Membranoproliferative Glomerulonephritis and C3 Glomerulopathy

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Introduction/Clinical Setting

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

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

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

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

Pathologic Findings

Light Microscopy

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

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

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

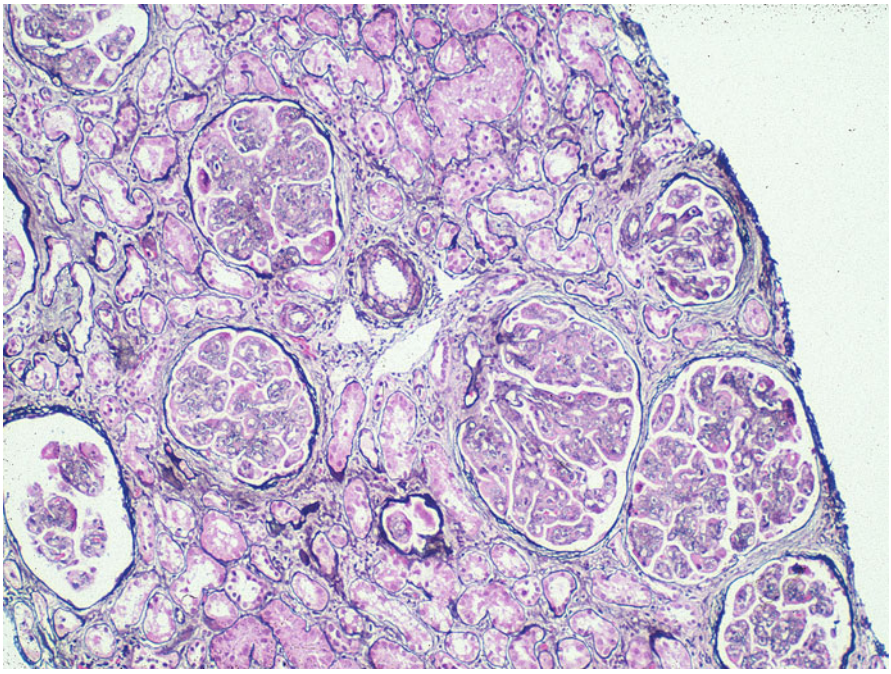

Fig. 3.1 Lobular appearance due to diffuse, global endocapillary proliferation of all glomeruli in immune complex-type membranoproliferative glomerulonephritis (MPGN) (Jones silver stain)

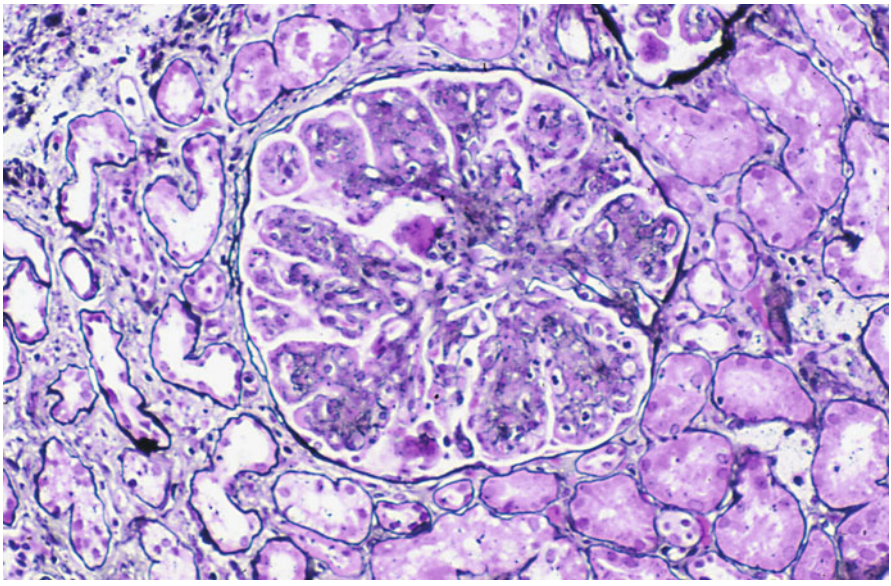

Fig. 3.2 Diffuse, global endocapillary proliferation with extensive glomerular basement membrane (GBM) double contours in immune complex-type MPGN (Jones silver stain)

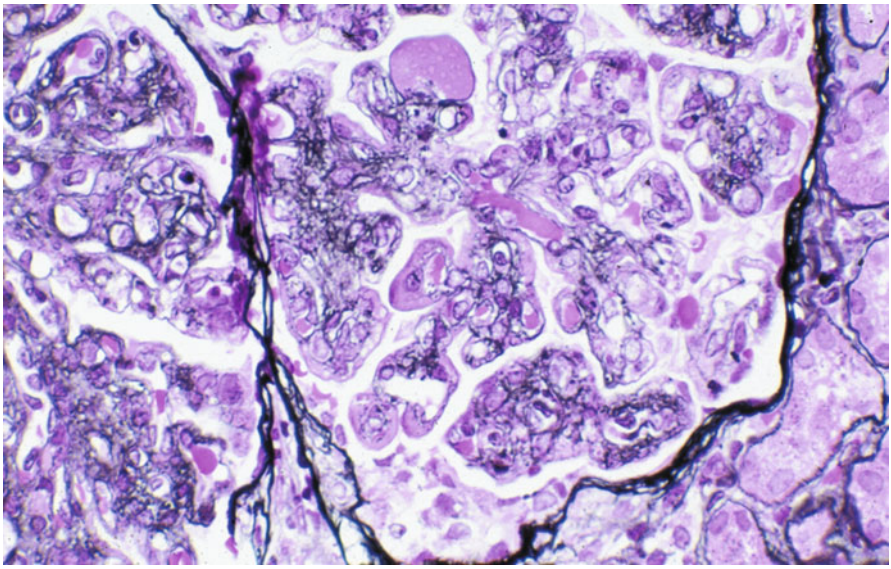

Fig. 3.3 Diffuse, global endocapillary proliferation with GBM double contours and visible large subendothelial deposits in immune complex-type MPGN (Jones silver stain)

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

Immunofluorescence Microscopy

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

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

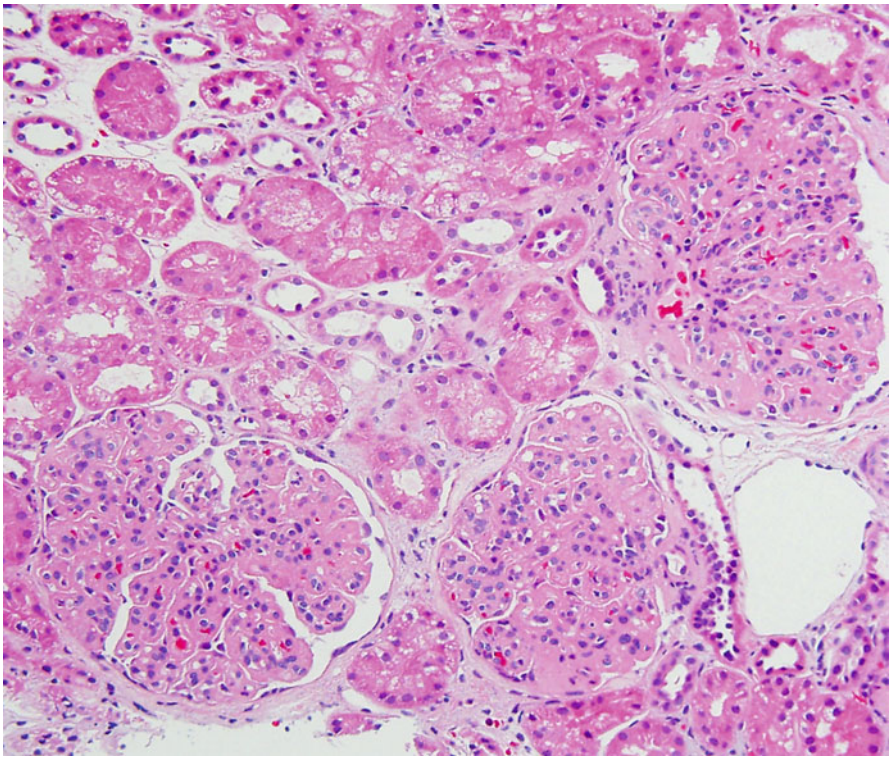

Fig. 3.4 Membranoproliferative pattern in C3 glomerulonephritis (H&E)

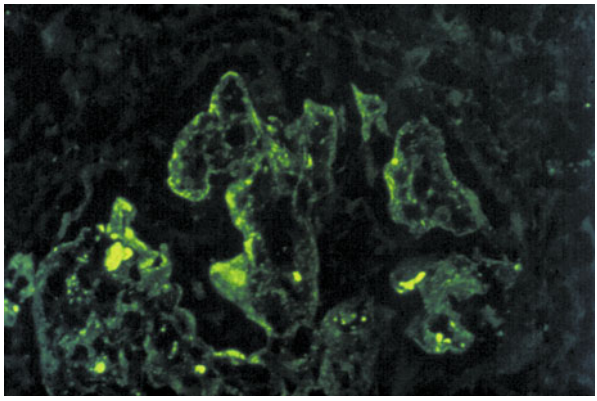

Fig. 3.5 Coarsely granular capillary loop and mesangial deposits in MPGN (anti-IgG antibody immunofluorescence)

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

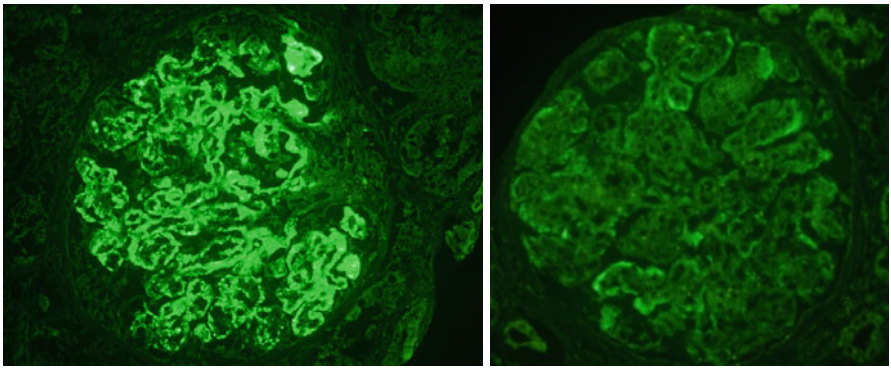

Fig. 3.6 Coarsely granular capillary loop and mesangial deposits in C3 glomerulonephritis, staining dominantly for C3 (*left*) with negligible staining for IgG (*right*) (immunofluorescence)

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

Electron Microscopy

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

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

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

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

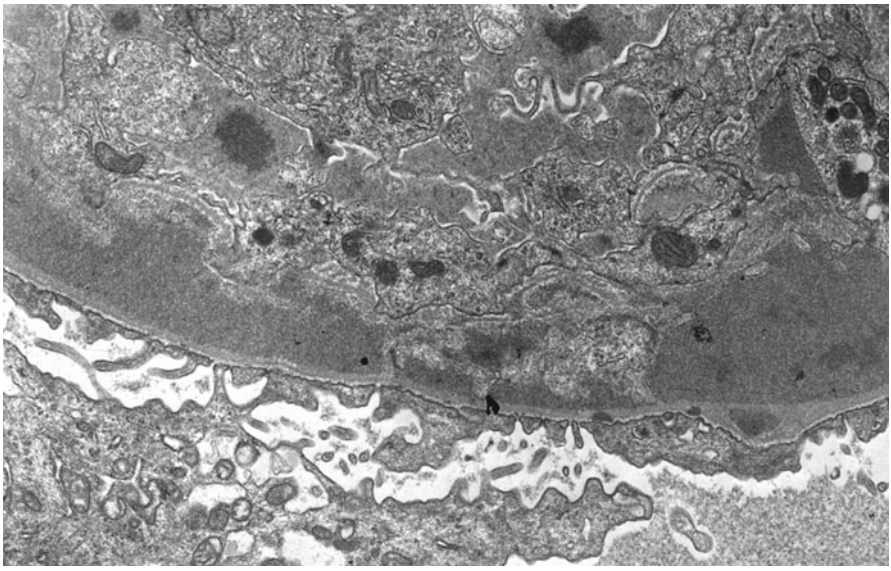

Fig. 3.7 Subendothelial immune complex deposits in immune complex-type MPGN (electron microscopy)

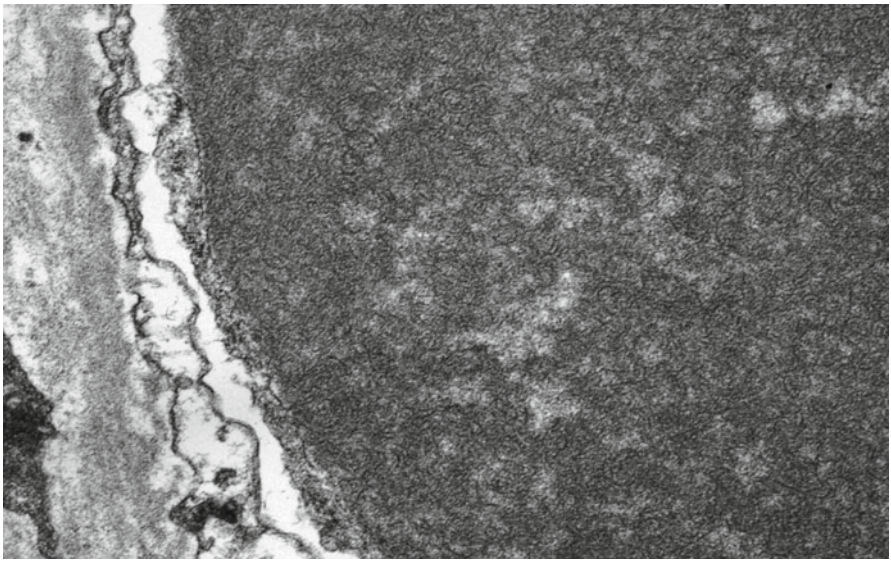

Fig. 3.8 Intracapillary deposits with vague, short fibrillary substructure, in MPGN caused by hepatitis C-associated cryoglobulin (electron microscopy)

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

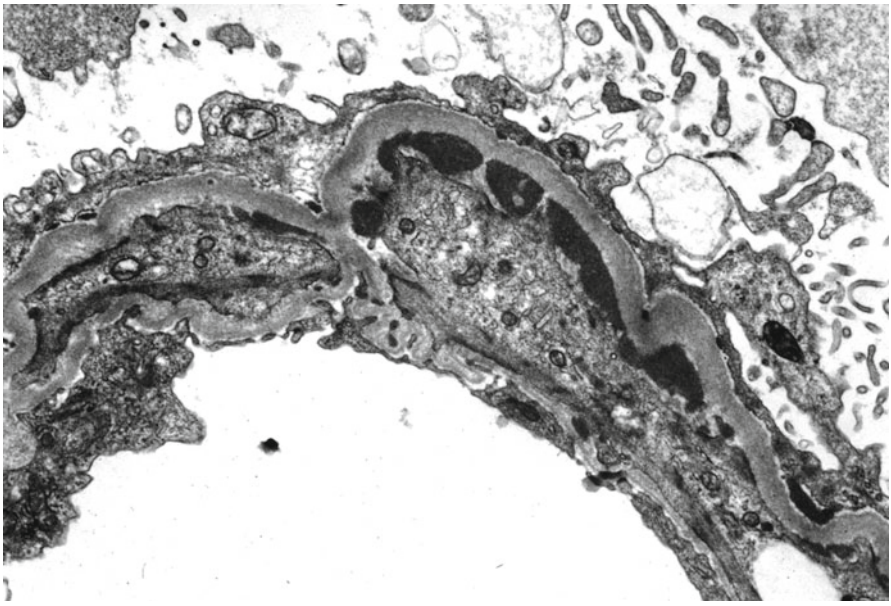

Fig. 3.9 Subendothelial deposits with underlying interposed cell (cellular interposition) and underlying new GBM formation, resulting in double contour appearance by light microscopy in MPGN (electron microscopy)

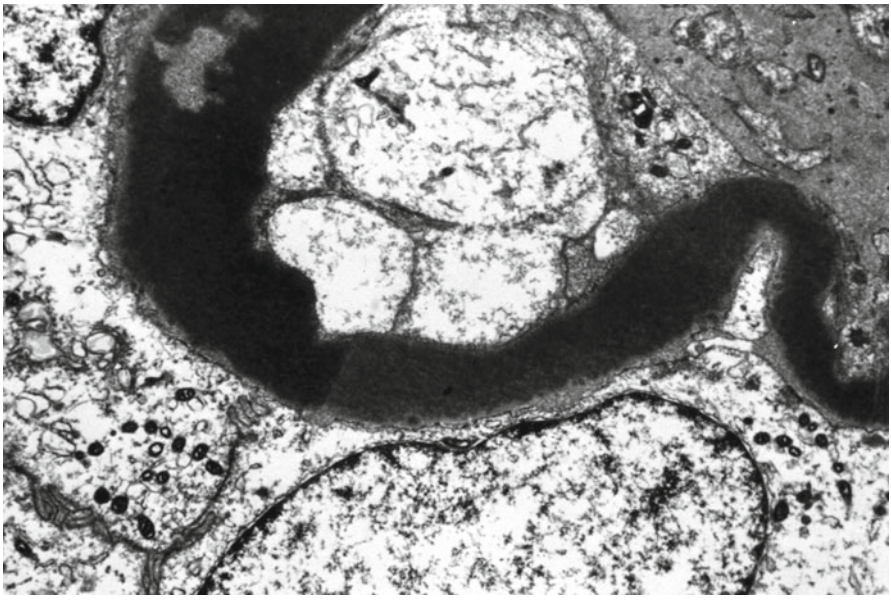

Fig. 3.10 Dense transformation of the GBM in dense deposit disease (electron microscopy)

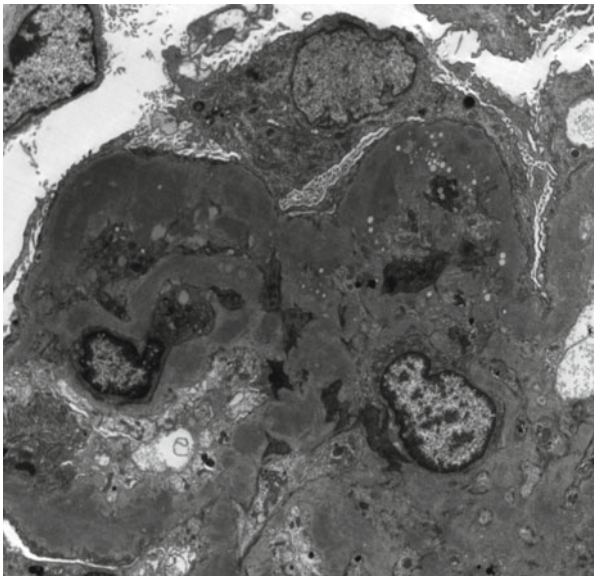

Fig. 3.11 In C3 glomerulonephritis, the deposits are typically mesangial and subendothelial/intramembranous, as in this case. Deposits often have a vague delineation from the GBM (electron microscopy)

Etiology/Pathogenesis

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

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

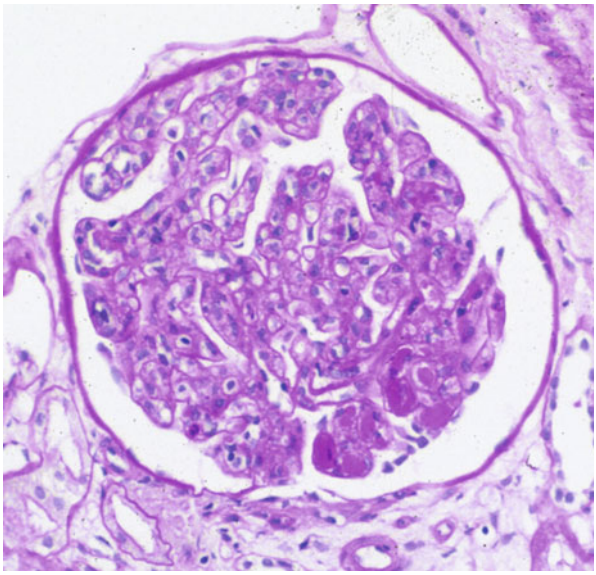

Fig. 3.12 Global endocapillary proliferation, double contours of GBM, and brightly PAS-positive so-called cryo-plugs in capillary lumina, characteristic of MPGN due to cryoglobulins (PAS)

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

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

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

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

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

Clinicopathologic Correlations

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

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

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