Acute Poststreptococcal Glomerulonephritis

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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

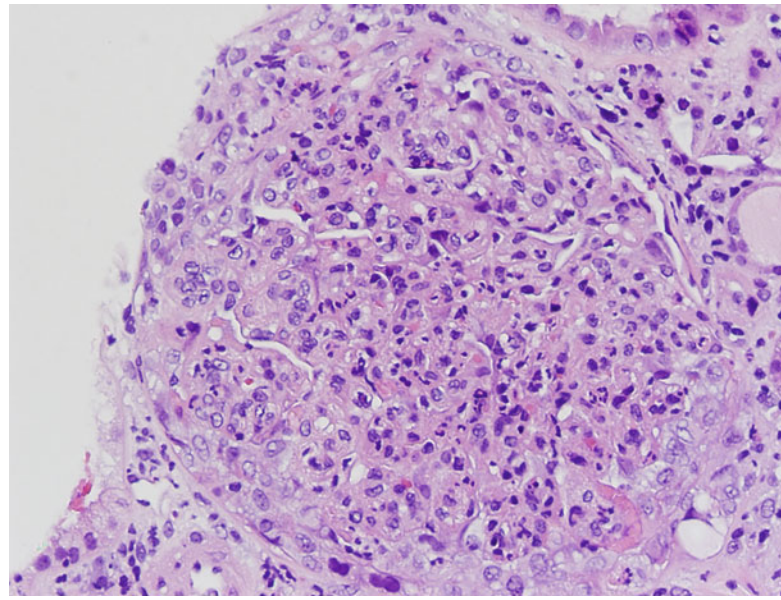

Fig. 1.1 An enlarged glomerulus shows diffuse endocapillary hypercellularity with numerous neutrophils and closure of all glomerular capillaries. The glomerulus is increased in size and cellularity, H&E, ×200

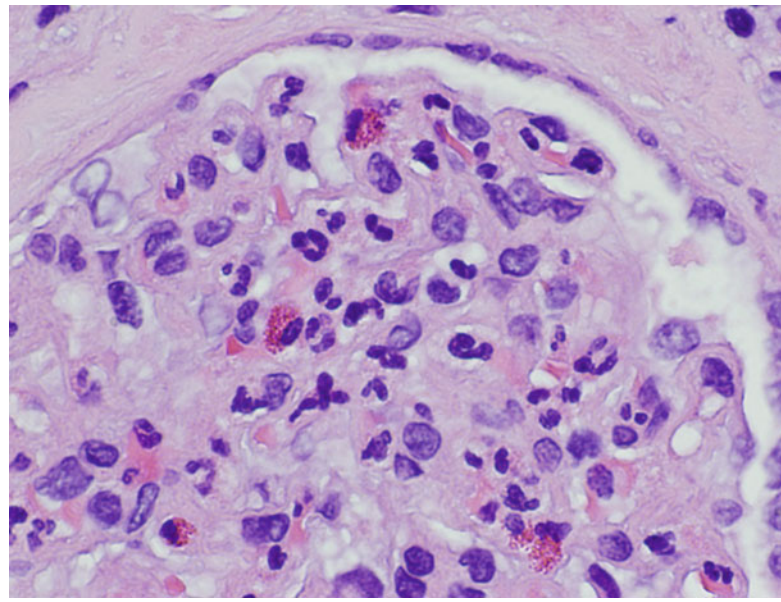

Fig. 1.2 Acute diffuse proliferative glomerulonephritis with considerable infiltration of the glomerulus not only by neutrophils but also by eosinophiles. H&E, ×400

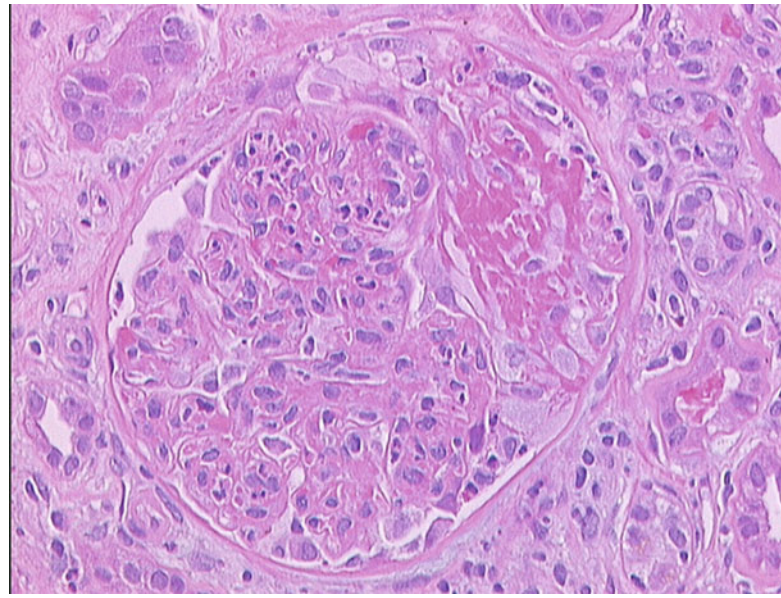

Fig. 1.3 Segmental glomerular necrosis with fibrin exudation into the Bowman's space. H&E, ×400

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

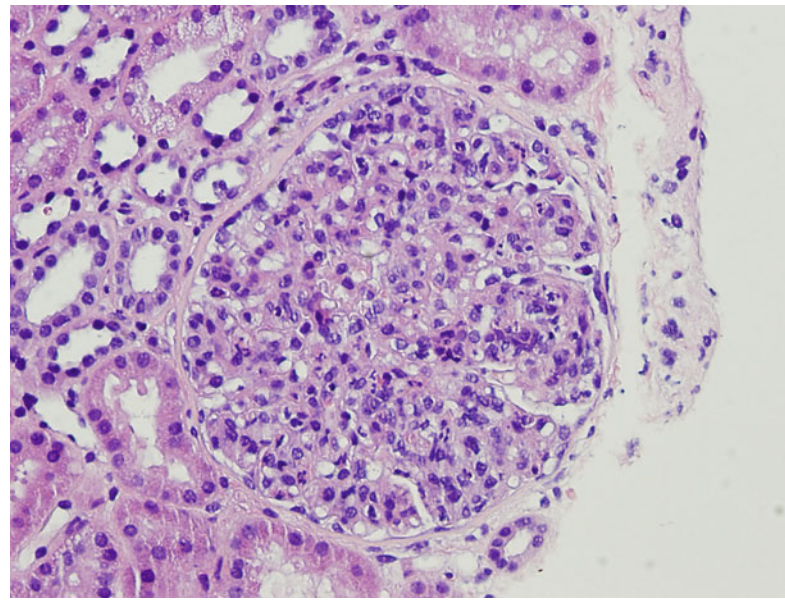

Fig. 1.4 A glomerulus with endocapillary hypercellularity. Because of the increased cellularity within each lobule, there is an accentuation of the lobularity. H&E, ×200

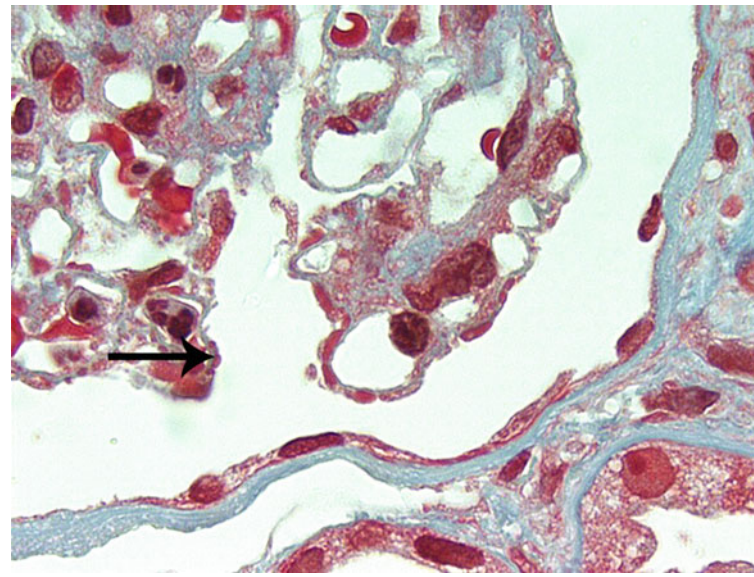

Fig. 1.5 The subepithelial humps may be seen as fuchsinophilic red dots (*arrow*) under high magnification, using Masson's trichrome stain, (×1000)

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

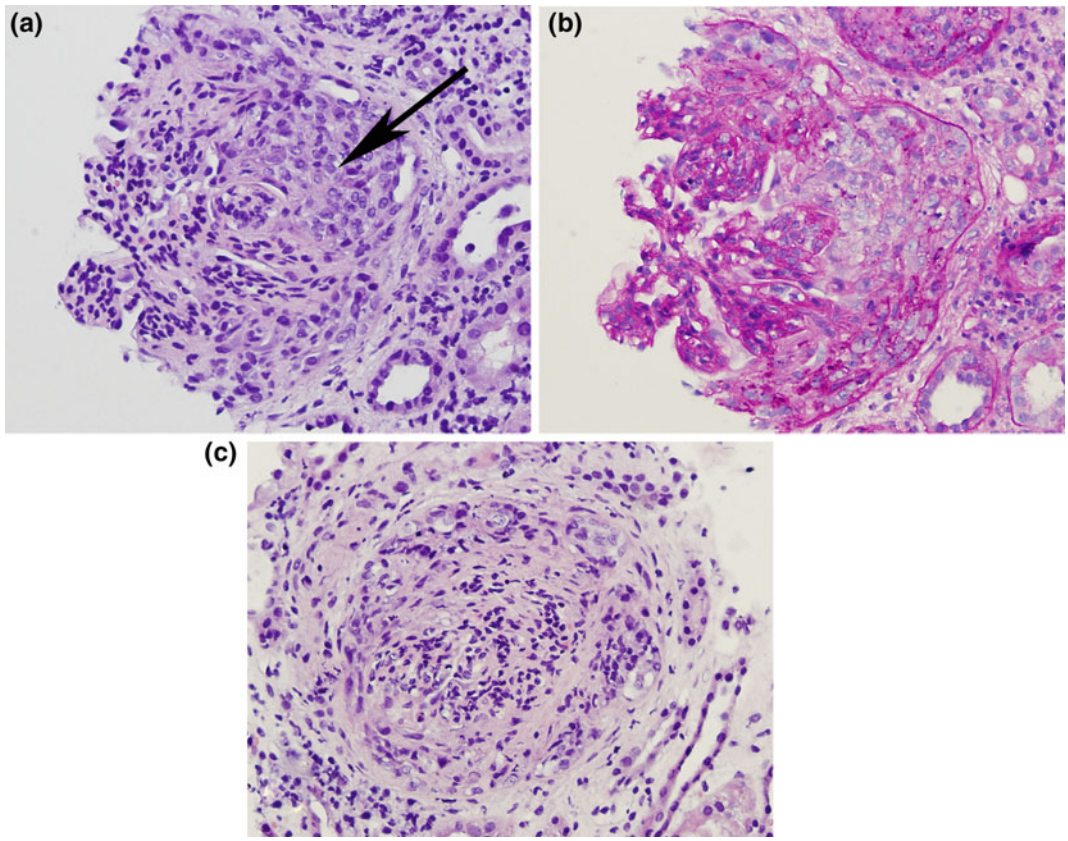

Fig. 1.6 Crescent formation in APSGN. **a** This cellular crescent (*arrow*) was noted in the renal biopsy of a 7-year-old girl with APSGN associated with acute kidney injury. Note that the compressed glomerular capillaries appear hypercellular. H&E, ×400. **b** The same glomerulus stained with PAS,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

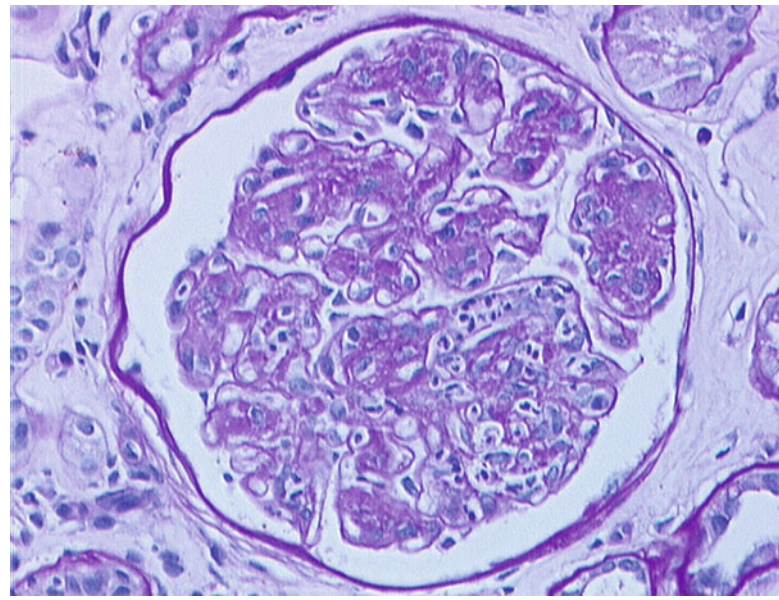

Fig. 1.7 APSGN in a patient with underlying diabetic glomerulosclerosis. The patient developed acute glomerulonephritis with very high ASO titers and low serum C3 levels after a "sore throat". *Note* the endocapillary hypercellularity superimposed on the preexisting mesangial expansion. PAS, ×400

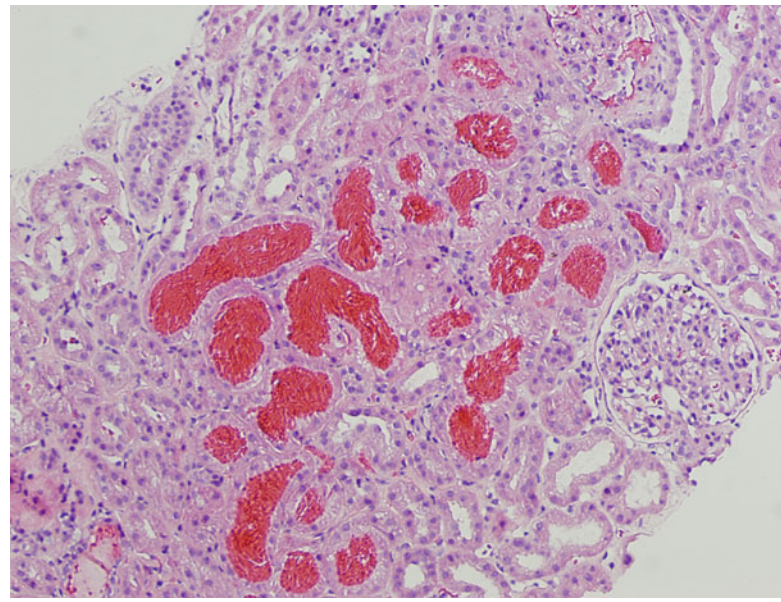

Fig. 1.8 Red blood cell casts persisting in a 45-year-old patient with resolving APSGN. The biopsy was done several weeks after the onset of proteinuria, hematuria and low serum C3 levels (the proteinuria improved from 3 to 0.5 g/24 h at the time of biopsy), H&E, ×100

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].

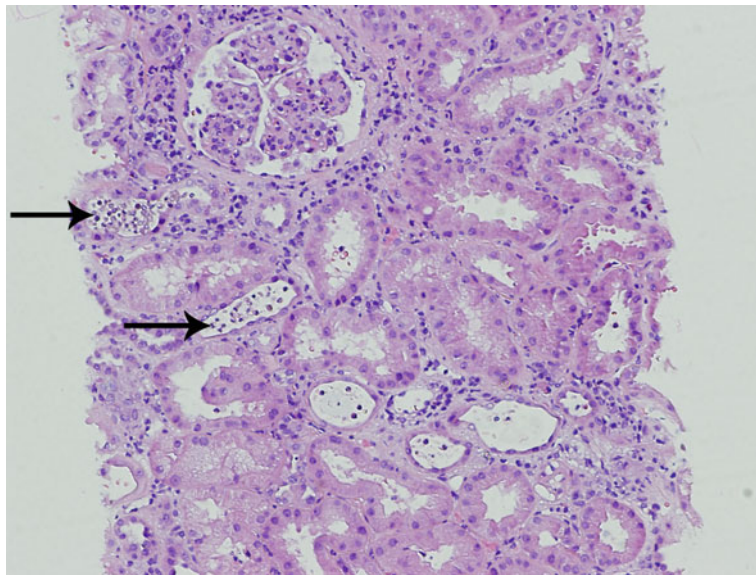

Fig. 1.9 Acute tubular necrosis in a 68-year-old nondiabetic male with APSGN. Note the several apoptotic tubular epithelial cells in dilated tubules (*arrows*). Such apoptotic cells should not be misinterpreted as neutrophil granulocytes, H&E, ×100

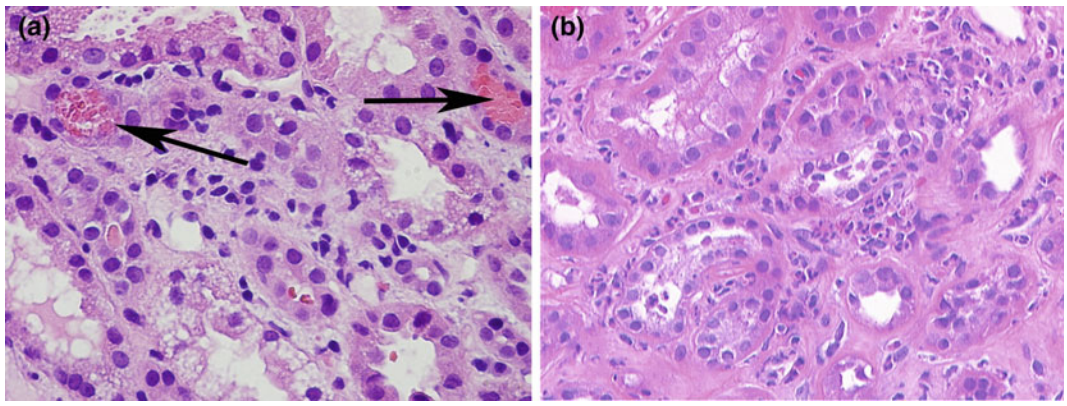

Fig. 1.10 Interstitial inflammation in APSGN. **a** ATN in a case of severe pediatric APSGN. *Note* the interstitial edema, inflammation and the tubular injury with epithelial irregularities, and vacuolization of the tubular epithelium. Few tubules contain red blood cells (*arrows*), H&E, ×400. **b** 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].

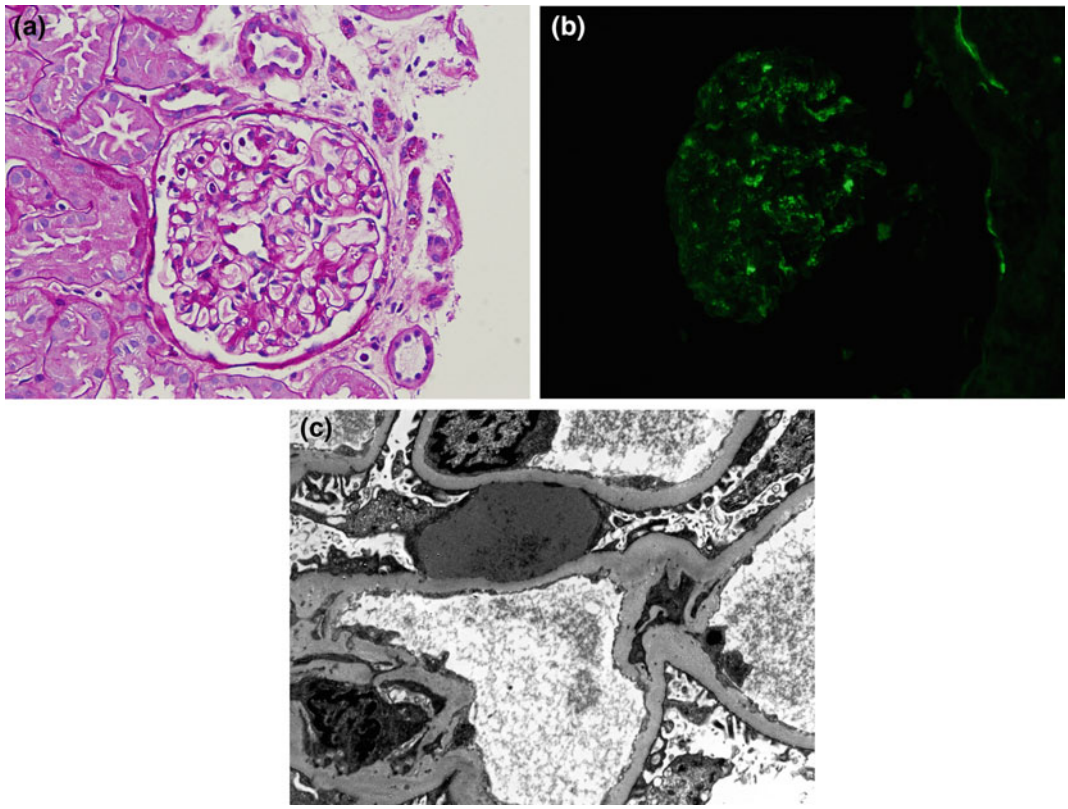

Fig. 1.11 **a** Normal appearing glomerulus in the biopsy of a hepatitis C virus positive patient who developed microscopic hematuria and mild proteinuria. Immunofluorescence and electron microscopy detected C3-positive subepithelial humps, PAS, ×200. **b** Granular C3 deposits. No immunoglobulins were 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]

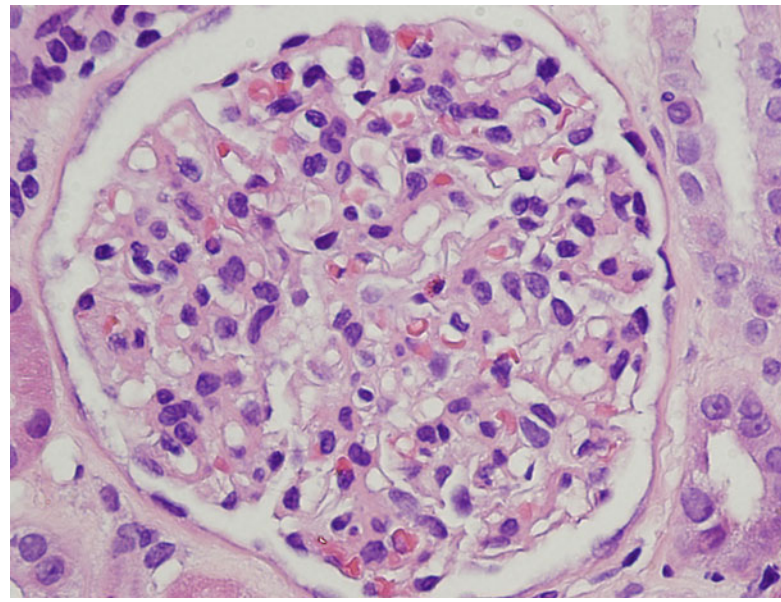

Fig. 1.12 Mesangial hypercellularity in a patient with resolving APSGN (same biopsy as Fig. 1.8), H&E, ×400

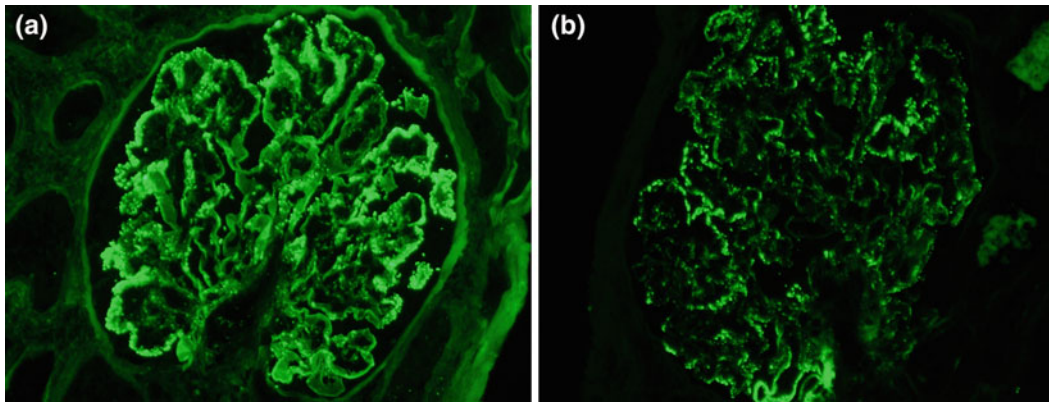

Fig. 1.13 Garland pattern of immunofluorescence staining. The coarsely granular staining along the glomerular capillary loops may be segmentally confluent. **a** IgG, **b** C3 staining from the same case, ×400

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

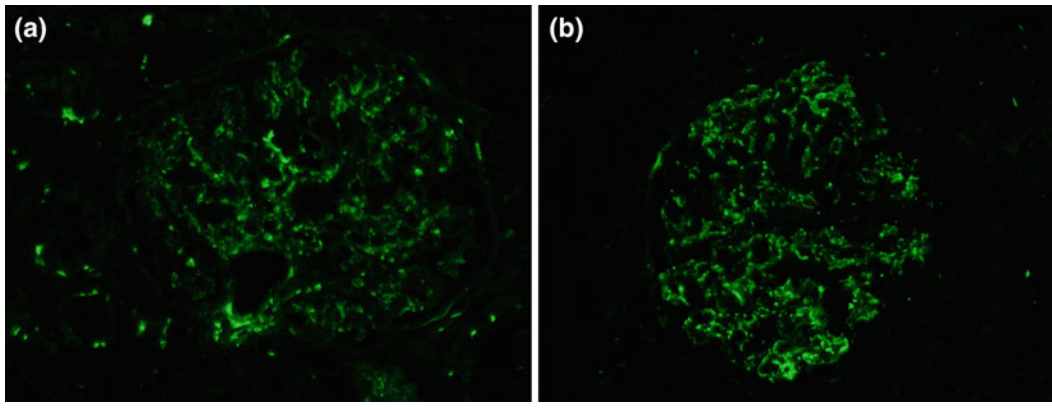

Fig. 1.14 The "starry sky pattern" of immunofluorescence. **a** The finely to coarsely granular deposits are randomly distributes across the glomerulus. Direct immunofluorescence with an antibody to C3, ×400. **b** More widespread mesangial and segmental C3 positive glomerular capillary deposits, ×400

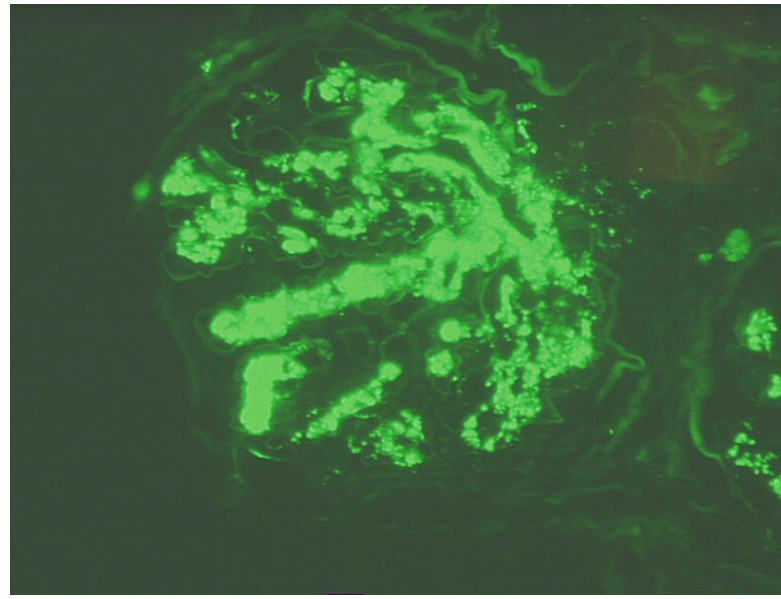

Fig. 1.15 Mesangial pattern of immunofluorescence in APSGN with granular C3 staining in the mesangium, ×400

("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

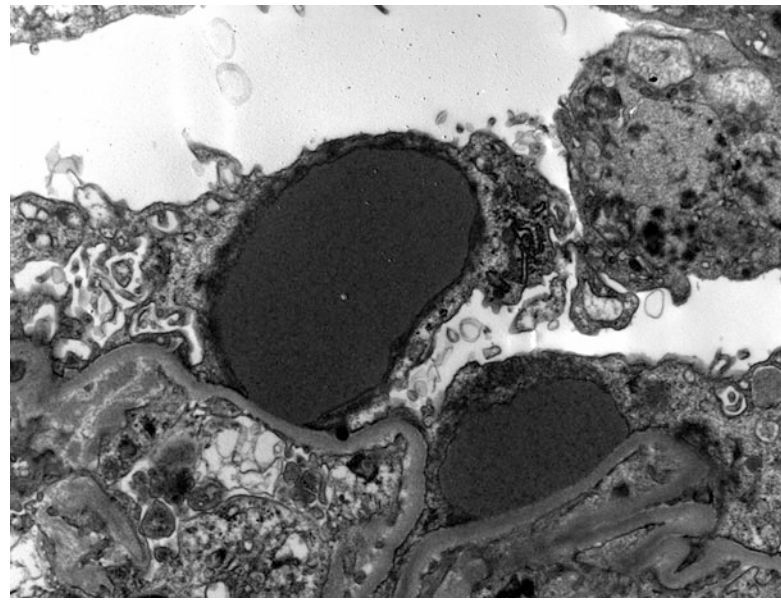

Fig. 1.16 Large dome-shaped subepithelial deposits (humps) are the hallmark ultrastructural finding in APSGN. Uranyl acetate–lead citrate, ×10,000

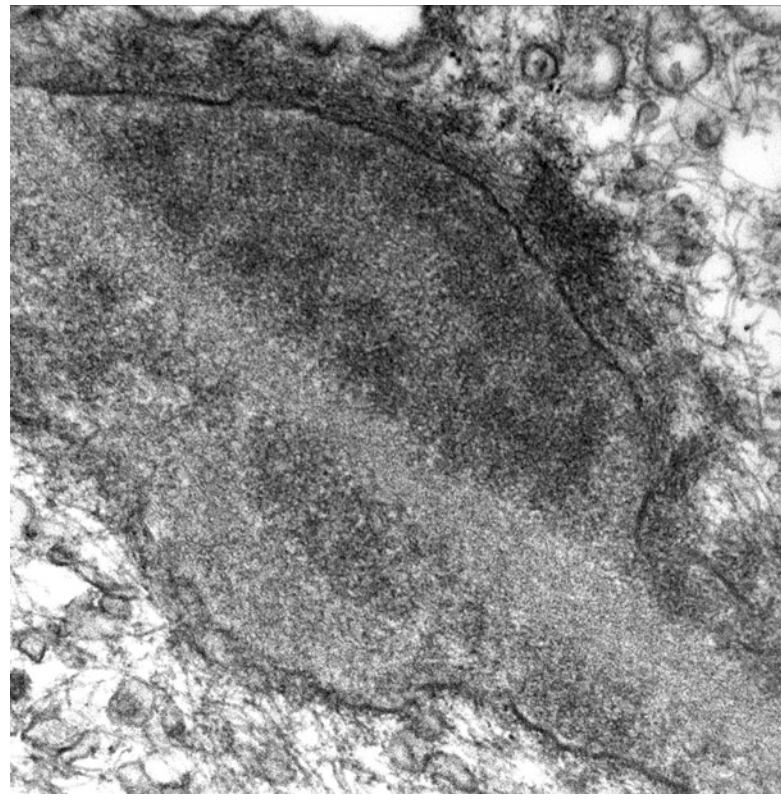

Fig. 1.17 A subepithelial hump with decreased and variegated electron density. This finding is thought to represent resolving immune complex deposits. Uranyl acetate–lead citrate, ×80,000

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

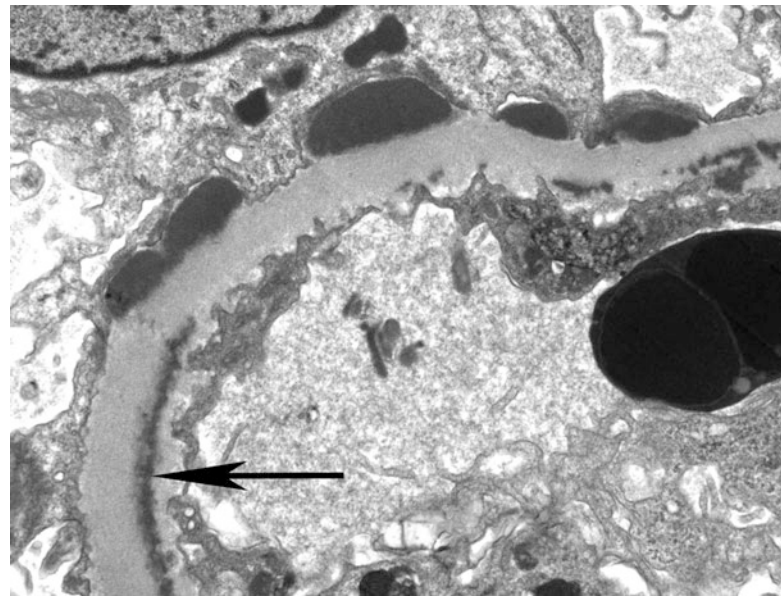

Fig. 1.18 Numerous subepithelial humps of various sizes along the GBM. This is frequently seen in biopsies with the garland pattern of immunofluorescence. Note that there are subendothelial deposits as well (*arrow*). Uranyl acetate–lead citrate, ×1100

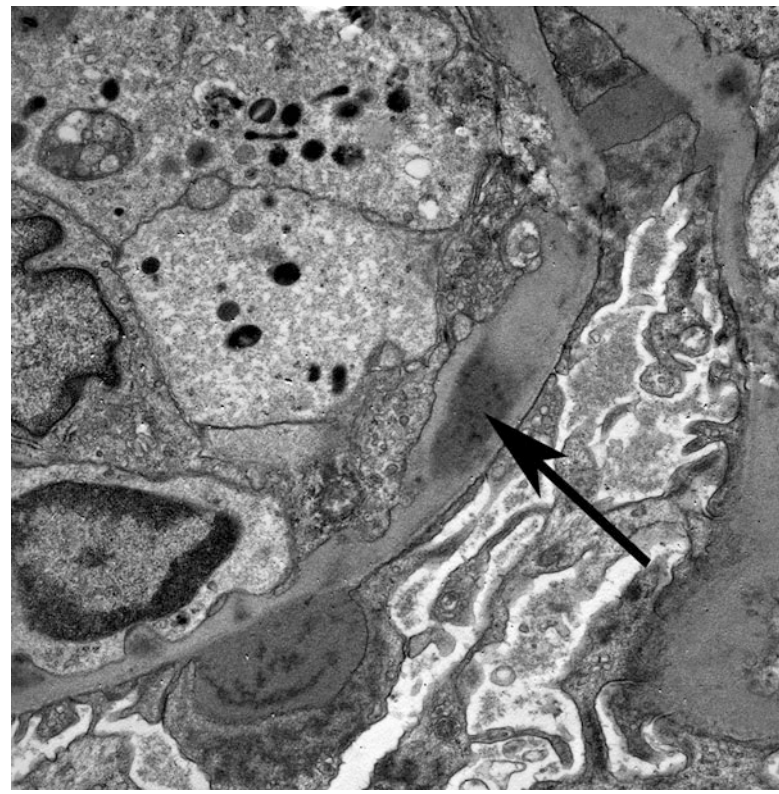

Fig. 1.19 In addition to subepithelial deposits, intramembranous deposits (*arrow*) are also common. Uranyl acetate–lead citrate, ×15,000

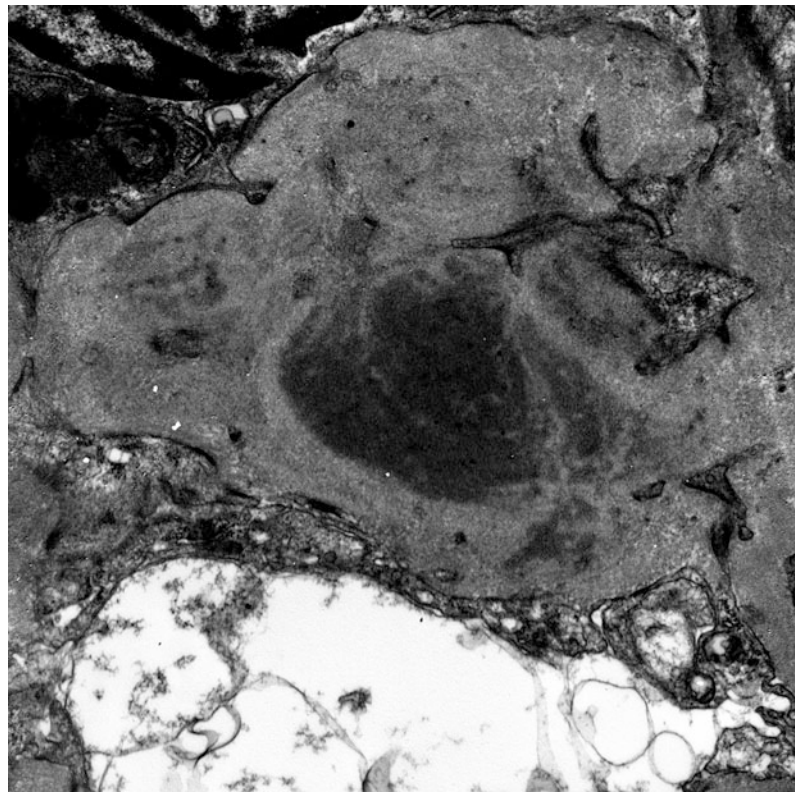

Fig. 1.20 Mesangial electron dense deposit in a case of APSGN. Uranyl acetate–lead citrate, ×20,000

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

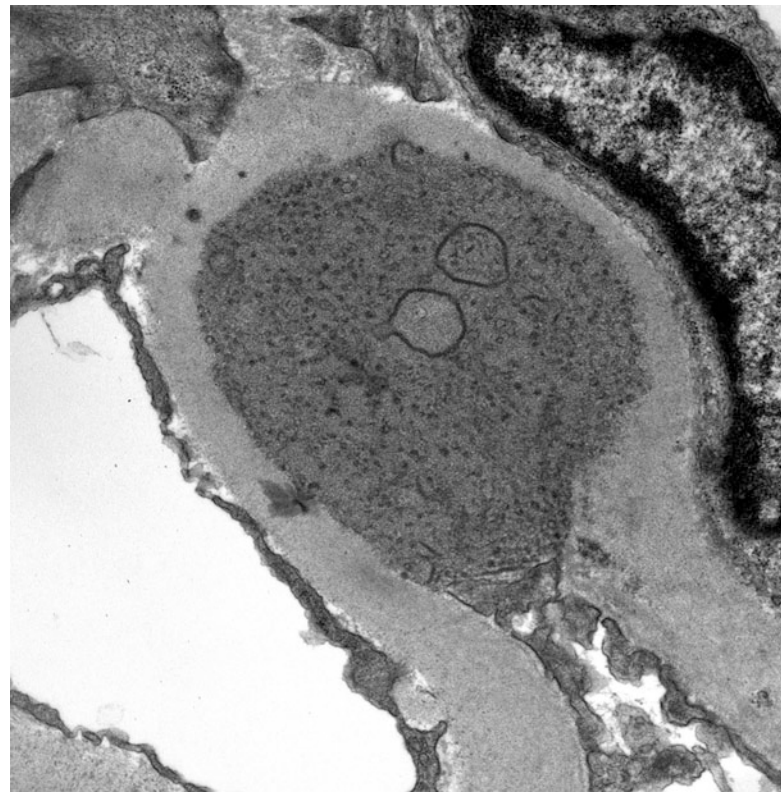

Fig. 1.21 A large subepithelial deposit in a mesangial groove (notch) region. In our experience, such deposits, particularly if they have microspheres and membrane-like inclusions in them, usually represent a nonspecific degenerative change. Uranyl acetate–lead citrate, ×25,000

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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