Postinfectious Glomerulonephritis

5

Introduction/Clinical Setting

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

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

A.B. Fogo et al., *Fundamentals of Renal Pathology*,
DOI 10.1007/978-3-642-39080-7_5, © Springer-Verlag Berlin Heidelberg 2014

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

Pathologic Findings

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

Light Microscopy

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

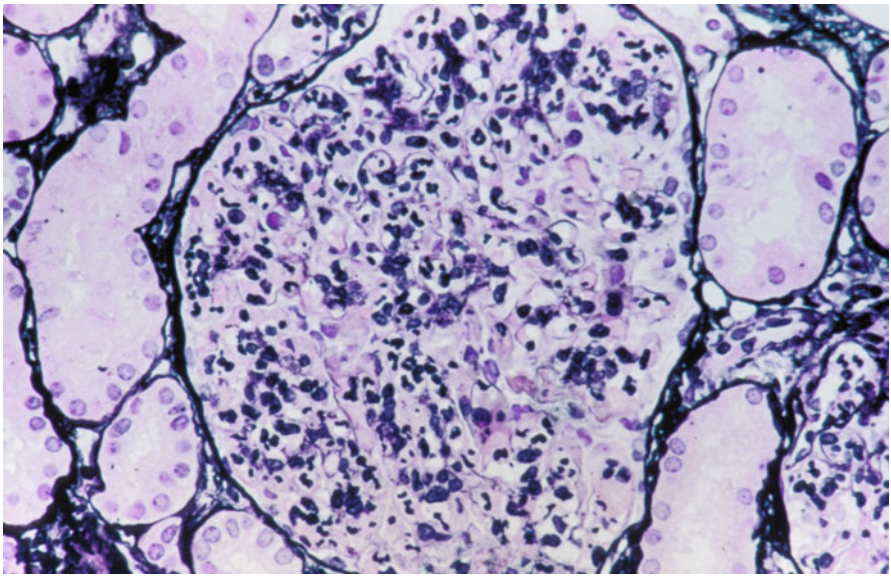

Fig. 5.1 Diffusely hypercellular glomerulus in acute postinfectious glomerulonephritis with massive influx of neutrophils (Jones silver stain)

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

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

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

Immunofluorescence Microscopy

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

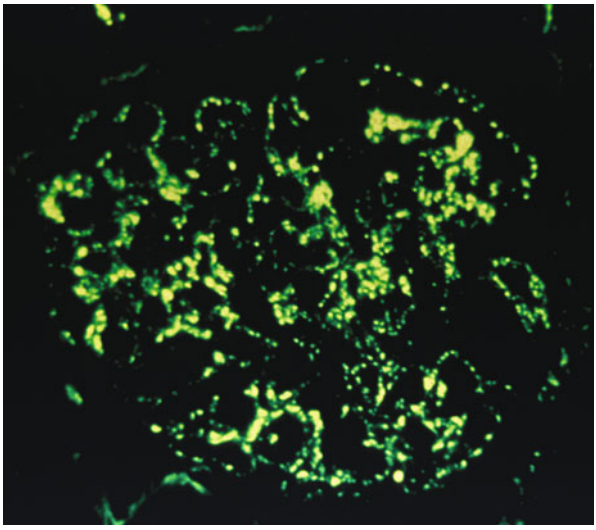

Fig.5.2 Immunofluorescence showing distribution of IgG in a "punctate" pattern in acute postinfectious glomerulonephritis

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

Electron Microscopy

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

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

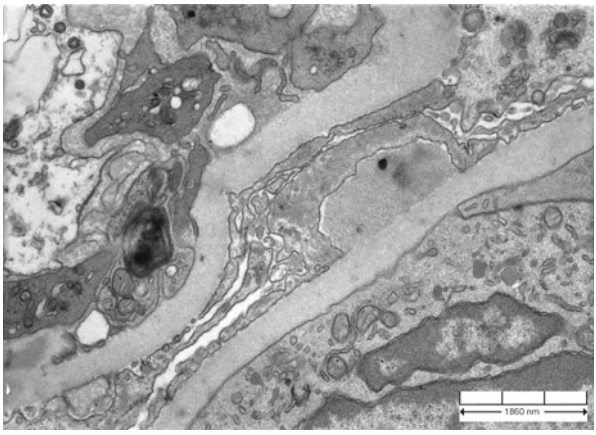

Fig. 5.3 Electron microscopy showing large subepithelial electron-dense deposits ("humps") and obliteration of overlying podocyte foot processes in acute postinfectious glomerulonephritis. Note the absence of glomerular basement membrane (GBM) thickenings and spikes

Etiology/Pathogenesis

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

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

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

Clinicopathologic Correlations

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

References

1. Couser WG (1999) Glomerulonephritis. Lancet 353:1509–1515
2. Carapetis JR, Steer AC, Mulholland EK, Weber M (2005) The global burden of group A streptococcal diseases. Lancet Infect Dis 5:685–694
3. Kanjanabuch T, Kittikowit W, Eiam-Ong S (2009) An update on acute postinfectious glomerulonephritis worldwide. Nat Rev Nephrol 5:259–269
4. Montseny JJ, Meyrier A, Kleinknecht D, Callard P (1995) The current spectrum of infectious glomerulonephritis. Experience with 76 patients and review of the literature. Medicine (Baltimore) 74:63–73
5. Nasr SH, Markowitz GS, Stokes MB, Said SM, Valeri AM, D'Agati VD (2008) Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine (Baltimore) 87:21–32
6. Nast CC (2012) Infection-related glomerulonephritis: changing demographics and outcomes. Adv Chronic Kidney Dis 19:68–75
7. Rodriguez-Iturbe B, Musser JM (2008) The current state of poststreptococcal glomerulonephritis. J Am Soc Nephrol 19:1855–1864
8. Eison TM, Ault BH, Jones DP, Chesney RW, Wyatt RJ (2011) Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol 26:165–180
9. Hricik DE, Chung-Park M, Sedor JR (1998) Glomerulonephritis. N Engl J Med 339:888–899
10. Rodriguez-Iturbe B (2000) Postinfectious glomerulonephritis. Am J Kidney Dis 35: XLVI–XLVIII
11. Rodriguez-Iturbe B, Batsford S (2007) Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int 71:1094–1104
12. Haas M (2003) Incidental healed postinfectious glomerulonephritis: a study of 1012 renal biopsy specimens examined by electron microscopy. Hum Pathol 34:3–10
13. Ruiz P, Soares MF (2003) Acute postinfectious glomerulonephritis: an immune response gone bad? Hum Pathol 34:1–2
14. Vernon KA, Goicoechea de Jorge E, Hall AE, Fremeaux-Bacchi V, Aitman TJ, Cook HT, Hangartner R, Koziell A, Pickering MC (2012) Acute presentation and persistent glomerulonephritis following streptococcal infection in a patient with heterozygous complement factor H-related protein 5 deficiency. Am J Kidney Dis 60:121–125

15. Edelstein CL, Bates WD (1992) Subtypes of acute postinfectious glomerulonephritis: a clinico-pathological correlation. Clin Nephrol 38:311–317
16. Sorger K, Gessler M, Hubner FK, Kohler H, Olbing H, Schulz W, Thoenes GH, Thoenes W (1987) Follow-up studies of three subtypes of acute postinfectious glomerulonephritis ascertained by renal biopsy. Clin Nephrol 27:111–124
17. Haas M, Racusen LC, Bagnasco SM (2008) IgA-dominant postinfectious glomerulonephritis: a report of 13 cases with common ultrastructural features. Hum Pathol 39:1309–1316
18. Nasr SH, Markowitz GS, Whelan JD, Albanese JJ, Rosen RM, Fein DA, Kim SS, D'Agati VD (2003) IgA-dominant acute poststaphylococcal glomerulonephritis complicating diabetic nephropathy. Hum Pathol 34:1235–1241
19. Ltlle JD, Seegal D, Loeb EN, Jost EL (1938) The serum anti-streptolysin titer in acute glomerulonephritis. J Clin Invest 17:631–639
20. Couser WG (2012) Basic and translational concepts of immune-mediated glomerular diseases. J Am Soc Nephrol 23:381–399