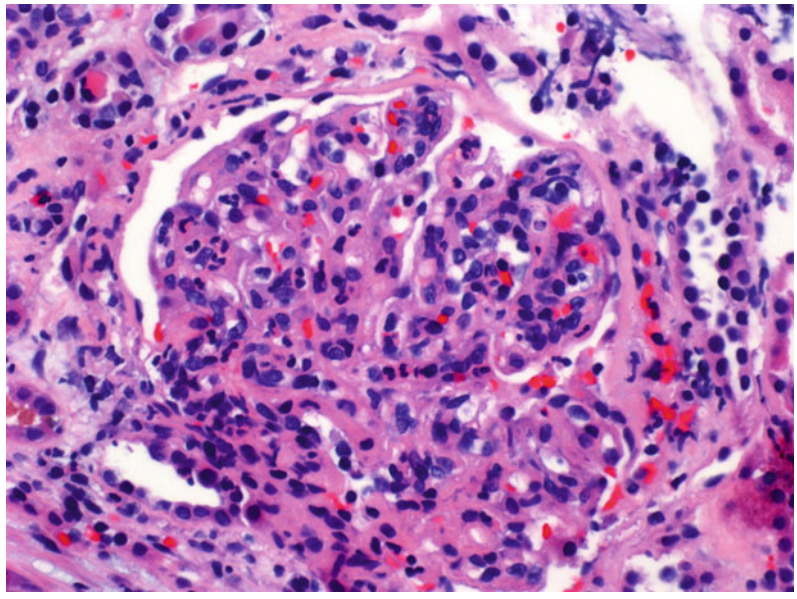

Fig. 4.17 Global endocapillary hypercellularity in a 66-year-old male with aortic valve *Coxiella burnetii* endocarditis. The patient was c-ANCA positive and had normal serum complement levels. The patient succumbed to his illness and died 1.5 months after the biopsy was performed (hematoxylin and eosin; ×400)

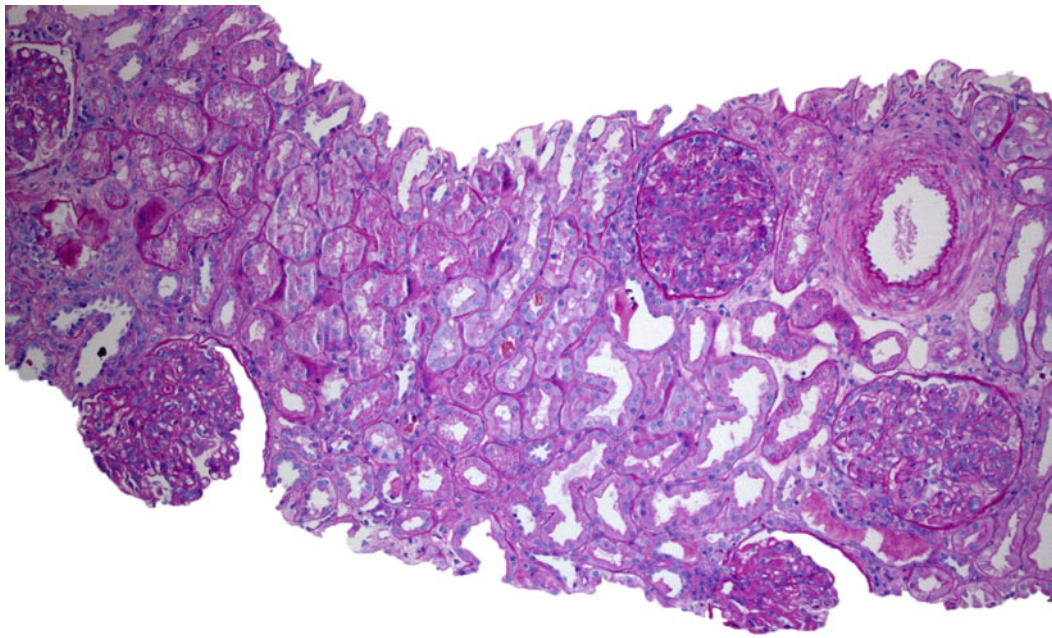

Fig. 4.18 Diffuse endocapillary hypercellularity in a 31-year-old male with methicillin-sensitive *Staphylococcus aureus* infective endocarditis. The patient was ANCA negative, and was treated with antibiotics, prednisone, and plasma exchange, leading to a full renal recovery (periodic acid-Schiff; ×100)

recurrent attacks of endocarditis-associated glomerulonephritis (data not previously reported). Both patients were females in their late 40s with history of intravenous drug use and hepatitis C virus infection. One had methicillin sensitive *S. aureus* (MSSA) pulmonic and tricuspid valve endocarditis treated with antibiotics leading to full recovery of renal function, followed by recurrent MSSA endocarditis two years later requiring tricuspid valve replacement. The other patient had Enterococcus mitral valve endocarditis treated with antibiotics and five months later mitral valve replacement and AV fistula, followed by recurrent infective endocarditis and infected shunt with fever, methicillin resistant *S. aureus* bacteremia, seizures, and stroke.

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The Management of Bacterial Infection-Associated Glomerulonephritis

5

Samir V. Parikh, Anthony S. Alvarado and Lee A. Hebert

Introduction

The association between infection and acute glomerulonephritis (GN) has been recognized for several centuries. What is now recognized as post-streptococcal GN was initially described in the seventeenth century as "edematous swelling" and "dark or suppressed urine" that developed as a life-threatening complication during the convalescent period of scarlet fever [1]. This syndrome was later shown to be the result of infection with group A, β-hemolytic streptococcus species [2]. Post-streptococcal GN is now a well-defined renal disease and historically, the most common form of infection-associated GN. However, over the past three decades there has been a shift in the epidemiology of infection-associated glomerular diseases. The incidence of post-streptococcal GN has decreased worldwide while the incidence of other forms of bacterial infection-associated GN has increased, particularly in adults [3, 4]. Most conspicuous is staphylococcal-associated GN. In adults, it is now as common as post-streptococcal GN and 3 times more common than post-streptococcal GN in the elderly [5]. A crucial distinction between post-streptococcal GN and the GN associated with staphylococcal infection is that post-streptococcal GN emerges after the infection has resolved whereas staphylococcal-associated GN usually emerges during active staphylococcal infection. The present work addresses all forms of bacterial infection-associated GN but focuses on the GN caused by β-hemolytic streptococcus and staphylococcus species because these are the most common forms of bacterial infection-associated GN.

Distinguishing Post-infectious GN from the GN of Active Infection

Earle and Jennings appear to be the first to publish the term "post-streptococcal GN" to describe a syndrome in which an acute GN occurred during the convalescent phase of an infection with β-hemolytic streptococcus [6]. However, about 15 years ago, there have been numerous reports of "post-staphylococcal GN". The stated rationale for the term "post-staphylococcal GN" is that the GN occurred after the onset of staphylococcal infection. However, as has been recently pointed out, the use of the term "post-staphylococcal" is incorrect for many reasons:

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1. Not historically accurate. The original meaning of the prefix "post" refers to a GN which emerges only after the infection has resolved (healed) and followed by a clear infection-free latent period. It does not include those glomerulonephritides that emerge with the onset of infection or during the course of an infection.
2. Not logical. There is no basis for "pre-infection GN" (the GN emerges before the infection).
3. Redundant. If staphylococcus-associated GN merits the term "post-infectious" than all forms of GN that emerge during an active or chronic infection would require the prefix "post". For example, HIV-associated nephropathy (HIVAN) would become "post-HIVAN", Hepatitis B associated membranous glomerulonephritis would become post-infectious membranous GN, or endocarditis-associated GN would become "post-endocarditis GN" [7].

On this basis, it is recommended that the term "post-staphylococcal GN" should not be used. Table 5.1 provides an overview of infection-related GN, using the paradigm of post-streptococcal GN and staphylococcal-associated GN to describe the clinical and histologic differences between post-infectious GN and the GN of active infection.

Post-infectious GN

Post-streptococcal GN is the only proven cause of post-infectious GN. Therefore our discussion will focus on the management of post-streptococcal GN.

Post-streptococcal GN

Acute post-streptococcal GN (APSGN) occurs as an isolated case or in epidemic outbreaks. The incidence of APSGN has decreased significantly worldwide and especially in industrialized nations, but in developing nations, remains an important complication of group A streptococcus (GAS) and rarely streptococcus group C infections [3, 8]. The decrease in incidence of APSGN is attributed to earlier recognition of infection and treatment of infection with an appropriate antibiotic. In developing countries, the annual incidence of APSGN ranges from 9.5 to 28.5 new cases per 100,000 persons per year which is approximately 4 times higher than in developed countries [8]. Worldwide, APSGN still predominantly affects children, representing over 85% of reported cases [9].

APSGN is an immune complex mediated GN thought to develop after nephritogenic antigens are released into circulation during a GAS infection. The acute infection is commonly a pharyngitis or skin infection. Despite extensive study the causal nephritogenic antigens are yet to be elucidated, however the nephritis-associated plasmin receptor (NAPlr) and the streptococcal pyogenic exotoxin B (SPEB) and its zymogen precursor (zSPEB) seem most plausible [10, 11]. These nephritogenic antigens are released into circulation and deposit in glomeruli. An antibody response is mounted and these antibodies combine with the circulating antigens to form immune complexes which then deposit in the glomeruli. Additionally, the antibodies bind to the streptococcal antigens already deposited in the glomeruli leading to in situ immune complex formation. These autoantibodies are classically IgG autoantibodies and activate the alternative complement pathway as evidenced by the presence of C3 in the glomerular immune deposits in APSGN. Infiltrating leukocytes including neutrophils, T helper cells, and macrophages are responsible for the mesangial and endocapillary hypercellularity of APSGN [12].

Autoantibodies have also been detected in patients with APSGN including anti-DNA antibodies, anti-C1q antibodies, and antineutrophil cytoplasmic antibodies (ANCA) [13, 14]. Indeed, ANCA has been found in up to 70% of APSGN that present with necrotizing and crescentic GN on biopsy [13]. The clinical relevance of these autoantibodies is unclear but they likely represent an epiphenomenon related to the autoimmunity caused by the GAS infection, and not

Table 5.1 Key clinical features of post-streptococcal GN and staphylococcal-associated GN

	APSGN	SAGN
Time of GN onset	1–4 weeks after infection has resolved	During the course of active infection. Typically weeks to months after infection starts
Pathogen species	Group A β-hemolytic streptococcus, Group C streptococcus	Staphylococcal aureus, staphylococcal epidermidis, any other staphylococcal strain
Age of onset	Most commonly affects children between ages 5–15 years old	Most commonly affects adults with chronic illness such as diabetes mellitus or malignancy
Site of infection	β-hemolytic streptococcal pharyngitis, cellulitis, otitis media, sinusitis, or other sites	Cellulitis, chronic leg ulcers, osteomyelitis, endocarditis, dental infection, pneumonia or other sites. Upper respiratory tract would not be consistent with SAGN
Natural history	Usually resolves within several weeks but microscopic hematuria may persists for months	GN does not resolve until the infection resolves
Histology findings	Focal or diffuse proliferative immune complex glomerulonephritis with IgG and heavy C3 staining. Electron microscopy with classic subepithelial humps	Focal or diffuse proliferative immune complex glomerulonephritis in MPGN pattern with IgA and heavy C3 staining. Electron microscopy reveals mesangial and subendothelial immune complexes and may show subepithelial humps
Renal prognosis	Excellent—renal recovery occurs within 4–8 weeks of disease onset	Variable—persistent renal dysfunction common. Presence of underlying diabetic nephropathy or advanced interstitial fibrosis are predictors of poor renal outcome
Treatment	Supportive care. Steroids may be considered in severe cases with crescentic GN	Eradicate the infection. Steroids/immunosuppression is not recommended. Recurrent sepsis or death may occur if immunosuppression is used, even in those receiving antimicrobial therapy

independent processes. For more details on pathogenesis, see Chap. 7.

Clinical Manifestations and Differential Diagnosis

APSGN is characterized by an abrupt onset of hematuria. In severe cases, oliguria and renal failure with associated edema and hypertension rapidly follow. APSGN usually occurs 1–2 weeks after a pharyngeal infection and 2–4 weeks after a skin infection. APSGN typically lasts for 2–4 weeks with clinical improvement starting 1 week after presentation [9]. Subclinical disease can occur and is manifested by microscopic hematuria, low serum C3 levels, and hypertension. In children with APSGN, nephrotic range proteinuria and severe azotemia are uncommon [8]. In adults with APSGN, up to 20% may present with nephrotic range proteinuria and over 60% present with severe azotemia [8]. The hematuria associated with APSGN is characterized by gross hematuria or "tea-colored" urine (30–50%). Generalized edema (60–70%) is common, as is new onset hypertension (50–90%), and renal dysfunction (REF). Severe, rapidly progressive, necrotizing and crescentic GN is rare and may predict a poor long-term prognosis [15–17].

Laboratory findings show "nephritic" urine sediment consisting of dysmorphic red blood cells (especially acanthocytes), red blood cell casts, and mixed red and white blood cell casts. Pyuria (neutrophils) can be extensive. Still, red cells typically outnumber neutrophils. The serologic hallmark of APSGN is activation of the alternative complement pathway (low serum C3, normal serum C4). In approximately 90% of cases, serum C3 and CH50 levels are suppressed early in the disease course, and then return to normal levels at remission [18]. Serum C4 levels

are usually normal or only slightly low consistent with alternative, but not classical complement pathway activation.

There are several serologic studies available to assess for recent GAS infection. The streptozyme test measures five different antibodies that target various extracellular streptococcal products and is positive in 95% of patients with a pharyngeal infection and in 80% of patients with skin infection [9, 19]. Generally, the anti-streptolysin antibody (ASO) titer is increased after a pharyngeal infection with peak titer occurring about 3 weeks after presentation [20]. However, the ASO titer is not a good indicator if pyoderma is the inciting infection [19]. Instead, anti-DNAse B antibody titers are more likely to be elevated after streptococcal skin infections [20]. These studies are particularly helpful in cases where the infection history is unclear and can help distinguish APSGN from other forms of acute nephritis, especially in adults.

The features that differentiate APSGN from other forms of acute nephritis are shown in Table 5.2. The differential diagnosis for APSGN includes autoimmune diseases that cause acute nephritis. Lupus nephritis, Henoch–Schönlein purpura (HSP), IgA nephropathy, and membranoproliferative GN (MPGN) may all present similarly to APSGN. C3 nephritis or dense deposit disease may be indistinguishable from APSGN clinically as both present with evidence of nephritis and signs of alternative complement pathway activation. In patients with MPGN, however, the clinical abnormalities persist and do not remit spontaneously. Both IgA nephropathy and HSP may present after an upper respiratory tract infection but the infection is typically synpharyngitic and occurs 1–2 days after a mucosal infection. Additionally, serum complement levels are usually normal. Lupus nephritis is an immune complex mediated GN and can present with acute nephritis similar to APSGN, however, gross hematuria is not usually seen in LN. In contrast to APSGN, the classical complement pathway is activated during lupus nephritis flare and there is no apparent relationship to a preceding infection. Finally, GN related to chronic, ongoing infections, such as staphylococcus-associated GN (discussed below) may also present with clinical features similar to APSGN, including acute nephritis with activation of the alternative complement pathway.

Differentiating APSGN from other forms of acute nephritis may be challenging, particularly in adults. Only 10–20% of pharyngitic infections are caused by GAS [21] so APSGN may be diagnosed mistakenly in patients with other forms of acute nephritis if the pharyngitis is presumed to be secondary to GAS. Also staphylococcus does not cause a pharyngitis in immunocompetent patients. An alternative diagnosis should be sought in cases where the GN does not resolve after 4–8 weeks of supportive care. However, if an alternative diagnosis is present, such as a C3 nephritis or lupus nephritis, waiting for several weeks to confirm the diagnosis will delay therapy and expose the patient to chronic kidney damage. The kidney biopsy is invaluable in such cases and maybe necessary to definitively diagnose the cause of the acute nephritis.

Role of the Kidney Biopsy in Suspected APSGN

The kidney biopsy, while the gold standard for diagnosis of most glomerular diseases, is not routinely done in patients suspected to have APSGN. The rationale is that the processes of APSGN can usually be deduced from its characteristic presentation and laboratory findings (see Table 5.2). Kidney biopsy is considered when atypical clinical features are present. For example, if the ASO or streptokinase titers are not elevated and the renal failure is severe (GFR < 30 ml/min/1.73 m^2), or the nephritis is a recurrent problem then a kidney biopsy should be considered [22, 23]. The classic histologic features of APSGN include light microscopy findings of diffuse mesangial and endocapillary hypercellularity with neutrophil infiltration of the glomerular tuft, by immunofluorescence granular deposition of IgG and C3 in the capillary loops, and by electron microscopy showing the hallmark subepithelial humps. The presence of cellular crescents is uncommon but may be seen in

Table 5.2 Features that distinguish APSGN from other immune-mediated glomerular diseases

	APSGN	SLE	IgAN	C3 nephritis	Staph-associated GN	ANCA vasculitis
Clinical presentation	Acute proliferative GN that occurs 1–4 weeks after group A streptococcal infection	Lupus nephritis develops in 50% of cases of SLE. Commonly occurs alongside extra-renal manifestations of SLE	Acute GN may occur 1–3 days after developing a viral or upper respiratory tract infection	Acute GN may occur 1–3 days after viral infection	Acute proliferative GN that occurs during an active staphylococcal infection that has not yet been effectively treated	Rapidly progressive GN usually with systemic features including lung, skin and joint involvement
Age of onset	Most commonly children 5–15 years old, rarely adults	Typically 16–40 years of age, predominantly female. Children also can be affected	Variable but usually affects 20–40 year olds	Usually develops in childhood, but adults affected as well	Most commonly occurs in adults and particularly in elderly patients with comorbidities such as diabetes mellitus	Usually affects older adults
Histology	Immune complex mediated disease with IgG and C3, classic subepithelial "humps"	Immune complex mediated disease with "full house" pattern on immunofluorescence	IgA dominant or codominant with IgG immune complex mediated disease, mild C3 staining	No immunoglobulin, C3 only deposits in MPGN pattern, may have dense deposits	Proliferative GN with variable IgA and bright C3 staining by immunofluorescence	Pauci-immune crescentic glomerulonephritis. Few if any immune deposits identified. Severe, proliferative GN common
Autoimmune serologies	Positive ASO, streptozyme test, ANCA titer may be positive in some cases	Positive ANA, positive anti-dsDNA, positive anti-SM antibodies	Negative	Negative	ANCA titers may be positive in some cases, otherwise negative	Positive C-ANCA or P-ANCA with either PR3 or MPO common
Serum complement	Low C3 (90%), normal C4	Low C3, low C4 common	Normal C3, C4	Low C3, normal C4	Low C3 (50%) of cases, normal C4	Normal C3, C4
Microbial pathogens	Group A, B-hemolytic streptococcus	None	None	None	Staphylococcal species, especially staph aureus	None
Treatment	Supportive care. Steroids may be considered in severe cases with crescentic GN	Immunosuppression	Supportive care. If severe, then immunosuppression	Immunosuppression?	Eradicate the infection. Steroids/immunosuppression is not recommended	Immunosuppression
Prognosis	Excellent—renal recovery usually occurs within 4–8 weeks of disease onset	Relapsing/remitting disease prognosis is variable. 30% of patients with LN progress to ESRD	Most have a very good prognosis. Slowly progressive CKD occurs in many. ESRD risk of 20% at 20 years	Chronic GN variable prognosis, with reported risk of ESRD ranging from 16 to 76%	Acute GN with variable prognosis—persistent renal dysfunction common	Relapsing/remitting disease with guarded renal prognosis. Risk for substantial CKD high. ESRD risk 10–26%

severe cases. Since disease remission is based on resolution of clinical manifestations of nephritis, histologic remission is not typically considered but to have implications for long-term prognosis. For details on renal biopsy findings, see Chap. 1.

Treatment of APSGN

At present, there is no specific treatment for APSGN. The current approach is supportive and focuses on treating hypertension and volume overload. Acute infection has usually subsided by the time nephritis develops, thus antibiotic therapy is not usually helpful. Antibiotic therapy is, of course, recommended during the acute infection to reduce the triggers of APSGN and to prevent outbreaks. In the setting of epidemics or in high risk locations, prophylactic antibiotics should be provided to family members and other close contacts of APSGN patients [8]. This has been shown to decrease the incidence of disease in those settings [24]. As mentioned above, renal biopsy is not typically recommended since the disease is typically transient and usually goes into remission spontaneously. Clinical manifestations commonly begin to resolve 1 week after disease onset and renal function returns to baseline levels 3–4 weeks after disease onset. This is true even in cases of acute renal failure and in cases where kidney biopsy was performed and showed crescentic GN [25]. Microscopic hematuria may persist for up to 1–2 years and proteinuria may be slow to resolve [8]. Approximately 20% of patients will continue to have abnormal urine findings (hematuria or proteinuria) during long-term follow-up [26]. Overall most patients have an excellent outcome with supportive therapy alone, and disease recurrence is rare.

Supportive therapy includes symptomatic management of the acute nephritis. Sodium and fluid restriction along with diuretic therapy is considered as first line therapy to treat hypertension and volume overload. Angiotensin converting enzyme inhibitors may be used to manage hypertension, however, these agents are commonly avoided due to the potential for worsening renal function acutely and causing hyperkalemia. Additionally, APSGN usually remits within several weeks so the long-term benefit of renin-angiotensin-system blockade may be negligible. Vasodilators are commonly used if additional anti-hypertensive therapy is required. Hypertensive encephalopathy may also occur and requires parenteral therapy such as intravenous nicardipine. If volume overload persists, or metabolic derangements including hyperkalemia develop, dialysis should be considered until the APSGN remits and renal function improves.

Steroid/Immunosuppressive Therapy in APSGN. In patients with rapidly progressive crescentic GN, intravenous pulses of methylprednisolone are commonly recommended to treat the acute inflammation. However, whether immunosuppression is beneficial in crescentic GN due to APSGN is unclear. The available evidence is shown in Table 5.3. As shown, most of the evidence is from small retrospective studies [27–29]. In the only available prospective study, 10 children with crescentic GN due to APSGN were stratified to receiving either immunosuppression plus anticoagulation or supportive care alone [25]. For immunosuppression, five patients were selected to receive quintuple therapy with cyclophosphamide, azathioprine, prednisone, dipyridamole, and systemic anticoagulation. The other five patients were selected to receive supportive care only. All patients had greater than 50% crescents on the initial biopsy and repeat biopsy was performed in 8 of the 10 patients. After 3 months of treatment, the clinical and histologic outcomes were similar in both groups. However, at each interval up until 3 months of follow-up, the treatment group had a more rapid improvement in creatinine clearance [25]. After 60 months of follow-up, the serum creatinine and proteinuria levels were similar between the groups. There was no correlation between severity of crescent involvement and outcome. Also, most patients in both groups attained a complete remission after 6 months of follow-up. Additionally, the level of parenchymal scarring at repeat biopsy was similar between the groups.

In a more recent study, the outcomes of 27 children from New Zealand with severe APSGN

Table 5.3 Long-term renal prognosis in APSGN

Study location	Study year	Patient number	Patient population	Follow-up (yrs)	Albuminuria/proteinuria (%)	Persistent hematuria	Hypertension	Chronic kidney disease
Trinidad [32]	1982	534	Children	12–17	3.2	1.5%	3.5%	2%
United States [26]	1974	24	Mixed children and adults	10–18	50	N/A	50%	50%
Venezuela [8]	2005	110	Mixed children and adults	15–18	7.2	5.4%	13.7	0.9%
Italy [34]	1994	26	Mixed children and adults	11	34.6	N/A	N/A	7.7%
United Kingdom [30]	1988	33	Children	9.5–19	10	10%	2.7%	0%
Brazil [63][a]	2005	56	Adults	5	22	N/A	30%	49%
United States (Native American Epidemic) [31]	1964	61	Native American Children	10	6.6	8.2%	3.3%	0%
Australia [35]	1979	57	Adults	7	1.9	19%	17%	1.9%
Australia [33]	2012	200	Aboriginal children	>10	57.6	13%	Similar to controls	Similar to controls

[a]Strep zooepidemicus. Mostly adult population

were studied retrospectively. At baseline, 11 of the 27 patients had a crescentic GN. These patients were more likely to require acute dialysis at presentation [28]. Each of the patients with crescentic GN was treated with immunosuppression, either pulse methylprednisolone followed by oral prednisone alone, or in combination of cyclophosphamide. Renal outcomes were similar between the immunosuppressed group and the supportive care group. However, none of the patients who received supportive care only manifested crescentic GN at baseline [28]. This suggests that immunosuppression may have been beneficial because the group treated with immunosuppression started with worse APSGN but achieved the same outcome as those with less severe disease.

Clear conclusions cannot be made from the available evidence. Nevertheless, we suggest that immunosuppression, particularly with corticosteroids, may be helpful in severe cases of APSGN to suppress acute inflammation, limit chronic renal damage, and help facilitate a more rapid renal recovery. Figure 5.1 provides an algorithmic approach to the management of APSGN.

APSGN Prognosis and Long-Term Outcomes

The prognosis for patients with APSGN is generally excellent especially in children [30–32]. This is true even for a patient who presents with acute renal failure and the renal biopsy shows crescentic GN [25]. Determining the long-term prognosis for children with APSGN has been an area of extensive study. Earlier studies suggested that the long-term prognosis was excellent but this was based on short follow-up. Studies with longer follow-up (5–18 years) showed that approximately 20% of APSGN patients have a persistently abnormal urinalysis (hematuria, proteinuria or both) but elevated serum creatinine is rare [26]. For example, in one study, after 18 years of follow-up, 7% of children with APSGN had persistent subnephrotic range proteinuria and 5% had microscopic hematuria [26]. However, less than 1% developed end-stage renal disease. However, in another study of 200 well-characterized Australian Aboriginal children, the risk of developing persistent albuminuria after 5 years of follow-up was 3–4 times greater in those with a history of APSGN [33].

Adults with APSGN have a worse renal and overall prognosis than children [26, 34]. APSGN in adults commonly occurs in elderly patients with significant comorbidities such as alcoholism or malignancy. In these patients, azotemia, congestive heart failure, and nephrotic range proteinuria were common during the acute illness. During follow-up, 30–50% of these patients will have residual hypertension, persistently abnormal urinalysis, or chronic kidney damage [26, 35, 36]. These abnormalities are likely related to the development of glomerulosclerosis from the APSGN [26]. This was initially suggested by Baldwin and colleagues in the 1970s, after they conducted a landmark study of 118 well-characterized patients with APSGN who underwent repeat renal biopsy and were followed for at least 2 years [26]. They found that glomerulosclerosis increased from 18% at diagnosis to 56% after 5–18 years of follow-up. Proliferative lesions decreased from 93% to 11% during this same time period. Overall, 60% of patients developed at least one histologic or clinical marker of chronic damage (proteinuria, hypertension, or decreased GFR). The outcomes in children were better with only 40% having at least one manifestation of chronic damage. However, the extent to which APSGN results in end-stage renal disease is still unclear. The general experience is that APSGN rarely results in end-stage renal disease and long-term prognosis is excellent.

Glomerulonephritis Associated with Active Infection

Acute GN has long been known to occur in the setting of active infections. The earliest descriptions occurred in the setting of infective endocarditis and ventriculo-atrial shunt infections [37]. This form of acute GN occurs in the setting of an active, often subacute or chronic infection and is increasing in incidence, particularly in the

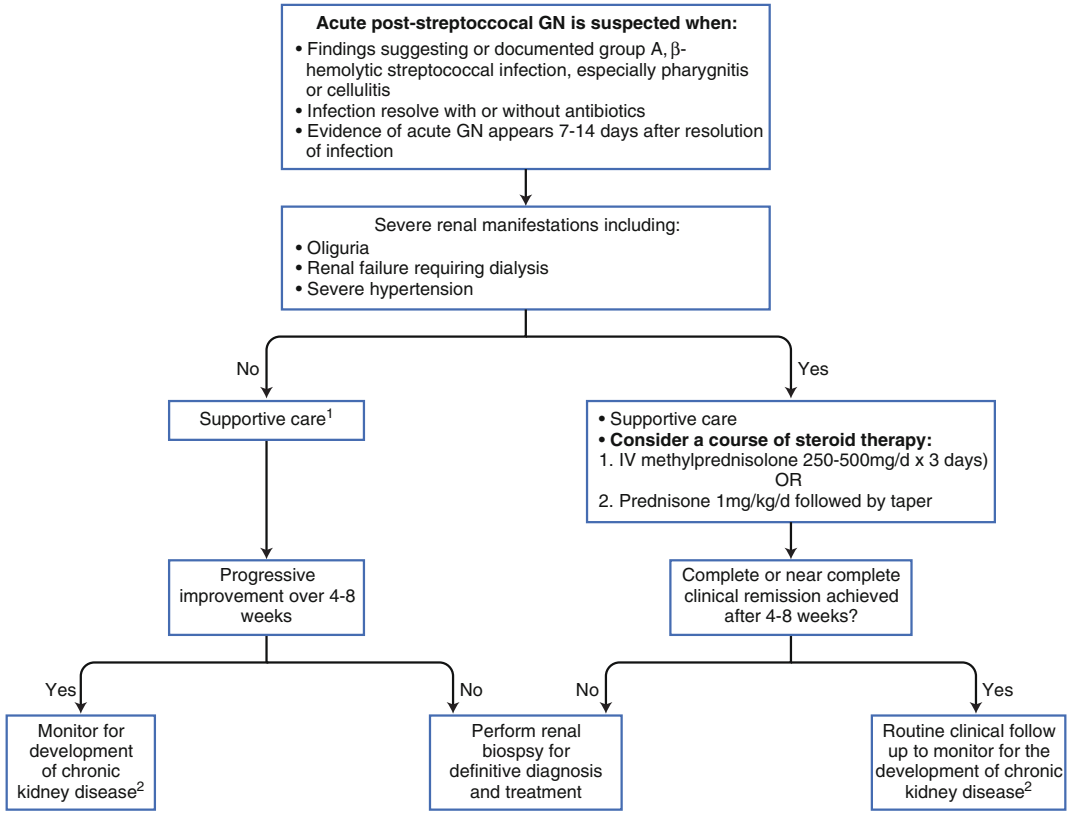

Fig. 5.1 Algorithmic approach to the management of acute post-streptococcal GN (APSGN). The patient presents with a history of recent infection (either pharyngitis or cellulitis) due to group A, β-hemolytic streptococcus infection. The infection resolved either with anti-microbial therapy or not. The patient now presents 1–2 weeks after the infection with signs suggestive of acute GN. Supportive care should be provided, as the GN is typically self-limited. However, if severe manifestations are present (oliguria, severe hypertension, renal failure) then treatment with corticosteroids can be considered to suppress the acute inflammation and limit chronic kidney damage. APSGN usually remits within 4–8 weeks. If the GN does not remit within this time frame, a kidney biopsy should be performed for definitive diagnosis and treatment

elderly population or in patients with multiple comorbidities [4, 5]. While it is recognized that the GN associated with infective endocarditis and ventriculo-atrial shunt infection is most commonly due to staphylococcal infection, we will discuss these entities separately from staphylococcal-associated glomerulonephritis (SAGN).

Staphylococcus-Associated GN

Staphylococcus, especially *Staphylococcus aureus,* is a major cause of bacteremia with increasing incidence and increasing antibiotic resistance [38]. The incidence of *S. aureus* bacteremia, particularly methicillin-resistant strains or MRSA, has increased dramatically in the past decade in industrialized nations. Due to increasing antibiotic resistance, staphylococcal strains are not easily suppressed and the ongoing antigen exposure may lead to visceral complications including SAGN. SAGN has only recently been recognized and is an emerging cause of infection-associated GN.

SAGN most commonly affects older adults who are immunosuppressed or have debilitating comorbidities such as diabetes mellitus, vasculopathy, liver cirrhosis, neoplasia, alcoholism, or intravenous drug abuse [5]. SAGN is thought to

be a rare manifestation of *S. aureus* infection but is likely underreported [39]. For example, in the setting of acute infection, acute kidney injury is most commonly attributed to acute tubular necrosis (ATN), thus a diagnosis of SAGN may be easily missed. Also, histology is needed to confirm the diagnosis of SAGN and since kidney biopsy is not routinely performed in the setting of acute kidney injury, the GN associated with an active infection may often be missed.

Similar to APSGN, SAGN is an immune complex mediated GN. The pathogenesis of SAGN has not been extensively studied but likely involves glomerular deposition of preformed circulating immune complexes and possibly in situ formation of immune complexes with antibody binding to already deposited staphylococcal antigens [4, 40, 41]. The staphylococcal antigen is suspected to act as a super antigen that causes a large increase in circulating immunoglobulin [42]. This superantigen binds directly to major histocompatibility II molecules on antigen presenting cells, and causes massive T cell and subsequent B cell activation. This leads to the release of pro-inflammatory cytokines and the production of immunoglobulins (IgG, IgA, and IgM). IgA has been shown to have an affinity for the staphylococcal antigen and binds to the antigen creating an immune complex [43, 44]. These complexes then deposit in the kidney. The result is an immune complex GN that is IgA dominant or codominant with IgG [45]. Activation of the alternative complement pathway is evident by heavy C3 staining seen on immunofluorescence microscopy. However, hypocomplementemia occurs in only 30% of cases [45]. The lack of overt hypocomplementemia likely is due to the fact that IgA is the dominant immunoglobulin in SAGN and is a poor activator of complement. In comparison, in APSGN, IgG is the dominant immunoglobulin and IgG is a potent activator of complement.

Clinical Manifestations and Differential Diagnosis

The clinical manifestations of SAGN are similar to other glomerular diseases except patients usually present with clinical signs of an active, untreated infection. For example, consider a patient with a chronic foot ulcer that only presents for evaluation after it has progressively worsened for several weeks. The infection has not healed and requires antimicrobial therapy. The untreated infection has led to several weeks of antigen production and an acute nephritis develops. Clinically the acute nephritis is indistinguishable from other forms of acute nephritis, including APSGN. The proteinuria may be nephrotic range in approximately 20–30% of cases [39]. Peripheral edema and new onset hypertension may also develop. In some patients, a cutaneous vasculitis may develop in addition to the acute GN and mimic a systemic vasculitis such as Henoch–Schönlein purpura (IgA vasculitis) [46, 47]. The site of infection in SAGN is variable but the most common site is a skin such as in the setting of a cellulitis or ulcer. Deep-seated infections such as osteomyelitis or a dental abscess, endocarditis, and pneumonia are also common sites of infection [47]. It is important to note that, unlike APSGN, the upper respiratory tract is not a common site of infection in SAGN.

The diagnostic workup includes a urine microscopy evaluation, which usually reveals nephritic sediment with evidence of dysmorphic red blood cells, red blood cell casts, and pyuria. Blood cultures may be positive for staphylococcal species however in many cases, especially in the setting of deep-seated infections, blood cultures may be negative. In this scenario, a high index of suspicion is needed to facilitate diagnosis and ensure appropriate treatment is given. The presence of hypocomplementemia and acute nephritis may suggest SAGN in the correct clinical context even if there is no obvious sign of infection. In this case, kidney biopsy should be performed to facilitate diagnosis. If there is suspicion for SAGN but an obvious source of infection has not been identified, an extensive search for a deep-seated infection should be conducted. This may include a CT scan of chest, abdomen and pelvis, dental X-ray (Panorex), and 2D-echocardiogram. Transesophageal echocardiogram should be considered if 2D-echo is non-diagnostic or if there is a high suspicion of endocarditis.

The kidney biopsy in SAGN reveals a proliferative, exudative GN with endocapillary proliferation by light microscopy and electron-dense subepithelial deposits or "humps" by electron microscopy [45]. The histology differs from APSGN in that the immunofluorescence is classically IgA dominant or codominant with IgG in addition to heavy C3 staining. Cellular crescents are not uncommon and may be seen in severe cases. These histologic findings are similar to IgA nephropathy so the clinical history is important [47]. It is important that the clinician maintains a high index of suspicion for SAGN even if blood cultures are negative and especially in the setting of a middle aged or elderly patient with multiple comorbidities [4, 5]. The morphologic findings are detailed in Chap. 2.

Treatment and Prognosis

An algorithmic approach to management of SAGN is shown in Fig. 5.2. The primary goal of treatment in SAGN is to eradicate the underlying infection and to control the symptoms associated with the acute nephritis. When possible culture-driven antimicrobial therapy should be given as soon as possible and dosed for renal function. While identification of *S. aureus* species is important, distinguishing between methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) strains is also necessary to guide antibiotic therapy. If, however, all culture data are negative, empiric antibiotic coverage should be used. Finally, surgery should be performed to eradicate the infection when indicated.

Supportive care involves management of the symptoms associated with acute nephritis. This includes management of hypertension, fluid overload, and the metabolic disturbances associated with renal failure. Hypertension and volume overload is managed with diuretic therapy and salt restriction similar to other forms of acute nephritis. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers may be used if the renal function is stable. Calcium channel blockers are commonly used for additional blood pressure control. Dialysis may be necessary when the renal failure is severe to correct electrolyte disturbances and for volume control.

Immunosuppression for SAGN

Immunosuppression for treatment of SAGN is not recommended. While it has not been well studied, treatment of SAGN with immunosuppressive therapy, such as high-dose corticosteroids, may exacerbate the underlying infection and increase the risk for clinical deterioration and death [5, 48]. Table 5.4 summarizes the current literature on the use of immunosuppression for SAGN. In a study of 109 elderly patients with infection-related GN (46% had SAGN), 22 patients were treated with corticosteroids [5]. Only 3 of the 22 patients had resolution of renal injury after corticosteroid use. The majority of patients had persistent renal disease of progressed to end-stage renal disease. Additionally, four patients died of recurrent sepsis. In another study of 76 patients with infection-related GN, corticosteroids alone or in combination with cyclophosphamide was given to 17 patients, 12 of whom had crescentic GN on biopsy [38]. SAGN was the cause of infection-related GN in 13 of these 76 patients. Overall, only five of the patients who received some form of immunosuppression attained a clinical remission but only after the infection was completely eradicated. In a similar study, 17 of 52 patients with infection-related GN were treated with corticosteroids for more than 3 months [39]. Out of 17, 16 patients were nondiabetic. Diabetic patients were not given steroid treatment. In this cohort, 24% of the patients had a SAGN. There were no significant differences in renal outcome between the corticosteroid-treated group and patients treated with antibiotics alone. In a study of 49 patients, 53% of which had SAGN related to endocarditis. Corticosteroids alone or in combination with cytotoxic agents were used in 14 of these patients [48]. Overall, 23.5% of the immunosuppressed patients died compared to 10% of the patients treated with antibiotics alone. The rate of renal remission was similar between the groups. Finally, in two smaller studies, 6/16 patients were treated with corticosteroids. In the first study, 2/8 patients were treated with steroids

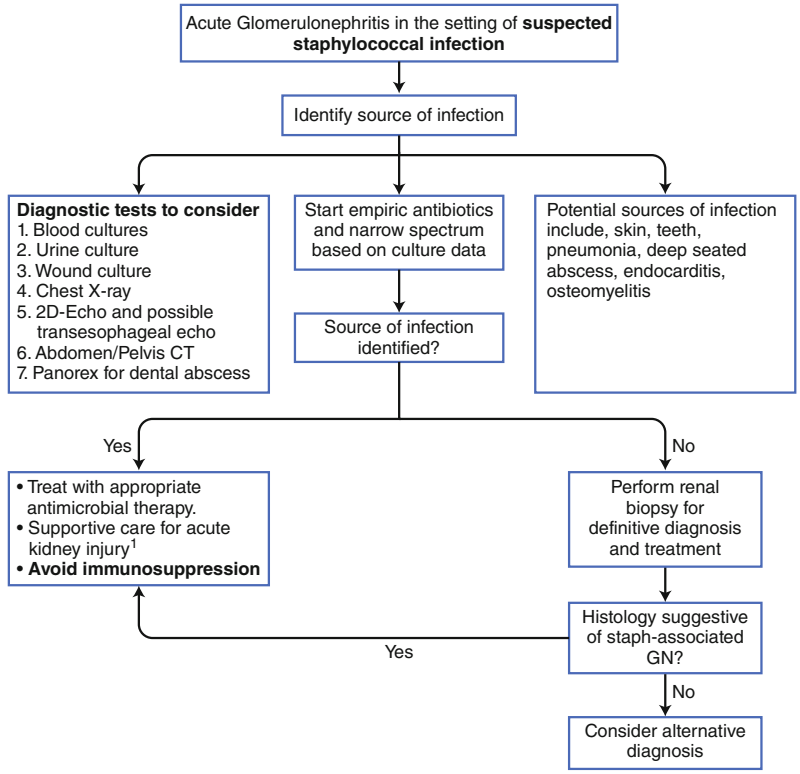

Fig. 5.2 Algorithmic approach to the management of staphylococcal-associated GN (SAGN). The patient presents with signs of acute GN in the setting of an active infection. The GN is likely due to the underlying infection. Usually, the clinical presentation is indicative of an active staphylococcal infection, which may be subacute or chronic in nature. During the course of the infection, an acute glomerulonephritis may develop that is consistent with SAGN. A thorough workup is often required to identify the source of infection. Treatment with appropriate antibiotics is necessary to eradicate the infection and resolve the GN. Treatment is supportive and *immunosuppression should be avoided*. If the source of the infection cannot be elucidated, then a kidney biopsy is recommended for definitive diagnosis

after the infection was thought to be eradicated. Unfortunately, the staphylococcal infection reappeared after steroids were initiated and both patients died from sepsis [49]. In a later study with SAGN, 4/8 patients were treated with steroids. None of the steroid-treated patients achieved a complete renal recovery. All four patients developed chronic renal failure and one patient developed sepsis [46].

Relevant to this discussion, is the CORTICUS study, which was a prospective controlled, double-blind, randomized trial in patients presenting with documented bacterial sepsis and hypotension [50]. The patients were assigned to standard of care, including appropriate antimicrobial therapy and either placebo or the glucocorticoid equivalent to prednisone 40 mg daily, which was tapered to 0 mg over 10 days. Compared to placebo, the glucocorticoids resulted in no important benefit but increased the risk of septic shock and superinfections. Taken together, these data suggest that immunosuppression should be avoided during active infection in SAGN.

SAGN Prognosis

The renal prognosis for patients with SAGN is not nearly as favorable as that for APSGN. Eradication of the infection should eventually lead to resolution of the GN but glomerular healing may take months. There are few studies available that evaluated the renal prognosis in

Table 5.4 Outcomes for staph-associated glomerulonephritis treated with immunosuppression

Study	*N*	Pathogenic organisms	Immunosuppression regimen	Renal recovery rate (%)	CKD rate (%)	ESRD (%)	Mortality (%)
Nasr et al. [5]	22	Staph species only (46% 50/109 patients had SAGN)	Corticosteroids only variable duration	13.6	54.5	31.8	18.2
Montseny et al. [38]	17	17% of cases due to staphylococcal species	Corticosteroids ± cyclophosphamide	29	47	12	12
Nasr et al. [39]	17	24.4% of cases due to staphylococcal species	Corticosteroids	70	18	12	0
Boils et al. [48]	14	53% of cases due to staph species	Corticosteroids ± cyclophosphamide	28.6	42.9	7.1	23.5
Nagaba et al. [49]	2	MRSA infection only; 8 patients followed and 2 received immunosuppression	Corticosteroids	N/A	N/A	N/A	100[a]
Satoskar et al. [46]	4	Staph species only; 8 patients followed and 4 received immunosuppression	Corticosteroids	0	100	25	0

[a]Both patients died from sepsis

patients with SAGN alone. Most studies evaluated both post-infectious GN and SAGN together and reported cumulative outcomes. For example, in one large, single center study of 86 patients with either post-infectious of infection-associated GN, only 50% of patients had a complete renal recovery [39]. Underlying diabetic glomerulosclerosis or advanced age was independent predictors of poor renal outcomes in these patients with the majority of these patients having had SAGN. Similarly, in a study of 76 older adults, SAGN was the most common form of infection-related glomerular disease identified [38]. In this study, 16% of patients had a complete renal recovery while 41% developed chronic kidney disease and 43% progressed to end-stage renal disease. Finally, in a study of elderly patients in which most had a SAGN, approximately half required dialysis at presentation, and of the 72 patients followed for at least 3 months, 77% either had persistent REF or progressed to end-stage renal disease [5]. Predictors of poor renal outcome included a history of diabetes mellitus, higher serum creatinine at presentation, presence of diabetic glomerulosclerosis, and presence of greater interstitial fibrosis on kidney biopsy. These findings suggest that patients who develop SAGN and have underlying diabetic nephropathy or advanced interstitial fibrosis on biopsy have a poorer renal prognosis and are more likely to have persistent chronic renal damage.

From this discussion however, another question emerges. Should immunosuppression be considered in SAGN patients in whom the disease persists but the infection appears to have been eradicated? Successfully eradicating the infection in SAGN should theoretically abrogate the associated GN; however, as mentioned above, this is not always the case. Whether immunosuppression would be beneficial in cases where the GN appears to persist after the infection has been successfully eradicated is unclear. A repeat kidney biopsy may be necessary in this scenario to determine whether the persistent renal injury is due to ongoing inflammation or simply reflecting sustained chronic kidney damage.

On the other hand, one could argue that, as in APSGN, once the antigen is gone the GN is destined to resolve. So, if anti-inflammatory therapy were to be helpful, it would be only in a narrow window after the infection has been eradicated and inflammation still persists. This window, if present, is likely small and since these patients tend to be debilitated, exposure to high-dose steroids may expose these patients to high risk a minimal prospect of benefit.

GN Associated with Bacterial Endocarditis

Acute GN is a well-described complication of infective endocarditis with the first reports occurring well over 100 years ago [51]. Most cases occur in the setting of subacute bacterial endocarditis. The severity of acute nephritis is generally related to the duration of infection and antigen exposure prior to antimicrobial therapy. *S. aureus* and *strepotococcus* species are the most common pathogens associated with GN due to endocarditis [39, 52]. In a recent study 53% of the cases were due to *S. aureus* and 23% were due to *streptococcus* species [48]. Of the cases with *S. aureus* endocarditis, 56% were methicillin resistant. Several different species of gram-negative bacteria causing GN were also reported in this cases series and include *Bartonella henslae, Coxiella burnetti,* and *Cardiobacterium hominis*. Many other gram-negative bacteria have been reported in the literature to cause infection-related GN but SAGN remains the most commonly associated pathogen. The presentation most commonly associated with GN in this study was a staphylococcal tricuspid valve endocarditis associated with intravenous drug use.

In general, the clinical presentation is consistent with acute kidney injury and evidence of acute nephritis in the setting of an infective endocarditis. Low C3 and C4 is reported in over 50% of cases and up to 28% of cases will have a positive anti-neutrophilic cytoplasmic antibody (ANCA) titer [48, 53]. Both C-ANCA and P-ANCA and both myeloperoxidase (MPO) and proteinase 3 (PR3) positivity has been reported in the setting of infective endocarditis [53]. A necrotizing and crescentic GN is the most common histologic feature found in GN associated with endocarditis. Additionally, a cutaneous vasculitis or pulmonary hemorrhage suggestive of a small vessel vasculitis may be seen. Cryoglobulins may also be present in the circulation [54]. It is important to recognize that the small vessel vasculitis is due to the ongoing infection and not due to a secondary process such as an ANCA-associated vasculitis [55]. This is important because treatment of ANCA-associated vasculitis requires aggressive immunosuppressive therapy but in the case of small vessel vasculitis associated with infective endocarditis, immunosuppression is harmful and may lead to death. Instead, treatment with long-term intravenous antibiotics and potentially valve replacement if necessary is recommended. That provides the best chance for renal recovery and resolution of the GN [48, 54]. Still, renal recovery is often incomplete. For example, in a recent retrospective study, 50% of the patients with GN associated with infective endocarditis had persistent REF or developed end-stage renal disease. Additionally, 22% of these patients died [48]. Immunosuppression, mostly with high-dose corticosteroids, was given to 15 of the 38 patients. It did not improve outcomes and was associated with 50% of the deaths in the study [48]. Therefore, similar to SAGN, immunosuppression has no role in the treatment of GN associated with infective endocarditis even in the setting of a necrotizing and crescentic GN. Prompt therapy with appropriate antimicrobials and supportive treatment of the acute nephritis provides the best opportunity for the patient to achieve a good long-term prognosis.

Shunt Nephritis

Infection associated with ventriculo-atrial shunts, commonly used to treat hydrocephalous, has long been known to cause GN and is referred to as shunt nephritis. Shunt nephritis was first described in 1965 in two children who developed "lobular proliferative" GN after developing a

staphylococcal shunt infection causing sepsis and eventually nephritis [56]. Since then shunt nephritis has been well described in the literature. Most of the cases are associated with a *Staphylococcus epidermidis* infection [37]. As this staphylococcal strain is less virulent, the infection commonly presents in a subacute fashion. These infections are less common with the extravascular ventriculo-peritoneal shunts currently being used in clinical practice but still occur [57]. Clinically, patients present with an acute nephritis and histologically a membranoproliferative GN similar to SAGN is seen. Treatment is supportive with appropriate antibiotic therapy and removal of the shunt. There is little evidence regarding renal prognosis in these patients but the few studies available suggest renal prognosis is favorable with improvement in most patients after the shunt is removed and antibiotic therapy is completed [37].

Antibiotic-Associated Nephrotoxicity

Infection-related glomerulonephritis must be distinguished from other forms of acute kidney injury. Acute kidney injury that occurs in the setting of an infection that is actively being treated may be due to the antibiotic being used to treat the infection. Depending on the type of antibiotic two types of kidney injury may develop: ATN or acute interstitial nephritis (AIN). Antibiotics known to cause ATN and AIN are shown in Table 5.5. The distinction between drug-induced renal injury and infection-related GN can often be made based on the timing of injury. Infection-related GN usually occurs at the peak of infection and commonly before antibiotics have been initiated. Antibiotic-associated nephrotoxicity usually occurs several days to weeks after the antibiotic has been initiated. For example, aminoglycosides are a well-known nephrotoxin that causes direct toxicity to the proximal tubule and manifests clinically as ATN [58]. The toxicity is cumulative and it typically takes >5 days before ATN will become clinically apparent. The urine sediment in ATN is different from acute GN. The urine sediment may be bland or show granular or "muddy brown" casts which are consistent with ATN. Additionally epithelial cells and epithelial cell casts may be seen. Red blood cell casts and pyuria are not consistent with ATN. An emerging cause of antibiotic-associated ATN is vancomycin [59]. Increasing resistance of MRSA has led to more intense dosing schedules for vancomycin in patients with MRSA infections. An increase in vancomycin trough goals has led to an increase in frequency of vancomycin-associated ATN. Treatment for antibiotic-associated ATN is supportive and starts with removing the offending agent. Renal failure is usually non-oliguric and most patients recover renal function. However, the acute kidney injury that occurs can be severe and may lead to chronic kidney damage or dialysis dependence. It may also lead to an increase in length-of-stay and associated comorbidity. Appropriate antimicrobial dosing and close monitoring of trough levels are critical to preventing nephrotoxicity. Importantly, a multidisciplinary effort between the clinician and pharmacist is needed to ensure antibiotic dosing is appropriate, levels are

Table 5.5 Antibiotics associated with nephrotoxicity

Acute tubular necrosis	Acute interstitial nephritis
Aminoglycosides	Penicillin
Colistin	Cephalosporin
Vancomycin	Rifampin
	Trimethoprim-sulfamethoxazole
	Ciprofloxacin
	Vancomycin
	Tetracycline
	Isoniazid

monitored carefully and the drug is promptly stopped when acute kidney injury occurs.

AIN is also a well-known complication of antibiotic therapy and has been associated with several different antibiotics (Table 5.5). AIN shares several clinical features with infection-related GN. Microscopic hematuria may occur but red blood cell casts are uncommon. Proteinuria is usually mild and renal insufficiency is common. Pyuria and white blood cell casts may be seen in both AIN and infection-related GN but pyuria is a hallmark finding in AIN. At least 7–10 days of antibiotic exposure is generally required for AIN to develop [60]. However, AIN is not dose dependent and may recur after second exposure. The classic triad of fever (27%), macular-papular rash (15%), and peripheral eosinophilia (23%) may be seen but the triad is only seen in approximately 10% of cases [61]. Kidney biopsy is required for definitive diagnosis. Treatment is largely supportive, especially in the setting of ongoing infection, and starts with removal of the offending antibiotic. If the infection has resolved, a course of corticosteroids may be considered if renal failure is severe or slow to resolve after removing the offending agent [62].

Conclusion

In summary, the management and prognosis of bacterial infection-related GN is dependent on the timing of the development of the acute nephritis. Post-infectious GN, such as APSGN, most commonly occurs in children and the GN typically occurs after the infection has resolved. The incidence is decreasing worldwide but when GN does develop, treatment is largely supportive and the renal prognosis is excellent in children but in adults chronic kidney disease may develop. In severe cases, the use of immunosuppression may be considered to suppress inflammation and prevent chronic renal damage. In contrast, infection-associated GN, such as SAGN, typically occurs in older adults and the renal prognosis is variable. The incidence appears to be increasing due to increasing prevalence of anti-microbial resistant staphylococcal strains. Histologically, SAGN is distinct from APSGN and appears similar to IgA nephropathy. Therefore the entire clinical picture is needed to determine the etiology of the GN and to ensure appropriate treatment is provided. Treatment for SAGN is largely supportive and importantly, immunosuppression should be avoided. The prognosis for infection-associated GN is not as favorable as APSGN and many patients are left with significant chronic renal damage or dialysis dependence. Antibiotic-associated nephrotoxicity must be considered in the differential of infection-related GN and may manifest as ATN or AIN. Acute kidney injury due to antibiotics is distinguished from infection-related GN in that it usually occurs several days after antibiotic exposure while infection-related GN usually occurs prior to antibiotic exposure. Overall, bacterial infections may lead to renal injury in a variety of ways. Early recognition and treatment is required to preserve renal parenchyma and ensure good long-term prognosis.

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Infection-Associated Thrombotic Microangiopathy

6

Anatoly Urisman and Zoltan G. Laszik

Introduction

Thrombotic microangiopathy (TMA) is a histopathologically defined lesion characterized by microvascular injury with formation of microthrombi, subendothelial and intimal swelling, and luminal occlusion. In the kidney, TMA typically involves the glomerular capillaries and the arterioles, however, interlobular arteries can also be affected. It can be associated with well-defined clinical disorders such as hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), and also a number of other diverse conditions including systemic infections, malignancy, pregnancy, autoimmune connective tissue diseases, abnormal metabolism and coagulation, and transplantation. Clinically, TMA is defined by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia with no apparent alternative explanation for thrombocytopenia and anemia. Other common clinical features include renal functional and neurologic abnormalities, abdominal symptoms, and fever. With advancements in understanding of the underlying etiologies and ongoing development of specific diagnostic tests to distinguish among the many types of TMA-associated conditions, etiology-based classification is becoming widely accepted. Various infectious causes were among the first recognized etiologies of TMA, which are the main focus of this chapter.

Classification

The term *hemolytic uremic syndrome* was first introduced in a 1955 report by Gasser et al. [1], which described a fatal syndrome in children characterized by hemolytic anemia, thrombocytopenia, and severe renal failure. It is now recognized that over 90% of cases of HUS are caused by infection with Shiga toxin-producing gram-negative bacteria and are typically preceded by diarrhea, often bloody diarrhea. Historically, these cases of HUS have been referred to as *diarrhea-positive* (D+), *classic*, or *epidemic* HUS, however, the introduction of tests for Shiga toxin detection in the stool now allows specific diagnosis of Shiga toxin-associated HUS (ST-HUS). The term *atypical HUS* (aHUS) historically referred to as *diarrhea-negative* (D−) HUS, but recognition of specific etiologies of aHUS over the past several decades has resulted in ongoing subdivisions within this category. Invasive infections with *Streptococcus pneumoniae* are associated with a distinctive form of HUS, which accounts for approximately 40% of ST-negative cases [2]. Other infectious agents,

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including HIV, influenza virus, and several other viral and bacterial pathogens, have also been reported in association with HUS. Large proportion of the remaining aHUS cases are associated with either genetic (both familial and sporadic) or acquired disorders of complement regulation. Although the term aHUS is still in use, we prefer the more specific term *complement-mediated* TMA for this group of patients [3]. A rare inherited disorder of cobalamin C metabolism causes a distinctive form of perinatal HUS [4–6]. Other conditions associated with the clinical phenotype of HUS include pregnancy, HELLP syndrome, autoimmune connective tissue disorders, and a variety of drug toxicities [3]. TTP is a rare disorder that can affect any age group [7, 8] with the peak incidence in the third decade of life. Although classically characterized by the clinical pentad of thrombocytopenia, MAHA, fever, neurological abnormalities, and renal dysfunction, current diagnostic criteria require only thrombocytopenia and MAHA to consider the diagnosis of TTP. In contrast to HUS, renal involvement is typically mild in TTP, with mild elevation in serum creatinine, microscopic hematuria, and sub-nephrotic range proteinuria; acute renal failure is present in only a minority of cases. TTP is caused by functional deficiency of ADAMTS13 protease that cleaves multimeric forms of von Willebrand factor (vWF) expressed on endothelial cells, resulting in microvascular platelet aggregation and thrombosis. Approximately 5% of the cases are inherited and are caused by a variety of genetic mutations in the ADAMTS13 gene, which are associated with varying severity and time of presentation from early neonatal period to adulthood. The majority of the cases are caused by acquired autoantibodies to ADAMTS13, which can be detected by laboratory assays. TMA with the clinical phenotype of TTP has also been reported in association with multiple drugs, including quinine, antiplatelet agents, calcineurin inhibitors, chemotherapeutic agents. Other associated conditions include infections, pregnancy and HELLP syndrome, and autoimmune connective tissue disorders. Although classically TTP was distinguished from disseminated intravascular coagulation (DIC) based on normal coagulation times in TTP, many TMA-associated conditions have significant clinical overlap with DIC [9, 10].

Several etiology-based classification systems for TMA have been proposed over the past decade. This includes the 2006 HUS/TTP classification by the International Society of Nephrology [11], and the 2013 TMA classification by George and Nester (Table 6.1) [3]. In the etiologic classification those with well-characterized pathogenesis are classified as primary TMA; cases with TMA but without well-defined specific etiology and pathogenesis are classified as secondary TMA. The secondary forms are associated with a broad range of various conditions including systemic infections, *Streptococcus pneumoniae* infection, malignancy, pregnancy, malignant hypertension, autoimmune disorders, stem cell and solid organ transplantation, and primary glomerular disorders. From the diagnostic point of view, clinical recognition of the TMA hallmarks—thrombocytopenia and MAHA—should trigger a diagnostic evaluation for known TMA-associated conditions (Fig. 6.1).

Pathological Findings of TMA

In general, the histologic features of TMA in the kidneys are similar and independent of the cause. Clinical history and laboratory data are critical when considering the possible etiologies. Cases of classic ST-HUS tend to have a characteristic clinical presentation and usually do not require a renal biopsy. Occasionally, TMA develops in the background of other pathologic abnormalities which may provide important histologic clues to the etiology. For example, features of lupus nephritis in combination with TMA might suggest SLE as the primary etiology. Similarly, inflammatory changes may be helpful in identifying cases of TMA associated with systemic infections and viral cytopathic changes may point to a specific viral etiology.

Table 6.1 Etiology-based classification of TMA

Primary TMA syndromes
Hereditary disorders
ADAMTS13 deficiency-mediated TMA (also called TTP)
Complement-mediated TMA
Coagulation-mediated TMA
Acquired disorders
ADAMTS13 deficiency-mediated TMA (also called TTP)
Shiga toxin-mediated TMA (also called ST-HUS)
Drug-mediated TMA (immune reaction)
Drug-mediated TMA (toxic dose-related reaction)
Complement-mediated TMA
Secondary TMA (common conditions associated with MAHA and thrombocytopenia)
Systemic infection
Malignancy
Preeclampsia, eclampsia, HELLP syndrome
Malignant hypertension
Autoimmune connective tissue disorders
Hematopoietic stem cell or solid organ transplantation

Modified from George and Nester [3]

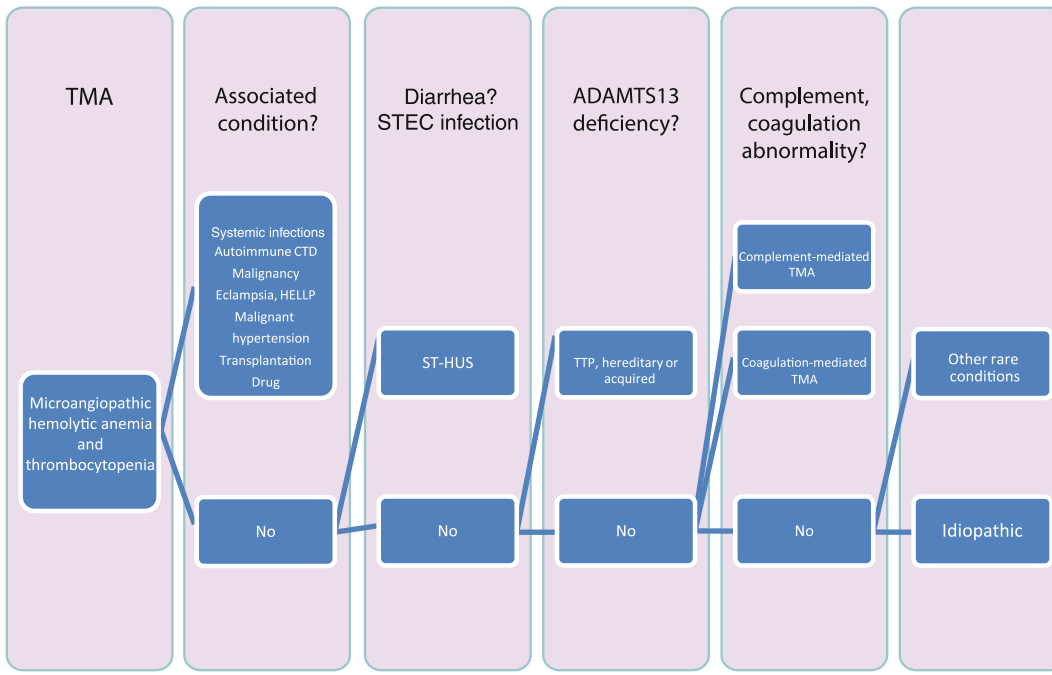

Fig. 6.1 Clinical algorithm for diagnosis of TMA-associated conditions

Gross Appearance

Gross evaluation typically occurs in fatal cases that require autopsy. Another context for gross assessment is in cases that progress to ESRD and also uncontrolled hypertension, which require bilateral nephrectomy for blood pressure control. In the early acute phase of the disease, the kidneys may be swollen and have areas of hemorrhage and cortical necrosis. Petechiae may be seen on the capsular surface and pelvic mucosa. In the late chronic stage, the kidneys can be reduced in size. Areas of old cortical necrosis may be recognized as retracted scars, which sometimes contain calcifications. Other chronic changes may include cystic degeneration and vascular changes of long-term dialysis.

Light Microscopy

Renal core biopsy is frequently used in the evaluation of TMA-associated conditions, particularly in cases where alternative diagnoses are being considered or the underlying etiology is not immediately apparent. Biopsy may also be useful in some chronic or relapsing cases to estimate the extent of chronic damage and ongoing active injury. Depending on the timing of the biopsy, the findings may be dominated by acute (early) or chronic (late) changes. Although these changes exist on a continuum, and significant overlap may be present in some cases, in general, acute changes are seen in biopsies taken within days to a couple of weeks after the disease onset, while chronic changes are more typical of biopsies performed weeks to months following the onset. Changes encountered in the autopsy specimens may be biased toward the severe end of the spectrum.

Early glomerular changes include capillary loop wall thickening and closure of the lumina by swollen endothelial cells. When prominent, this creates the characteristic appearance of *bloodless* glomeruli on the H&E stain, in which the tufts appear solidified and capillary loops cannot be easily distinguished from the mesangium (Fig. 6.2). Glomerular basement membrane (GBM) reduplication, which is best seen on PAS and silver stains, typically develops later in the disease. However, more severe cases may have rapid development of GBM double contours, which typically show irregular complex patterns (Fig. 6.3).

Microthrombi within the glomerular capillary lumina are present in most cases of TMA, but the

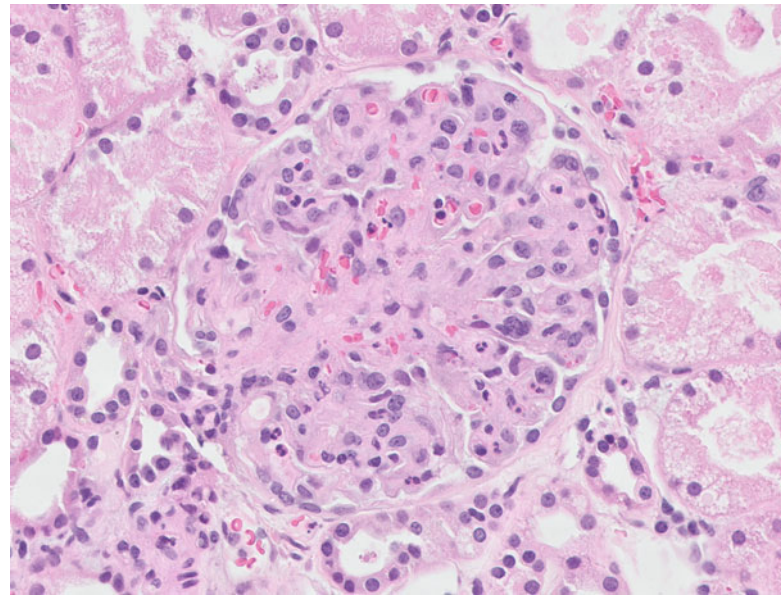

Fig. 6.2 Classic hemolytic uremic syndrome, ST-HUS. Endothelial cell swelling. The glomerulus sows closure of the capillary loops by endothelial cell swelling. Scattered endocapillary neutrophils are also seen (H&E)

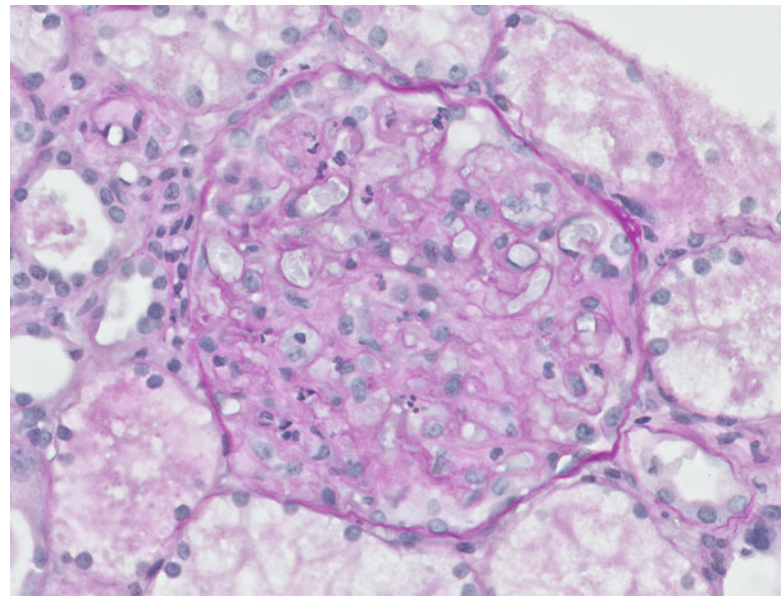

Fig. 6.3 Classic hemolytic uremic syndrome, ST-HUS. Early glomerular basement membrane reduplication and mesangial edema. Subtle glomerular basement membrane double contours and more complex reduplication are seen. The mesangium appears swollen and spongiform (PAS)

frequency and severity of this acute finding may vary significantly from case to case. In mild cases, focal fibrin accumulation may be seen along the internal aspect of the capillary walls in some of the loops (Fig. 6.4). More severe cases typically demonstrate large fibrin and platelet thrombi that may involve several capillary loops (Fig. 6.5). A common location for microthrombi formation is at the point of entry of the afferent arteriole into the glomerular tuft. These so-called *infundibular* thrombi may be quite large and create aneurysmal dilatation of the affected arterioles (Fig. 6.6). In some cases, such afferent arteriolar thrombi extend into the capillary walls or into the mesangium creating the appearance of fibrinoid necrosis. Karyorrhexis and small

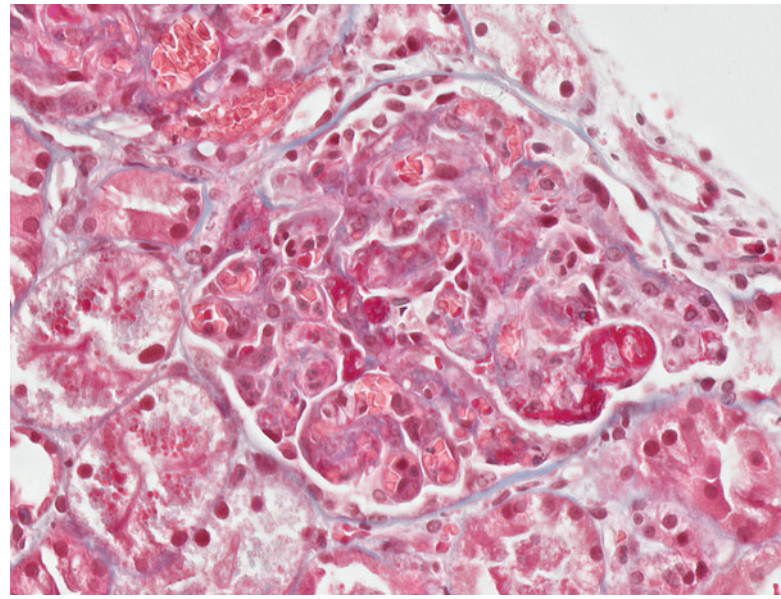

Fig. 6.4 Classic hemolytic uremic syndrome, ST-HUS. Endocapillary thrombi. The endocapillary thrombi appear as *bright red* (fuchsinophilic) aggregates along the inner aspects of the capillary loop walls on trichrome staining (Masson's Trichrome)

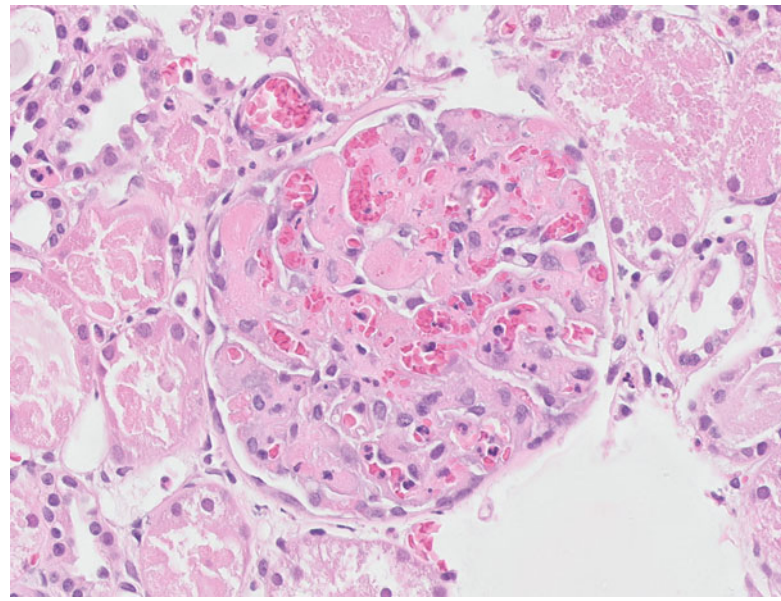

Fig. 6.5 Classic hemolytic uremic syndrome, ST-HUS. Endocapillary thrombi. Large thrombi fill and expand the lumina of multiple glomerular capillary loops (H&E)

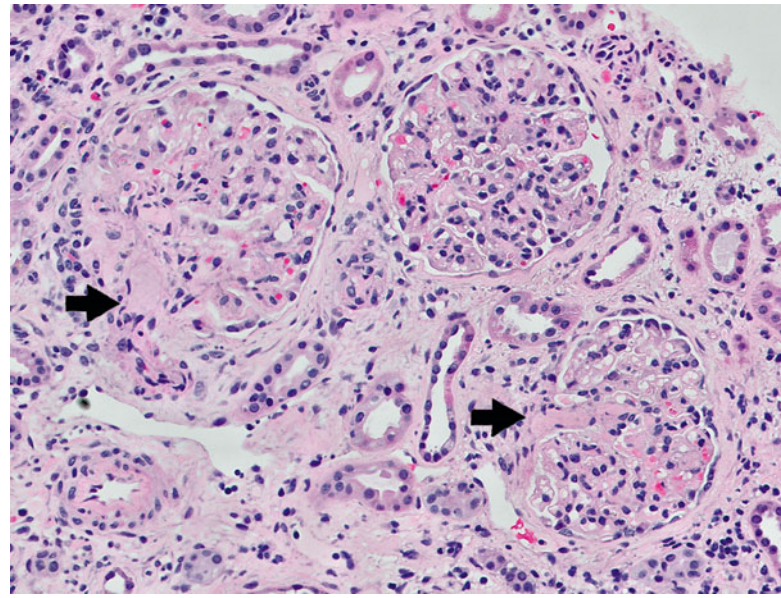

Fig. 6.6 Histologic changes of TMA. Infundibular thrombi. Two glomeruli show prominent infundibular thrombi (*arrows*). Glomerular capillary loop walls appear thickened, and occasional double contours are seen (H&E)

crescents with fibrin may also be present occasionally.

Glomerular capillary loop congestion by red blood cells is another common finding in TMA (Fig. 6.7), particularly in cases with significant extraglomerular arteriolar involvement. This finding is sometimes described as *glomerular paralysis*, because it is classically observed in combination with a thrombotic lesion in the afferent arteriole or terminal interlobular artery upstream of the involved glomerulus.

Fragmented red blood cells (schistocytes) may be a subtle finding in mild cases, but in most cases they are easily identified within the glomerular capillary loops, embedded in fibrin thrombi, and in the mesangium (Fig. 6.8).

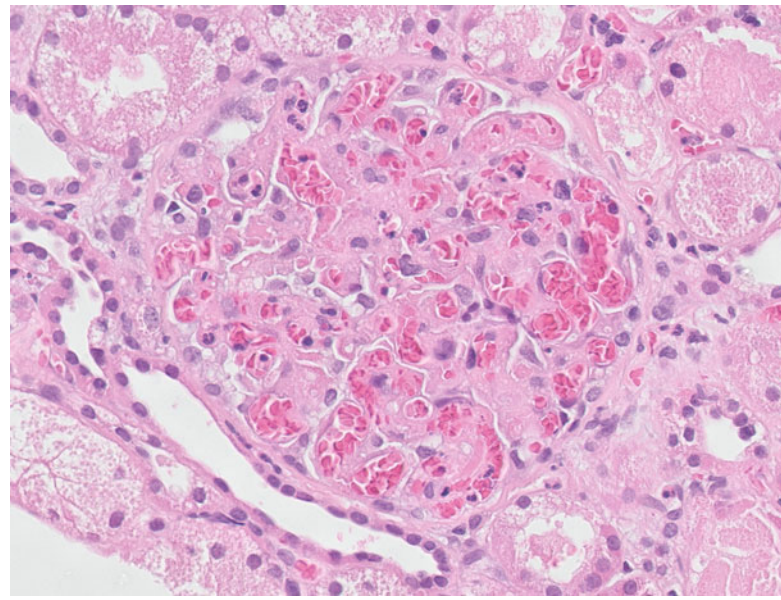

Fig. 6.7 Classic hemolytic uremic syndrome, ST-HUS. Glomerular congestion. The glomerular capillary loops are dilated and congested by red blood cells. Occasional endocapillary neutrophils are also present (H&E)

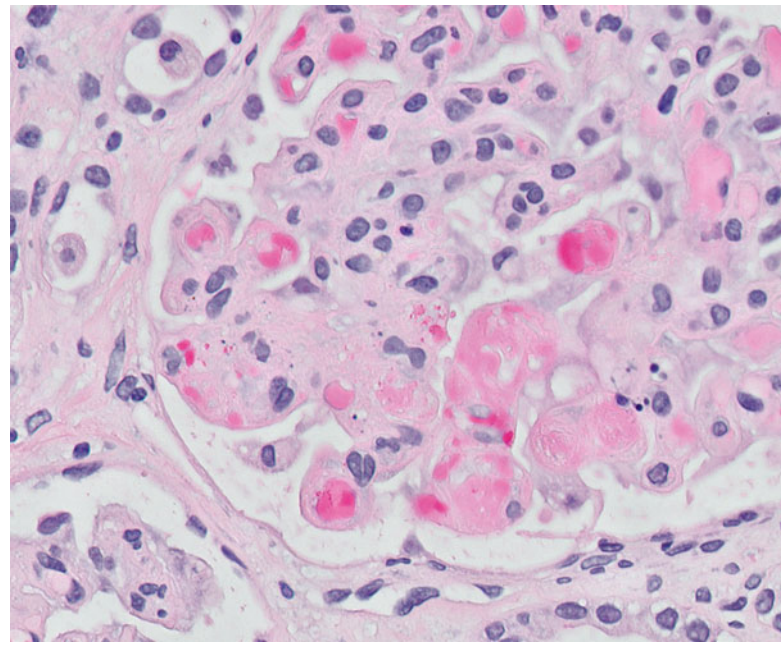

Fig. 6.8 Histologic changes of TMA. Schistocytes. Fragmented red blood cells (schistocytes) are seen in some of the capillary loops and focally in the mesangium. Prominent endocapillary thrombi and apoptotic nuclear debris are also present (H&E)

Mesangial edema with spongiform mesangial appearance is sometimes present as an early finding and is usually not associated with mesangial hypercellularity (Fig. 6.3). Mesangiolysis with capillary loop microaneurysm formation is also occasionally observed, most commonly in more severe cases.

Arterioles, particularly afferent arterioles, and sometimes interlobular arteries may demonstrate luminal microthrombi with associated endothelial cell swelling, and subendothelial edema. In more severe cases, mural fibrinoid necrosis may be present (Fig. 6.9), but mural inflammation such as that seen in cases of leukocytoclastic

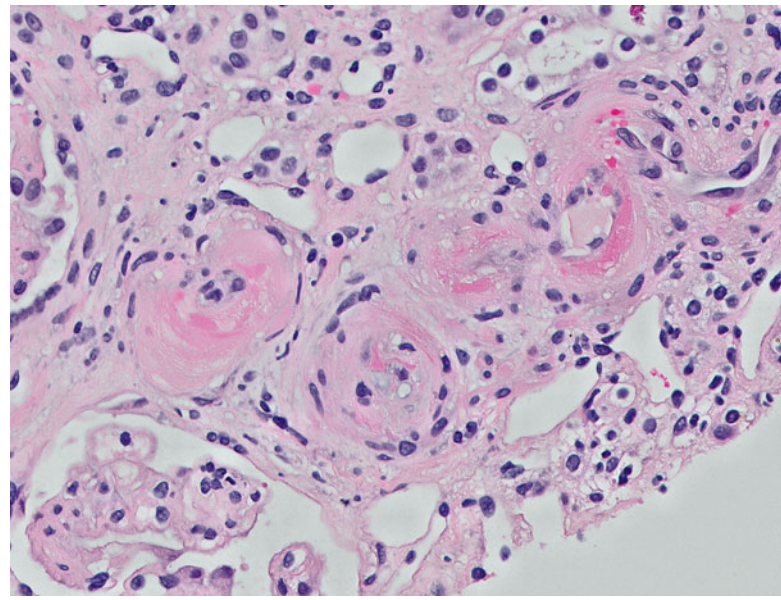

Fig. 6.9 Histologic changes of TMA. Arteriolar thrombi and fibrinoid necrosis. Several arterioles demonstrate fibrin thrombi and mural fibrinoid necrosis (H&E)

vasculitis is not typically observed. With advancing chronicity, the arterioles and arteries develop prominent subendothelial intimal thickening due to proliferating smooth muscle and myointimal cells, with characteristic *onion skin* appearance (Fig. 6.10). Subendothelial accumulation of myxoid matrix, *mucoid intimal hyperplasia*, is also frequently present. In some cases, arteriolar *glomeruloid* lesions are detected, which resemble plexiform lesions of pulmonary arterial hypertension and are also thought to represent sequelae of prior thrombosis with subsequent recanalization.

Chronic changes in the glomeruli vary depending on the severity of the acute injury and whether ongoing active disease is present. In

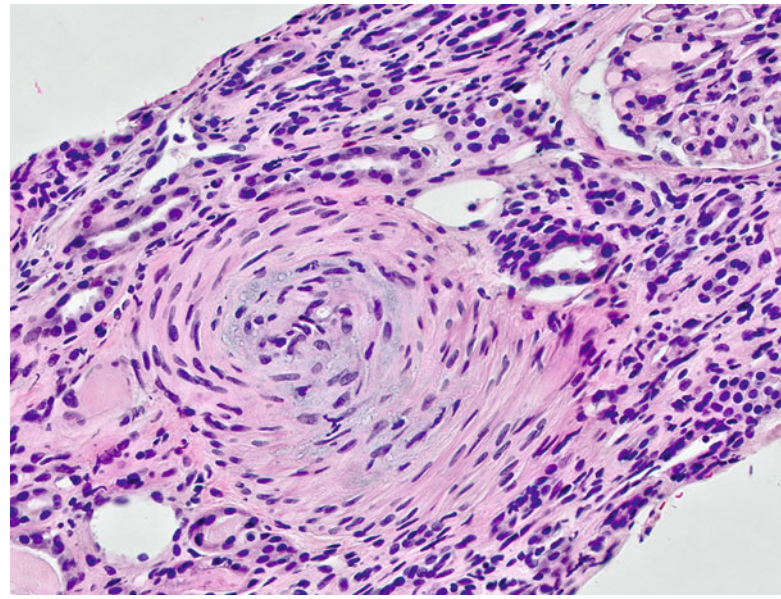

Fig. 6.10 Histologic changes of TMA. Arteriosclerosis with mucoid hyperplasia in a chronic stage case. A terminal interlobular artery shows prominent medial thickening with "onion skin" appearance and mucoid intimal fibroplasia (H&E)

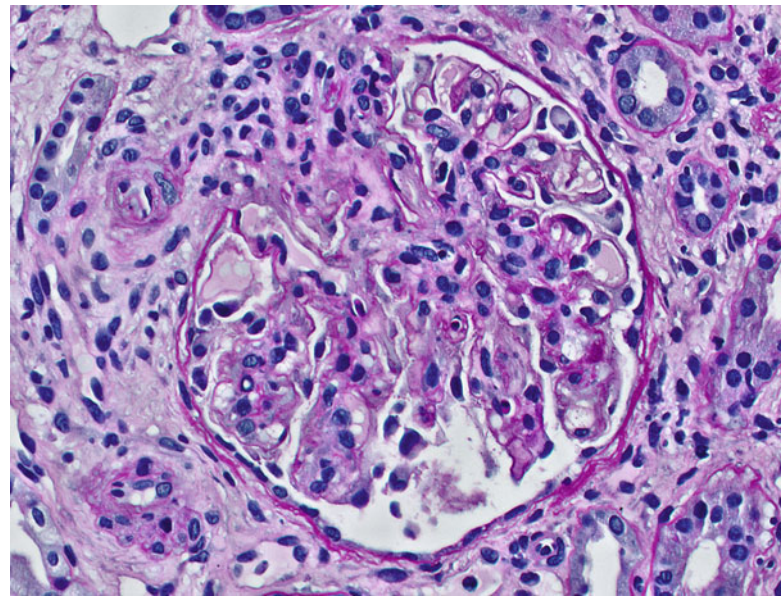

Fig. 6.11 Histologic changes of TMA. Glomerular basement membrane reduplication. The glomerular basement membranes show focal wrinkling, and reduplication can be seen in some of the loops (PAS)

cases without significant ongoing activity, the light microscopic findings become relatively nonspecific. Variable mesangial matrix accumulation with mild mesangial hypercellularity is usually present. GBM double contours on silver and PAS stains may be focal in mild cases or more widespread in more severe cases, resembling the pattern observed in membranoproliferative glomerulonephritis (Fig. 6.11). Focal segmental sclerosis may be observed as a sequela of prior glomerular injury. The adaptive (secondary) form of focal segmental glomerulosclerosis (FSGS) may develop in cases with significant chronicity. Ischemic glomerular changes are common and include thickening and wrinkling of the capillary walls, retraction of the tuft with widening of the Bowman's space, thickening of the Bowman's capsule, collagen "halos" inside the Bowman's space, and periglomerular fibrosis. Significant hyaline arteriolosclerosis may develop as a result of arteriolar injury. Marked arteriosclerosis is also common, both in cases that develop hypertension as a consequence of renal failure and those with preexisting hypertension.

Tubulointerstitial changes are largely nonspecific. In acute disease, variable amounts of red blood cells and red blood cell casts, and sometimes heme pigment can be seen in the tubules. This might be accompanied by mild tubular epithelial cell injury. Mild interstitial edema with sparse lymphocytic or lymphoplasmacytic inflammation may be present. Tubular epithelial protein resorption droplets may accompany cases with proteinuria. In severe cases, areas of cortical coagulative necrosis may occur (Fig. 6.12), which is thought to be ischemic in nature. Dystrophic calcifications are a common finding in such areas. Tubular atrophy and interstitial fibrosis develop with the progression of chronicity (Fig. 6.13).

Immunofluorescence

The most prominent immunofluorescence (IF) finding in TMA is the presence of fibrinogen or fibrin staining in the areas that correspond to glomerular endocapillary microthrombi and thrombi in the extraglomerular vessels (Fig. 6.14). In mild cases, only focal linear fibrinogen staining along the endothelial aspect of the GBM may be detected. Conversely, more severe cases may feature segmental glomerular staining corresponding to large endocapillary thrombi and areas of fibrinoid necrosis.

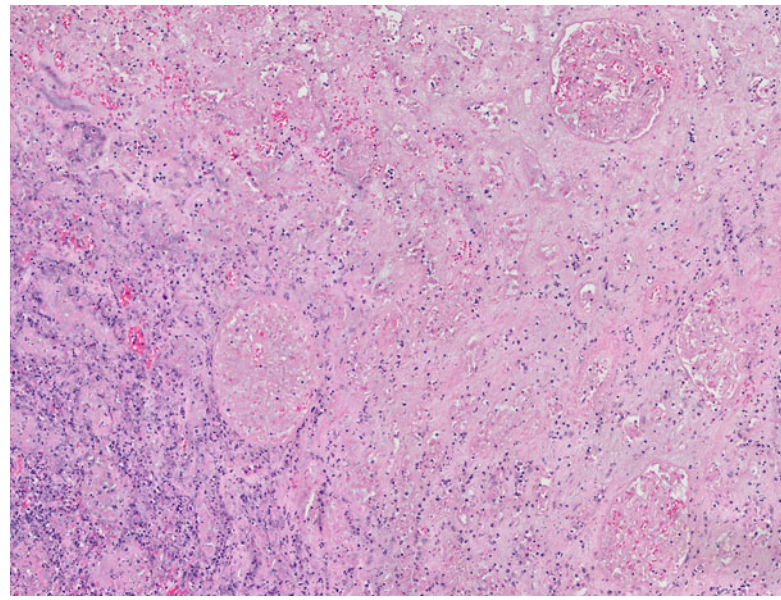

Fig. 6.12 Histologic changes of TMA. Cortical necrosis. Wide area of cortical necrosis with infarct-like appearance is present (H&E)

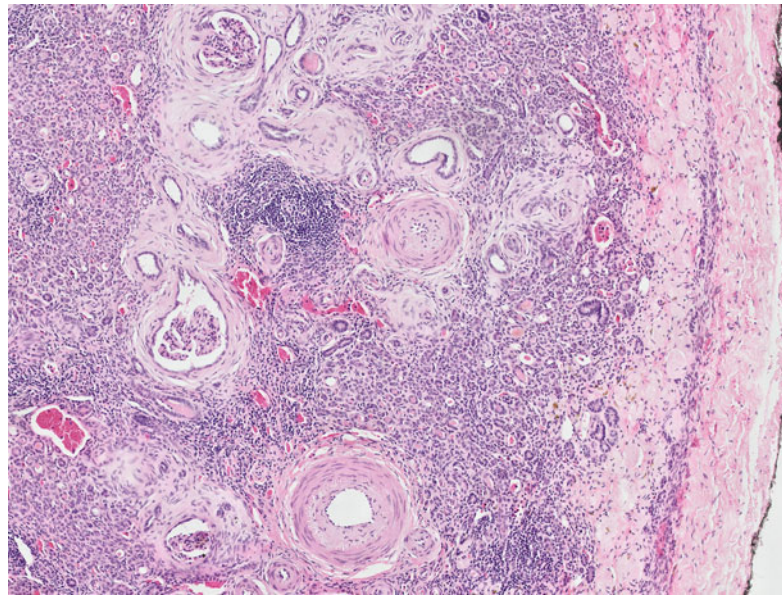

Fig. 6.13 End-stage kidney disease following an episode of classic hemolytic uremic syndrome, ST-HUS. Subcapsular cortex is replaced by a thin layer of fibrosis with small obsolete glomerular "ghosts" still recognizable. A few severely ischemic glomeruli are seen deeper in the parenchyma. There is widespread tubular atrophy and interstitial fibrosis. Arteries and arterioles show prominent medial hypertrophy and intimal fibroplasia (H&E)

Extraglomerular arterioles and small arteries may show staining along the endothelium, within luminal thrombi, or transmural staining corresponding to areas of fibrinoid necrosis. Mesangial fibrinogen staining may also be observed.

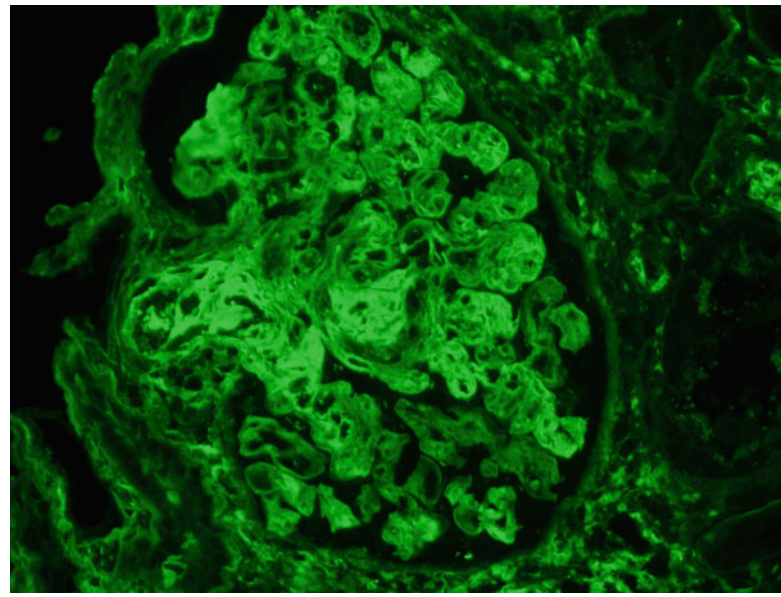

Fig. 6.14 *Clostridium difficile* associated HUS. Fibrinogen immunofluorescence staining. Fibrinogen deposition is seen within the large endocapillary thrombi and in the mesangial areas (Courtesy of Dr. Tibor Nadasdy)

Variable staining for C3 and sometimes C1q complement proteins is usually observed in a distribution similar to fibrinogen. Nonspecific and usually focal staining with antibodies against immunoglobulins, particularly IgM, may also be observed, but significant staining for IgG, IgA, or kappa and/or lambda light chains is not a typical finding.

Several studies compared the composition of microthrombi in TMA cases associated with classic ST-HUS and TTP using IF staining with antibodies against fibrin or fibrinogen to detect fibrin thrombi and antibodies against vWF to detect platelet thrombi [12, 13]. Although more significant staining for fibrin products was reported in cases of HUS compared to TTP, and conversely vWF staining was more significant in cases of TTP compared to HUS, this approach has not found widespread application due to significant overlap in the staining patterns, particularly in cases where the etiology of TMA is uncertain.

Electron Microscopy

Ultrastructural evaluation is an important component in the diagnosis of TMA. It is particularly useful in chronic or subacute cases, where diagnostic features of acute injury may not be readily detected by light microscopy.

In acute phase, glomerular capillary loops demonstrate prominent endothelial cell swelling with diffuse endothelial cell separation from the glomerular basement membranes and subendothelial accumulation of electron-lucent flocculent or granular material (Fig. 6.15). The endothelial fenestrae often disappear because of endothelial swelling. The characteristic *subendothelial widening* is a consistent finding in TMA, which tends to persist beyond the early acute period and can be useful in cases lacking other morphologic features of TMA. With time, new GBM deposition by the endothelial cells results in easily identifiable GBM double contours. Complex multilayered reduplication may be encountered in some cases. Mesangial cell interposition, i.e., extension of the mesangial cell cytoplasm into the capillary loops along the glomerular basement membranes under the endothelial cells, develops soon after the initial injury and usually persists in chronic cases.

In the acute phase, electron-dense strands of fibrin are readily recognized within the capillary loops, often accompanied by variable numbers of platelets and fragmented red blood cells (Fig. 6.16). Mesangial rarefication with

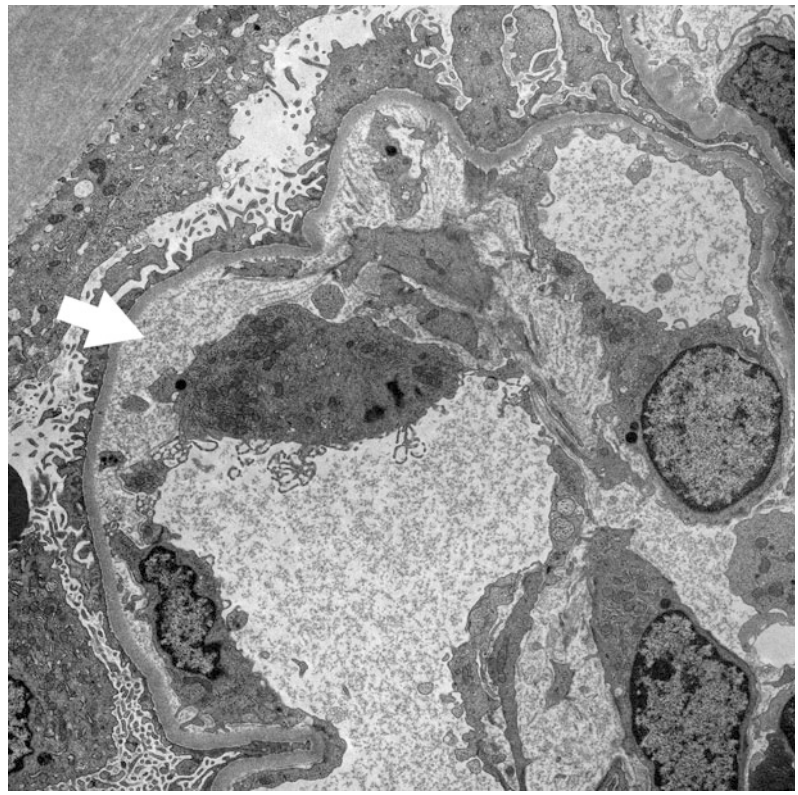

Fig. 6.15 Electron microscopy findings in TMA. Subendothelial widening. Endothelial cells show loss of fenestrae and endothelial cell cytoplasm separation from the glomerular basement membrane with accumulation of electron-lucent granular or flocculent material (*arrow*)

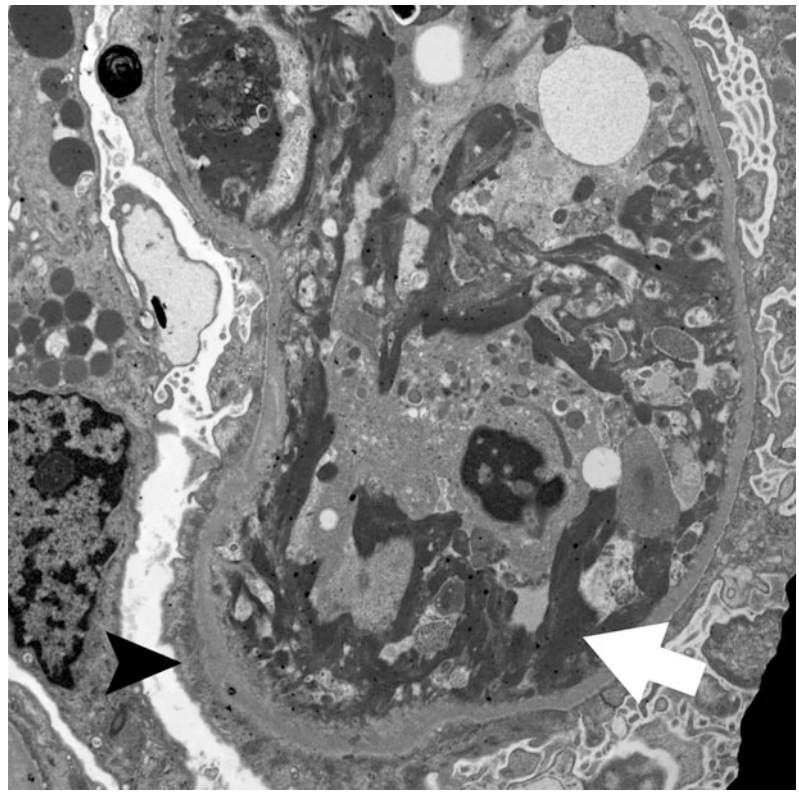

Fig. 6.16 Electron microscopy findings in TMA. Endocapillary fibrin. Abundant irregular electron-dense fibrin strands are seen within a glomerular capillary loop (*arrow*). The capillary lumen is closed by swollen endothelial cells and necrotic/apoptotic cell debris. Significant podocyte foot process effacement is also present (*arrowhead*)

accumulation of granular material similar to that seen in subendothelial widening may be observed. Large dilated capillary loops may be visualized as a consequence of mesangiolysis. Podocyte foot process effacement is typically focal or patchy, not widespread.

Findings in arterioles and small arteries resemble those seen in the glomerular capillary loops. These include endothelial cell swelling, endothelial separation from the basement membrane, and subendothelial accumulation of granular material. Endoluminal fibrin, platelets, and schistocytes may be identified. Basement membrane multilayering is sometimes observed in more chronic cases.

Shiga Toxin-Associated HUS (ST-HUS)

Epidemiology

In the 1980s, Shiga toxin-producing *E. coli* (STEC) emerged as the major etiologic factor in the development of classic HUS, first in two epidemic outbreaks reported by Riley et al. [14] and later in a series of sporadic cases described by Karmali et al. [15, 16]. Since then, several major epidemic outbreaks of STEC-associated HUS have been documented. In 1992–1993, a multistate outbreak in the United States was caused by STEC O157:H7 transmitted via contaminated hamburger meat at a fast food restaurant chain. Among 501 cases (median age 8 years; range 4 months–88 years), 45 developed HUS (9%), and 3 patients died [17]. Two large *E. coli* O157:H7 outbreaks occurred in Japan in 1990 [18] and in 1996 [19]. The 1996 outbreak in Osaka, Japan affected 12,680 school children with the median age of 7 years through contaminated school lunches. Among them, 121 patients developed HUS (0.9%), and 3 children died. Another outbreak occurred in the United States in 2008 among patrons of a buffet style restaurant in Oklahoma, which was caused by a non-O157 *E. coli* strain, STEC O111. This outbreak affected mostly adults (median age 44 years), with 26 cases of HUS (17%) and one death recorded among 156 confirmed cases [20]. A more recent outbreak involving an unusual hybrid strain of STEC O104:H4 in Germany in 2011 resulted in 3816 cases, 845 of which (22%) developed HUS (median age 42 years), and 54 patients died [21]. A retrospective analysis of STEC O157 outbreaks reported to the Centers for Disease Control and Prevention identified 350 outbreaks between 1992 and 2002 with 8598 cases total, among which 354 (4%) developed HUS [22]. Although data from North America and Western Europe indicate that STEC O157:H7 is responsible for the great majority (63–83%) of diarrhea-associated HUS cases [21, 23, 24], non-O157:H7 strains are responsible for a larger proportion of HUS cases worldwide [25, 26]. Additionally, emerging evidence from studies using direct detection of Shiga toxin in the stool indicates that non-O157:H7 STEC strains may account for 20–50% of all STEC infections in the United States [27]. The annual incidence of ST-HUS in the US, Canada, and Western Europe has been estimated at 1–20 cases per 1 million population [28–32], but is likely several fold higher in the regions where STEC strains are considered endemic [33].

Shigellosis is another well-established cause of classic HUS. Shiga toxin was originally characterized as an enterotoxin produced by *Shigella dysenteriae* serotype 1 strains [34]. It has been estimated that there are 165–250 million cases of Shigella infection causing 0.6–1.1 million deaths annually, with over 99% of the cases occurring in the developing countries where poor sanitation is thought to play a key role in the disease transmission [34, 35]. Although numerous *Shigella* species produce Shiga toxin and cause diarrheal illness, *S. dysenteriae* type 1 is responsible for a significantly higher proportion of cases with more severe clinical course and a higher proportion of cases of HUS [35, 36]. Most cases of Shigellosis and associated complications, including death, occur in children <5 years of age [35, 37, 38].

Clinical Course and Treatment

The average incubation time with STEC infection is 3–8 days, which varies depending on the strain [17, 19–21, 29]. Symptoms usually begin with abdominal cramps and diarrhea. Hemorrhagic diarrhea develops in 40–60% of epidemic cases, and up to 20% of cases progress to HUS (compared to <10% in sporadic cases) [39, 40]. Cases of hemorrhagic colitis not complicated by HUS are self-limiting and are not known to be associated with a long-term risk of hypertension or renal dysfunction [41]. Among STEC cases that do develop HUS, prodromal bloody diarrhea is present in about 70% of cases; fever occurs in 30% and vomiting in 30–60% of cases. Neurologic involvement, including stroke, seizures, or coma, is present in 25% of cases. Blood transfusions may be required in 70% of cases and dialysis in up 50% of cases [39, 42, 43]. STEC may be detected in the stool for several weeks after the symptoms resolve, particularly in children <5 years of age [44]. Risk factors associated with the development of HUS in STEC infections include bloody diarrhea, fever, elevated white blood count, vomiting, extremes of age, female gender, use of antimotility agents [39, 45]. In a meta-analysis study of 3476 patients with average follow-up of 4.4 years, patients who survived an episode of ST-HUS had an increased risk of long-term kidney dysfunction, including ESRD (12%) and significantly reduced GFR (25%) [43]. The outbreak of STEC O104:H4 in Germany in 2011 was characterized by unusually severe symptoms and outcomes compared to prior outbreaks, with 50% neurologic involvement, 20% frequency of seizures, 20% dialysis-dependent renal failure, and 6% mortality (vs. 1%) [46].

Treatment of ST-HUS is largely based on supportive management of anemia, renal failure, and fluid and electrolyte imbalances. Early intravenous fluid administration may limit the severity of renal dysfunction and need for dialysis [47]. Bowel rest is usually recommended in cases with bloody diarrhea, and antimotility agents should be avoided. Although an early study suggested that use of antibiotics in STEC infections may increase the risk of HUS by 17-fold [48], a meta-analysis of 26 studies failed to show a statistically significant correlation between antibiotic and HUS [49]. Nevertheless, with the exception of rare cases with bacteremia [50], antibiotics should be avoided in STEC colitis, as their use has not resulted in improved outcomes. Vigilant blood pressure control in patients with chronic kidney insufficiency following an episode of ST-HUS may be beneficial in slowing down the progression of renal function decline [51, 52]. An oral Shiga toxin-binding agent has been developed, but a prospective randomized clinical trial failed to demonstrate any clinical benefit of the therapy [53]. Plasma infusion, plasma exchange and intravenous IgG therapy have been used in critically ill patients on individual basis [54–57], but randomized studies are lacking to assess the efficacy of these interventions. Similarly, the use of anti-C5 monoclonal antibody eculizumab which showed promise in the initial trials [56, 58], has been put into question in follow-up studies [59], and a randomized prospective phase 3 trial is currently under way. Kidney transplantation should be considered in patients who progress to ESRD.

Presentation and clinical course of illness caused by *S. dysenteriae* type 1 are similar to those of STEC. An important exception might be a higher rate of bacteremia in Shigellosis (up to 6% vs. <1% in STEC) [60–62], and evidence that empiric antibacterial therapy in endemic regions shortens the duration of symptoms and reduces the incidence of complications [63, 64].

Pathologic Findings

Gross and histologic findings of ST-HUS are largely the same as those of other conditions characterized by TMA (see above). Although no specific histopathologic characteristics that distinguish ST-HUS from other TMA-associated conditions exist, a few typical observations are worth mentioning. Petechial subcapsular and parenchymal hemorrhages, which can be recognized both grossly and microscopically, are less common in HUS than in TTP [65]. Glomerular involvement is usually present. Capillary wall

thickening is the earliest and most readily recognized abnormality. Mesangiolysis is present in most cases and may be subtle or very prominent in the more severe cases. Hilar and infundibular fuchsinophilic thrombi are common and are often surrounded by arteriolar fibrinoid necrosis. Focal crescents may be found in up to 5% of the cases [65]. Although cortical necrosis in HUS associated with STEC as well as *S. dysenteriae* type 1 is well documented in older autopsy series [1, 66], it likely develops only in a minority of cases with the most severe disease. Several studies have demonstrated that the presence of significant extraglomerular arterial involvement is an important prognostic factor associated with poor long-term clinical outcomes and more rapid progression to ESRD [67–70].

Mechanisms

The general underlying pathophysiological mechanisms that result in the development of TMA are thought to be shared by the different TMA-associated conditions and include endothelial cell damage and local activation of complement and coagulation pathways. In ST-HUS, Shiga toxin produces a multifactorial response mediated by both intrinsic properties of the toxin as well as host response mechanisms (Fig. 6.17).

STEC strains produce two serotypically different types of Shiga toxin, Stx1 and Stx2, while Stx refers to the prototype Shiga toxin originally discovered in *S. dysenteriae* type 1. Stx and Stx1 are nearly identical with only a single amino acid difference in their protein sequence [71]. Stx1 and Stx2 amino acid sequences are only 56% identical, but the two toxins share the same domain structure and mechanism of action [72]. Multiple variants of the prototypical Stx1 (renamed Stx1a) and Stx2 (renamed Stx2a) have been identified, including Stx1c, Stx2c, Stx2e, Stx2f, and Stx2g, which share 84–99% sequence identity with the prototypes [73, 74]. Shiga toxins are encoded by diverse lambdoid bacteriophages, which are an important vehicle for horizontal gene transfer and rapid acquisition of pathogenicity in gram-negative bacteria. Stx genes encode two subunits, A and B, which assemble into AB_5 configuration formed by a single A subunit which non-covalently inserts into a doughnut-shaped pentamer of B subunits [75, 76].

Both Stx/Stx1 and Stx2 interact with the same cellular receptor, glycosphingolipid globotriaosylceramide (Gb3, also known as CD77), on the surface of mammalian cells [77–79]. Binding of the B pentamer induces clathrin-independent endocytosis and retrograde transport of the toxin into the endoplasmic reticulum (ER), where the catalytic A subunit is released into the ER lumen [80, 81]. The A subunit is an RNA *N*-glycosidase that cleaves a specific adenine base in 28S ribosomal RNA (rRNA), which blocks elongation factor-dependent aminoacyl tRNA binding and inhibits translation [82–84]. In addition to the inhibition of protein biosynthesis, Stx-induced structural modification in the 3′ end of the 28S rRNA induces a stereotypic response pathway called ribotoxic stress, which results in activation of pro-apoptotic signaling cascades (including JNK1) and leads to cell death [71, 85].

It has also been shown that even at low concentrations of Shiga toxin with minor effects on protein biosynthesis, major signaling changes are induced in endothelial cells [86, 87]. These changes include upregulation of the NF-κB and TNFα pathways, which promote expression of numerous proinflammatory cytokines and chemokines (MCP-1, IL-8, IL-1, IL-6, CXCR4 and SDF-1) as well as various cell adhesion molecules (E-selectin, ICAM-1, VCAM-1, and PECAM-1). Together, these changes are thought to result in recruitment of inflammatory cells such as neutrophils, monocytes and macrophages, with further elaboration of proinflammatory cytokines and tissue factor (TF) leading to downstream activation of platelet adhesion, extrinsic coagulation pathway, and C3-dependent alternative complement pathway [88–94]. TNFα and IL-1 have also been shown to induce upregulation of the Stx glycolipid receptor, Gb3, in endothelial cells, which may further promote binding of Stx to the endothelial cells [95].

In vitro evidence suggests that Stx can directly interact with vWF and induce the formation of

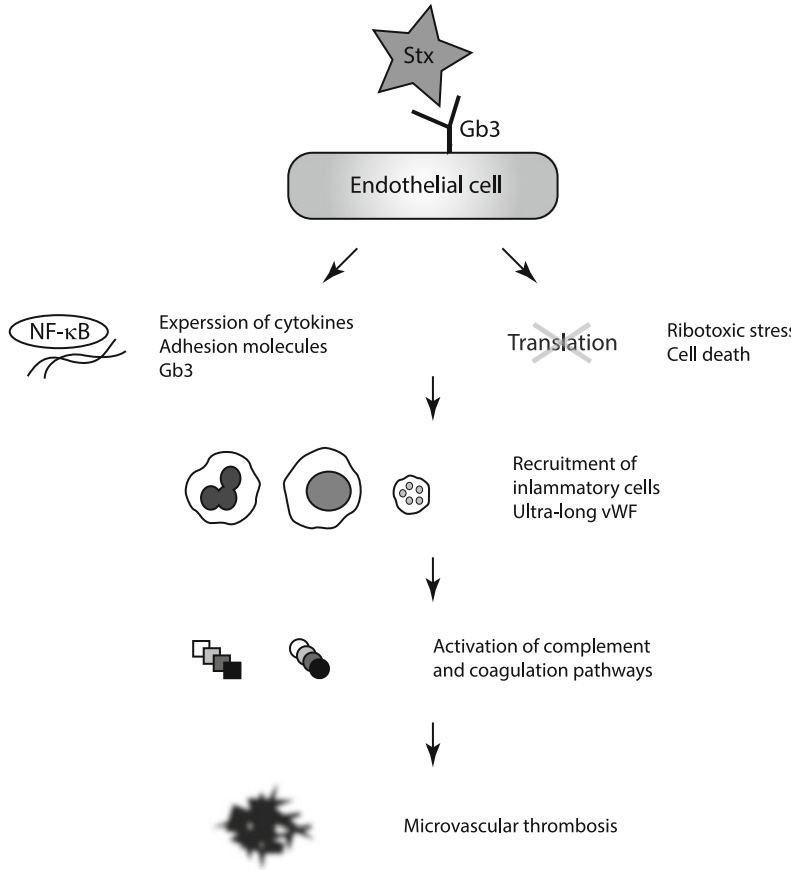

Fig. 6.17 Mechanism of Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS). Shiga toxin (Stx) binds to its cellular receptor Gb3 on the endothelial cells and induces endothelial cell injury through direct inhibition of translation and NF-κB dependent transcriptional changes. Direct ribosomal inhibition by Stx produces *ribotoxic* stress and leads to cell death. Activation of NF-κB induces expression of numerous cytokines and cellular adhesion molecules, which leads to local recruitment of inflammatory cells. Stx binding to endothelial cells is promoted by upregulation of Gb3 expression. Stx binds von Willebrand Factor (vWF) and induces formation of ultra-long vWF, which promotes platelet recruitment and aggregation. Concurrent activation of complement and coagulation pathways ultimately results in formation of thrombi

ultra-long vWF multimers (UL-vWF) [96]. Although the formation of UL-vWF is dependent on B subunits in both Stx1 and Stx2, the precise mechanisms by which Stx1 and Stx2 induce UL-vWF may be different [97, 98]. Independent of the mechanism, formation of UL-vWF promotes platelet aggregation and activation of the clotting cascade in a manner similar to TTP.

It has been noted that Stx2-producing STEC strains tend to produce severe disease, including neurological symptoms and HUS, more frequently than Stx1-producing strains [99]. These differences have been attributed to the differences in binding properties of the two toxins to their receptor. Stx1 and Stx2 use different epitopes on Gb3, and although Stx1 has a 10-fold higher affinity for the receptor, Stx2 has a 200-fold slower dissociation from the receptor [100, 101].

Streptococcus Pneumoniae-Associated HUS (SP-HUS)

Severe systemic infections caused by *S. pneumoniae*, including pneumonia and less frequently meningitis, are the most common cause of

non-diarrheal (D−) HUS. A study from the United States estimated that SP-HUS accounts for up to 38% of D− HUS and up to 4.7% of all HUS cases [2]. SP-HUS affects predominantly children under 2 years and is associated with high morbidity. A recent and largest to date retrospective study from North America of 37 cases of SP-HUS occurring between 1997 and 2009 reported 3% mortality [102] compared to up to 25% mortality in older studies [103–105]. In that study, 95% of patients required admission to the intensive care unit, 73% required dialysis during hospitalization, 23% remained dialysis dependent after 6 months of follow-up, and 10% underwent renal transplantation. The clinical outcomes are strongly dependent on prompt initiation and the effectiveness of antibacterial therapy.

Several studies from the US, Canada, and the UK documented an increase in annual incidence of SP-HUS following the introduction in 2000 of the heptavalent pneumococcal conjugate vaccine (PCV-7) [106–108]. Following 2001, serotype 19 which was not included in PCV7 has emerged as the most prevalent serotype associated with invasive *S. pneumoniae* infections. The serotype *replacement* has been argued to have occurred as a result of the introduction of the vaccine and/or antibiotic selection [109–111]. The more recently introduced broader-coverage PCV-10 and PCV-13 have been estimated to produce a significant reduction in the incidence of invasive infections caused by vaccine serotypes [112]. However, serotype tracking data following the introduction of the 10 and 13-valent vaccines, also suggests rapid emergence of non-vaccine strains [113–117], including those with multidrug antibiotic resistance [113, 117].

The proposed mechanism of SP-HUS involves cleavage of sialic acid on the surface of the red blood cells, platelets, and renal endothelial cells by the bacterial neuraminidase to expose Thomsen–Friedenreich antigen (Gal-GalNAc, also known as T-antigen) [104]. Naturally occurring cold IgM antibodies cause erythrocyte agglutination in vitro, which is the reason for positive Coombs test in SP-HUS unlike other forms of HUS [104, 118, 119]. Although T-antigen is thought to be involved in the pathogenesis, the role of anti-T IgM antibodies has been questioned [120]. A recent study examined the role of complement in five SP-HUS patients and found significantly decreased levels of the classical and alternative complement pathway components during the acute phase of the disease [121], suggesting acute activation of the complement pathways and consumption of its components. Importantly, three of the five patients also showed evidence of genetic alterations in the complement genes, including a previously described variant of Factor I (P50A) and two novel variants in Factor H (R1149X) and Thrombomodulin (T44I). Although these results provide novel evidence of complement activation in SP-HUS, a mechanistic understanding of the events leading to this activation is currently lacking. Additionally, these findings provide further evidence that the pathogenesis of many forms of TMA is multifactorial and that abnormal activation of complement is an important component in many forms of TMA with various triggering etiologic factors.

Human Immunodeficiency Virus (HIV)-Associated TMA

Although bacterial infections are the most common cause of TMA, TMA is also well-documented in association with some forms of viral infections. Therefore, viral infection-associated TMA is briefly discussed. The first case of TMA associated in an AIDS patient was published in 1984 [122], just a couple of years following the description of AIDS [123], and the same year HIV was proposed as the causative agent of AIDS [124]. The incidence of HIV-associated TMA prior to the introduction of highly active antiretroviral therapy (HAART) varied in different studies from 0 to 83% [125–133], likely due to the differences in case selection criteria and perhaps geographical variation among the studied populations. The incidence of HIV-associated TMA has likely declined after the introduction of the HAART [129, 130]. In a large US cohort of over 6000 HIV patients, 0.3% had TMA [129]. Of those with TMA, approximately 11% had clinical manifestations of TTP while the remaining 89% had HUS. TMA was

associated with significantly lower CD4 counts and higher HIV RNA loads. Mortality from HIV-associated TMA also appears to have declined in the era of HAART and with the use of plasma exchange, with recent mortality estimates around 4% [134].

Clinically, HIV-associated TMA is characterized by the classic manifestations of TMA with MAHA, thrombocytopenia, and elevated LDH levels. In some cases, TMA is the presenting manifestation of HIV infection [135–137]. A component of renal failure is usually present and may vary from mild elevation in creatinine to acute oliguric renal failure requiring dialysis. Based on the severity of renal involvement, HIV-associated TMA cases were sometimes classified as TTP or HUS [130]. However, following the discovery of ADAMTS13 cleaving protease and of its role in the pathogenesis of TTP [138], HIV-associated TMA cases could be classified more precisely based on the measurements of ADAMTS13 activity. A study from South Africa found that in a cohort of 20 patients with clinically diagnosed HIV-associated TTP 14 patients (70%) had severely reduced ADAMTS13 activity, of whom 5 also had evidence of ADAMTS13 inhibitor [139]. In that study, reduced ADAMTS13 activity was also correlated with lower CD4 counts and higher vWF levels. Similarly, a multicenter study from France of 29 patients with HIV-associated TMA (identified among the total of 236 patients in the French Network on TMA) demonstrated that 59% of the patients had severe reduction of ADAMTS13 activity (<5%) [140]. Importantly, patients in this group had fewer AIDS-related complications (24% vs. 92%), higher CD4 counts, and lower mortality (12% vs. 50%) compared to those with higher ADAMTS13 activity. Although mortality in the group with severely reduced ADAMTS13 activity was similar to that of idiopathic (HIV-negative) TTP in this study, a study from England suggested a more favorable prognosis in HIV-associated TTP compared to idiopathic TTP [134].

The treatment of HIV-associated TMA includes early initiation of plasma exchange, even before the results of ADAMTS13 testing are available, and consideration of anti-complement therapy in cases with normal ADAMTS13 activity [141]. Although the efficacy of anti-complement therapy is still being evaluated, some reports show promising results with the use of eculizumab (anti-C5 monoclonal antibody) in the setting of HIV-associated TMA [141, 142].

Influenza-Associated TMA

Several cases of TMA have been reported in association with influenza A virus [143–145], which share a TTP-like phenotype characterized by thrombocytopenia, MAHA and significantly reduced ADAMTS13 levels. In at least one case ADAMTS13 inhibitor could be detected [143]. Since influenza A virus expresses neuraminidase on the surface of its envelope, a TTP mechanisms similar to that produced by streptococcal neuraminidase has been proposed [146]. However, given the apparent disconnect between the very high worldwide incidence of influenza A virus and the rarity of TMA in association with the virus, other host factors likely play a predisposing role in the pathogenesis. For example, autoantibodies similar to those detected in autoimmune connective tissue disease were detected in the acute phase in one patient with Influenza A virus-associated TMA [147], and in another recent case a heterozygous factor S deficiency was identified [148].

TMA Associated with Other Infections

TMA has been reported in association with numerous other pathogens. Bacterial causes include systemic infections with both gram-positive and gram-negative bacteria [149, 150]. Viral triggers of TMA include both DNA viruses such as cytomegalovirus (CMV) (particularly in renal transplant patients [151]), Ebstein–Barr virus (EBV), adenovirus, and parvovirus, as well as RNA viruses such as HIV, HTLV, Hepatitis C, picornaviruses, and orthomyxoviruses [152]. TMA in patients with

tissue-invasive fungal infections, most commonly in immunocompromised patients, have also been reported [153–155].

Although the exact mechanisms of pathogen-mediated TMA may be different with various pathogens, the general mechanisms that have been proposed are direct endothelial cell injury, cytokine storm-mediated endothelial cell injury, ADAMTS13 inhibition/deficiency, and complement dysregulation [146, 152, 156].

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Direct Bacterial Infection of the Renal Parenchyma: Pyelonephritis in Native Kidneys

7

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Acute Pyelonephritis in Adults

Introduction

Acute pyelonephritis (APN) is a direct and, more often, focal bacterial infection of the renal parenchyma, which frequently develops in young women.

In uncomplicated forms diagnosis is simple and could be made solely on a clinical ground: flank pain associated with fever and preliminary dysuria. Some simple cases may be treated at home for a week.

However, APN may prove to be an insidious disease, since even apparently simple cases may subtend other pathologic situations or may behave in atypical ways which is why a more in-depth evaluation must be conducted in every patient.

Patients usually present at Emergency Rooms where they undergo blood tests and ultrasound examination (US). This is the correct procedure since the severity of the infection can be determined through the inflammatory parameters, and moreover hydronephrosis and the presence of urinary tract stones ruled out.

However, even with this approach there may be other pitfalls. In the majority of cases, differential diagnosis with important clinical conditions which may simulate APN, such as pelvic inflammatory disease, renal infarction, or appendicitis, may not be possible by US alone. Moreover, complicated APN, such as cases with intra- o perirenal abscesses, are most often not detected by ultrasound.

Thus, the need for further examination by CT or by magnetic resonance (NMR) (which is preferable due to the frequency of young patients) should be evaluated and if possible performed in all cases.

Moreover, other clinical traps may include the frequent finding of negative urine cultures, the reason being that many patients have already taken antibiotics prescribed by their family doctor or even self-prescribed. This implies that the antibiotic strategy is empirical in most cases and cannot correctly be targeted on the basis of an antibiogram. Additional problems include the increasing resistance of germs to the antibiotics that are most commonly used to treat urinary tract infections (UTIs) (such as fluoroquinolones) and that differences in resistance are observed in various geographical areas.

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This is an even greater problem in APN complicated by abscesses, which require longer duration of therapy.

While single episodes of APN are likely completely irrelevant as regards renal function outcome, relapsing cases may lead to the development of cortical scars and to chronic pyelonephritis. Some of these patients come to the nephrologist's attention only late in life for unspecific symptoms and various alterations of renal function. When a history of recurrent APN is accompanied by the presence of renal scars, the existence of VUR as the primary disease must be taken into account. As the VUR often disappears by the fifth year of age, the diagnosis of such a VUR nephropathy may be difficult.

Even if APN is more and more frequently observed in hospitals, our knowledge is still evolving slowly. In fact, no standardization has yet been reached regarding diagnostic criteria, indication to imaging, need for hospitalization, length of antibiotic treatment, need for long-term re-evaluation, and management of abscesses.

The aim of this chapter is therefore to attempt to clarify these nebulous points, even through our own direct experience.

– *Definitions*

Lower UTIs (cystitis and asymptomatic bacteriuria) must be differentiated from APN, in which the infection is localized in the kidney.

Asymptomatic bacteriuria is the presence of 10^5 colony-forming units (cfu)/ml of bacteria in at least two subsequent urine cultures in asymptomatic women or in just one urine culture in asymptomatic men [1].

Uncomplicated cystitis is a bladder infection, presenting frequent or urgent urination, dysuria, and even suprapubic pain.

Acute pyelonephritis (APN) is an infection of the renal parenchyma and pelvis, which may be sometimes severe.

C*omplicated* APN are those arising in the context of clinical situations that make patients susceptible to such infections: age above 65 years, diabetes, presence of urinary tract abnormalities, pregnancy, transplantation, immunosuppression, multiresistant bacteria, hospital-acquired infection, functional or anatomic abnormality of the urinary tract, symptoms for seven or more days, urinary tract obstruction, presence of an indwelling urethral catheter, stent, and nephrostomy tube or urinary diversion. All urinary infections in men are considered complicated [2].

Unfortunately the same expression, i.e., *complicated*, is also used to refer to other conditions, thus sometimes generating misunderstandings. C*omplicated* APN also refers to forms characterized by severe clinical presentation or by a greater extent of the infection or by the appearance of abscesses or emphysematous evolution [2] (Table 7.1).

Recurrent UTI is caused by a different strain of microorganism than the one that was responsible for the original infection. The term refers to ≥ 2 infections in 6 months or ≥ 3 infections in 1 year [3].

Relapsing infections are those appearing within two weeks of the completion of treatment for the original infection [3].

Epidemiology

APN has been estimated to have an incidence of 250,000 cases/year in the U.S. [4], and the direct and indirect cost amounts to about 2,140,000,000 US dollars per year [5].

Women are infected five times more often than men, even though they have a lower mortality rate (7.3 vs. 16.5 deaths/1000 cases [4]).

APN is common among diabetics with an incidence of 51.4 and 147.9/1000 person-years for men and women, respectively [6].

The incidence of APN during pregnancy was 0.5% in a series of 543,430 patients [7].

Renal and perirenal abscesses, which may be either of ascending or hematogenic origin, may complicate an infection of the renal parenchyma [8, 9]. Although the problem of renal abscesses is underestimated in the literature, their frequency is high: in the U.S. they are responsible for 1–10/10,000 hospitalizations yearly with a mortality of 0.7–1.6% [9].

Table 7.1 Complicated acute pyelonephritis

(a) Conditions favoring APN and increasing the clinical severity
Age >65 years
Diabetes
Cancer
Pregnancy
Urinary tract obstruction
Urinary tract anatomic/functional abnormalities
Immunosuppression
Broad antibiotic resistance
Neurologic bladder
Hospital-acquired infection
Urethral catheter, stent, nephrostomy tube, or urinary diversion
(b) Conditions which may complicate APN
Abscesses
Septic shock
Emphysematous pyelonephritis
Papillary necrosis
Acute kidney injury

APN: Acute pyelonephritis. The term *complicated APN* may refer either to the conditions favoring the occurrence of APN and making them more severe, either to clinical situations superimposed on APN which make them clinically severe

Clinical Presentation and Laboratory Data (Table 7.2)

The spectrum of APN manifestations ranges from mild symptoms to a full septic syndrome.

The clinical presentation is traditionally a triad, including loin pain, fever, and bacteriuria and/or pyuria [10]; however, it has been demonstrated that bacteriuria and pyuria may not be present, even in cases of APN which have been confirmed by imaging [11–13].

Loin pain is present in 86% of cases, fever in 77%, and at least one of these symptoms in 95% of cases [14], but one-third of elderly patients present without fever and in 20% of cases symptoms are gastrointestinal or pulmonary [15]. Symptoms that are typical of cystitis may accompany or precede the onset of APN in 83% of cases.

Acute renal failure rarely occurs [16], and may be due to dehydration, septic shock, tubular toxicity by gram-negative microorganisms, tubular injury due to diffuse interstitial infiltration of polymorphonuclear cells and bacteria. It is always present when the infection has spread bilaterally throughout the entire renal parenchyma.

– *Diagnostic criteria*

Although in most cases the clinical features are typical and allow the diagnosis to be made, the literature indicates the need for microbiological positive finding.

– *Urine cultures*

Sobel and Kaye [10] for the Infectious Disease Society of America (IDSA) defined APN as the pathology in which a growth of at least 10,000 cfu/ml is found in the urine in the presence of typical symptoms. Lower levels of bacterial growth (1000–10,000 cfu/ml) may be significant in pregnant women and in men.

Table 7.2 Clinical presentation and laboratory examination

Clinical presentation and laboratory examinations	Frequency (%)
Flank pain/costovertebral tenderness [14]	86
Fever [14]	77
Either pain or fever [14]	95
Dysuria [14]	83
Gastrointestinal or pulmonary signs [14]	20
Acute renal failure [16]	Rare
Mortality [4]	1.5–15
Leukocytosis [11]	82.6
High C-reactive protein [11]	100

Other diagnostic criteria include isolation of the same microorganism in the urine and in the blood [10, 17], or the concomitant presence of loin pain, fever (axillary >38 °C), pyuria (>10^3 WBC/high microscopic field—hmf), and positive urine culture (>10^5 cfu/ml).

However, a review of the literature suggests that this definition is outdated: in fact Gupta and Hooton [12, 13] state that pyuria and bacteriuria may be absent if the infection is not communicating with the urinary tract, or if an obstruction is present.

In a study performed by our group involving 223 patients (202 women, mean age 37.77 ± 17.61 years) tested at their arrival in the Emergency Unit of our hospital, urine culture was positive in only 30% of patients and pyuria in 65% [11]. Moreover, among 196 patients who underwent CT/NMR, only 46 (23.4%) had a positive urine culture. In 98 patients who had positive CT/NMR urine or blood cultures were negative [11].

The low frequency of positive urine cultures may be explained by previous antibiotic treatment, either self-prescribed or prescribed by the general practitioner, and by the possibility that the infection is confined to the renal parenchyma. Moreover, atypical organisms, such as Ureaplasma urealyticum (responsible for 4.8% of APN cases [9]) and Mycoplasma hominis, are not found unless particular culture media containing arginine and urea are used.

Obtaining an antibiogram is very important in order to give the patient a targeted antibiotic. Therefore, we recommend collecting urine as soon as possible before starting antibiotics. However, we believe that a urine culture is not essential nowadays in order to diagnose APN. The same considerations hold true for pyuria.

– *Blood cultures*

Blood cultures are positive in about 20% of cases [15] (21.4% of cases in our series [11]), and there is no evidence that they indicate a more severe form of APN [18], or that they should modify the therapeutic strategy [19, 20].

Blood cultures are indicated in case of diagnostic doubt, in a situation of immunosuppression or when a hematogenic source is suspected [19].

– *Parameters of inflammation* (Table 7.2)

Leukocytosis was present in 82.6% of cases and elevated C-reactive protein (CRP) in 100% of cases in our series. Mean CRP was 15.65 ± 8.56 mg/dl [11].

These two parameters, which are commonly tested in clinical practice, may be helpful together with the presence of fever to distinguish a renal colic from an APN.

– *Imaging*

US is the first investigation that must be performed in order to exclude hydronephrosis, stones, or urinary abnormalities.

US examination can show ureteral thickening, irregular, and focal parenchymal echogenicity (usually hyperechogenicity), increase in kidney size or hypotonia of the intra-renal cavities (Figs. 7.1 and 7.2a, b), while it only rarely evidences abscesses.

Several authors [11, 21–24] envisage that it is necessary to document APN with CT or NMR. These examinations allow a better definition of the extent of the inflammatory lesions, and confirm the diagnosis in case of clinical doubt (atypical pain or negative urine culture). Moreover, CT and NMR are more sensitive at detecting intra- and perirenal abscesses than US [25].

CT must be performed with contrast medium. It shows triangular areas of hypodense parenchyma, the apex being toward the papilla and the base toward the renal cortex. These areas may be multiple and bilateral (Figs. 7.3, 7.4, 7.5 and 7.6a, b).

In APN, no hypodense areas can be seen in the arterial phase, as they only become evident in the nephrographic phase and are better demonstrated in the venous phase (Fig. 7.7a, b). Sometimes they appear as hyperdense lesions in a late phase of the test, 2 h after the injection of the contrast medium.

In renal infarction, an avascular area of renal parenchyma can be seen in the arterial and venous phases; the lesion has sharper margins than APN areas.

The attenuation of density depends on the focal reduction of perfusion due to vessel compression by edema, intravascular granulocyte aggregation, and defective tubular function with altered contrast medium tubular transport and concentration.

NMR has a sensitivity and a specificity similar to that of CT and it is therefore preferable in young women (Figs. 7.8 and 7.9).

«Diffusion NMR» is useful in case of renal failure because it allows good imaging even without contrast medium (Fig. 7.10).

In our study, US was normal in 109 cases (52.1%). CT scan was performed in 183/223 (82.06%) patients and showed lesions suggestive of APN in 170 cases (92.8%), with evidence of single or multiple areas of parenchymal hypodensity. Concordance between CT and US was 49% [11].

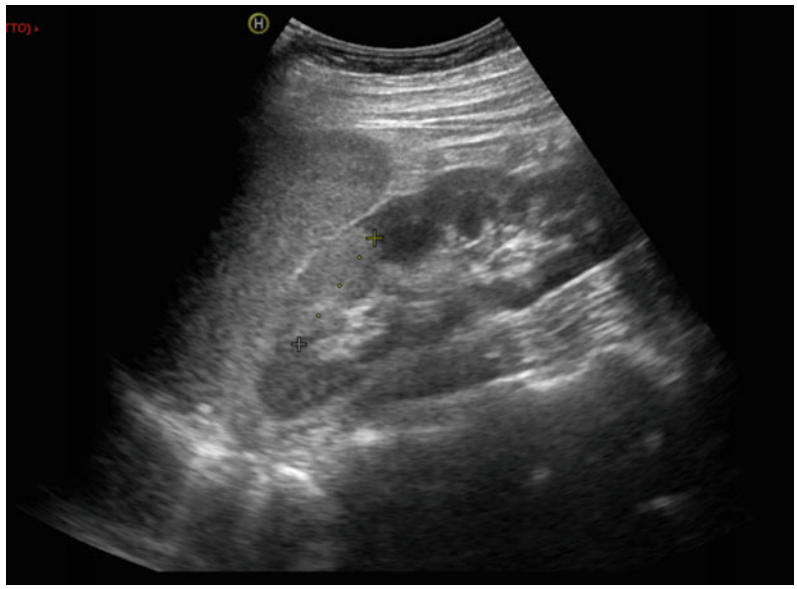


Fig. 7.1 US scan of the left kidney shows a wedge-shaped hyperechoic focus in the upper pole related to acute bacterial pyelonephritis

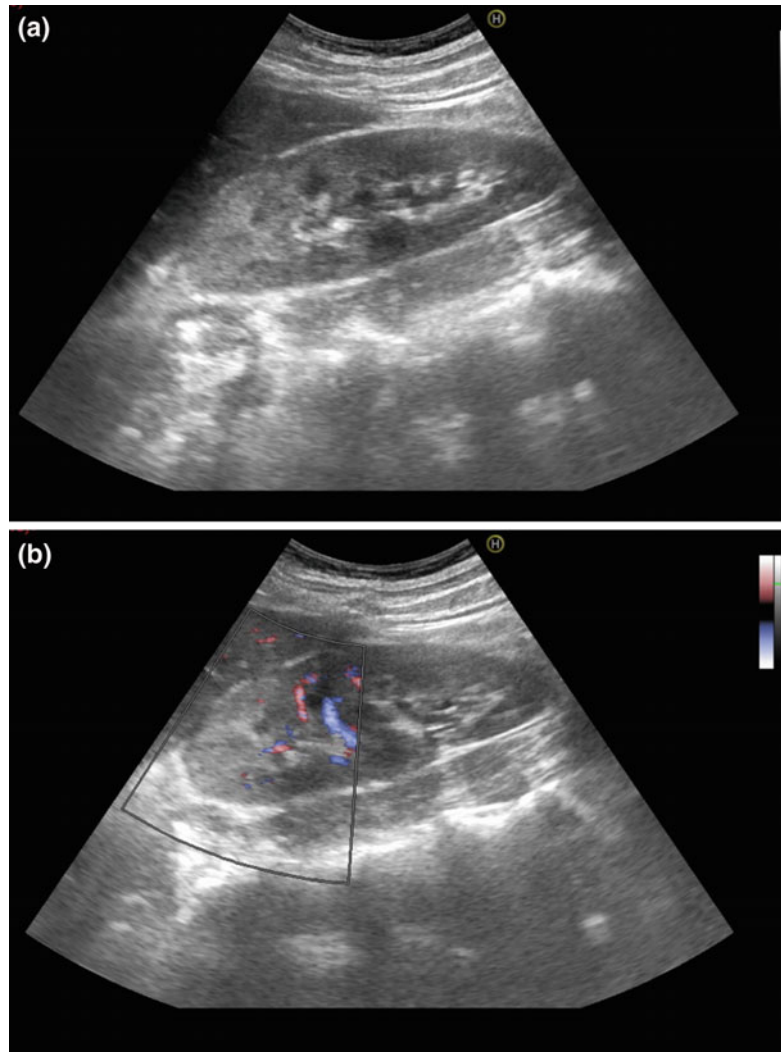


Fig. 7.2 US scan demonstrates an enlarged and hyperechoic upper pole of the right kidney (**a**) and color flow US image shows diminished blood flow through the involved area (**b**)

NMR was performed in 57 cases (47 positive, 10 negative).

Altogether, 213 patients underwent CT and/or NMR (95.5%) with radiologic confirmation of APN in 196/223 patients (87.9%). Among these patients, only 46 (23.5%) had positive urine cultures, 31 (15.3%) had positive blood cultures, and 15 (7.6%) had positive cultures of both urine and blood. Urine or blood cultures were negative in 98 patients in whom CT/NMR was positive for APN. In 12 patients CT was normal while blood or urine cultures were positive [11] (Table 7.3).

No differences were found between patients with positive or negative CT/NMR as regards body temperature at admission, leukocytosis, CRP, or duration of symptoms before hospitalization.

Similar data were reported in another study and no differences were found between patients with single or multiple inflammatory lesions [25].

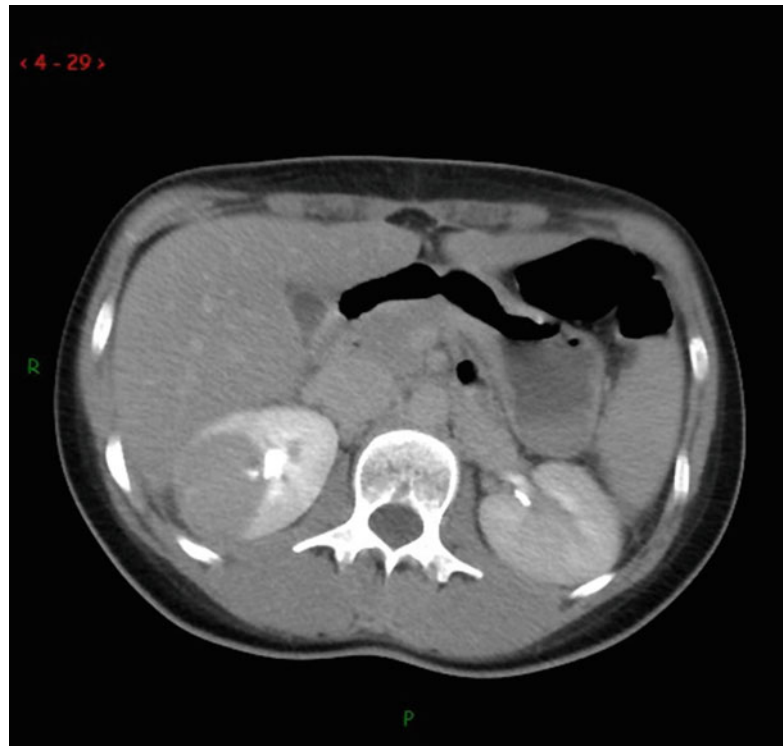


Fig. 7.3 The excretory phase of axial spiral CT scan obtained after intravenous administration of contrast agent demonstrates a large area of parenchymal hypo-attenuation of the right kidney related to acute pyelonephritis

We found single or multiple abscesses in 23.5% of patients who underwent CT/NMR, which were evident at US examination in only 2 patients.

We believe that NMR (especially in young women) or CT should be routinely performed in patients with APN since evidence of an abscess would influence the following therapeutic strategy.

– *Differential diagnosis*

Differential diagnosis must be made with several other situations, the most similar to APN is renal infarction, which may present similar clinical manifestations at onset, including fever [26]. CT may distinguish the two disorders, even though the radiologic features can sometimes be difficult to interpret [27] (Figs. 7.11a, b and 7.12).

Pelvic inflammatory disease, cholecystitis, appendicitis, lower lobe pneumonia, ovary or uterine torsion, abdominal abscesses, ovarian cysts, intestinal perforation, and Herpes zoster prodromes may also mimic APN.

– ***APN in Pregnancy***

Asymptomatic bacteriuria occurs in 2–10% of pregnancies and, if untreated, up to 30% of these patients may develop APN during pregnancy [28].

APN is especially dangerous in pregnancy; therefore, urine cultures must be monitored regularly during pregnancy, and in case of previous APN they must be repeated every week.

APN is more frequent in the second trimester of pregnancy [7]. It seems to be more frequent in nulliparous and in young women [7], and may lead to acute renal dysfunction and spontaneous preterm delivery. Most of the preterm births in the study by Wing et al. occurred between 33 and 36 weeks of gestation (9.1%) [7].

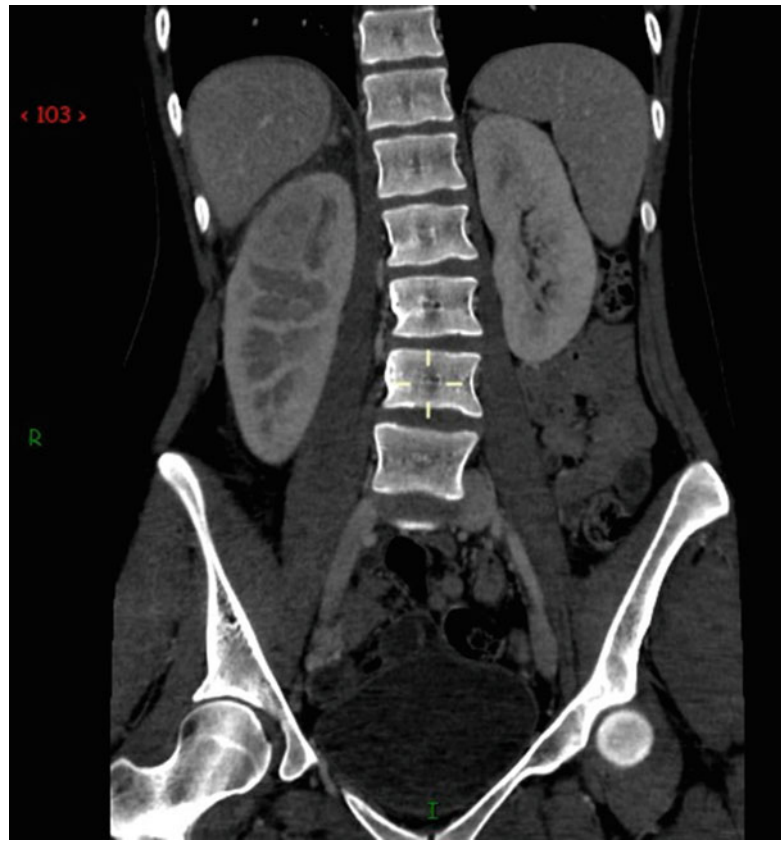


Fig. 7.4 The coronary nephrographic phase demonstrates a large well-defined focus of decreased attenuation in the upper pole of the right kidney

Relapses occurred in 25% of cases [7].

The most frequent etiologic agents are *Escherichia coli* (70%) and gram-positive microorganisms, especially beta-hemolytic Streptococci (10%).

– ***APN in Diabetes***

Diabetes is a common predisposing factor for UTIs, entailing a relative risk of 1.2–2.2 [29]. APN in diabetic patients is 5–10 times more frequent than in nondiabetic patients of both genders [30].

The reason for this is not clear. Geerlings [31] reports increased vaginal colonization by *E. coli* in diabetic patients, perhaps due to greater bacteria adherence to the cells of the uroepithelium or to an altered or delayed inflammatory response and cytokine secretion.

Klebsiella, Enterobacter, Clostridium, or Candida are the microorganisms that are most often responsible for APN in diabetics.

Kumar et al. [32] evaluated 105 cases of APN in diabetic patients: 24.8% had emphysematous pyelonephritis (EP), 3.8% had renal papillary necrosis, 12.3% had renal abscesses, 39% had bacteremia, and 17% had renal failure.

The outcome in diabetic patients can be poor, and an 11% mortality rate has been reported [32].

– ***Emphysematous pyelonephritis***

Careful attention must be paid to EP [15]. This is a necrotizing infection with gas formation

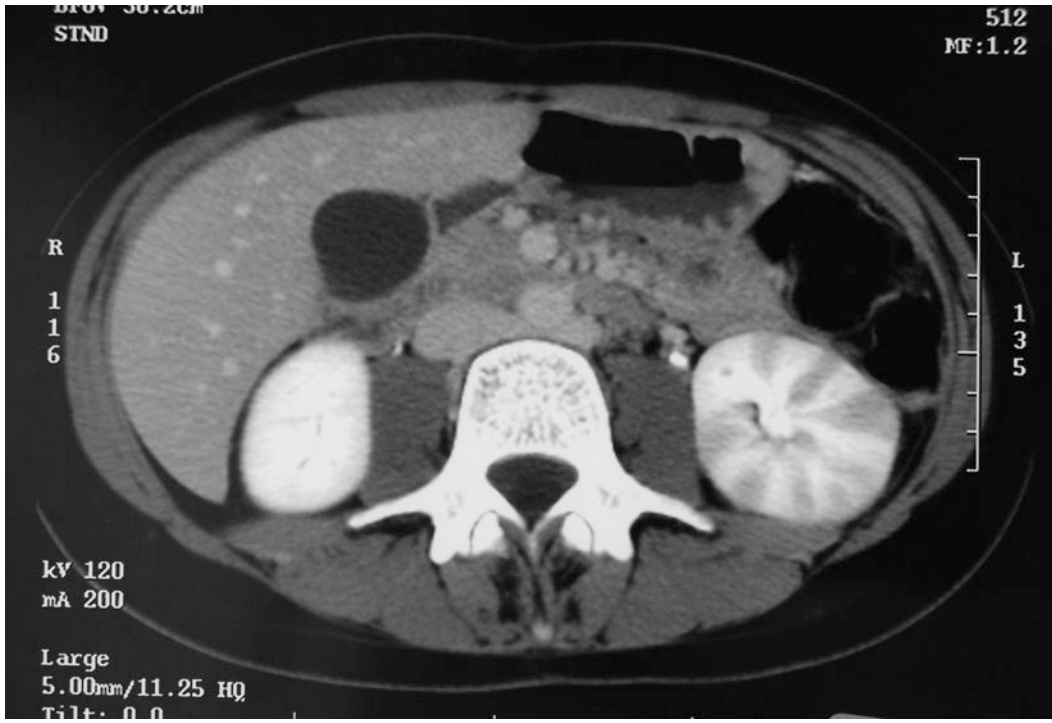


Fig. 7.5 Spiral CT after intravenous administration of contrast agent shows multiple foci of parenchymal hypo-attenuation of the left kidney, with striped aspect

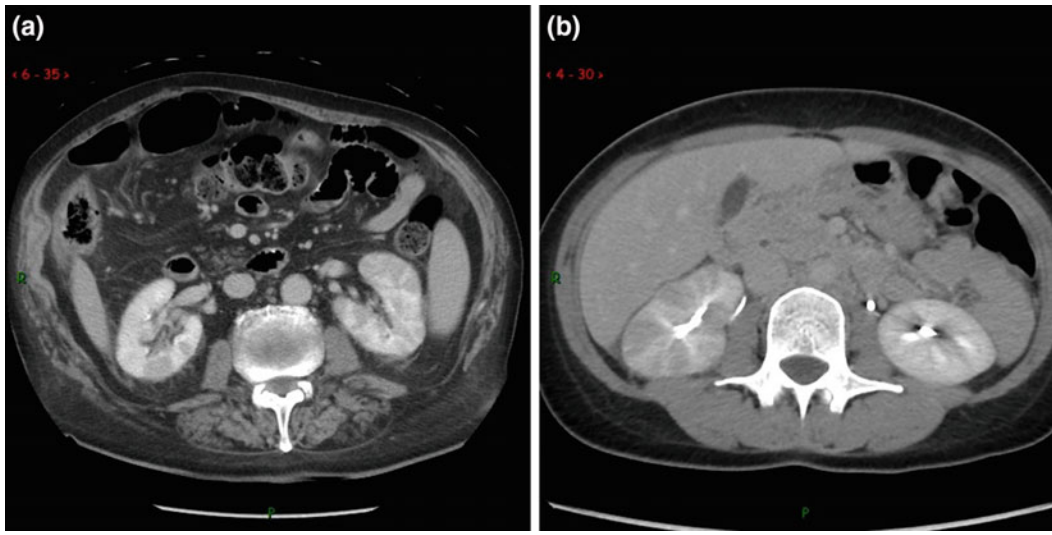


Fig. 7.6 CT scan demonstrates bilateral multiple foci of hypo-attenuation in nephrographic **a** and excretory **b** phase

in the renal parenchyma, collecting system or perinephric tissue that develops almost exclusively in diabetic patients. Therefore, it is necessary to maintain a high degree of suspicion and to perform imaging studies early during the course of APN in diabetic patients.

Hyperglycemia has been postulated to be an important factor for gas formation, which

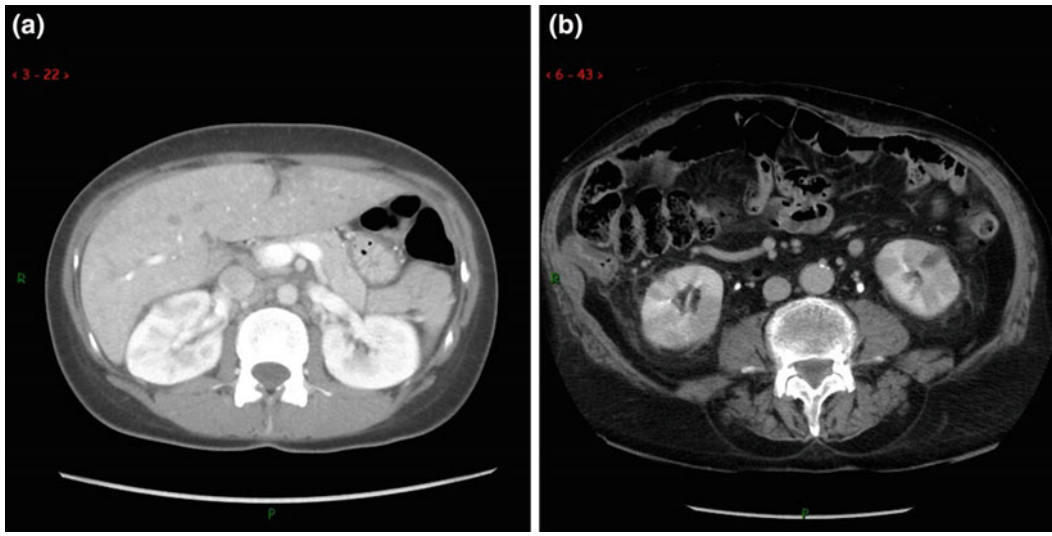


Fig. 7.7 The nephrographic phase of spiral CT (**a**) shows multiple small areas of parenchymal hypo-attenuation, which become more evident in the excretory phase (**b**), assuming a striped aspect

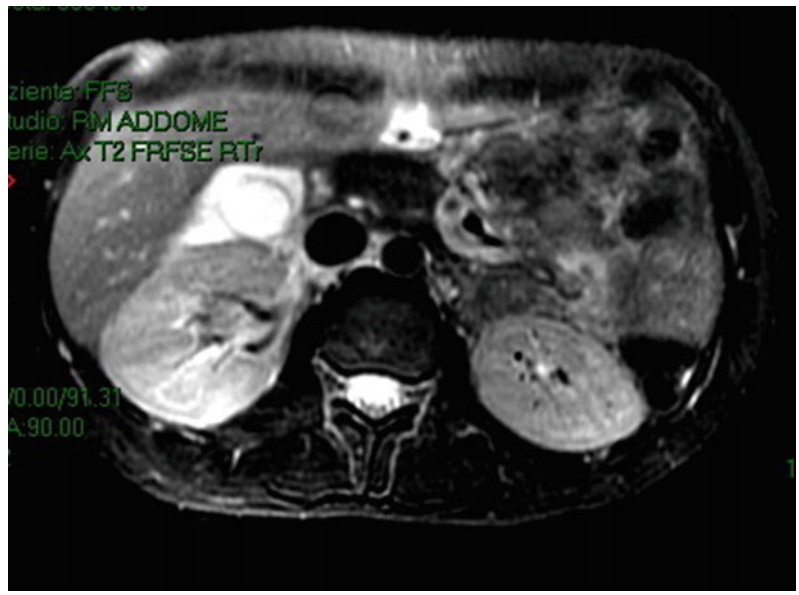


Fig. 7.8 Axial T2-weighted NMR with fat suppression shows globally enlarged right kidney with thickening of the collecting system due to bacterial pyelonephritis

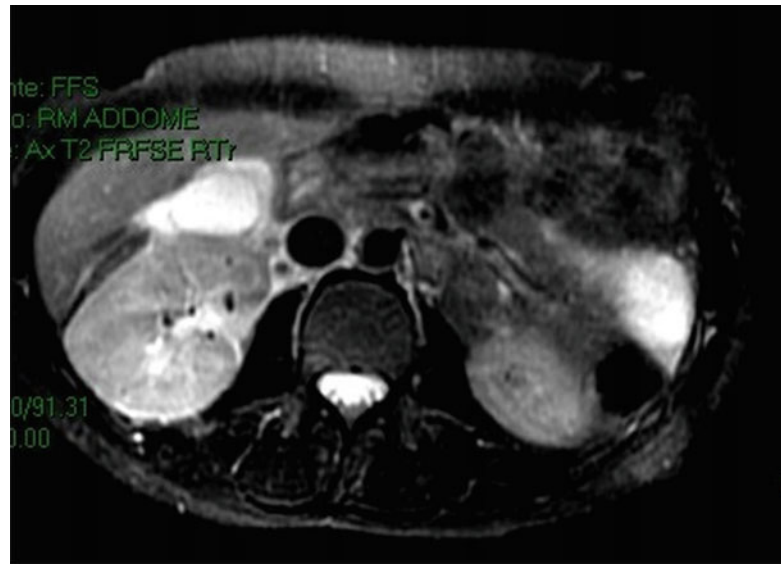


Fig. 7.9 T2-weighted NMR with contrast medium and fat suppression demonstrates multiple areas of altered signal in the right kidney

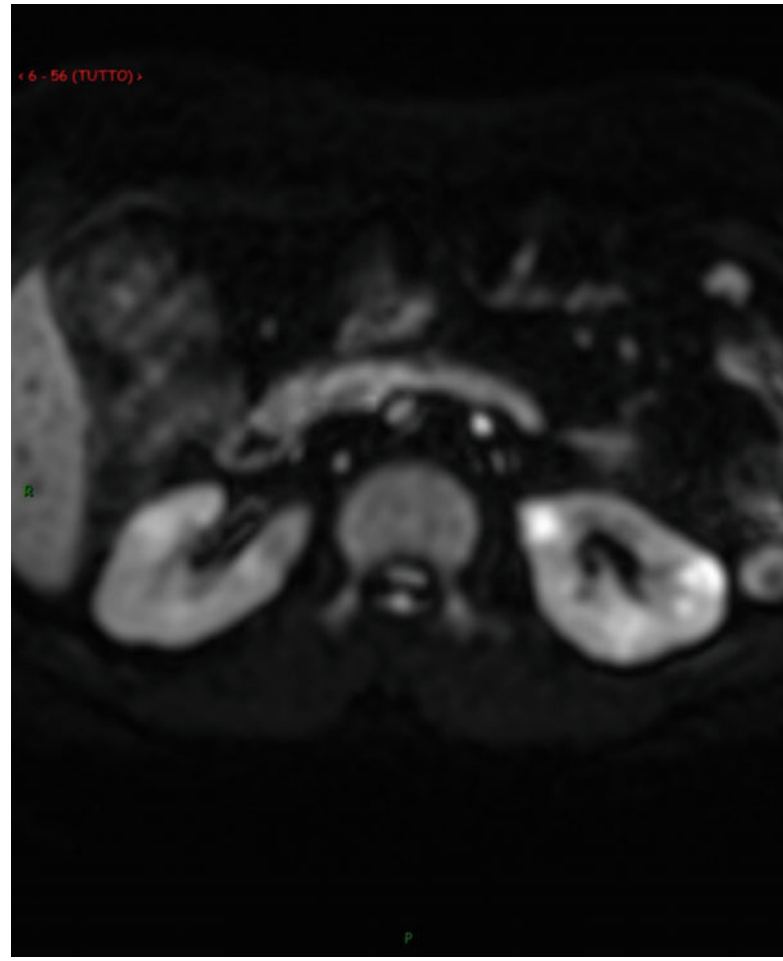
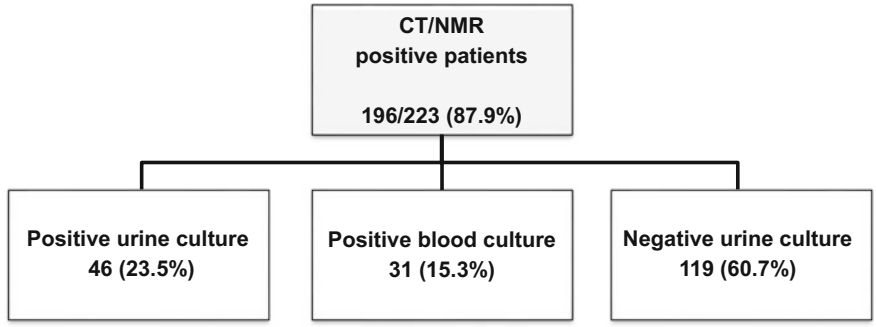


Fig. 7.10 Diffusion NMR shows multiple areas of hyper-intensity of the left kidney

Table 7.3 Frequency of urine and blood cultures in patients with CT and/or NMR demonstrating acute pyelonephritis [11]



requires anaerobic metabolism of glucose [33]. In fact, in the series of diabetic patients reported by Kumar [32], 24.8% with EP, patients with EP had poorer sugar control than patients without EP.

The reported sensitivities of plain X-ray, US, and CT scan for detecting EP are 65, 69, and 100%, respectively [34].

EP may be extremely severe, so that nephrectomy rates in these patients were higher than in non-emphysematous pyelonephritis patients ($P < 0.05$), and mortality was 30.8% [32].

– ***Abscesses***

Renal and perirenal abscesses may complicate an infection of the renal parenchyma, and they may be either of ascending or hematogenic origin [8, 9].

Risk factors for developing abscesses include urinary tract obstruction, multiresistant pathogens, diabetes, recurrent UTIs (66% of cases), stones (30%), instrumentation of the urinary tract, association with VUR, neurogenic bladder, cancer-causing urinary obstruction, simple cysts, and renal polycystic disease [35].

Abscesses may be cortical (75% of cases are observed in men) and cortico-medullar (with similar distribution in genders).

In our series, 50/213 patients studied by CT/NMR had abscesses (23.5%) [11], with only two abscesses being detected by US.

CT shows a defect of perfusion during the arterial phase due to the occlusion of the small vessels by inflammatory cells and edema. During the venous phase, the capsule of the abscess may be evident, becoming hyperdense. In a late phase a lack of concentration of the contrast medium can be observed (Figs. 7.13 and 7.14).

CT without contrast medium detects only large abscesses.

At NMR, the image in T2 is hyperintense in the acute phase because of edema, and hypo-intense in a later phase. After gadolinium injection, hypoperfusion in the arterial phase, delimitation of the rim in the venous phase, and lack of contrast absorption in a late phase are observed (Figs. 7.15 and 7.16).

Another useful examination is «diffusion NMR», which requires only a few minutes when added to a routine NMR, and allows good imaging without contrast medium [36]. Diffusion NMR is a type of functional imaging, where the image contrast is derived from differences in the Brownian motion of water molecules in tissues [37]. Since the signal is derived from the inherent tissue contrast, the administration of intravenous contrast medium is not required. The imaging signal confers information about the biophysical properties of tissues, such as cell organization and density.

In a study on 42 patients with APN, diffusion NMR showed a higher sensitivity (95.3%) than that of contrast-enhanced CT (88.1%) [38].

In another study, agreement between CT and diffusion NMR was 94.3% [39].

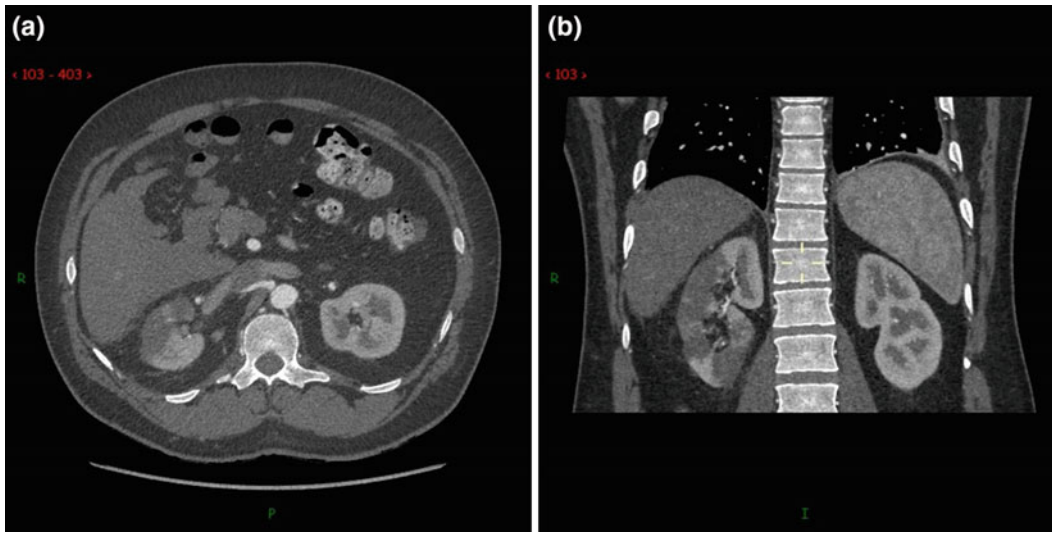


Fig. 7.11 Multiple well-defined areas of hypo-attenuation of the right kidney in the arterial phase of axial (**a**) and coronal (**b**) spiral CT related to infarction

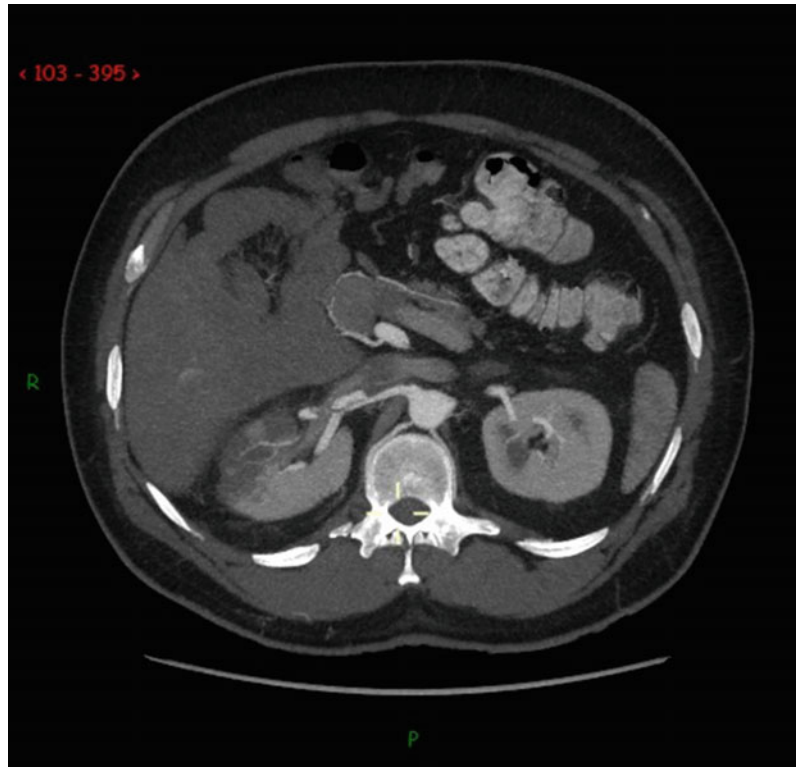


Fig. 7.12 The CT arterial phase demonstrates dissection of right renal artery with parenchymal infarction

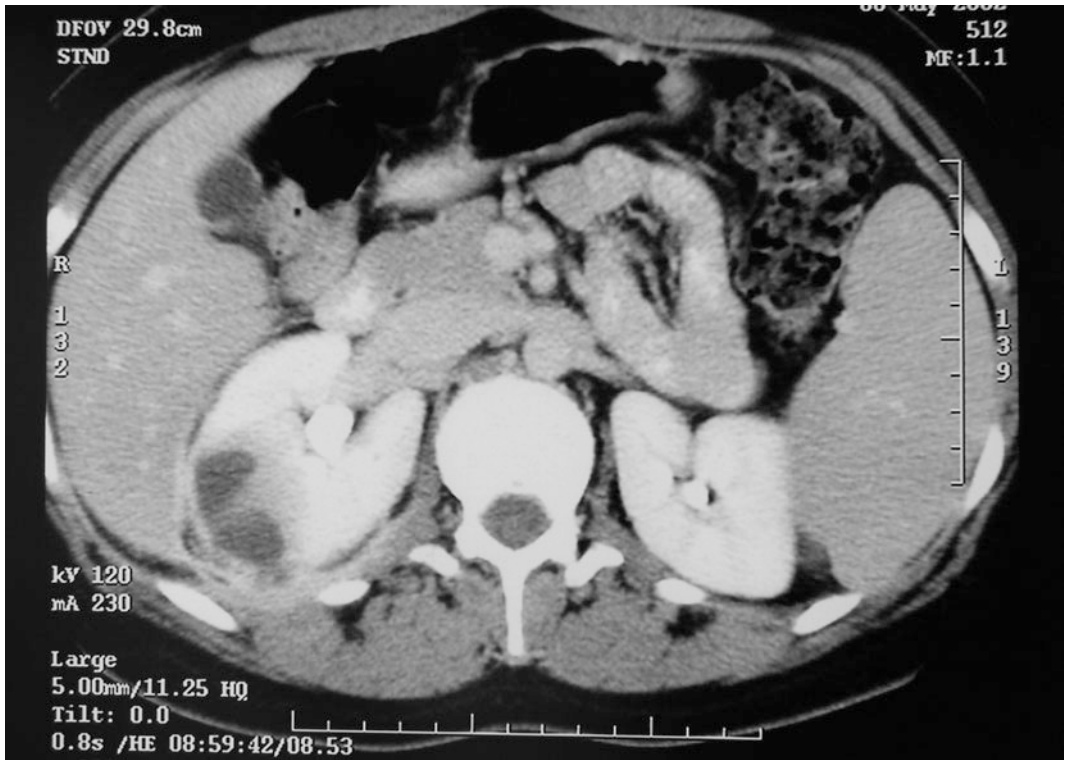


Fig. 7.13 Axial CT shows a large focus of hypo-attenuation of the right kidney, well defined in the excretory phase, related to an abscess without perinephric extension

Diffusion-weighted imaging appears to be reliable in the diagnosis and follow up of APN and could provide a reasonable alternative to contrast-enhanced magnetic resonance imaging [39].

In our series of patients no differences were found between patients with or without abscesses as regards body temperature (39.3 ± 0.66 vs. 39.16 ± 0.81 °C), leukocytosis (16,912.72 ± 6676.36 vs. 14,979.67 ± 6434/mm^3), duration of fever (5.48 ± 4.23 vs. 5.44 ± 7.52 days), duration of symptoms before hospitalization, CRP, pyuria, and urine culture positivity (20 vs. 31.5%). Patients with abscesses were hospitalized for longer periods of time [11] Table 7.4.

Table 7.4 Clinical data of patients with or without abscesses [11]

	Abscess present	Abscess absent	P
Leukocytosis (/mm^3)	16912.72 ± 6676.36	14979.67 ± 6434	0.11
CRP (mg/dl)	14.87 ± 9.09	16.06 ± 8.48	0.4
Fever (number of days)	5.48 ± 4.23	5.44 ± 7.52	0.88
Temperature (°C)	39.38 ± 0.66	39.16 ± 0.81	0.12
Hospitalization (number of days)	16.68 ± 14.15	8.63 ± 9.67	0.000008
Time elapsed between symptoms and diagnosis (number of days)	4.51 ± 4.16	6.23 ± 12.69	0.36
Pyuria (presence)	30/48 (62.5%)	102/153 (66.6%)	0.59
Urine culture (positive)	10/50 (20%)	47/149 (31.5%)	0.07

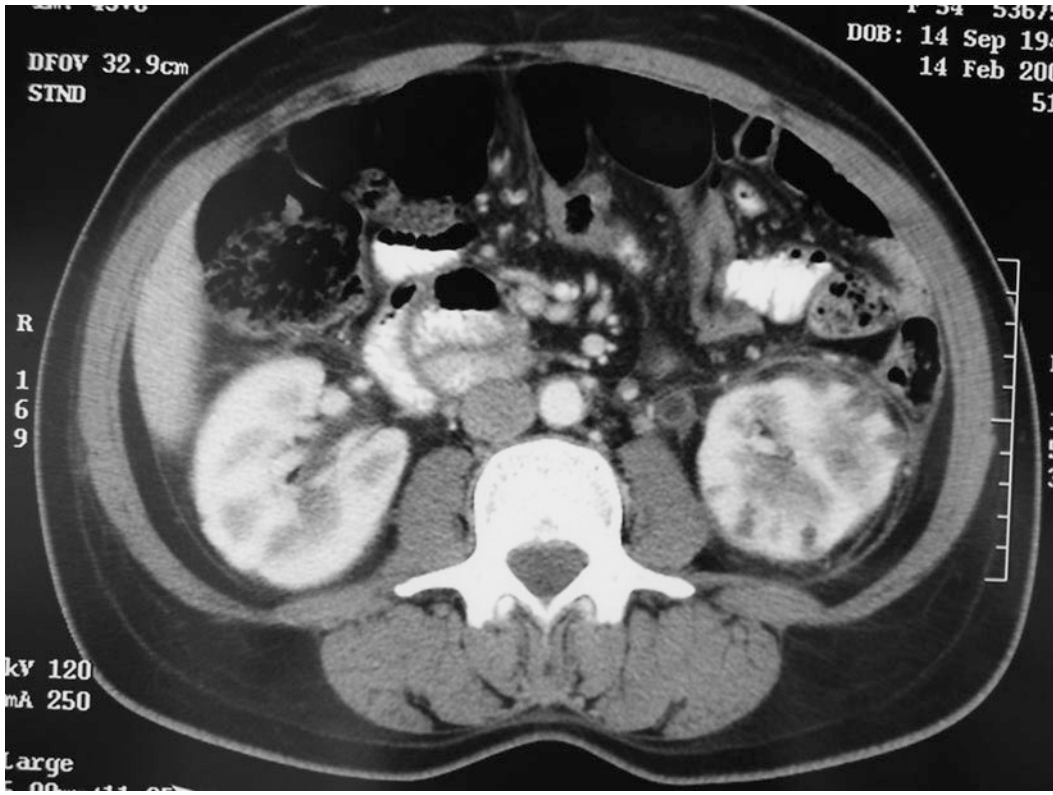


Fig. 7.14 The Nephrographic phase of axial CT demonstrates multiple small hypodense foci of the left kidney related to abscesses

Mortality of patients with abscesses is reported to vary from 1.5 to 15% [9], while in uncomplicated APN mortality is reported to be 0.7–1.6% (4).

Pathologic Findings and Clinical Pathological Correlations

APN is diagnosed clinically. Therefore, renal biopsy is rarely necessary, being performed only in case of acute renal failure or diagnostic doubt. In these cases, the process is more often diffuse and the disease could be better defined as *acute infectious tubulointerstitial nephritis*.

In APN at macroscopic examination the kidney appears enlarged and edematous. The surface may look variegated by the presence of yellowish areas of different extensions, which represent parenchymal abscesses.

When the kidney is cut, abscesses localize prevalently in the cortex but exudation may extend to the collecting ducts. Sometimes the lesions attain the perirenal connective tissue.

The distribution of the lesions may be casual, even though the renal poles are more frequently involved.

The renal pelvis is usually dilated; its mucosa may be edematous, reddish, or covered by pus.

In most severe cases the renal papillae are ulcerated or necrotic (papillary necrosis).

The histologic aspect is dominated, at least in the initial phases of the disease, by neutrophil infiltration, which may be diffused or organized in abscesses. Neutrophil infiltration localizes in the interstitium, in tubules and in the interior of the collecting ducts, which appear dilated and, in severe forms, necrotic (Fig. 7.17). Neutrophils collecting in the tubules can form casts (*pus*

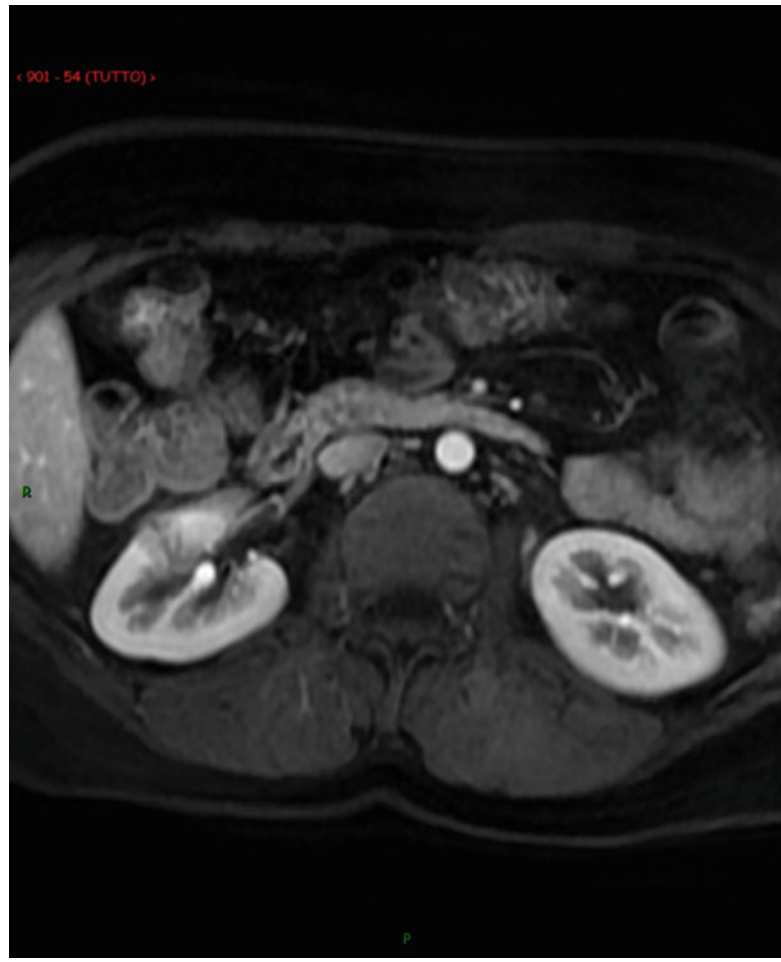


Fig. 7.15 T1-weighted NMR with contrast medium and fat suppression shows an hypo-intense abscess in the right kidney

casts), which may be found in the urine. Leukocytes sometimes organize to form a granuloma.

Zones with inflammatory infiltrates alternate with spared areas.

Interstitial edema is an early feature, and usually occurs in concert with cellular infiltration [40].

In the early phases, glomeruli and vessels are usually spared, except in hematogenous APN, in which medullary involvement is milder and less frequent.

An infiltration by lymphocytes, plasma cells, and rarely by eosinophils may be associated and become prevalent in late phases.

Pyelocalyceal mucosa is always involved in the inflammatory process in ascending APN where it appears swollen. Infiltrates by granulocytes can be present also on the intraluminal surface.

Special dyes may be useful or even essential to establish the bacterial (Gram) or the fungal etiology (PAS, Silver Metenamine, Grocott).

In chronic pyelonephritis lymphocytes and plasma cells are seen together with interstitial fibrosis and tubular atrophy. Collapsed tubules combine with dilated tubules.

– *Abscesses*

The size of the affected kidney may be normal or slightly enlarged.

In the ascending pathway of infection, the pyelocalyceal mucosa presents purulent exudate.

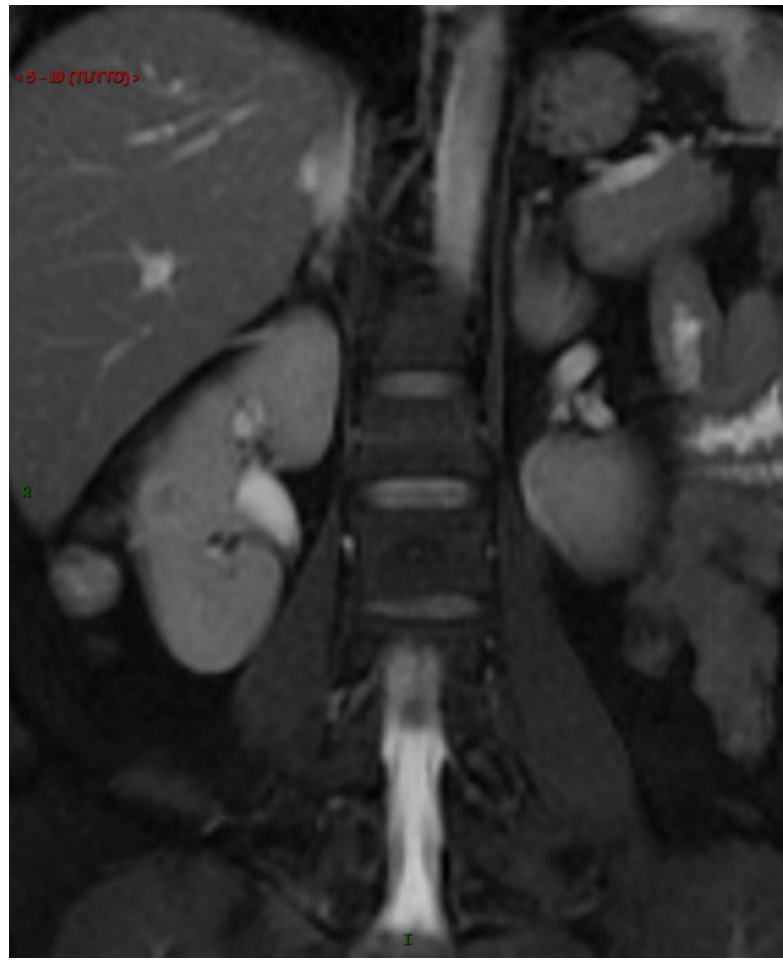


Fig. 7.16 T1-weighted NMR with contrast medium and fat suppression shows a hypo-intense abscess in the right kidney—coronal plane

The inflammation and the abscesses have a radial distribution, from the calyces to the renal cortex.

In the hematogenous infection, multiple, isolated pale-yellowish abscesses (1–5 mm in diameter) with a hyperemic halo can be seen on the cut surface, especially in the cortical area and on the surface of the kidney.

Microabscesses may merge and create large purulent cavities.

Etiology and Pathogenesis

E. coli represents by far the prevalent etiologic agent, and is present in 56.4% of cases. Enterococci are found in 10.7% of cases, Staphylococcus species in 8%, *Proteus mirabilis* in 6%, Enterobacter species in 5.3%, and *Pseudomonas aeruginosa* in 5.3% of cases [17].

In our series [11], we detected *E. coli* in 56 patients of the 64 with positive urine culture (87.5%). Other pathogens included *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, and *Klebsiella pneumoniae* plus *Enterococcus faecalis*.

Blood cultures were positive in 39/182 patients (21.4%): *E. coli* in 35 patients, *Acinetobacter lwoffii* in 1 patient, *Proteus mirabilis* in 1 patient, *Streptococcus saprophyticus* in 1 patient, and *Staphylococcus hominis* in 1 patient [11].

E. coli is less frequently found in elderly patients because, bladder catheters and the

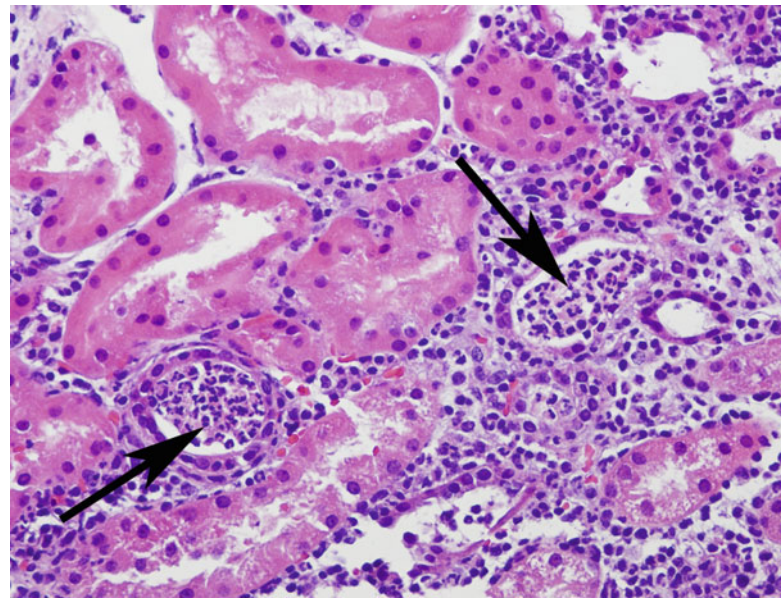


Fig. 7.17 Acute pyelonephritis. Heavily inflamed renal cortex with polymorphonuclear granulocytes accumulating in tubular lumina (*arrows*) in a patient with acute pyelonephritis and urine cultures growing vancomycin-resistant Enterococcus. Hematoxylin–Eosin, ×400 (Courtesy of Drs. Anjali Satoskar and Tibor Nadasdy)

frequent instrumentation allow the selection of different microorganisms, above all gram-negative bacteria such as Proteus, Pseudomonas, Klebsiella, and Serratia [4].

The etiologic agents of cortico-medullary abscesses include *E. coli* (75%), Klebsiella, Proteus, Enterobacter, Serratia (15–20%), *Streptococcus faecalis*, and *Staphylococcus aureus* (5%) [9].

Cortical abscesses are prevalently due to *S. aureus* (90% of cases) [9].

Bacteria usually ascend through the urethra, bladder and ureters to the kidneys.

A healthy bladder can eliminate the microorganisms which have been introduced within two to three days. The defense mechanisms of the bladder include voiding, antibacterial properties of urine, and intrinsic defense mechanisms of the mucosa. Moreover, the acid milieu of the vaginal environment in women and of prostate secretions in men contributes to protect against infections.

Hematogenic infections are more frequent in frail patients and in those affected with chronic disease, or who are immunosuppressed.

Staphylococci and fungi may reach the kidney through the blood stream from distant foci, which may be anywhere, though they are most often found in the skin or bones [4].

Sexual activity in women plays a fundamental role in the pathogenesis of APN. A correlation has been found between APN and frequency, promiscuity, and characteristics of sexual intercourse [14].

The use of spermicides, previous urinary infections, familial (maternal) history of UTIs, smoking habit, and difficulty in holding urine are also significant risk factors for the development of APN [14].

In men, prostatitis and prostate hypertrophy predispose to APN [4].

Other predisposing conditions include urinary tract obstruction, diabetes, immunosuppression, urinary instrumentation, and use of estroprogestinic drugs.

– *Association with VUR in adults*

The association between VUR and APN is well known in children, while it is not clear in adults; therefore, there are no clear-cut indications to search for VUR in the context of APN.

In a study on 86 women affected by APN, only two cases with VUR were found [41]. In another study, 48 out of 603 women with APN (8%), who had recurrent episodes of APN, underwent a retrograde cystography [42].

Twenty-one had VUR: 12 of them (i.e., those who presented scars or ureteral duplication) received an anti-reflux endoscopy correction, after which no further recurrences developed in 11 women. Hence, these authors suggest using an anti-reflux procedure to treat patients with urinary tract abnormalities, such as double ureters, cortical scars, or abnormality of ureteral orifices, which may indicate VUR even in the absence of obvious signs of ongoing VUR. The hypothesis at the basis of this approach is the high probability of a preexisting or a transient VUR which can no longer be detected.

We usually perform retrograde cystography on patients with recurrent APN or those who present dilation of the urinary tract [11]. On the basis of these criteria, 43 patients in our series of 223 underwent retrograde urethrocystography: VUR was found in 9 of them (20.9%) [11].

Treatment

– *Hospitalization*

Home treatment can be undertaken if the patient's conditions are good, and fever and leukocytosis are mild.

Hospitalization is mandatory if the patient is suffering, vomits, presents signs of sepsis or risk factors, or a complicated form of APN.

Parenteral treatment may be started in hospital and continued at home.

– *Antibiotic administration*

Guidelines on APN treatment have been published by the IDSA [12], by the European Association of Urology [43], and by the Scottish Intercollegiate Guidelines Network [44].

In case of uncomplicated APN, the Guidelines suggest oral treatment with antibiotics at home or a rapid switch to oral treatment.

Non-severely ill patients may be treated by oral ciprofloxacin for 7 days, levofloxacin 750 mg per day for 5 days, or by trimethoprim/sulphamethoxazole (TMP/SMX) 320/1600 mg/day for 14 days if the sensitivity of the microorganism to this agent is known.

A single intravenous dose (ceftriaxone 2 g, gentamycin 3–5 mg/kg or a fluoroquinolone—i.e., ciprofloxacin 400 mg) may be administered before oral therapy.

More severely ill patients must be treated intravenously with a fluoroquinolone or an aminoglycoside with or without ampicillin, or a third-generation cephalosporin with or without an aminoglycoside or a carbapenem.

As regards gram-positive cocci, treatment with ampicillin/sulbactam (or amoxicillin/clavulanic acid) with or without an aminoglycoside is recommended.

Aminoglycosides have a wide spectrum of bactericidal action which is synergic with beta-lactam antibiotics. They are indicated in sepsis, in cases of suspected resistant gram-negative bacteria, and in association with beta-lactam antibiotics or fluoroquinolones until the microbes have been identified or in case of allergy to other antibiotics [45].

When an improvement is attained, antibiotic therapy may be administered orally. A fluoroquinolone or TMP/SMX is recommended (for gram-positive bacteria amoxicillin or amoxicillin/clavulanic acid).

Fever usually disappears within 72 h of beginning treatment. In a study performed in uncomplicated APN, fever disappeared in 26% of patients after 48 h and in 13% after 72 h [46]. Hence, the persistence of fever beyond 72 h does not necessarily require a change in therapy [47].

In our series of patients the mean duration of fever in cases of CT-confirmed APN was 5.44 ± 7.52 days in patients with no renal abscesses and 5.48 ± 4.23 (p 0.98) in patients with abscesses [11].

The two most frequent causes of treatment failure are the presence of resistant microorganisms and of kidney stones.

Gupta [12] suggests that a regular review of the treatment protocols should be carried out on the basis of the local prevalence of urinary pathogens and resistance to antibiotics. The recommended thresholds of community *E. coli* antibiotic

resistance are 20% as regards TMT-SMX, 10% as regards fluoroquinolones [13].

– *Duration of treatment*

The conditions of the host, the characteristics of the infection (duration, relapse, abscess), and the chosen drug (bactericidal or bacteriostatic agent) must be taken into account.

A general trend toward reducing the duration of treatment has been seen in the last years [48] (Table 7.5). The most recent indications suggest treatment with fluoroquinolone for 7–14 days [49–52].

American guidelines recommend 7 days with ciprofloxacin or 5 days with levofloxacin 750 mg once a day for mild to moderate pyelonephritis or 14 days with TMP/SMX if the sensitivity to this agent of the bacterium is known [12].

Men with neither urinary obstruction nor prostatitis have a favorable outcome when a 14 day treatment schedule is administered. In case of recurrent infections or acute prostatitis, treatment with doxycycline, TMP/SMX, or a fluoroquinolone should last 4 weeks [12].

In case of chronic prostatitis, treatment must be prolonged up to 12 weeks [12].

– *Pregnancy*

A recent Cochrane analysis [28] revealed that antibiotic treatment of asymptomatic bacteriuria, which is associated with low-birth weight babies and preterm birth, can reduce the incidence of APN in pregnant women.

If APN is diagnosed, the woman must be hospitalized, hydrated, and treated with antibiotics.

The first choice of treatment is amoxicillin or amoxicillin–clavulanic acid or a last generation cephalosporin.

Fluoroquinolones should not be used because of their potential teratogenic effect [15].

In relapsing cases, which make up about 25%, treatment with nitrofurantoin 100 mg/day may be indicated; however, the drug must be discontinued before delivery.

86% of pregnant women with APN have uterine contractions in the first hour of antibiotic administration and 50% up to 5 h afterward [53].

– *Diabetes*

The management of APN in diabetic patients is the same as in nondiabetic patients [31], but

Table 7.5 Comparison of Infectious Disease Society of America guidelines in 1999 and in 2012

	IDSA1999 [103]		IDSA2012 [12]	
	Non-severely ill patients	Severely ill patients	Non-severely ill patients	Severely ill patients
Oral therapy	Yes	Only when improvement is achieved	Yes	Only when improvement is achieved
i.v. antibiotic	1 dose	Until improvement	1 dose	Until improvement
First antibiotic	Fluoroquin.	i.v. fluoroquin. or aminoglyc. ± ampicillin cephalosporin ± aminoglyc.	Fluoroquin.	– i.v. fluoroquin. or aminoglyc. ± ampicillin – cephalosporin ± aminoglyc. – carbapenem
TMP/SMX	Only if sensitivity is known		Only if sensitivity is known	
Duration	6 weeks → 14 days → 7–14 days	14 days	5–7 days	10–14 days

Fluoroquin. Fluoroquinolone
Aminoglyc. Aminoglycoside
TMP/SMX Trimethoprim/sulphamethoxazole

with special attention to the possible development of EP.

– *Emphysematous pyelonephritis*

Nephrectomy must be carried out in patients who are refractory to antibiotics [54].

– *Abscesses*

Beta-lactam antibiotics associated with aminoglycosides, possibly based on the germ sensitivity, are recommended to treat abscesses [8].

The duration of treatment is not well defined. It should be intravenous for 24–48 h after the disappearance of symptoms, and should be continued for 4 weeks until complete clinical and radiographic recovery [9].

If abscesses are <3 cm in diameter antibiotic treatment may be effective in up to 100% of cases.

If the patient is unstable or presents abscesses >3 cm, or if there is no improvement after a week of antibiotic therapy, a surgical approach must be taken into consideration [9, 55]. In case of abscesses between 3 and 5 cm in diameter, the probability of recovery by antibiotic treatment alone is about 92%. If the abscess reaches a diameter >5 cm, percutaneous or surgical drainage is necessary [56]. However, these situations are quite infrequent and are usually related to late diagnosis or to the presence of urinary obstruction.

Perinephric abscesses of minor extension may require partial nephrectomy. Nephrectomy must be considered if the abscess reaches the perirenal fat [55].

Outcome

– *Long-term evolution*

Pediatric series report the development of scars, which are evident at ultrasound and are hypocaptant at renal scintigraphy. Renal scars are irreversible and develop if APN is treated late or inadequately.

In more severe cases, hypertension and renal failure may accompany the presence of scars [57]. In children it is difficult to understand whether there may have been previous renal dysplasia.

Genetic predisposition could represent a factor favoring scar formation: polymorphisms of genes coding for interleukin 1 and 6 [58], adhesion molecules [59], TGFβ [58], and uromodulin may also play a role.

Besides its anti-antimicrobial effect, the Tamm–Horsfall protein is a powerful immunoregulating agent [60]: knockout mice for the Tamm–Horsfall protein are prone to develop urinary infections [61].

Experiments have been carried out to evaluate the possible prevention of scar formation.

In APN secondary to surgically created VUR in piglets preventively treated with antibiotics or with steroids and antibiotics, scarring resulted more severe in the control group than in the steroid-treated group (59 vs. 31%). APN completely resolved in 40% of controls and in 51% of steroid-treated animals [62].

In another experiment in rats, combined antibiotics and ibuprofen significantly inhibited gross renal scarring compared with no treatment or with antibiotics alone [33]. Mice that were pretreated with losartan showed a more significant decrease in TGF-beta, IFN-gamma, and IL-6 levels at 3 and 8 weeks after APN as compared with controls [63].

Although these experiments gave interesting results, they can hardly be applied to humans.

In adults there is little concern about the outcome of APN. In a study evaluating the long-term evolution of APN, 63 women underwent 99mTc-DMSA renal scintigraphy 10–20 years after the acute episode [64]. Cortical scars were found in 46% of these women, of whom 17.2% had macroalbuminuria (>300 mg/day) and 13.7% had a glomerular filtration rate <75 ml/min.

It is difficult to predict which patients will evolve to renal failure. Patients with predisposing factors (anatomic–functional abnormalities, stones, immunosuppression, diabetes, urologic instrumentation) are at greater risk of unfavorable outcome than those with no risk factors.

Patients who present recurrent APN (which may suggest an ongoing or remote VUR) may show slowly progressing renal damage over a long period of time. This results in thinning of the renal cortex along with deep, segmental, coarse cortical scarring. Club-shaped deformity of the renal calyces occurs as the papillae retract into the scar. A single or several scars may be present in one or in both kidneys mainly in the upper and lower poles because of the frequency of VUR in these sites. These features are characteristic of the *chronic pyelonephritis* and of the *reflux nephropathy*, which may, in turn, complicate with a superimposed *focal segmental glomerulosclerosis.*

– *Need for re-evaluation*

The guidelines do not express any recommendations regarding the need for long-term monitoring. Hooton et al. [13] suggest that follow up urine cultures are not needed in patients with acute cystitis or pyelonephritis whose symptoms resolve with antibiotics.

It is a general rule in routine practice to monitor complicated cases, and it is advisable to follow up on patients who have risk factors for the development of renal failure and who may therefore require a longer time to heal [64].

Authors who evaluated patients by CT three months after the acute episode observed the disappearance of the parenchymal hypodensity lesions together with clinical improvement [22, 65].

Contrast-enhanced ultrasound (CEUS) is a noninvasive US with a contrast medium represented by microbubbles. It has a 95–98% sensitivity [66, 67] and a high predictive value in the detection of parenchymal lesions which can be seen at CT with contrast medium (78% globally and 100% in case of abscess).

Contrast-enhanced ultrasound might represent a noninvasive examination that would be useful in long-term monitoring [66, 68] in APN, while the possible role of NMR has not yet been defined.

Large abscesses should be regularly monitored by CT or by NMR.

Acute Pyelonephritis in Children

Introduction

Febrile UTIs, generally defined interchangeably as APN in pediatric literature, are amongst the most common severe bacterial infections in childhood [69], entailing a high risk of complications such as sepsis and meningitis in newborns and infants. A major concern in the past years was, moreover, the potential risk for chronic damage through scarring development; therefore, an aggressive approach through intensive imaging, prolonged treatment, and prophylaxis was adopted by most pediatric nephrologists. In the last thirty years these assumptions were progressively overcome by the evidences of a major role for congenital hypodysplasia on the progression of renal damage to end-stage renal failure even in the absence of infections or abnormalities of the urinary tract. A milder approach on imaging, treatment, and prophylaxis has progressively been adopted by scientific pediatric societies and most recent guidelines and a substantially different approach from APN in adults has derived.

Epidemiology

Seven to 8% of girls and 2% of boys are estimated to present with a UTI in the first 8 years of life [69, 70]. The severity of the acute infection is mainly due to dissemination of the infection to tissues, favored mainly by urine stasis, but also by an immature defense apparatus as in neonatal age.

APN in small children may often represent the first sign of a congenital abnormality of the urinary tract, in particular VUR [23, 69] and obstructive abnormalities missed in prenatal ultrasound.

The vast majority of APN in children are caused by *E. coli* with prevalence of about 80–90% [71], while in the remaining cases a number of other organisms such as Klebsiella, Enterococcus, Enterobacter, Proteus, and Pseudomonas are involved.

Some bacteria show specific characteristics that favor the onset of urinary infections, such as the P fimbriae facilitating uroepithelial attachment displayed by *E. coli*. However, in children with urinary tract malformations, abnormal urinary flow or residual urine after voiding even non-attaching bacteria may cause infection.

Clinical Presentation and Laboratory Data

Clinical presentation in newborns and infants can be ambiguous: fever (38.5 °C and over), often representing the only sign of APN, is commonly considered a marker of renal parenchymal involvement and is associated with an increased likelihood of urinary tract malformations. A diagnosis of APN has therefore to be taken into consideration in all infants with fever and no signs of localization [72]. It must also be noted that in newborns fever may not be present and the clinical symptoms may be aspecific until rapid worsening to sepsis.

Poor feeding, unsatisfactory weight gain, irritability, lethargy, hypotonia, abdominal pain, nausea, and vomiting might be symptoms of UTI.

More specific symptoms such as dysuria, frequency, malodorous urine, and urinary incontinence are associated with urethra and bladder involvement, generally defined as lower UTI and are typical of older ages. In this population, UTI is often secondary to voiding disturbances, including incontinence, enuresis, hyperactivity, and dysfunctional bladder emptying and are more typical of girls. Bowel and constipation may often play a role in bladder dysfunctions [72].

Diagnosis

As urine cultures require 24–48 h, the diagnosis of APN in children is initially made on the basis of clinical symptoms and urinalysis. While urinalysis performed in the laboratory is not always available in short time, urine dipstick test for nitrites and/or leukocyte esterase are accurate indicators of infection. Up to 4 h may be necessary to provide a sufficient quantity of nitrites for a dipstick to be positive; therefore, in case of frequent urination (infants), false negatives should always be considered.

If nitrite and leukocyte esterase are positive, the risk of UTI is high (requiring prompt antibiotic treatment), becoming lower if only leukocyte esterase is positive. Urinary infection is unlikely if nitrite and leukocyte esterase are both negative [73].

The diagnosis of AP is confirmed by the culture of a single strain of bacteria from an appropriately collected urine specimen [69].

Collecting a viable urine sample for urine culture in young children can be challenging. The clean voided mid-stream method [74] is the best option for toilet-trained children, but is feasible, albeit time consuming, also in very young children [75]. In non-toilet-trained children the other noninvasive method, represented by urine collection bags, entails a high risk for contamination. The American Academy of Pediatrics (AAP) guidelines [23] suggest the use of invasive methods only (suprapubic aspiration under ultrasound guidance or catheter sampling), while the National Institute for Health and Care Excellence (NICE) [73] guidelines recommend invasive techniques only in severely ill-appearing children. The European attitude and experience is mainly for clean catch as first choice, sterile bag as second option, and urethral catheterization in case of doubts, false-positive, or worsening clinical conditions.

Urine culture is considered positive if a single strain of bacteria is found at a concentration of 10,000 CFU/ml when the sample is obtained by catheter, $\geq$ 100,000 CFU/ml when urine are collected using the clean catch method, 1,000,000 CFU/ml if perineal bag is used, and at any concentration if suprapubic aspiration is performed [76].

Differentiating APN from lower UTIs can be challenging: the elevation of C-reactive protein levels and white blood cell count can suggest the presence of renal involvement, but sensitivity and specificity are low. Procalcitonin is a promising marker of renal parenchymal

involvement [77, 78]. Blood tests are not normally required in well-appearing children.

Imaging

UTI in children can be associated with urinary tract anomalies, such as obstruction or VUR, characterized by the retrograde flow of urine from the bladder to the kidneys (Fig. 7.18). Although intra-infective inflammatory processes may cause scars, a wide amount of evidences have demonstrated that renal damage, in the past mostly ascribed to acquired pyelonephritic scarring, is very often congenital and caused by alterations in kidney development, particularly hypodysplasia [79, 80] due to a variety of genetic abnormalities. Improved antenatal ultrasonographic techniques have resulted in frequent recognition of such developmental anomalies in utero, before the occurrence of UTI.

As the role played by acute infections in renal scarring and subsequent adverse outcome is being questioned, the indication to second-line imaging after the first infection in a child with normal prenatal US is still controversial.

First-line imaging is represented by renal ultrasound, recommended in all children after a first febrile UTI by AAP and Italian Society of Pediatric Nephrology guidelines, and proposed by NICE guidelines only in infants aged less than 6 months or presenting with complicated UTI (defined as seriously ill child, poor urine flow, abdominal or bladder mass, raised serum creatinine, septicemia, failure to respond to correct antibiotic treatment within 48 h, infection with an organisms other than *E. coli*) [73].

Second-line imaging is represented by retrograde cystography (aimed at finding VUR and/or urethral abnormalities) and DMSA scintigraphy (to evaluate the presence of residual renal scars or renal hypodysplasia), and should be reserved only to selected cases [72]. Less-aggressive imaging strategies after a first infection reduce radiation exposure and costs.

CT scan is exceptionally used in children due to the need for sedation or anesthesia, and the high dose of irradiation and the limited informative value.

Treatment

Empirical antibiotic treatment should be based on local resistance patterns, as no gold standard treatment is suggested by the literature.

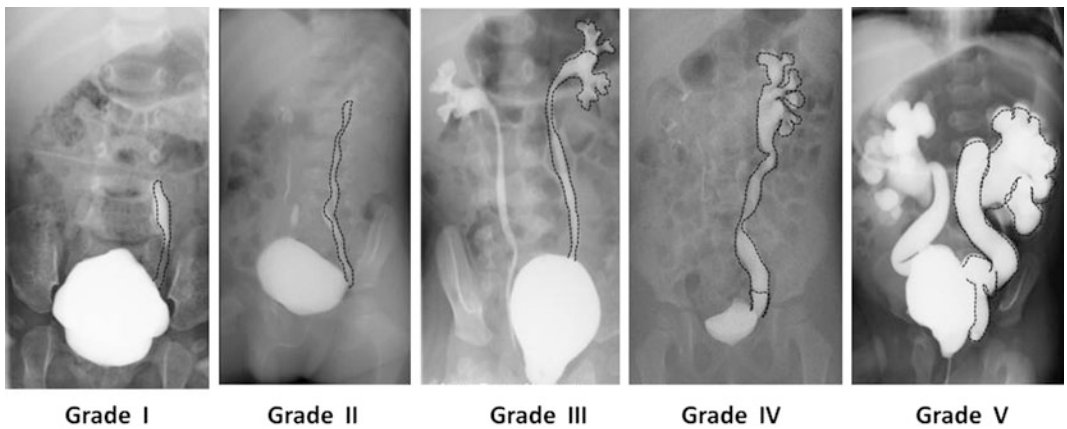


Fig. 7.18 International classification of vesicoureteral reflux. *Grade I* reflux into a non-dilated ureter only; *grade II* reflux into the renal pelvis and calyces without dilatation; *grade III* reflux into a mildly to moderately dilated ureter and renal pelvis with no or only slight blunting of fornices; *grade IV* moderate dilatation and tortuosity of the ureter and renal pelvis, with obliteration of the sharp angle of the fornices but maintenance of papillary impressions in most calyces; and *grade V* gross dilatation and tortuosity of the ureter, renal pelvis, and calyces with loss of papillary impressions [16]

While in the past the first approach was often a long course of intravenous antibiotic, recent evidences resumed in a Cochrane review [81] have demonstrated that the oral route is as effective as the intravenous and that 10 days did not produce better outcomes than 14 days.

In children older than 3 months appearing well, oral therapy and outpatient care should be the option of choice, with a maximum duration of 7–14 days.

Hospital admission and intravenous therapy are suggested for children less than 3 months old, in bad clinical condition, presenting with vomit or dehydration, or in case of poor familial compliance [23, 73, 82]. Parenteral therapy should be replaced by oral therapy when the child is no longer in critical conditions.

Dosage for the most commonly used antibiotics is reported in Table 7.6.

Antibiotic prophylaxis

The efficacy of antibiotic prophylaxis in preventing recurrence of UTI is still unclear and the emerging problem of antibiotic resistance makes its use even more questionable.

It has been suggested that prophylaxis can be withheld in children after the first UTI if neither VUR nor grade I or II VUR is detected. Conversely, prophylaxis seems appropriate in patients with grade III–V VUR, showing a much higher rate of reinfection, especially in girls.

The optimal duration of prophylaxis (usually administered for 12–24 months) has not been established; however, a proper balance between the risk of recurrence, possible surgical option, and occurrence of resistant strains should be evaluated in single cases.

Data from the last ten years have progressively reduced the indication of prophylaxis as an efficacious strategy to reduce the occurrence of scars, although useful to reduce UTI incidence, overcome by the evidences in favor of congenital dysplasia [83].

Prevention of recurrence

The true impact of frequently recurrent infections on the child's quality of life, growth, and occurrence of scars is still undefined and ad hoc controlled studies are being conducted.

While different approaches have been tempted from the most aggressive to the most conservative ones to avoid recurrence of UTI, the predisposing risk factors are still controversial.

Male gender, age lower than 6 months, and high-grade VUR are recognized in most series, while the role of circumcision is mainly recognized in American studies.

Table 7.6 Treatment in children

		Antibiotic	Daily dosage
Newborns		Ampicillin **plus**	100 mg/kg/day IV/IM divided q8 h
		Gentamicin	7.5 mg/kg/day IV/IM divided q8 h
		oramikacin	15 mg once per day IV/IM
Children 1–3 months	Outpatients	Trimethoprim/sulfamethoxazole	6–12 mg/kg/day PO divided q12 h
		Amoxicillin clavulanic acid	20–40 mg/kg/day divided q8 h
		Cefixime	8 mg/kg/day divided q 24 h
		Cefpodoxime	10 mg/kg/day divided q 12 h
		Ciprofloxacin	10–20 mg per kg twice per day
	Inpatients	Ceftriaxone	75 mg/kg/day IV/IM q 24 h
		Cefotaxime	150 mg/kg/day IV/IM divided q6-8 h
		Ceftazidime	100–150 mg/kg/day divided q8 h
		Piperacillin	300 mg/kg/day divided q 6-8 h

Complementary strategies for preventing UTI recurrence in older children include treatment of bladder and bowel dysfunction.

Surgical management remains a relevant option for those patients who have a dominant obstructive component as in high-grade VUR or complex megaureter or for those who fail conservative measures and present with frequent UTI or high-grade VUR persistence associated to recurrent APN after the third year of age, once functional bladder dysfunction has been excluded.

Chronic Pyelonephritis in Adults

Chronic interstitial nephritis (CIN) is a heterogeneous panel of alterations which primarily affect both cortical and medullary tubules and the interstitium, and secondarily other renal structures such as the glomeruli [84].

Chronic pyelonephritis (CPN) is the term used for infection-related CIN. VUR accounts for the overwhelming majority of cases of CPN [85], providing a direct route for infection to reach the kidney, but also by means of mechanical and immunological effects.

Renal changes often begin early in childhood as a result of chronic UTI superimposed on congenital VUR and intra-renal reflux.

CPN may be complicated by focal and segmental glomerulosclerosis leading to nephrotic-range proteinuria [86].

Clinical Presentation and Laboratory and Radiology Data

In adults, CPN is often a coincidental finding at US, as patients may present no symptoms, even though sometimes a history of relapsing APN or UTI is reported.

Renal function may be variably reduced, but it may also be normal if the lesion is monolateral. Urinary sediment is bland with a few white and red blood cells. Daily protein excretion is usually mild (less than 1.5 g/day), and hypertension is less common than in glomerular disease. Sodium wasting occurs, but mild and non-anion gap metabolic acidosis may result from proximal or distal renal tubular acidosis.

At US the kidney profile is irregular. Demarcation of cortex and medulla in the affected areas of the kidney is lost. The renal cortex is thinned and crossed by deep, segmental, coarse scarring. Renal scars are frequently found, in one or both kidneys, at the poles, and deformity of the renal calyces with blunt, dilated, or club-shaped calyces occurs as the papillae retract into the scars.

The presence of polar scars in an adult prompts the indication to retrograde cystography, since the possible presence of VUR must be searched.

The appearance of nephrotic-range proteinuria suggests the possible secondary development of focal segmental glomerulosclerosis. In this case a renal biopsy might be indicated.

Differential diagnosis

CIN must be differentiated from glomerular diseases: hypertension is less common, and usually daily protein excretion is mild and urinary sediment is poor with no need for renal biopsy.

CPN must be differentiated from idiopathic and genetic CIN, from toxic, drugs, myeloma, immune, and obstruction-related CIN forms.

Etiology and Pathogenesis

In most patients, renal damage occurs slowly over a long period of time in response to a chronic inflammatory process or relapsing or chronic infections.

Obstruction predisposes the kidney to infection, and chronic obstruction contributes to parenchymal atrophy.

Most scars develop in the upper and lower poles because of the frequency of reflux in these sites. VUR is the most common mechanism of renal scarring in CPN. VUR provides a direct route for infection to reach the kidney, and severe reflux may occur intra-renally, but also other mechanisms play a role in determining the renal injury.

Renal changes often begin early in childhood as a result of chronic UTI superimposed on

congenital VUR and intra-renal reflux. Scarring and atrophy lead to a loss of tubular functions, especially in the concentrating power.

Pathologic Findings

Renal biopsy is rarely indicated in CPN unless in the presence of nephrotic-range proteinuria that suggests a secondary focal segmental glomerulosclerosis [86].

Histologic changes are nonspecific and are represented by infiltrates of lymphocytes, fibrosis, and atrophic tubules with hyaline casts (Fig. 7.19).

In CIN tubulointerstitial fibrosis and glomerular scarring are present in a so-called geographic pattern [87]. This refers to irregular zones of scarring, with intervening preserved areas. There may be foci of polymorphonuclear neutrophils within tubules. Glomerular scarring may be present in a focal and segmental pattern.

Signs suggestive of CPN or reflux nephropathy as the underlying etiology include periglomerular scarring surrounding relatively intact glomeruli and thickened Bowman's capsule [87].

Uninvolved tissue may be locally hypertrophied.

Xanthogranulomatous pyelonephritis

Xanthogranulomatous pyelonephritis (XPN) is a rare variant of CPN occurring in middle-aged women with a history of recurrent UTIs.

In children it may be bilateral or, more frequently in girls, it may be localized and may mimic a tumor [88].

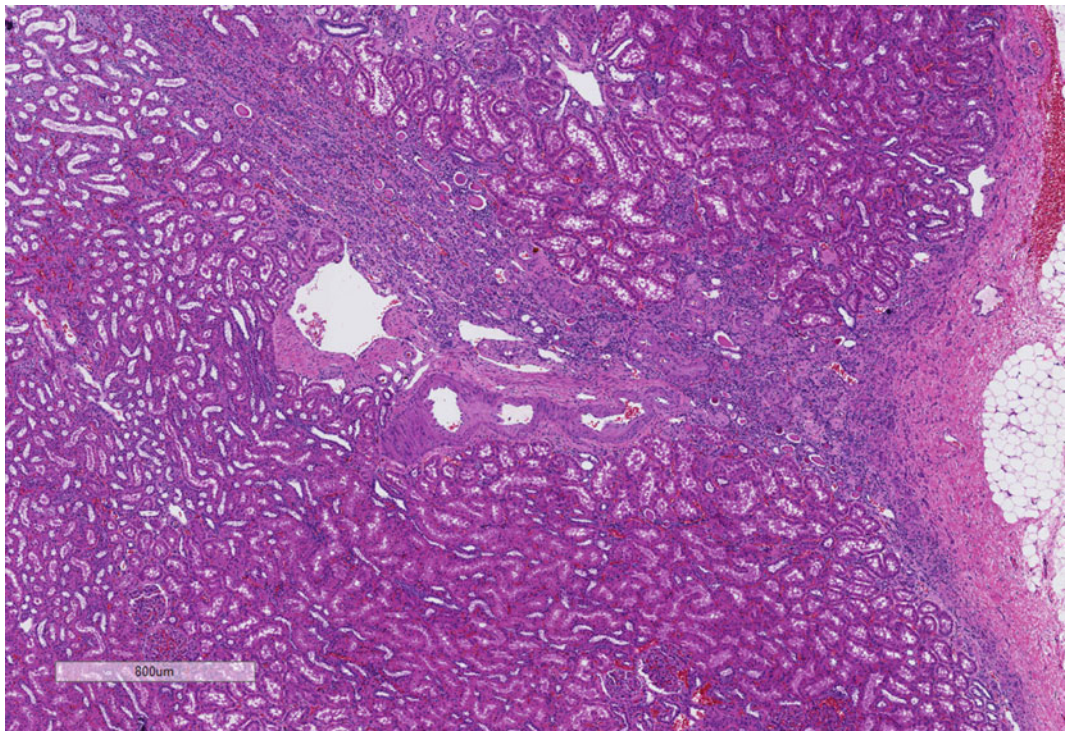


Fig. 7.19 Chronic pyelonephritis. A renal cortical scar extending from the medulla all the way to the renal capsule in a nephrectomy specimen from a patient with chronic pyelonephritis. These cortical scars usually contain mononuclear cell infiltrates and are alternating with well-preserved, normal appearing zones of renal cortex. Hematoxylin–Eosin, ×4. (Courtesy of Drs. Anjali Satoskar and Tibor Nadasdy)

Clinical Presentation and Laboratory Data

Presenting symptoms include flank pain, fever, malaise, anorexia, and weight loss. In children growth and weight retardation may be observed [89].

Blood tests show nonspecific inflammation; examination of the urine may confirm the presence of UTI. In an analysis of 21 patients, symptoms were present in all of them, the most common ones being flank pain and fever over 38 °C. Laboratory results showed anemia in 71.4% of cases, leukocytosis in 61.9%, and pyuria in 81.0% [90].

Another retrospective analysis of 35 patients affected with XPN showed that staghorn calculi were the most common cause (51.4%), and obstructing ureteral calculi the second most common (22.9%) cause [91].

US examination shows an enlarged and distorted renal outline, with loss of the normal renal architecture and often a centrally located shadowing stone.

CT scan shows the renal tissue replaced by several rounded, low-density areas, that are surrounded by an enhanced rim of contrast medium. The normal renal outline is lost and enlarged with paradoxical contracted renal pelvis. The calyces are dilated giving a multiloculated appearance that has been likened to the paw print of a bear (*bear's paw sign*) [92].

Sometimes there is perinephric extension with thickening of *Gerota's fascia*. Calcification can be better delineated on CT scan.

NMR appearances mirror the heterogeneous nature of the mass with solid and cystic components surrounding a central staghorn calculus.

Differential diagnosis

XPN is frequently confused with renal carcinoma in its clinical presentation and radiographic appearance [93], but must also be differentiated from renal parenchymal malakoplakia [94] and from renal abscesses [95].

In an analysis of 35 cases, 20% of cases were not thought to be an XGP prior to nephrectomy performed for a suspicious renal mass [91].

Etiology and Pathogenesis

The most common organisms associated with XPN are *E. coli*, *Proteus mirabilis*, Pseudomonas, *Enterococcus faecalis,* and Klebsiella [88].

Obstruction and infection, which are often due to infected renal stones, lead to infiltration of monocytes and lipid-filled macrophages which are the pathological hallmark of the disease.

Pathologic Findings

XPN is almost always unilateral.

Macroscopic examination reveals an enlarged kidney. Necrotic yellow material surrounded by layers of orange-colored tissue is typically seen. Renal stones are usually present within the mass.

The renal capsule is thickened, and may adhere to the perirenal fat connective tissue.

When the kidney is cut, calyces appear dilated, because of obstructive phenomena and the frequent association with stones (*staghorn calculi*).

The most typical macroscopic features are the presence of yellowish crumbly tissue surrounding calyces, pelvis, and the renal parenchyma, with a frequent extension to the perirenal and retroperitoneal tissue, adrenal glands, cava vein, which may be occupied by thrombi [96], and rarely to liver, spleen, or other organs [97].

In the most advanced forms fistulas may develop into the skin, while they are rarer into bronchi, colon, duodenum, and through the diaphragm [88, 98, 99].

XPN may mimic other pathologic processes, among which cancers, such as papillary or clear cell renal carcinoma, sarcoma, tuberculosis, and malakoplakia.

Microscopic examination shows the yellowish areas of a polymorphic inflammatory infiltration dominated by large aggregates of the characteristic lipid-laden foamy macrophages with abundant cholesterol crystals, lymphocytes sometimes aggregated in germinative centers, plasma cells, isolated or intratubular aggregated neutrophils forming microabscesses, and possibly giant cells.

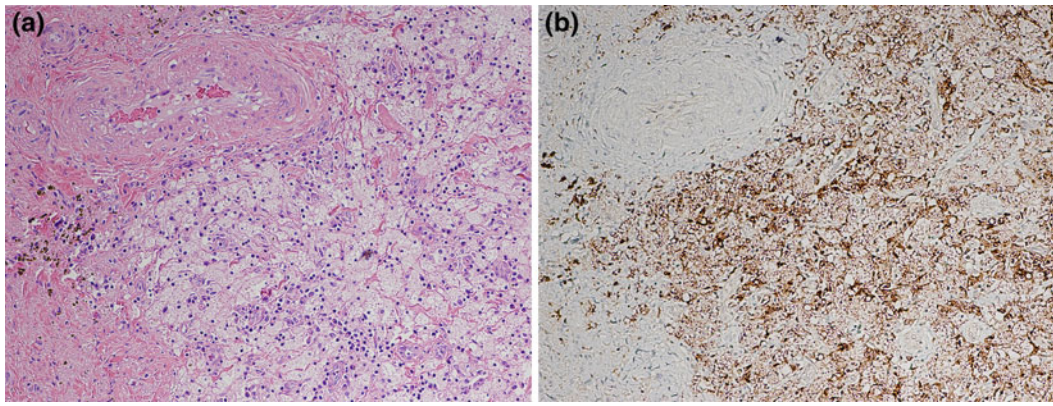


Fig. 7.20 **a** Xanthogranulomatous pyelonephritis in a nephrectomy specimen. Note the numerous foam cells admixed with a variety of inflammatory cells around a small artery. H&E, ×100. (Courtesy of Drs. Anjali Satoskar and Tibor Nadasdy). **b** The same area stained with an antibody to CD68, a macrophage marker. Note that the foamy histiocytes are positive (*brown color*). Immunoperoxidase, ×100. (Courtesy of Drs. Anjali Satoskar and Tibor Nadasdy)

The neighbouring renal parenchyma shows the signs of the associated obstructive lesions, acute and chronic inflammation, fibrosis and tubular atrophy, intimal fibrosis of small- or medium-size vessels and, rarely, areas of squamous metaplasia of the urothelium.

Immunohystochemical examination shows CD68 positivity in foamy cells that testify their histiocytic nature. α1-antitrypsin and lysozyme also play an important role in differential diagnosis (Fig. 7.20a, b).

Clear cell carcinoma, both in classic and papillary variants, is easily differentiated on a surgical piece, but not in pre-surgical samples of little size. Renal cell carcinomas are positive for EMA and CD10 and negative for CD68, what allows an easy differentiation between the two forms. The presence of tapered cells, which are frequently found in XPN, may suggest a sarcomatoid carcinoma, and benign and malignant mesenchymal lesions of leiomiosarcoma. The cells of sarcomatoid carcinoma show a high grade of atypic cytology and an elevated mitotic index, which lack to hystiocytes. Moreover, sarcomatoid carcinoma is positive, at least focally, for epithelial markers, such as cytokeratine and EMA.

Leiomiosarcoma is diffusely of focally positive for muscle-specific actin and desmin.

Renal tuberculosis is characterized by the typical necrotizing granulomas in which alcohol–acid-resistant Mycobacteria may be localized with the specific dyes.

Hallmark of malakoplakia and megalocytic interstitial nephritis is the presence of concentric PAS-positive diastase-resistant bodies, which lack in XPN.

Treatment

Treatment is surgical [100].

Renal malakoplakia

Malakoplakia is a similar condition to XPN, as another peculiar form of CPN, usually reported in the setting of immunocompromised patients, and involving various internal organs, most commonly the retroperitoneal area, the kidney, the bladder, or the colon with friable yellow soft plaques [101].

Variable clinical manifestations as well as the nonspecific radiological findings of malakoplakia can be misleading, making diagnosis quite difficult [102].

Defective macrophage killing of bacteria, most commonly *E. coli*, results in an

accumulation of bacterial degradation products. Deposition of calcium and iron on residual bacterial glycolipid, and eventually a granulomatous reaction, clinically manifest with the formation of a papule, a plaque, or an ulceration.

The presence of the resulting basophilic inclusion structure, the Michaelis–Gutmann body, is considered pathognomonic for malakoplakia.

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Bacterial Infection of the Renal Allograft

8

Uday S. Nori and Anjali A. Satoskar

Introduction

Kidney transplantation is the treatment of choice for patients with advanced chronic kidney disease or end-stage kidney disease. Transplantation provides improved quality of life as well as increased longevity as compared to dialysis. However, since the vast majority of the transplanted organs are from immunologically non-identical donors, maintenance immunosuppression for the life of the allograft is critical in prevention of acute and chronic rejection. These medications are well known to cause many long-term complications including heightened risk for infections, malignancies, metabolic complications such as new onset diabetes mellitus, hyperlipidemia. Infectious diseases include bacterial, viral, fungal, and parasitic etiologies. Many studies reported that the bacterial infections of the renal allograft to be the most common infectious complication among the transplant recipients. For reasons outlined below these infections are responsible for substantial morbidity, mortality, and financial burden on the society.

In the early days of transplantation, five decades ago, the incidence of acute rejection was >50% within the first year and mortality was up to 40% mainly from infections. With vast improvements in the immunosuppression regimens and other advances in transplantation medicine, both patient and allograft survival are now routinely >95% at 1 year and long-term outcomes became excellent. For this reason prevention and treatment of opportunistic infections has become the focus in further improving the patients' outcomes.

Urinary tract infections (UTIs) in renal transplant recipients (RTRs) include asymptomatic bacteriuria, simple cystitis, and pyelonephritis. As will be described elsewhere in this chapter, the clinical differentiation of these forms can be extremely challenging in the immunocompromised host. The definition of the UTI is the same as in the general population which, according to the Infectious Diseases Society of America's 2011 guidelines, is greater than 100,000 colony-forming units (CFU) per ml of urine [1]. Recurrent UTI is defined as ≥ 3 episodes during a 12-month period and complicated UTI is in individuals with either structural or function abnormalities of the urinary tract or any medical condition with high risk of UTI. Since all RTRs are immunocompromised, any UTI in these patients is regarded as complicated.

Epidemiology: UTI is the most common form of bacterial infection in the RTRs accounting for 45–72% of all infections [2]. A large prospective,

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randomized study comparing the efficacy of four different immunosuppression regimens showed that 25% of all patients developed symptomatic UTI within the first year of transplantation regardless of the regimen [3]. The incidence of UTI in the immediate post-transplant period is 25–45% and about half of them related to urinary catheters [4–8]. The incidence increased to 70% within the first six months [9]. The incidence of bacteremia as a result of UTI is about 3–7% [5, 6, 10, 11] and hospitalizations for septicemia were most commonly (30.6%) associated with urinary tract infection as a secondary diagnosis [12]. Recurrent UTI was reported in 2.6–27% [13] but given the relative lack of systemic and localized symptoms in these immunosuppressed patients, the true incidence of pyelonephritis is likely under recognized. The variation in the reporting of UTI incidence is also likely due to lack of uniform diagnostic criteria, inconsistent follow-up, and differences in antibiotic prophylaxis practices.

Unrecognized pyelonephritis can cause renal parenchymal damage leading to interstitial fibrosis and tubular atrophy. Even though these events likely cause increased risk of graft loss this remains controversial. A retrospective study [2] and a large database study [12] found a significant association between UTI and graft loss but two other studies found no such association [6–8]. It must be pointed out that the strength of the evidence in the latter two studies is weak and counter-intuitive compared to the former. Additionally, most studies have not distinguished between simple UTI (cystitis) and graft pyelonephritis. When assessed in more detail, the outcomes in this population are more complex. Early graft pyelonephritis (within the first 3 or 6 months) was found to be significantly more detrimental for graft outcome, irrespective of acute rejection episodes [13, 14]. Only larger prospective studies would be able to answer the question emphatically and more importantly, if graft outcomes are highly affected by other more common problems like rejection (acute and chronic), alloantibodies, toxic effects of drugs like cyclosporine, and metabolic issues including diabetes mellitus, hypertension, and obesity (often related to corticosteroid effects). It is practically very difficult to selectively assess the effect of UTIs (cystitis and/or pyelonephritis) on graft outcomes.

Emphysematous pyelonephritis, which is a potentially catastrophic complication requiring urgent nephrectomy, has been reported in transplanted kidneys in several case reports [15, 16]. They describe conservative management with percutaneous drains and antibiotic therapy to be very effective in preserving the renal allograft function.

There are many well-recognized risk factors for UTIs in the RTRs. These include donor-related factors, peri-transplant surgical complications, maintenance immunosuppression, altered urinary tract anatomy, and urinary bladder outflow problems. Although most of the bacterial infections are acquired in the ascending (retrograde) pathway, some infections are likely to be initiated by blood stream dissemination. Each of these risk factors will be discussed in detail in the following sections.

Recognition of frequent UTIs has led to the routine use of antibiotic prophylaxis starting immediately post-transplantation. Such a practice has not been uniformly effective and could contribute to high antibiotic-resistant strains as well as long-term colonization of the urinary tract with such strains. Besides, there remains a significant variation in the choice of antibiotics and the duration of the prophylaxis.

The specific areas of interest and controversy about UTIs in transplant recipients are the risk factors, clinical features, and the difficulty in arriving at the precise diagnosis. Therefore, the emphasis of this chapter is placed in these areas as opposed to the treatment strategies. The transplanted kidney is denervated and therefore may not experience the localized pain or discomfort expected with pyelonephritis. It adds to the difficulty in clinical diagnosis of acute pyelonephritis in the allograft as opposed to native kidney, increasing the need for biopsy. This is described in more detail under the section for pyelonephritis in the later half of this chapter.

Despite the high incidence and the risk of heightened allograft loss as a result of recurrent UTIs, specific guidelines regarding the

prevention and management of post-transplant UTI are lacking. This is mainly because there exists no 'gold standard' for the accurate diagnosis of the UTI.

Risk Factors for UTI in Kidney Transplant Recipients

Several unique factors are thought to contribute to UTI in transplant recipients compared to the general population. The traditional risk factors present from before the transplant, such as female gender and diabetes will be discussed elsewhere in the textbook. It is worth mentioning that patients with anatomical urinary tract abnormalities (e.g., vesicoureteral reflux, neurogenic bladder, ileac conduit for urinary diversion) tend to develop chronic kidney disease earlier in life and receive kidney transplantation and therefore are over-represented in the overall transplant population. Patients with 'neurogenic bladder,' either because of diabetes mellitus or spinal cord injury, are taught self-catheterization technique to be done up to several times a day. Some patients may require either a chronic indwelling Foley catheter or a supra pubic catheter because of the urinary bladder failure. Regardless of what technique is utilized the risk for UTIs is substantially high in these individuals. Congenital urological problems that result in altered urinary tract anatomy (e.g., prune belly syndrome, creation of an ileal conduit for urinary drainage) leading to ESRD requiring kidney transplantation are another sub-group of patients that fall into this category. Patients with these conditions are not contraindicated for transplantation but need careful and individualized risk assessment.

Risk Factors in the Perioperative Period

As with any invasive procedures transplant surgery itself poses a high risk in introducing infections to the urinary tract in the perioperative period. Indeed, in the early days of transplantation perioperative infection rates were as high as 25% but now occur in <1% cases. There is ample literature evidence to support a single dose of an intravenous (IV) broad-spectrum antibiotic, usually a first-generation cephalosporin. At our medical center we administer one dose of cefazolin 2 g IV as a single dose 30 min before the surgery. For combined kidney–pancreas transplantation we administer ampicillin–sulbactam 3 g, corrected to the renal function. Patients allergic to penicillin receive clindamycin 600 mg IV Q 6 h, for the duration of the surgery.

In addition to the generic perioperative risk, the transplanted kidney has certain unique anatomical features that need to be considered in the context of UTIs. First, the kidney is placed in either the right or the left lower quadrant of the abdomen without needing to disturb the native kidney anatomy. Because of this proximity to the urinary bladder the transplant ureter is shorter than the native ureter making the bacterial transit to the upper urinary tract easier. Second, the ureteric anastomosis (neocystostomy) to the urinary bladder is designed to have an anti-reflux mechanism but the trade-off is between too tight an anastomosis causing a stricture or allowing free urinary reflux into the ureter. Different surgical techniques were devised (e.g., Lich-Gregoir technique, which is the most common procedure) primarily to prevent the urinary reflux but the long-term efficacy of the anastomosis is heavily dependent on the experience and skill of the operating surgeon. Third, many surgeons prefer to place an indwelling ureteral pigtail catheter at the time of the surgery, to prevent stricture formation at the neocystostomy during the healing process. This catheter (also called a stent) is usually removed at around four to six weeks post-operatively. But for as long as the stent is in situ it serves as a potential nidus for infections. Fourth, in patients who are dialysis dependent for many years and are anuric during that period, the urinary bladder becomes inactive and contracted. The return of brisk urinary output after a successful transplantation in the context of a dysfunctional urinary bladder may lead to urinary incontinence or frequency. This may pose a threat of bacterial infection introduction. In this

context, it is worth remembering that the transplanted kidney lacks the Gerota's fascia that acts as a barrier in spread of the infection to the perirenal tissues in native kidneys. Finally, use of multiple and more potent immunosuppressive agents in the early post-operative period including lymphocyte antibodies, corticosteroids predispose the patient to increased risk of early UTI and graft pyelonephritis. Also, diagnosis can be difficult because it can be masked by delayed graft dysfunction which occurs in up to 10–40% of renal allografts.

Risk Associated with Maintenance Immunosuppression

Maintenance immunosuppression is critical in protecting the allograft from acute and chronic rejection. Successful allotransplantation (transplantation between members of the same species) in humans became possible more than 50 years after the surgical techniques were invented. The first successful kidney transplantation in humans occurred in 1954 between identical twins. The recipient required no immunosuppression since they had identical immune systems and the allograft functioned for several years only to ultimately fail from myocardial infarction 9 years post-operatively [17]. In the early days of transplantation immunosuppressive therapies, such as whole body irradiation, cytotoxic chemicals (e.g., 6-mercaptopurine) were used that were nonspecific and too toxic leading to annual mortality as high as 40–50%, principally from infections. Recognition and understanding of the transplant immunobiology and the mechanisms of alloantigen recognition led to the development of medications that targeted specific pathways. This approach immensely reduced the drug toxicity and improved the efficacy of the immunosuppressive medications over the past two decades. As a result the incidence, severity and outcomes of bacterial infections of the renal allograft have improved substantially. The primary targets of the modern immunosuppression protocols are the alloantigen recognition, lymphocyte activation, proliferation, and suppression of pro-inflammatory mediators (corticosteroids). These regimens have very specific mechanisms of action that help in the prevention of acute rejection of the allograft but preserve many other essential components of the immune system especially the innate system comprising the complement pathway, immunoglobulin activity, etc. Therefore, the ability of the recipient to prevent infections and respond to pathogens and neoplasms is largely preserved. Individually, these medications are still far too toxic for long-term use and therefore, combination regimens with synergistic pathways allowed the doses to be vastly reduced for clinical use, which in turn minimizes adverse reactions. Some of these medications, such as calcineurin inhibitors (cyclosporine and tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus), have unreliable pharmacokinetics and are dosed based on the therapeutic drug level monitoring.

Despite these advances the therapeutic drug index for these regimens remains very narrow thereby making over- and under-immunosuppression in clinical practice quite possible and frequent. No biomarker exists currently that can reliably and accurately measure the degree of immunosuppression. Quantitative immunoglobulin G levels (IgG), measurement of various T and B cell subtypes, pharmacogenomic methods, T cell ELISPOT test, and measurement of intracellular ATP levels in stimulated T cells have all been used with very limited success. A detailed discussion of these methods is beyond the scope of this chapter, but their lack of success underscores the complexity and redundancy of the human immune system. Thus, the clinicians' inability to reliably maintain the recipient's treatment within this narrow therapeutic index remains one of the most important drivers of the post-transplant bacterial infections.

Despite the waning interest in the use of IgG levels to monitor patients' immunosuppression, a recent meta-analysis by Florescu et al. [18], which included 18 clinical studies, concluded that in patients with severe hypogammaglobulinemia (<400 mg/dL) the odds of respiratory, cytomegalovirus, and fungal infections were

significantly higher. However, they were not able to show such association for UTIs.

Donor-Related Factors

Despite the diligent protocols in the management of the deceased donors during the process of organ procurement infections can be transmitted via the donor organ. By the nature of the clinical setting in which the organ donor is selected, infections are highly prevalent in such patients. Thorough screening for infections, prophylactic antibiotics and transporting the procured organs under strict sterile techniques have all contributed to the rarity of such infection transmissions. Unfortunately, some of the cultures report the final results only after 4–5 days of incubation and positive cultures are therefore noted well after the transplant surgery has occurred. Cases of methicillin-resistant staphylococcus aureus infection [19] and rabies [20], transmitted with the donor kidney, have been well described and led to improvement in the processes of donor evaluation. Additionally, in centers that used pulsatile perfusion pump to preserve organs, positive cultures from the perfusion solution were able to predict post-transplant infections in the recipients [21].

Other risk factors for UTI that were reported include delayed graft function, prolonged hospitalization of >21 days, prior episodes of UTI, use of third-generation cephalosporins, long history of dialysis, simultaneous double kidney transplantations, re-transplantation, cytomegalovirus infection, and glomerulonephritis as native kidney disease. Some of these factors are intuitively plausible, whereas some others appear to be described based on small case series and therefore, not well substantiated.

Clinical Presentation and Laboratory Data

The classic presentation of cystitis is with the tetrad of fever, suprapubic pain (and/or flank pain in pyelonephritis), dysuria, and urinary urgency. They may present with nonspecific symptoms such as nausea, vomiting, altered mentation, sweats, chills, rigors asthenia, or without symptoms of UTI. The proportion of patients presenting with asymptomatic bacteriuria is much higher than in the general population. This is because immunosuppression may mask the inflammatory response and because the surgically denervated inflamed transplanted kidney may remain non-tender. One prospective randomized study reported that 56.7% of renal allograft recipients developed bacteriuria during the first month after renal transplantation, of which 40% had no symptoms of a UTI [22]. Another study, retrospective in design, reported that 71% of all bacteriuria occurring in the first month after transplantation was asymptomatic [23]. It must be noted that the patients in this Polish study were given perioperative prophylactic antibiotics for 7 days which is certainly not the practice in most US centers. The treatment of asymptomatic bacteriuria remains controversial despite many studies reporting a high incidence of acute pyelonephritis. Fiorante et al. [24, 25] showed that the incidence of pyelonephritis in patients with asymptomatic bacteriuria was 7.6 episodes per 100 patient-years compared with 1.07 in those without asymptomatic bacteriuria. However, the same studies also failed to demonstrate a significant difference in the allograft survival in patients treated for pyelonephritis. None of the published studies were prospective or randomized.

As previously noted the incidence of bacteremia as a result of UTI is about 3–7% and hospitalizations for septicemia were most commonly (30.6%) associated with urinary tract infection as a secondary diagnosis. Patients with UTI frequently have elevated serum creatinine and leukocytosis, when there is accompanying pyelonephritis. Graft dysfunction is less common with cystitis alone. However, diagnosis of graft pyelonephritis based on clinical features alone can be difficult. Symptoms can be nonspecific and also they can overlap with those of acute rejection. This is described further under the section on graft pyelonephritis. Urinalysis reveals pyuria (defined as >10 white blood cells in a high

power field—in an unspun urine sample), leucocyte esterase and nitrites. However, these findings alone are not diagnostic and a positive culture is required to guide antibiotic therapy. Diagnostic pitfalls with urine culture results are described below under the section of graft pyelonephritis.

A number of case reports regarding emphysematous pyelonephritis in transplanted kidneys and their management were published. This is an acute, severe necrotizing infection of the renal parenchyma and perirenal tissue, resulting in the generation of gas within the renal parenchyma, collecting system, or perinephric tissue. It is a catastrophic and potentially lethal complication in immunocompetent individuals requiring emergency nephrectomy but can be managed non-surgically in some cases. Agreda Castaneda et al. [15] reviewed 23 such cases from the literature and concluded that out of 23 cases, 12 were treated with allograft nephrectomy (52%), 7 (30%) patients underwent percutaneous drainage, and the remaining 4 cases (17%) were treated only with antibiotics and supportive care. 82% of these patients were diabetic and none of them had urinary obstruction. The treatment choice appeared to be based on the radiological and clinical severity at presentation with septic patients with >50% parenchyma involved with gas requiring a nephrectomy.

The diagnosis of acute pyelonephritis (APN) in the native kidney is usually made based on the classic tetrad—fevers, costovertebral angle tenderness, history of lower urinary tract infection, and microbiological cultures of the urine. The native kidney is therefore rarely biopsied for APN. However, in the context of renal transplantation and immunosuppression, the classic clinical features of fever and pain are frequently subdued, and costovertebral angle tenderness is not an accompanying feature since the anatomic location of the transplanted kidney is different from the native kidney. Blood leukocyte counts can be altered by immunosuppressive medications. Pyelonephritis is therefore often coincidentally discovered on allograft biopsy, and a definitive diagnosis can only be made if there is a positive concomitant urine culture result. Therefore, it is recommended that a urinalysis and a urine culture with reflex antibiotic sensitivity must be ordered as early as possible. This must be done before administering any antibiotics for obvious reasons. It is also important, as with urine collection in any patient, to collect the specimen with the appropriate technique. In patients who have an indwelling urinary bladder catheter for >2 weeks the Infectious Diseases Society if America (IDSA) recommends removal of the catheter before obtaining a urine specimen either from a mid-stream collection or from a new catheter.

Laboratory Diagnosis of UTI

Urinalysis: The findings most predictive of a UTI in urinalysis are pyuria (>10 WBCs/hpf), positive leukocyte esterase, a product of WBCs, and nitrites a product of gram-negative bacterial conversion of urinary nitrates to nitrites. Sterile pyuria is common in RTRs and therefore a positive leukocyte esterase alone is not a reliable indicator for UTI. The usefulness of leukocyte esterase and nitrite screening by dipstick has not been confirmed in renal transplant recipients. Additionally, many organisms such as enterococci, *Staphylococcus saprophyticus*, and Acinetobacter are unable to reduce nitrate to nitrite giving a false-negative reaction to the dipstix.

Urine culture: A positive urine culture with >100,000 CFU of a known uropathogen in the appropriate clinical context remains the gold standard for the diagnosis of UTI. Not all organisms found in urine cultures are pathogens. For example, *Staphylococcus epidermidis* (except in the presence of ureteral stents), lactobacillus, and *Gardnerella vaginalis* are normal commensals in the female genital tract and are likely contaminants. Urine cultures containing multiple organisms (i.e., "mixed flora") indicate that contamination has likely occurred. Other true pathogens may not grow well on routine culture media (e.g., unusual pathogens such as *Corynebacterium urealyticum* or *M. tuberculosis*) and specific culture media may need to be requested in the appropriate clinical context.

Blood cultures: They are not obtained unless patients have symptoms or clinical evidence for a systemic inflammatory response syndrome. Skin contamination can lead to false-positive results. The standard technique of specimen collection is to obtain a minimum of 10 ml of blood from a venipuncture with strict aseptic precautions into each of the two bottles containing growth media for aerobic and anaerobic organisms.

Pyelonephritis in Renal Allografts—Difficulties and Pitfalls in Diagnosis

Ascending infection of the urinary tract can be complicated by acute pyelonephritis (APN). The classic tetrad of costovertebral angle tenderness, fever, elevated white blood cell count, positive urine culture used to diagnose acute pyelonephritis in the native kidney, is frequently not useful for renal allografts. Fevers and leukocytosis can be attenuated by immunosuppressive therapy. Graft tenderness may be absent because of the surgically denervated transplant kidney. Also, graft tenderness can be present both in acute rejection and in graft pyelonephritis. Costovertebral angle tenderness is not a useful feature. Urine cultures can be frequently negative in renal allograft patients with APN, since these immunosuppressed patients receive long-term prophylactic antibiotics [26]. Lack of positive urine cultures has also been reported in a high percentage of patients with native kidney pyelonephritis in a large case series of 223 patients by Rollino et al. [27] in which they report that only 23.5% of their patients had positive urine cultures. In our study [26] of 49 kidney transplant recipients with biopsy features diagnostic of APN in first two years post-transplant, we showed that only 32% (16/49) had concomitant positive urine cultures at biopsy and in 8 of these 16 patients, colony count was less than 10^5 CFU/ml. In 14/49 patients, positive urine culture did not coincide with the biopsy (had positive culture beyond 10 days before or after biopsy) and in 19/49 patients, urine cultures were negative. Urinalysis findings in patients with APN and acute rejection can also overlap and may not be specific. Differentiating between renal allograft APN and acute rejection based on clinical symptoms alone can be difficult. Biopsy therefore plays an important role in diagnosis of pyelonephritis in the renal allograft (as opposed to native kidney).

Role of Kidney Biopsy in the Diagnosis of Graft Pyelonephritis: Diagnostic Pitfalls

It must be emphasized that a transplant renal biopsy is not indicated to prove presence of UTI as a cause of renal dysfunction. This method is invasive, with its attendant complications. Biopsy becomes necessary when there is graft dysfunction, and other causes need to be excluded, most frequently acute rejection. Another indication may be if the infection is not improving despite antibiotic treatment. We have already pointed out that clinical features and urinalysis findings can be overlapping in APN and acute rejection. Even on biopsy, APN versus acute rejection can pose a differential diagnostic dilemma [28, 26, 29–31]. Both conditions are associated with tubulointerstitial inflammation [32, 33]. The classic pathological features of pyelonephritis include interstitial inflammation, frequently in a zonal distribution (Fig. 8.1). There is typically predominance of polymorphonuclear leukocytes (PMNs) in the interstitial infiltrates (Fig. 8.2) along with neutrophilic tubulitis and scattered intratubular PMNs forming microabscesses (Fig. 8.3). However, tubular microabscesses are usually focal in distribution and therefore may not get sampled in the biopsy specimen. Tubular apoptotic cell debris accompanying severe acute tubular necrosis (ATN) can mimic tubular microabscesses. Neutrophil-rich areas can be focally seen in acute rejection associated inflammatory infiltrates as well. Although there are well-defined Banff criteria for the diagnosis and grading of acute rejection (based on interstitial inflammation and tubulitis) [34], tubulitis also tends to be focal.

The other histologic features such as acute tubular necrosis (ATN) and interstitial edema can be seen in both acute pyelonephritis and acute

rejection. Interstitial hemorrhage, however, should make one suspicious of a rejection process. Thus, histologic features between pyelonephritis and acute rejection may overlap. All these factors can complicate the diagnosis of APN in renal allografts.

The clinical importance of making an accurate diagnosis in this situation cannot be over emphasized. The treatment of these two conditions is diametrically opposite—reduction of immunosuppression (along with antibiotics) for the former and aggressive immunosuppression for the latter.

Not only the diagnosis, but even treatment of acute pyelonephritis can be difficult in some patients. We have encountered cases where biopsy showed diagnostic features APN, but there was no improvement in graft function after antibiotic treatment. We had three such cases in our cohort of 49 patients (reference). Two of these recipients had positive urine cultures ($>10^5$ CFU/ml) at the time of the biopsy. The third recipient had negative urine cultures at the time of the biopsy but subsequently developed positive urine culture several days after biopsy. Additionally, two other recipients showed biopsy features of APN, but urine cultures were repeatedly negative. They showed improvement in graft function only after the addition of corticosteroids to their antibiotic regimen. Such cases pose a diagnostic and therapeutic dilemma.

Need for Novel Diagnostic Techniques

Because of this diagnostic difficulty, there is a need for novel techniques that can help differentiate between the specific etiologies causing interstitial inflammation in the kidney. Extensive efforts have been made to develop less-invasive tools such as blood and urine biomarkers. Interferon gamma-controlled chemokines (CXCL9, CXCL10) and cytotoxic T-lymphocyte granule contents (Granzyme B, perforin) have been shown to be highly expressed in acute rejection. *CXCL10* has been shown to be a candidate urinary biomarker for acute rejection [38, 39]. Our recent pilot study explored the utility of miRNA profiling (microRNA) by Nanostring technology using kidney allograft biopsy tissue [26]. This study by Oghumu et al. selected a group of 49 patients who had a transplant biopsy within the first 24 months after transplantation with interstitial inflammation characteristic of acute pyelonephritis. As described above 16/49 patients had concomitant positive urine cultures

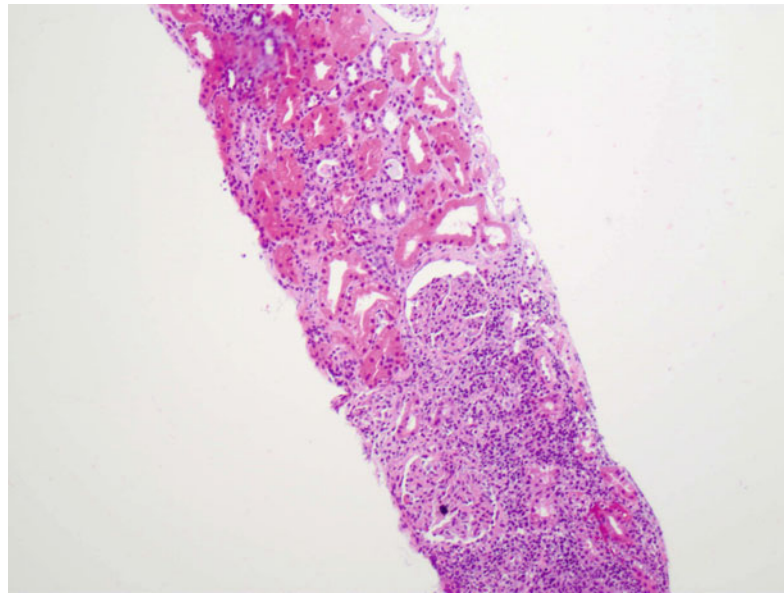

Fig. 8.1 Zonal pattern of inflammation is more common in pyelonephritis (as opposed to diffuse inflammation in acute rejection) in which inflamed areas of renal cortex are immediately juxtaposed to well-preserved renal cortex without inflammation (H&E, 200X). This is typically seen in ascending urinary tract infection

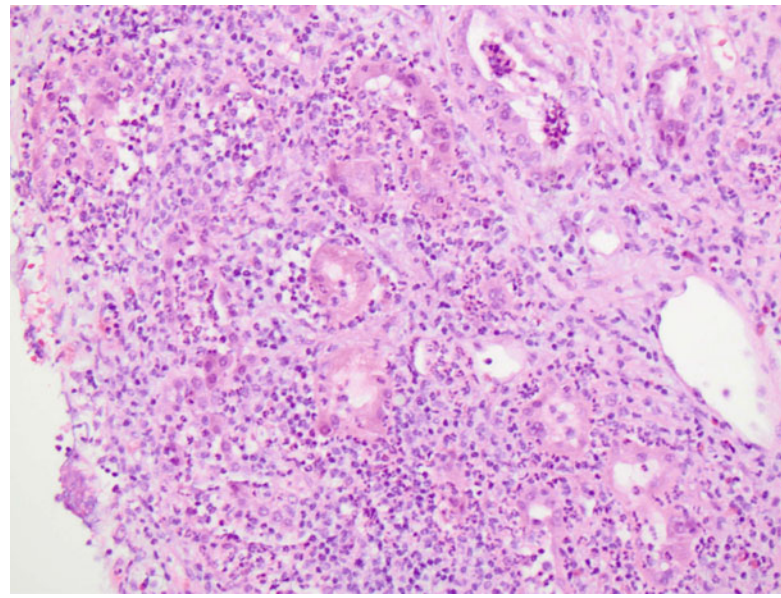

Fig. 8.2 Neutrophil-rich interstitial inflammation with neutrophilic tubulitis (H&E, 400X)

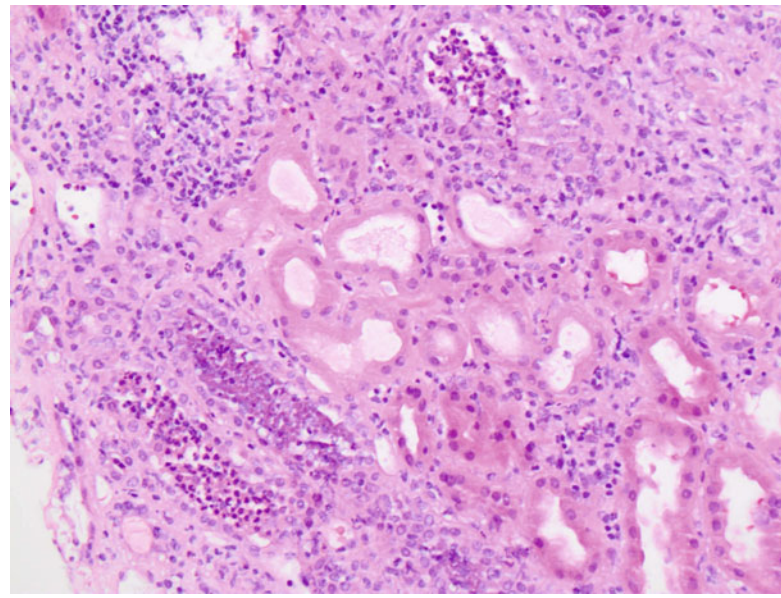

Fig. 8.3 Neutrophils and apoptotic cellular debris inside tubular lumens forming "tubular microabscesses" (H&E, 400X)

at biopsy, 14/49 patients had positive urine culture but it did not coincide with the biopsy (had positive culture beyond 10 days before or after biopsy), and in 19/49 patients, urine cultures were negative. Based on urine culture results at the time of the biopsy these patients were subdivided into groups of 'highly likely,' 'possible,' and 'equivocal' for pyelonephritis. Eleven patients representing these groups were selected for the miRNA testing and compared to five patients with unequivocal AR and four patients with normal (preimplantation) biopsies as controls. miRNAs profiles were analyzed using top 100 miRNAs and found that there was good intra-group clustering within the AR and the normal groups. Amongst the pyelonephritis

group intra-group clustering was poor. Several biopsies of graft pyelonephritis clustered with AR. We did, however, find a small group of miRs that showed statistical differences between the biopsies with AR and the cases of unequivocal graft pyelonephritis (miR-145, miR-99b, let-7b-5p, miR23b, and miR-30a). A follow-up study looking at gene expression (mRNA transcripts) was performed using Nanostring platform [29]. For this study we also added a group of biopsies with native kidney pyelonephritis. Gene transcripts for *CXCL1*, *CXCL2,* and lactoferrin (*LTF*) were found to be higher in pyelonephritis (both native kidney and graft pyelonephritis). CXCL1 and CXCL2 are known to be neutrophil chemoattractants [35]. LTF is an iron-binding glycoprotein in secondary granules of polymorphonuclear leukocytes, found in various body secretions such as saliva, tears, and milk. It has antimicrobial activity. Conversely, interferon gamma-controlled chemokine genes—*CXCL9*, *CXCL10*, and *CXCL11* (and also metabolic enzyme *IDO1*) are expressed significantly higher in acute rejection biopsies as compared to pyelonephritis (both native kidney and graft pyelonephritis). These are CXCR3 ligands and potent T-lymphocyte chemoattractants, universally induced during cell-mediated immune responses [36, 37]. *CXCL10* has been shown to be a candidate urinary biomarker for acute rejection [38, 39]. Surprisingly though, we found that gene expression in graft pyelonephritis does not exactly resemble that in native kidney pyelonephritis. In fact, *CXCL9*, *CXCL10*, and *CXCL11* transcript levels in graft pyelonephritis are significantly higher than in native kidney pyelonephritis (albeit lower than AR). In silico functional pathway analysis using Ingenuity software was also performed. Pathway analysis showed similarities between graft pyelonephritis and acute rejection. The T cell dominant upstream regulatory molecules (IFNγ, IFNα, IL-18, IL-12) are predicted to be activated in both AR and APN (culture positive and culture negative), but not in native kidney pyelonephritis. Differences between MAP kinase subfamilies (ERK1/2 and p38) were also seen between APN and native kidney pyelonephritis. Therefore, ineffective bacterial phagocytosis in APN resulting in lack of response to antibiotics in some cases may be speculated. Whether it is an effect of the immunosuppressive treatment is not known but is certainly a possibility. Also there is no predicted activation of TNF and NFκ-B in native kidney pyelonephritis as compared to graft APN and AR, probably suggesting a more controlled inflammatory reaction in NP as compared to AR and APN. Thus, the pathogenesis of allograft APN and native kidney pyelonephritis may not be exactly the same. We, therefore, think that graft pyelonephritis may also have a component of alloimmunity (in addition to antimicrobial immune response). Some cases of graft pyelonephritis do not completely recover with antibiotics alone. Selected cases may show some benefit with addition of steroids [29]. But since this method needs further validation and optimization the authors recommend using a 'gestalt' approach including clinical history, biopsy findings, culture results, immunosuppressive drug levels, C4d staining, and donor-specific antibody results in arriving at the best possible clinical diagnosis.

Recurrent UTI: This is reported as highly variable, 2.6–27% [40], based on several retrospective studies. A CT scan with contrast to study the native kidneys, transplant kidney, ureters, and the bladder will identify strictures, obstruction, abscesses, stones, or complex cysts. For instance, if the native kidney appears to harbor a persistent reservoir of infection and transmitting the infection to the transplanted kidney, a native nephrectomy would be potentially curative. A post-void ultrasonogram of the urinary bladder would diagnose inadequate emptying and patients may respond to bladder training, medical therapy or frequent self-catheterization. In cases without an obvious etiology, a referral to the Urology department is appropriate to investigate urinary tract anomalies. Fiberoptic cystoscopy to diagnose urethral and bladder lesions, voiding cystourethrogram to diagnose ureteral reflux, urodynamic studies to diagnose detrusor dysfunction, and functional outflow problems are all appropriate tests. In cases with all negative results but with suspicion

for an infected nidus in one of the kidneys, the urologists at our institution have performed a selective ureteral urine sampling from each of the two native ureters and the transplant ureter via cystoscopy after sterilizing the bladder. A positive culture would then identify the culprit kidney allowing a selective treatment approach, such as native nephrectomy or prolonged antibiotic therapy. Among men rare causes for UTI are prostatitis and epididymitis and in women weak pelvic floor muscles causing urogenital prolapse and atrophic vaginitis from post-menopausal estrogen deficiency.

Etiology and Pathogenesis

Etiology: Many retrospective studies reported that the most common pathogens causing UTI are enteric gram-negative bacilli such as *Escherichia coli*, Klebsiella sp., Pseudomonas sp., and *Enterococcus faecalis*. Resistant strains are more common than in the general population, up to 17.2% reported by Valera et al. [41]. A prospective, randomized study from 1990 comparing trimethoprim/sulfamethoxazole (TMP/SMX) to placebo, a significantly higher proportion of UTIs in the treatment group, was due to multi-drug-resistant bacteria (62% vs. 18%) [42]. Similarly, Samra et al., from a large tertiary care center, reported that from an outbreak of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-3 (carbapenemase producing *K. pneumoniae* type 3), 11% of all the isolates were from RTRs [43]. Green et al. did a meta-analysis of all the prophylaxis studies and concluded that no significant reduction was found in the all-cause mortality and adverse events rates [44]. In this analysis, prophylaxis significantly reduced bacteriuria and sepsis with bacteremia but impact on graft survival could not be demonstrated. Maillard et al. reported the emergence of ampicillin-resistant *Enterococcus faecium* strains (ARE) in a kidney transplant ward and noted that prior cephalosporin use and patient-to-patient transmission were associated with the emergence of ARE [45]. This strain has the potential for clonal dissemination and further outbreaks but also is thought to represent an important step in the emergence of vancomycin resistance, which is highly prevalent as a nosocomial infection today [46]. In summary, even though antibiotic prophylaxis appears to be an important factor in the emergence of resistant bacteria it is difficult to prove this conclusively based on the retrospective, single-center studies that used a variety of regimens for prophylaxis.

Pathogenesis is similar to that in native kidney pyelonephritis. Ascending infections from the lower urinary tract are more common. Shorter ureter due to pelvic location of the transplanted kidney, absence of the natural anti-reflux mechanisms at the junction of the urinary bladder and surgically implanted ureter, post-surgical tissue injury, ureteral edema and stenosis, and suppressed immune system all together contribute to the ease of bacterial attachment to the urothelium, survival, and spread through the urinary tract.

Treatment

In general, as is the case with the general population, initial treatment of UTI is decided based on the clinical context, risk factors, and severity of the presentation. Results of the urine and blood cultures will ultimately decide the specific antibiotic regimen, the duration, and follow-up. There have been no prospective, randomized clinical trials comparing antibiotic choice or duration and therefore, the treatment should be individualized and must take into account the local center's bacterial culture profiles and patient's risk factors.

Asymptomatic bacteriuria: Treatment of patients with incidental positive bacterial cultures but without symptoms remains controversial. As described before, the incidence of asymptomatic bacteriuria is very high in the early post-transplant period and continues to be a significant event even in the long-term. The clinical outcomes appear to be worse with antibiotic treatment if not the same. El Amari et al. [47] showed in a retrospective study that 45% of the asymptomatic bacteriuria patients

treated with antibiotics had persistent bacteriuria and 35% of them with emergence of antibiotic-resistant strains. Among cases not treated with antibiotics 59% cases had spontaneous resolution of the bacteriuria. Similarly, Green et al. [44] showed that treating asymptomatic bacteriuria resulted in a three times higher risk for symptomatic UTI. This evidence, along with the risk for emergence of antibiotic resistance strains as well as the significant adverse effects of antibiotic exposure, e.g., Clostridium difficile, Candida infections question the efficacy of routine antibiotic treatment of asymptomatic bacteriuria.

Symptomatic UTI: Treatment in these patients is based on the clinical context. Treatment of the first episode of an uncomplicated UTI is according to the standard IDSA guidelines but with cases of recurrent UTI, recent instrumentation, nosocomial infections, and other risk factors the antibiotic selection can be broadened. Since antibiotic strains are on the rise, local center's microbiological sensitivities must be taken into consideration. Many transplant centers, as with ours, have dedicated infectious disease physicians who are consulted for recommendations and whenever available this service should be made use of. Patients with resistant bacterial strains may need to be treated with intravenous antibiotics for extended periods of time as outpatients. Treatment should also be extended to address the underlying risk factors such as urinary tract anomalies, which may require surgical or cystoscopy procedures. For example, ongoing ureteral reflux can be treated with collagen injection to the vesicoureteral junction via cystoscopy.

Antibiotic prophylaxis: Since bacterial infections are highly prevalent during the first year of transplantation, antibiotic prophylaxis for all the recipients has become common practice. The regimens used and their duration are varied between centers although trimethoprim–sulfamethoxazole (TMP–SMX) appears to be the most favored agent since it is the drug of choice for the prevention of pneumocystis jeruvici pneumonia. Most of the studies on antibiotic prophylaxis were done more than 30 years ago before the more potent immunosuppressive regimens came into use and therefore a detailed review of those studies would probably be considered inadequate evidence. As mentioned before, a randomized, prospective, double-blind, placebo-controlled study by Fox et al. [42] using TMP–SMX showed a significant decrease in the UTI in patients on the antibiotic compared to the placebo; however, their infections were more likely to be caused by resistant bacteria than infections in patients in the placebo group (62% vs. 18%, $p < 0.001$). More recent studies have shown a continuing trend of bacterial resistance in patients treated with antibiotic prophylaxis and indeterminate benefit from UTI prevention. While no recent studies were conducted on this subject, the prevalent notion seems to be that TMP–SMX seems to be the antibiotic of choice for at least 6–12 months of the post-transplant period.

Where appropriate, women who appear to have recurrent UTI related to sexual intercourse should be given post-coital antibiotic prophylaxis. Post-coital voiding may be helpful. Post-menopausal women with atrophic vaginitis might benefit from topical estrogen applications.

In rare instances, with failure of response to the above measures, methenamine hippurate has been used with relative success. This is a FDA-approved antibacterial agent, which exerts its activity because the methenamine component is hydrolyzed to formaldehyde in acid urine [48]. Hippuric acid, the other component, acts to keep the urine acid. The minimal inhibitory concentrations are significantly lower in more acidic media. At a dose of 1 g BID it can be used safely for periods of up to 6–12 months with very low adverse effect rate and without the risk for antibiotic resistance. A systematic review of all the clinical studies showed that this drug is effective in the prevention of UTI but none of the studies involved transplant recipients [49].

Summary

UTI is the most common infection in kidney transplant recipients, especially in the early post-transplant period. Lower urinary tract

infections are much more frequent as compared to pyelonephritis (involvement of the graft kidney). Pyelonephritis is usually associated with graft dysfunction. Based on clinical and urinary findings alone, distinguishing acute graft pyelonephritis from acute rejection is usually not possible. Kidney biopsy therefore becomes important. Histological diagnosis of acute graft pyelonephritis is easy if characteristic features like neutrophilic inflammatory infiltrate and tubular microabscesses are seen in association with positive concomitant urine culture results. But these histologic findings are not absolutely specific and occasionally biopsies with acute rejection can also show neutrophil-rich inflammation. Tubular microabscesses can be seen with severe acute tubular necrosis as well. Additionally, urine cultures can show low bacterial counts or may be even negative presumably because of prophylactic long-term antibiotics in transplant recipients. In such cases, diagnosis of pyelonephritis can be difficult. Inflammatory cytokine biomarkers in blood and urine are currently being investigated as tools for diagnosis, especially for acute rejection. However, since both rejection and pyelonephritis are associated with inflammation in the kidney, some degree of overlap even in these cytokine biomarkers can occur. These diagnostic pitfalls must be kept in mind. There is no single gold standard test for the diagnosis of graft pyelonephritis. A gestalt approach is important. Also, response to antibiotic treatment may not be as rapid and complete as in an uncomplicated native kidney pyelonephritis. Graft recipients are chronically immunosuppressed. Uncommon resistant microbial infections can occur. Severe inflammation may not resolve with antibiotics alone. Superimposed rejection process may also occur. Antibiotic and corticosteroids in combination may become necessary in carefully selected patients.

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