CHAPTER

# 50 Membranoproliferative Glomerulonephritis and Dense Deposit Disease

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Membranoproliferative glomerulonephritis (MPGN), sometimes referred to as mesangiocapillary glomerulonephritis, describes a pathologic pattern of injury characterized by thickening of peripheral capillary walls (membrano-), glomerular hypercellularity (-proliferative), with mesangial expansion leading to an accentuated lobular appearance of the glomerular tuft. Although there are idiopathic forms of this condition, the majority of cases of MPGN are associated with secondary causes—in particular, hepatitis C (Table 50.1). The various forms of MPGN have very different clinical courses and are described separately.

## CLASSIFICATION

Prior classifications of MPGN have subdivided this entity into three different classes according to pathologic characteristics (Table 1). Type I is the most common and is an immune complex mediated disorder with primarily subendothelial and mesangial immune deposits leading to activation of the classical pathway of complement. Type III was described as having a similar histologic pattern, but with the additional finding of subepithelial immune deposits or a distinctive appearance of the capillary wall deposits identified by electron microscopy. It is increasingly recognized that cases previously considered as Type III MPGN do not represent a separate disorder, but rather are best considered a variant of Type I MPGN, or more commonly, a form of the recently described entity C3 glomerulopathy. Dense deposit disease (DDD; type II) results from dysregulation of the alternate pathway of complement, and it has become clear that only a minority of cases of DDD demonstrate an MPGN pattern on biopsy. In view of these points, we prefer to classify MPGN into primary and secondary causes (Table 50.2), and we follow an emerging consensus that DDD and C3 glomerulopathy are separate entities altogether.[1]

## PRIMARY MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

### Epidemiology

Primary MPGN is a relatively rare form of glomerulonephritis in developed countries, where secondary forms of MPGN are much more common. The disease is usually found in children and young adults and, interestingly, the incidence appears to be decreasing worldwide.[2–5] This may be due to a true decrease in disease incidence, partly due to improved hygiene and environmental factors reducing the incidence of bacterial infections, but may also reflect the increased ability to detect secondary forms of MPGN (e.g., viral infections, monoclonal gammopathies). In developing countries, MPGN remains one of the most common forms of glomerulonephritis. [6–8] This classically has been considered secondary to the increased incidence of bacterial infections in these countries, but this has been questioned by Johnson et al., who found little evidence for active infection in cases of MPGN in Peru.[8] They have proposed that a shift in Th1/Th2 immune balance, induced by environmental and hygienic factors, may determine the incidence of a range of glomerular diseases worldwide.[9,10]

Primary MPGN is more common among whites than among black or Asian populations. A genetic susceptibility is supported by the finding of an extended HLA haplotype—HLA-B8, DR3, SCO1, GLO2—more frequently in patients with MPGN I and III (13%) than in the general Caucasian population (1%), although this haplotype is not specific for MPGN.[11] Familial forms of MPGN have been described, but these are rare.[12] Some of these may be secondary to mutations encoding complement proteins or their inhibitors (discussed below).

### Pathogenesis

Primary MPGN is considered to be an adaptive immune response to a chronic antigenic stimulus leading either to the subendothelial and mesangial deposition of circulating immune complexes consisting of immunoglobulin G (IgG), C3, and antigen, or deposition of circulating antigens in the glomerular capillary walls (planted antigens) which then serve as a nidus for immune complex formation in situ. In secondary forms of MPGN a wide range of antigens (primarily infectious agents) have been implicated, but in primary MPGN the causative antigen remains unknown. The binding of the Fc portion of IgG or IgM in the immune complexes

## 50.1 Former Classification of Membranoproliferative Glomerulonephritis

| Classification | Pathologic Characteristics |
|---|---|
| Type I | Enlarged, lobulated glomerulus, mesangial hypercellularity<br>Influx of mononuclear leukocytes<br>Duplication of GBM with cellular interposition<br>IgG, C1q, C3 deposition in mesangium and capillary wall<br>Mesangial and subendothelial immune deposits |
| Type II (dense deposit disease) | Variable pattern on light microscopy<br>C3 deposition in absence of IgG or C1q<br>Ribbonlike dense deposits within GBM on electron microscopy |
| Type III | Histologic and immunofluorescence features similar to type I MPGN<br>Additional subepithelial deposits with thickened irregular GBM |

GBM, glomerular basement membranes; IgG, immunoglobulin G; MPGN, membranoproliferative glomerulonephritis.

## 50.2 Current Classification of Membranoproliferative Glomerulonephritis

| Classification | Associated Disorders |
|---|---|
| **Primary MPGN** | None |
| **Secondary MPGN** | |
| Infectious Disease | Viral: hepatitis C, hepatitis B, HIV<br>Bacterial: shunt nephritis, visceral abscess, endocarditis<br>Protozoan: quartan malaria, schistosomiasis, leprosy |
| Autoimmune Disease | Systemic lupus erythematosus, mixed cryoglobulinemia, scleroderma, Sjögren syndrome, hypocomplementemic urticarial vasculitis |
| Monoclonal Gammopathy | Monoclonal gammopathy of uncertain significance (MGUS), multiple myeloma, B cell lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia |
| Chronic Liver Disease | Chronic hepatitis, cirrhosis, α1-antitrypsin deficiency |
| Miscellaneous | Solid organ tumors; cystic fibrosis, sarcoidosis, sickle cell disease, hemolytic uremic syndrome, transplant glomerulopathy, drugs (heroin, α-interferon) |
| **C3 Glomerulopathy** | |
| Dense Deposit Disease (formerly type II MPGN) | Dysregulation of the alternate pathway of complement<br>■ C3 nephritic factor (partial lipodystrophy, retinal drusen)<br>■ Antifactor B autoantibody<br>■ Factor H dysfunction (inherited and acquired) |
| C3 Glomerulonephritis | Dysregulation of the alternate pathway of complement<br>■ C3 nephritic factor<br>■ Mutations in complement regulatory proteins (factor H, factor I, membrane cofactor protein) |

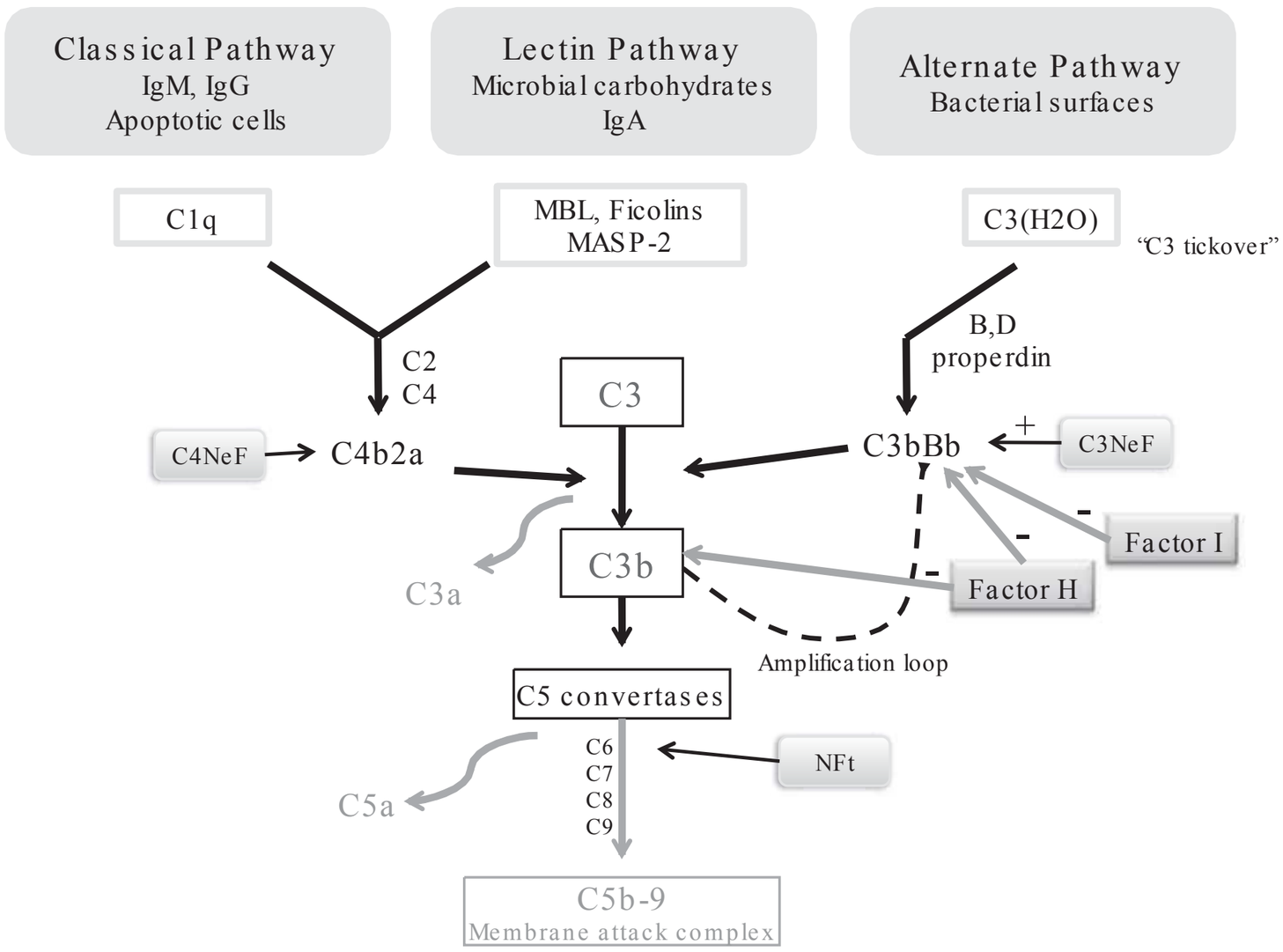



**FIGURE 50.1** Complement pathways. Complement may be activated by one of three pathways. In MPGN type 1, the Fc portion of IgG or IgM in immune complexes binds C1q and activates the classical pathway, cleaving C3 to C3b. This process may be amplified by the alternate pathway (amplification loop). Cleavage fragment C3a acts as an anaphylatoxin, C3b binds to surfaces as an opsonin and further promotes the generation of the C5 convertases. These cleave C5 to form C5a (chemotactic factor), and lead to the formation of the membrane attack complex (C5b-9). In dense deposit disease, the usual low level activation (tickover) of the alternate pathway, which generates small amounts of C3 convertase (C3bBb), is dysregulated (either by C3 nephritic factor [C3NeF] or failure of factor H regulation) leading to a more profound activation of the alternate pathway and the generation of large amounts of C3b. Factor H is the major regulator of the alternate pathway. *MBL*, mannose binding lectin; *C4NeF*, C4 nephritic factor; *NFt*, nephritic factor of the terminal pathway; *C4b2a*, C3 convertase of classical pathway; *C3bBb*, C3 convertase of alternate pathway.

to C1q triggers activation of the complement via the classical pathway, but this initial activation may be amplified by the alternate pathway (amplification loop). The subsequent cleavage of C5 leads to the production of chemotactic factors (C5a), opsonins (C3b), and the membrane attack complex (C5b-9) (Fig. 50.1). In some cases, complement activation is enhanced by nephritic factors that stabilize either the classical pathway C3 convertase (C4 nephritic factor, C4NeF) or the alternate pathway C3 convertase (C3 nephritic factor, C3NeF) which may enhance the amplification loop.[13,14]

It is likely that the prominent monocyte influx that characterizes MPGN is the result of complex interactions including Fc portions of immunoglobulins within deposited immune complexes engaging Fc receptors on the surface of monocytes, as well as release of chemoattractant cytokines (e.g., colony stimulating factor 1 [CSF-1]) and other proinflammatory mediators by resident glomerular cells as a response to injury.[15,16] It is unknown whether the monocytes infiltrating human glomerulonephritis (GN) have a homogeneous phenotype, and are proinflammatory, or whether some or even a majority of these cells infiltrating at different time points of the disease course may be engaged in activities primarily directed to opsonization and phagocytosis of immune complexes, stabilization of disease, and repair of glomerular injury. Recent studies suggest systemic and local innate immune responses may also contribute to the pathogenesis of MPGN. For example, studies have demonstrated toll-like receptor 3 in human MPGN associated with viral infection,[17] and upregulated expression of toll-like receptor 4 on glomerular cells has been identified in an animal model of cryoglobulinemic MPGN,[18] but more specific immune mechanisms leading to glomerulonephritis have not been established.

Following an initial proliferative phase, a second reparative phase develops, which is characterized by the development of mesangial expansion and the formation of new basement membrane matrices resulting in double contours. These duplicated basement membrane matrices lead to the sequestering of immune complexes and entrapment of cells or cell processes between the matrices (cellular interposition) and presumably this sequestration reduces the stimulation for an acute inflammatory response by circulating leukocytes.

## PATHOLOGY

The overall appearance of both primary and secondary types of MPGN often reveals enlarged glomeruli with accentuation of the normal lobular architecture (Fig. 50.2). Hypercellularity is mostly due to a combination of mesangial cell proliferation and infiltrating leukocytes. The mesangium is

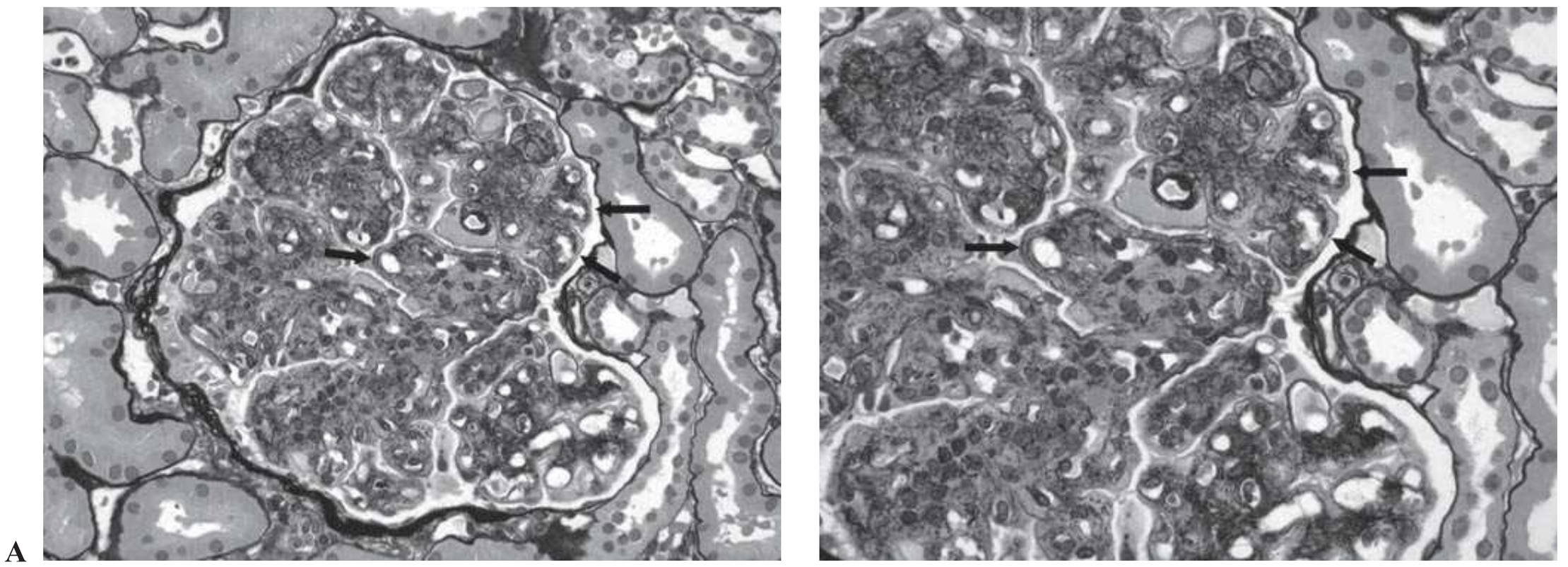



**FIGURE 50.2** Membranoproliferative glomerulonephritis. **A:** Light microscopy showing prominent mesangial expansion due to increased cellularity and accumulation of extracellular eosinophilic material, diffuse thickening of glomerular basement membranes with segmental splitting (*arrows*), and influx of leukocytes (endocapillary proliferation). Jones' silver methenamine stain. **B:** Higher power view of this glomerulus shows the mesangial cell proliferation, the irregular thickening and focal splitting/duplication of basement membranes (*arrows*), and accumulation of acellular eosinophilic material, most likely deposits of immune complexes, in capillary walls and some mesangial regions. Jones' silver methenamine stain.

prominently expanded, both by increased matrix as well as increased cellularity, which may reduce the number of open capillary loops. PAS or methenamine silver stains of histologic sections may show a characteristic feature of duplication (sometimes referred to as splitting) of the glomerular basement membranes (GBM) due to the synthesis of new basement membrane material, with interposition of cells (mesangial, endothelial, or leukocyte) between the duplicated basement membrane matrices.

Immunofluorescence typically shows the presence of IgG and C3 in a peripheral capillary wall distribution (Fig. 50.3). C1q and C4 are also commonly present in keeping with activation by the classical pathway. IgM is not prominent in primary MPGN and, if present, may suggest the presence of a secondary form of MPGN (e.g., hepatitis C). Glomerulonephritis with an MPGN pattern but in which deposition of immune reactants is limited to C3 has traditionally been considered part of the spectrum of MPGN I or

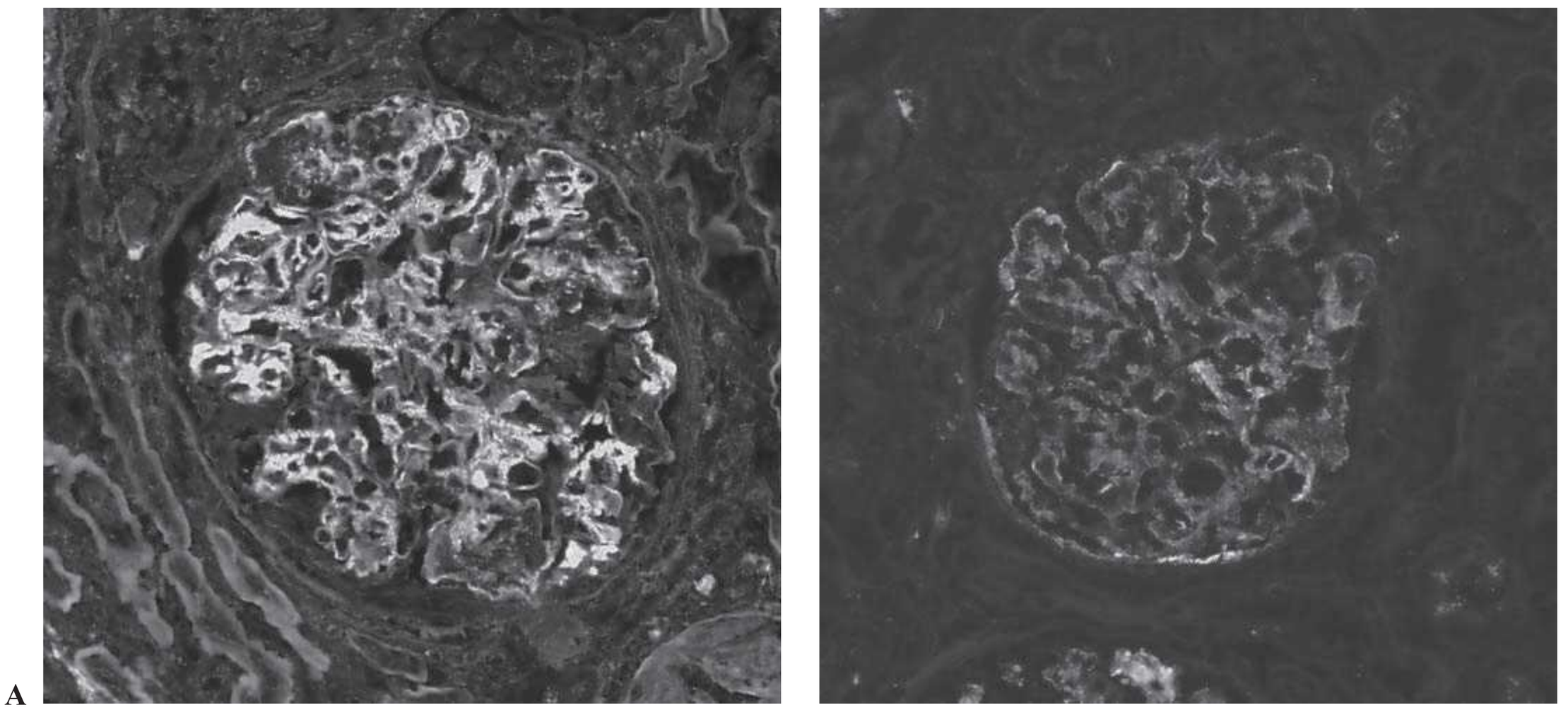



**FIGURE 50.3** Membranoproliferative glomerulonephritis type I with characteristic deposition of **(A)** IgG and **(B)** C3 primarily involving peripheral capillary walls, with a granular pattern. Mesangial deposits are also present.

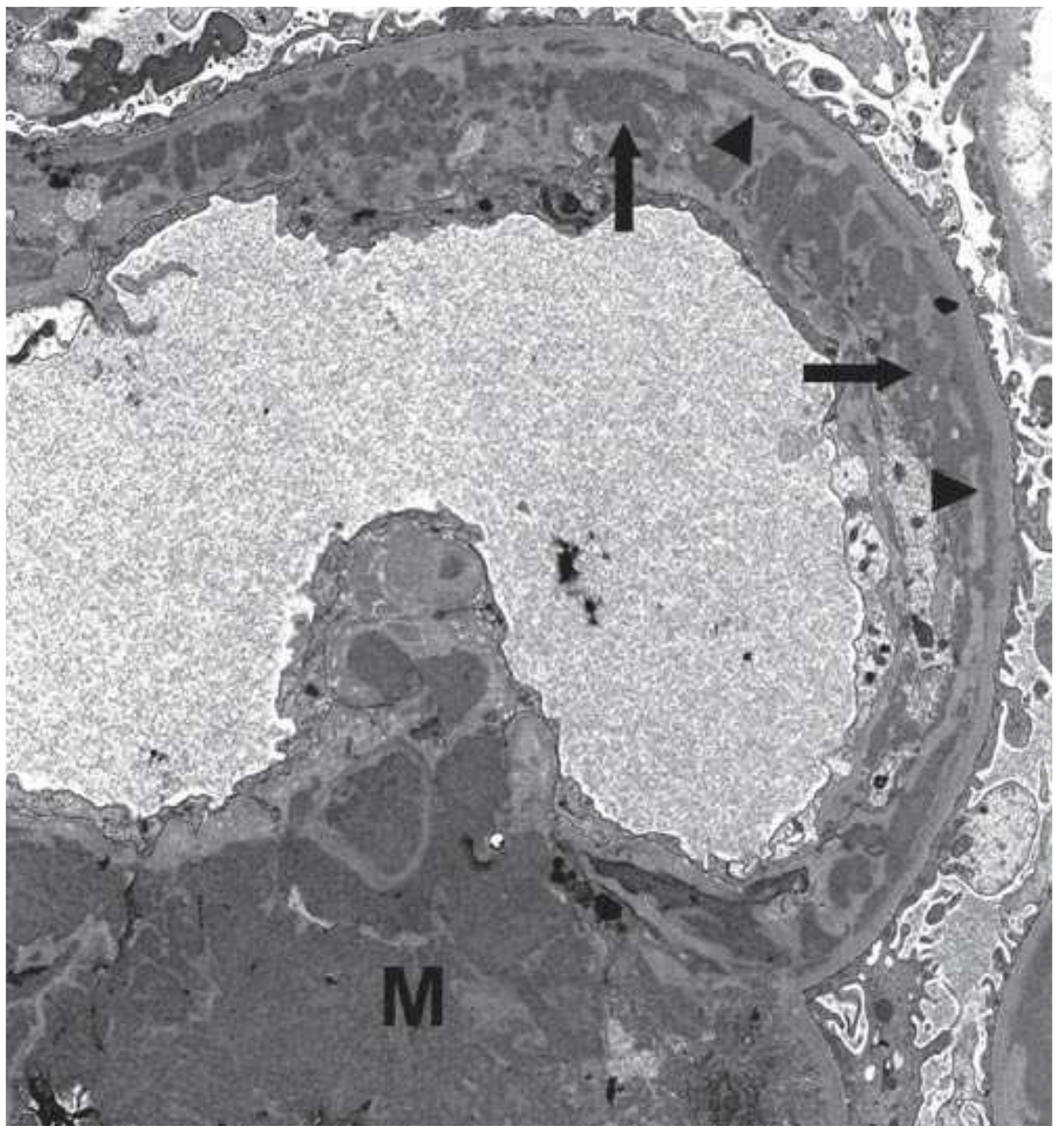



**FIGURE 50.4** Membranoproliferative glomerulonephritis type I with characteristic discrete electron-dense immune complex deposits along the subendothelial aspect (*arrowheads*) of the original glomerular basement membrane and between duplicated basement membranes (*arrows*). Large, confluent electron-dense deposits are also identified within mesangial regions (*M*).

the former MPGN II. Recent data has suggested that many, if not all, of these cases can now be classified as DDD or manifestations of a distinct group of disorders tentatively termed C3 glomerulopathy (see later).[19]

On electron microscopy, subendothelial and mesangial deposits are typically present (Fig. 50.4). Subepithelial deposits may be present, but are usually scanty. Prominent subepithelial deposits are found in some patients, and some authors advocate a separate classification for this entity, MPGN type III, as described later.

It is usually impossible to differentiate secondary forms of MPGN from the primary disease, but suggestive features from common forms are described in Table 50.3. It should also be recognized that other clinical disorders may present with an MPGN pattern on renal biopsy. We have mentioned DDD, but other imitators may include thrombotic microangiopathy and other rare diseases (Table 50.4).

## Clinical Features (Presentation and Clinical Manifestations)

Type 1 MPGN often presents in childhood or early teens with edema and nephrotic syndrome, and is often associated with hematuria and an active urine sediment (dysmorphic red cells and red cell casts). Constitutional symptoms including lassitude, fatigue, and weight loss may be present.

**50.3 Pathologic Features Suggestive of Underlying Secondary Disorders**

| | |
|---|---|
| Hepatitis C | Prominent IgM deposition<br>Intracapillary eosinophilic globules (hyaline thrombi)<br>Fibrillary or microtubular substructure to deposits (cryoglobulinemia) |
| Systemic lupus erythematosus | Hyaline thrombi or "wire loops" by histology<br>C1q deposition and full house immunofluorescence<br>Tubuloreticular structures |
| Monoclonal lympho-plasmacytic disorders | Heavy or light chain restriction of deposited immune reactants |

**50.4 Disorders That Can Mimic MPGN on Renal Biopsy**

| | |
|---|---|
| Monoclonal lympho-plasmacytic disorders | Light chain deposition disease, immunotactoid glomerulonephritis, type 1 cryoglobulinemia; proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) |
| Thrombotic microangiopathy | See Chapter 55 |
| Fibrillary glomerulonephritis and immunotactoid glomerulopathy | |
| Rare diseases | Collagen III glomerulopathy, fibronectin glomerulopathy, LCAT deficiency nephropathy |
| Transplant glomerulopathy | |

LCAT, lecithin-cholesterol acyltransferase

A range of other modes of presentation may be found ranging from asymptomatic microhematuria or proteinuria on screening to an acute nephritic syndrome with gross hematuria, renal impairment, and hypertension. This is often initially diagnosed as a postinfectious glomerulonephritis, but the persistent hypocomplementemia and failure to resolve usually prompt a renal biopsy, if not already performed. In children the course is often slowly progressive, with 20% to 60% of treated patients progressing to end-stage renal disease (ESRD) over 10 to 15 years.[20–23] Risk factors for progression include the presence of nephrotic syndrome and a raised serum creatinine at presentation.

In adults, primary MPGN typically presents with an overlap between nephrotic and nephritic syndrome. Nephrotic range proteinuria is common, as are microhematuria, renal impairment, and hypertension, which may be prominent. The course is variable, but in the absence of a secondary cause, a progressive course is common.

## Laboratory Findings

A major clinical clue to the diagnosis of MPGN is the presence of hypocomplementemia, due to activation of the classical pathway (Table 50.5). CH50, C3, and C4 are all depressed and may be persistent. C3 nephritic factor (C3NeF), an autoantibody stabilizing the C3 convertase of the alternate pathway, may occasionally be found (see dense deposit disease section).[13,14] C4 nephritic factor (C4NeF), an autoantibody stabilizing the classical pathway C3 convertase or a nephritic factor of the terminal pathway (Nft), have also been described,[24] occurring in ~20% of cases, either alone or with C3NeF.

**50.5 Causes of Hypocomplementemia in Kidney Disease**[a]

| Classical Pathway (↓C3, ↓C4) | Alternate Pathway (↓C3, ↔ C4) |
|---|---|
| Lupus nephritis | Postinfectious glomerulonephritis |
| Membranoproliferative glomerulonephritis (MPGN types I and III) | Dense deposit disease (C3 glomerulopathy) |
| Cryoglobulinemia (MPGN) | Hemolytic uremic syndrome |
| Endocarditis (MPGN) | |
| Shunt nephritis/ abscess (MPGN) | |

[a]Low C3 levels may also be seen in atheroembolism, liver disease, sepsis, and, rarely, heavy chain disease, rheumatoid vasculitis.

## Treatment

The initial key to management is to rule out secondary causes with appropriate investigations. These may include screening for infections (e.g., hepatitis C, hepatitis B, endocarditis), autoimmune diseases (e.g., antinuclear antibody), monoclonal gammopathies (serum free light chains, serum protein electrophoresis), and complement disorders (e.g., nephritic factors).

Nonimmunosuppressive therapy is similar to that used in other forms of proteinuric kidney disease (see Chapter 75). Achieving excellent blood pressure control and renin angiotensin aldosterone system (RAAS) blockade with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers is the cornerstone of therapy. Supplemental therapies may include vitamin D supplementation, HMG-CoA synthetase inhibitors (statins), and aspirin. As with most glomerular disease there is an increased risk of cardiovascular disease.

### Immunosuppressive Therapy

The role of immunosuppression is predicated on the accurate exclusion of secondary causes. The majority of evidence in children (mostly retrospective cohort studies) supports the use of an alternate day steroid regimen for prolonged periods of time. One report from the Cincinnati group, using prednisone 2 mg per kg alternate days for a minimum of 2 years, showed an 80% 10-year renal survival.[21] An early randomized controlled trial compared prolonged oral prednisone (40 mg per $m^2$) with placebo in 80 children with MPGN (a variety of subtypes), with a mean follow-up of 5.25 years. [25] Treatment failure was defined as an increase in serum creatinine >30% over baseline, or by 0.4 mg per dL, and was found in 33% of the prednisone group versus 58% of the placebo group. Adults with nephrotic syndrome or renal impairment are also typically treated with a 3- to 6-month course of steroids (prednisone 1 mg/kg/day). Notably, patients with subnephrotic proteinuria have a much better prognosis and may be treated more conservatively.[26]

The role of other immunosuppressive agents is less clear and, given the rarity of this condition, there is limited evidence to support their use. Two controlled prospective trials showed no benefit with dypiridamole[27] or combination cyclophosphamide, warfarin, and dypiridamole.[28] There are small series reporting beneficial results in steroid resistant disease with cyclosporine[29] or tacrolimus,[30] and with mycophenolate. [31] Rituximab may be considered, especially in the presence of a nephritic factor.[32]

Following kidney transplantation, idiopathic type 1 MPGN recurs in 20% to 30% of patients, and leads to graft loss in approximately 50% of these, although this historic data does not take into account the effect of separating cases of typical MPGN from those with C3 deposits only.[33]

## MPGN TYPE III

MPGN Type III was originally described by Burkholder et al. in the 1970's as a separate entity with pathological features that overlap between membranous nephropathy and a proliferative glomerulonephritis.[34] It was characterized by the presence of epimembranous "spikes" of silver staining projections of matrix from the glomerular basement membranes, in addition to the usual features of MPGN, absent C1q and C4 deposition on immunofluorescence, and by the presence of prominent sub-epithelial immune deposits with thickening and irregularity of the GBM on electron microscopy (Figure 5). A second pattern of injury was described by the groups of Strife[35] and Anders[36], with histologic features of MPGN characterized ultrastructurally by permeation of an irregularly thickened glomerular basement membrane by electron dense deposits that are frequently poorly demarcated from the glomerular basement membrane, but are less electron dense than the deposits encountered in MPGN type I or dense deposit disease, and frequently contain areas of electron lucency. The clinical presentation of MPGN III is similar to MPGN type I, but patients tend to be older, with a more insidious presentation and hypertension is less common. Low C3 levels are typically found (~85%), but C4 is usually normal in keeping with activation of the alternate pathway.

It is now generally considered that MPGN III is not a separate class of MPGN, and modern classifications, as recently proposed by Sethi et al.[1], omit the use of this term (Figure 6). When immune complexes containing immunoglobulins are present, there is no compelling reason to consider MPGN III as a separate entity from MPGN I, as a distinct clinical course or outcome has not been defined, and pathologic features overlap with MPGN I. When only deposits of C3 are detected by immunofluorescence, a pattern present in most of the cases of Strife and Anders type, these cases fall into the broadly defined category of C3 glomerulopathy.

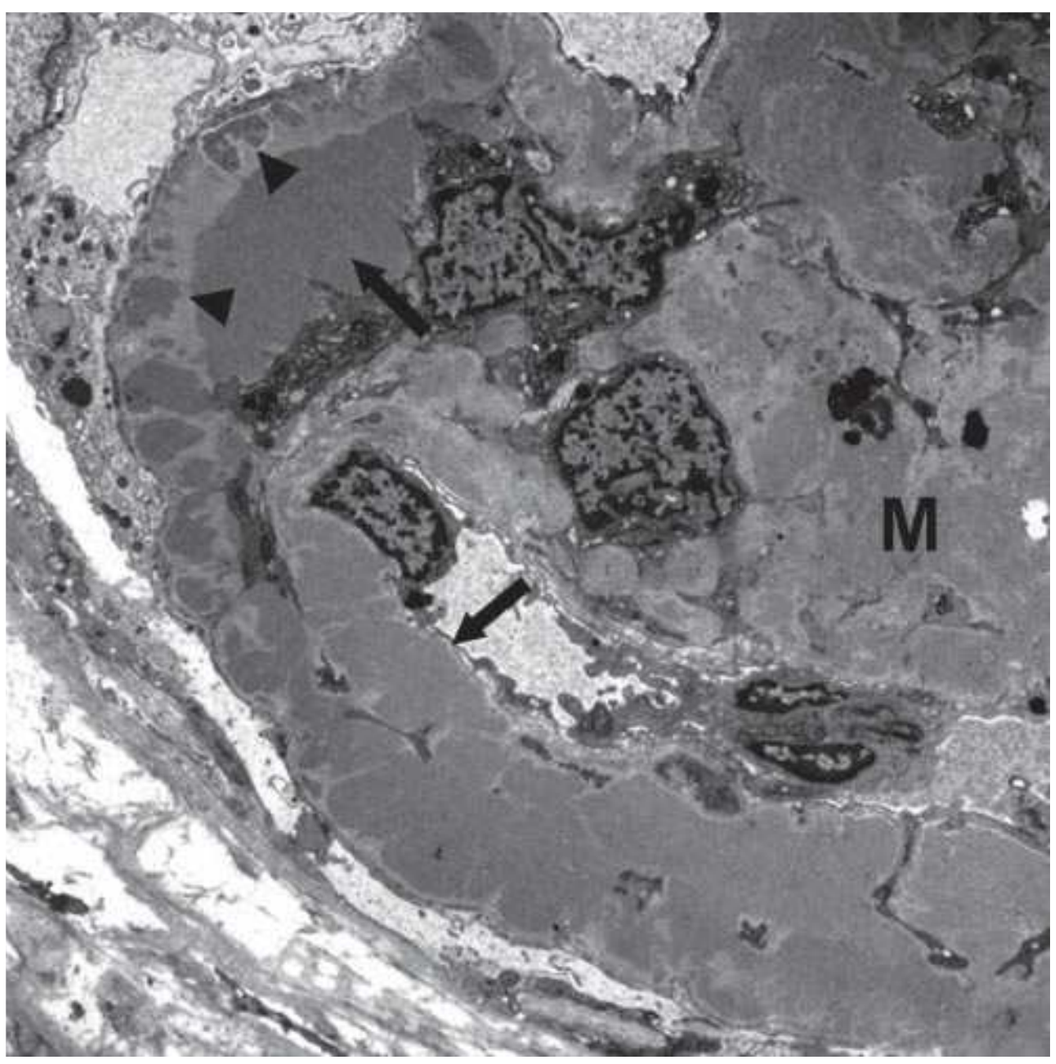



**FIGURE 50.5** Membranoproliferative glomerulonephritis type III (Burkholder), now considered to be a variant of membranoproliferative glomerulonephritis, type I. There are thickened peripheral capillary walls showing massive electron dense deposits in subendothelial (*arrows*), intramembranous, and subepithelial locations (*arrowheads*). Similar deposits are also present in mesangial regions (*M*). There is extensive effacement of foot processes.

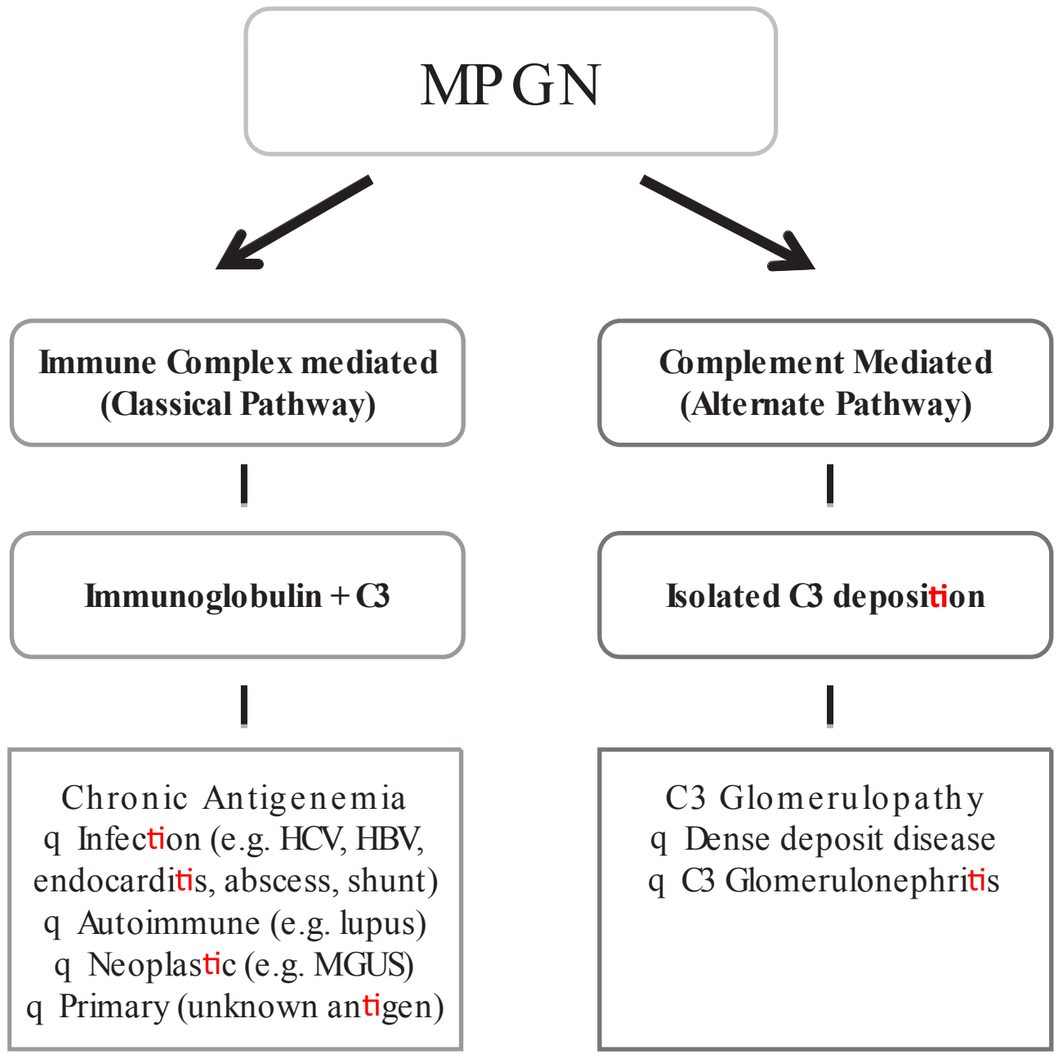



**FIGURE 50.6** Pathophysiological classification of MPGN. MPGN may be subdivided into immune complex mediated and complement mediated pathways. Immune complexes derived from a chronic antigenic stimulus activate the classical pathway and are characterized by the glomerular deposition of both immunoglobulin and C3 seen by immunofluorescence microscopy. The finding of isolated C3 deposition by immunofluorescence, in the absence of immunoglobulin, suggests a form of C3 glomerulopathy due to dysregulated activation of the alternate pathway.

## HEPATITIS C-ASSOCIATED MPGN

Hepatitis C virus (HCV) is a single-stranded RNA virus estimated to infect 170 million people worldwide. It is transmitted primarily by transfusion of blood products and intravenous drug use. Chronic infection occurs in 85% to 90% of exposed individuals and may progress to chronic active hepatitis, liver cirrhosis, and hepatocellular carcinoma. The association of HCV with cryoglobulinemic MPGN was first reported in 1993,[37] but a range of other renal diseases have also been reported with HCV infection (Table 50.6).

### Cryoglobulinemic MPGN

Cryoglobulinemia refers to the presence of serum immunoglobulins that reversibly precipitate when cooled to 4°C,

## 50.6 Renal Manifestations of Hepatitis C Infection

| Renal Compartment | Mechanism | Clinical Disorder |
|---|---|---|
| Glomerular disease | Secondary to cryoglobulinemia | Membranoproliferative glomerulonephritis (type I and III)<br>Immunotactoid glomerulopathy<br>Fibrillary glomerulonephritis<br>Crescentic necrotizing glomerulonephritis<br>Amyloidosis |
| | Not associated with cryoglobulinemia | Membranoproliferative glomerulonephritis<br>Mesangial-proliferative glomerulonephritis<br>Membranous nephropathy<br>Focal segmental glomerulosclerosis |
| Tubulointerstitial | Unknown | Hepatitis C-associated interstitial nephritis |
| Vascular | Secondary to cryoglobulinemia | Cryoglobulinemic vasculitis |

and is classified according to the composition of the circulating cryoglobulins (Table 50.7). Type I cryoglobulins are composed of monoclonal immunoglobulins secondary to B cell disorders such as Waldenström macroglobulinemia or multiple myeloma. Type II and type III are mixed cryoglobulins consisting of polyclonal IgG complexed to another immunoglobulin which acts as an antiglobulin (anti-IgG rheumatoid factor [RF]). In type II this antiglobulin (usually IgM) is monoclonal, whereas in type III it is polyclonal. Evidence of HCV infection has been found in up to 95% of cases of type II cryoglobulinemia and 50% of type III cryoglobulinemia in some series.[38,39] The circulating cryoglobulins are typically composed of HCV antigen and anti-HCV antibody complexed to an IgM with rheumatoid factor activity. HCV RNA is found to be concentrated 10 to 100 times in the cryoprecipitate.[37,40]

The exact pathogenesis of the rheumatoid factor generation in HCV infected patients is still unknown, but may relate to B cell dysregulation following HCV infection. The E2 envelope protein of HCV has been shown to bind

## 50.7 Brouet Classification of Cryoglobulinemia[118]

| Type | Composition | Associated Disorders |
|---|---|---|
| I | Monoclonal IgG, IgM, or IgA | Monoclonal gammopathy of uncertain significance, multiple myeloma, B cell lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia |
| II | Polyclonal IgG with monoclonal IgM (positive rheumatoid factor) | Hepatitis C (~95% of cases); rarely hepatitis B, Epstein-Barr virus<br>Lymphoproliferative disorders (especially B cell lymphoma)<br>Essential mixed cryoglobulinemia<br>Autoimmune disease (Sjögren syndrome, systemic lupus erythematosus) |
| III | Polyclonal IgG with polyclonal IgM | Infection: viral (hepatitis C [~50% of cases], hepatitis B, Epstein-Barr virus, HIV, cytomegalovirus); bacterial (endocarditis, poststreptococcal infection; leprosy); parasitic (schistosomiasis, toxoplasmosis, malaria)<br>Autoimmune disease: systemic lupus erythematosus; rheumatoid arthritis<br>Lymphoproliferative disorders<br>Chronic liver disease<br>Essential |

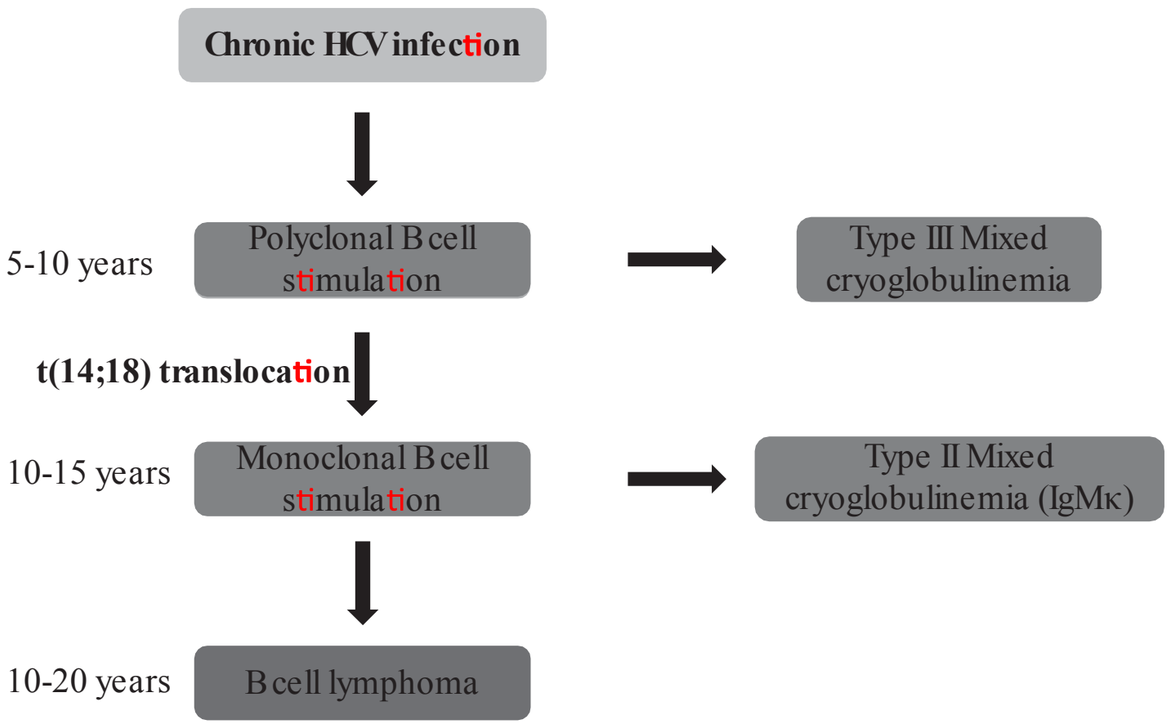



**FIGURE 50.7** Hepatitis C-associated cryoglobulinemia. Binding of hepatitis C viral antigens to B cells leads to polyclonal proliferation and activation, with the development of a type II mixed cryoglobulinemia. Further clonal selection may generate a monoclonial type II mixed cryoglobulinemia, and long-term is a risk of developing B cell lymphoma. The figure depicts a postulated sequence but does not imply that a type III cryoglobulinemia always precedes type II cryoglobulinemia.

directly to B lymphocytes via CD-81 receptors leading to activation and proliferation.[41] A range of autoantibodies are commonly found with HCV infection with an increased incidence of autoimmune diseases such as thyroid disease, diabetes, and Sjögren syndrome. It is likely that earlier in the course of HCV infection, B cell stimulation produces polyclonal IgM leading to a type III cryoglobulinemia. Over time, a B cell clone emerges, due to the acquisition of somatic genetic alterations which enhance B cell survival, leading to a monoclonal IgM antiglobulin and type II cryoglobulinemia (Fig. 50.7). Notably, a t(14;18) translocation, which may lead to overexpression of the antiapoptotic gene bcl-2, has been described in 80% of patients with HCV and cryoglobulinemia, but is rare (<10%) in HCV patients without circulating cryoglobulins.[42]

The association of HCV with cryoglobulinemic MPGN is clear, although there remains debate over the role of HCV in noncryoglobulinemic MPGN.[43,44] Johnson et al. described 14 of 34 patients with MPGN and HCV infection that had no detectable cryoglobulins at presentation and, although many developed cryoglobulin positivity during follow-up, five remained persistently negative.[45] It is recognized that circulating cryoglobulins can be difficult to detect, and cryoglobulinemia may be missed. The clinical features and course appear to be identical to the cryoglobulinemic group.

## Pathogenesis

Although there may be direct cytopathic effects of the virus on renal cells, the kidney disease is primarily felt to be a result of the host's adaptive immune response to viral infection. Circulating cryoglobulins may deposit in the glomerular capillaries and in the mesangial matrix, possibly due to the high affinity of the IgMκ constituent for fibronectin.[46] Viral RNA has been detected in glomerular tissue by in situ hybridization, and amplified from laser microdissected nephrons.[47] Some investigators[48,49] have been able to demonstrate the presence of HCV antigens in renal tissue using either immunohistochemistry or immunoelectron microscopy, but this has been difficult to replicate due in part to limitations of the detection methodology. The immune deposits likely consist of HCV antigen and anti-HCV antibody. Notably, in cryoglobulinemic MPGN, IgM is the predominant immunoglobulin, whereas in noncryoglobulinemic disease, IgG1 and IgG3 deposits are more commonly seen.[50] Cryoglobulinemia develops late in the course of HCV infection, often occurring years to decades after initial infection. The events that trigger the late development of cryoglobulinemia are unknown, as are the factors that cause only a small subset of HCV infected patients with evidence of cryoglobulinemia to develop MPGN or other HCV-associated glomerulopathies. Even the physiochemical properties that cause cryoglobulins to precipitate in the cold remain obscure.

## Pathology

Histology reveals a pattern resembling type I MPGN; however, there are often more intense macrophage infiltrates and occasionally extensive hyaline thrombi (representing subendothelial and intraluminal cryoglobulinemic immune deposits) are found in glomerular capillary lumina (Fig. 50.8). A necrotizing vasculitis of small and medium vessels with glomerular crescents may occasionally be found. Immunofluorescence reveals C3 and IgG with predominant IgM deposition (Fig. 50.9). On electron microscopy the mesangial, subendothelial, and intraluminal deposits may have a distinct substructure, ranging from bundles of finely fibrillar tactoids similar in appearance to fibrin, to large microtubules similar to those encountered in immunotactoid glomerulopathy (Fig. 50.10). Demonstration of such features in a renal biopsy may suggest the diagnosis of otherwise clinically unsuspected cryoglobulinemia.

## Clinical Presentation

Glomerulonephritis is typically a late complication of HCV, often occurring decades after the initial infection. The renal presentation usually includes microscopic hematuria, moderate to severe proteinuria, and mild renal impairment (chronic mixed nephritic/nephrotic picture). Hypertension is often prominent and difficult to control. Rarely, an acute oliguric presentation may occur. Extrarenal manifestations

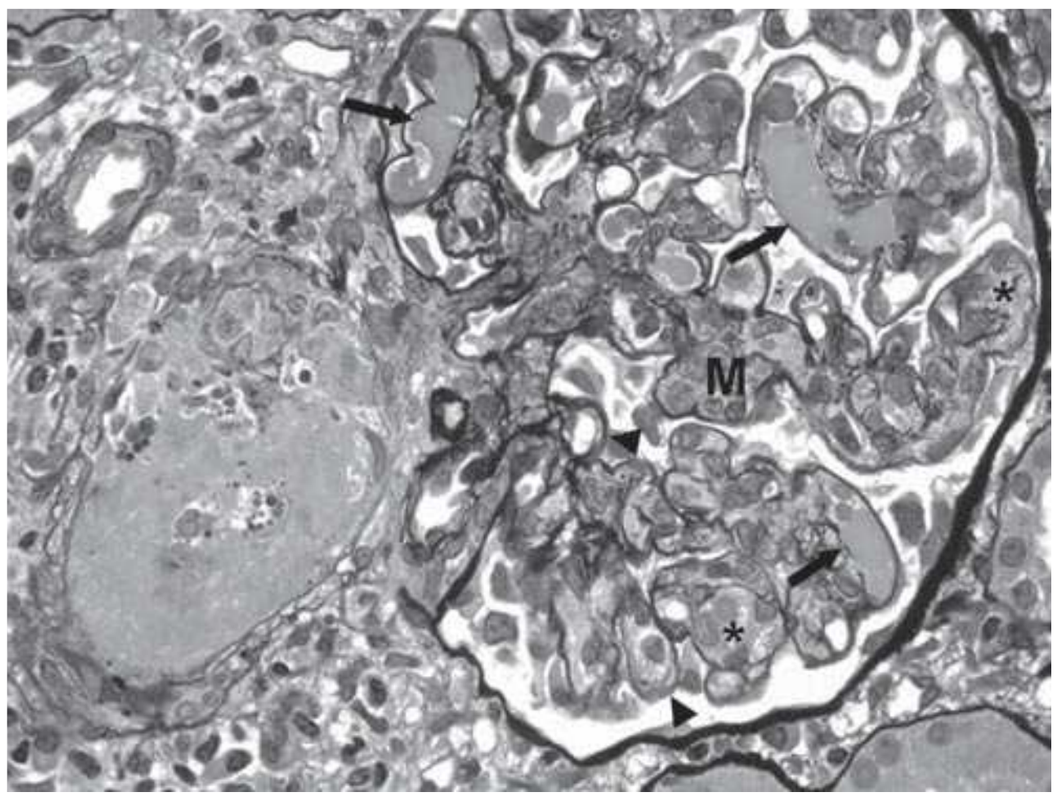



**FIGURE 50.8** Cryoglobulinemic glomerulonephritis. Light microscopy showing accumulation of mononuclear leukocytes within capillary lumina and swelling of endothelial cells (endocapillary proliferation [*]), mesangial cell proliferation (*M*), and capillary wall abnormalities characterized by subendothelial accumulation of eosinophilic material and duplication of basement membrane matrices (*arrowheads*). Many capillaries are partially or completely occluded by globules of eosinophilic material, which are intracapillary aggregates of immune complexes in which cryoglobulins are a major component (*arrows*). The hilar arteriole is occluded by luminal accumulation of immune complexes similar to those present in glomerular capillaries. Jones' silver methenamine stain.

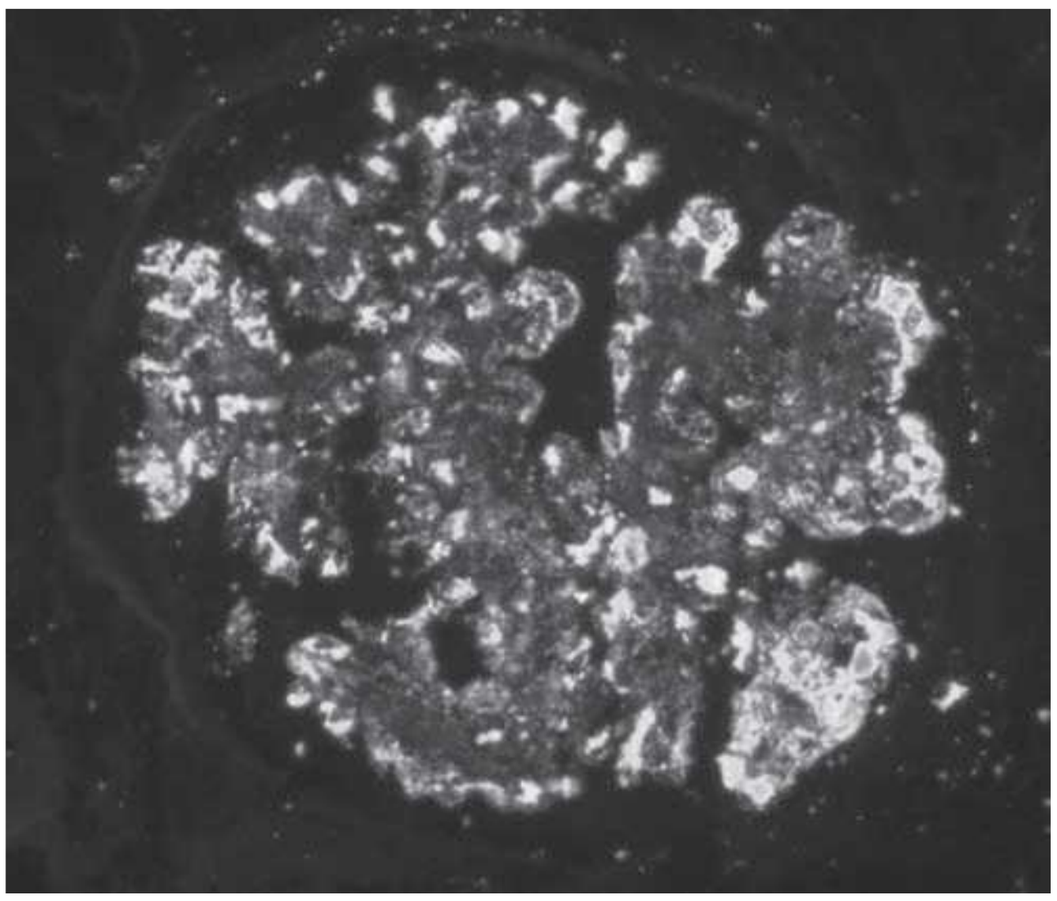
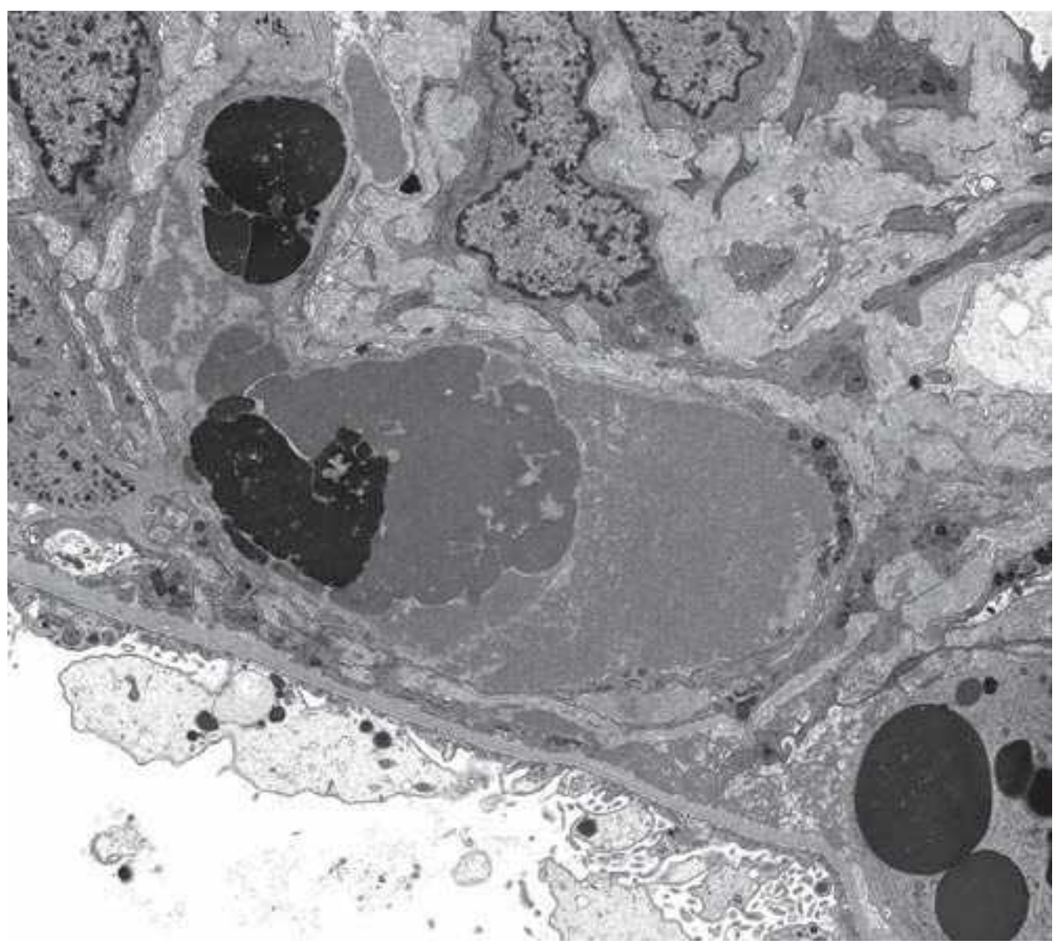
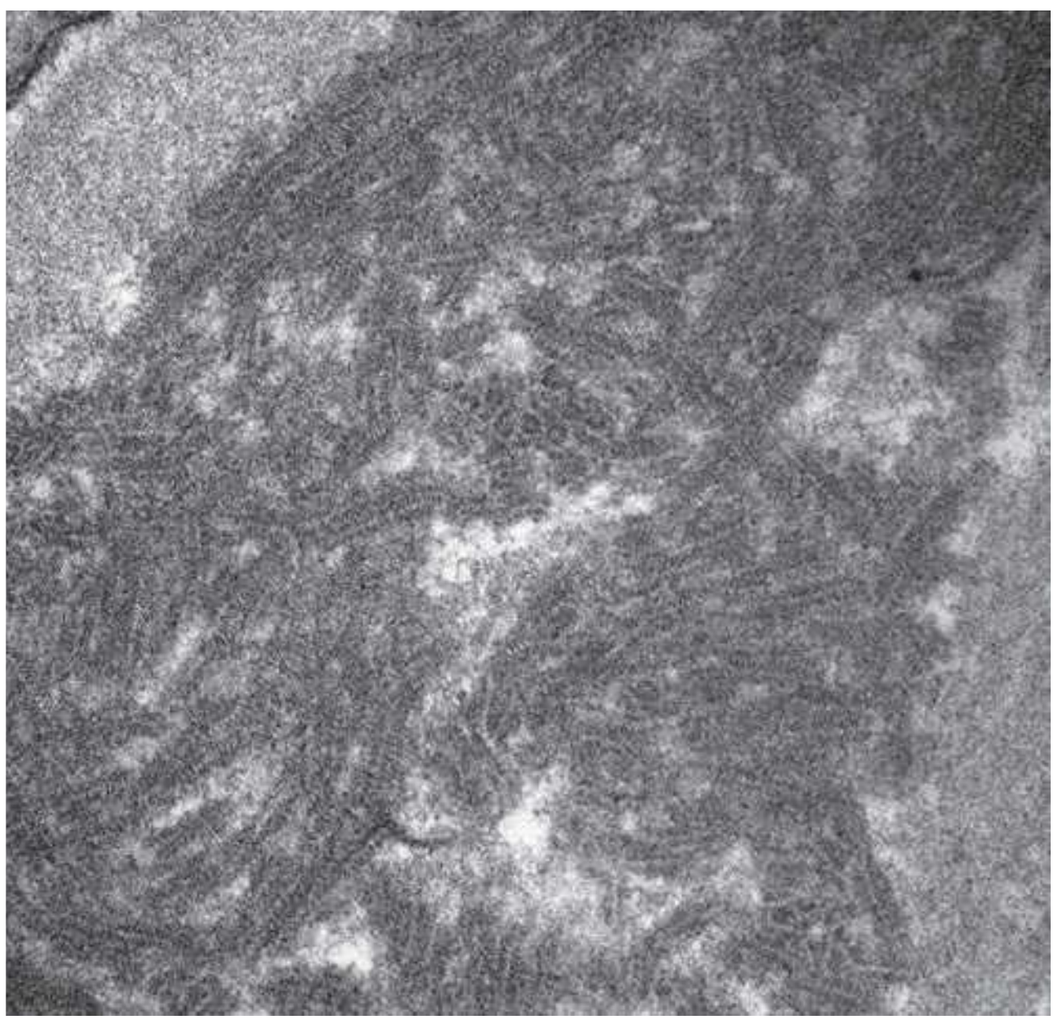


**FIGURE 50.9** Cryoglobulinemic membranoproliferative glomerulonephritis with granular deposits of IgM along peripheral capillary walls. Note globular deposits of immune reactants (which also stain for IgG and C3 [not shown]) within capillary lumina that correspond to the intracapillary globules seen histologically in Figure 50.8.



A



B

**FIGURE 50.10** Cryoglobulinemic membranoproliferative glomerulonephritis. **A:** There are massive accumulations of electron dense deposits of immune complexes within some capillary loops, corresponding to the globules seen histologically in Figure 50.8 and the immune complexes identified in Figure 50.9. More discrete deposits are also present along the subendothelial aspect of the glomerular basement membrane. **B:** At higher magnification, the deposits reveal a microtubular substructure.

of the mixed cryoglobulinemia are often mild with palpable purpura, fatigue, and arthralgia, but more severe features of cryoglobulinemic vasculitis may develop including skin necrosis, peripheral neuropathy, central nervous system (CNS) vasculitis, or abdominal pain secondary to mesenteric vasculitis. Notably, the majority of HCV infected patients with cryoglobulinemia are asymptomatic, or have minimal nonspecific symptoms. In addition, clinically silent MPGN has been described in 27% of HCV infected patients who had normal urinalysis and renal function but underwent protocol renal biopsies at the time of liver transplantation.[51]

Investigations reveal hypocomplementemia with depression in CH50 (90%), C3 (50%), and often a marked decrease in C4 (75%). Circulating cryoglobulins can be detected (~75%), usually a type II mixed cryoglobulin in which the monoclonal rheumatoid factor is an IgMκ. Quantification of cryoglobulins (cryocrit) correlates poorly with organ involvement. Mild elevations of transaminases are commonly found (70%), and although patients may have no clinical evidence of liver disease, liver biopsy often reveals significant hepatic injury.[37] It should also be recognized that occasionally HCV antigens and antibody are bound up in the circulating cryoglobulins and false negative testing for HCV infection (anti-HCV IgG and HCV viremia by polymerase chain reaction) may occur. A high index of suspicion is required in this setting, and the diagnosis can be confirmed by polymerase chain reaction of the rewarmed cryoprecipitate.[52]

The clinical course of HCV-associated MPGN is usually indolent and, in general, the renal prognosis is good with only around 10% progressing to ESRD.[53,54] The extrarenal manifestations often follow a waxing and waning pattern, with long periods of quiescence. Mortality is much greater, however, secondary to a very high incidence of infection and cardiovascular disease. Indicators of a good outcome have not been clearly defined for this condition, but those with heavy proteinuria, renal dysfunction, high levels of viremia, and biopsy findings of marked monocyte infiltration or extensive glomerular deposits may be at greater risk of progression.

## Treatment of HCV-MPGN

The primary treatment of HCV-MPGN is directed at eradication of the underlying hepatitis C, and thereby reducing the downstream B cell clonal expansion and generation of cryoglobulinemic antibodies. In cases with a more fulminant renal presentation, or with marked extrarenal manifestations of cryoglobulinemia, immunosuppression and/or plasmapheresis may be used prior to antiviral therapy (see Table 50.8).

### Antiviral Therapy

Eradication of the virus by the host is limited as the virus has a high mutation rate with numerous subtypes allowing evasion from the immune system. Patients with mixed cryoglobulinemia and HCV viremia are candidates for antiviral therapy. A sustained viral response (SVR) is defined as clearance of HCV viremia during therapy that persists for 6 months post antiviral therapy. The most common antiviral therapy is currently a combination of ribavirin (a nucleoside antimetabolite) with pegylated interferon (PEG-IFN). HCV genotypes 1 and 4 are more resistant to therapy and require a longer duration of therapy (48 weeks) compared to genotypes 2 and 3 which are typically treated for 24 weeks. SVR occurs in only 30% to 50% of patients with genotype 1, compared to 65% to 90% with genotypes 2 or 3.[55] Factors predicting a poor response to treatment include a high viral load (>2 million copies per mL), viral genotype 1 or 4, liver cirrhosis, hepatic iron deposition in the liver, and longstanding infection.[56]

IFNα is often poorly tolerated secondary to adverse effects including flulike symptoms, weight loss, hypoalbuminemia,

**50.8 Treatment of Hepatitis C-Associated Membranoproliferative Glomerulonephritis**

| Clinical Presentation | Treatment |
|---|---|
| Nonnephrotic, normal renal function | Supportive therapy<br>Consider antiviral therapy based on liver biopsy and/or renal course |
| Nephrotic or impaired renal function or extrarenal features of cryoglobulinemia | Pegylated interferon alfa-2a (180 μg weekly) + ribavirin (800–1200 mg/day) ( + telaprevir)<br>Consider addition of rituximab (375 mg/m$^2$ weekly × 4) |
| Rapidly progressive glomerulonephritis (RPGN) or features of severe cryoglobulinemic vasculitis | Plasmapheresis (3 L ×3 per week for 2 to 3 weeks)<br>IV methylprednisone 0.5 to 1 g × 3 days, oral prednisone 60 mg daily with slow taper over 2 to 3 months<br>Rituximab or cyclophosphamide (2 mg/kg, adjusted for renal function)<br>Antiviral therapy when cyclophosphamide discontinued and prednisone less than 20 mg/day |

and anemia. It also has immuno-stimulatory effects which may induce autoimmune disorders such as thyroid or liver disease, or worsen the underlying glomerular disease in patients who do not achieve viral clearance.[57] Ribavirin is taken orally and is generally well tolerated, although the dose is often limited by the development of a reversible hemolytic anemia. As ribavirin is mainly eliminated through the kidneys, this adverse event is more common in kidney disease, and the drug must be used with caution when creatinine clearance is less than 50 mL per min.

Recent studies have demonstrated a dramatic increase in the SVR for genotype I patients using the NS3/4A protease inhibitors telaprevir[58,59] and boceprevir,[60,61] when added to standard anti-viral therapy of PEG-IFN and ribavirin.

### Role of Immunosuppression and Plasmapheresis

Plasmapheresis (to remove circulating cryoglobulins) and immunosuppression (to decrease inflammation and reduce further cryoglobulin production) are reserved for those with a more aggressive renal or cryoglobulinemic disease during the acute phase. Typically this consists of intravenous methylprednisolone 0.5 to 1g for three days, followed by oral steroids (60 mg daily with slow taper over 2 to 3 months), plasmapheresis (3 L alternate × 3/week for 2 to 3 weeks) with warmed replacement fluid and cyclophosphamide 2 mg per kg for 2 to 4 months. This often controls the acute phase of the disease but is associated with a high relapse rate. Notably, although short courses of steroid do lead to increased HCV viremia, unlike chronic hepatitis B infection, a marked worsening of the underlying liver disease is uncommon.[62] Specific antiviral therapy is usually initiated as the immunosuppression is weaned (usually when the prednisone level is reduced to 20 mg per day or less).

Recent evidence suggests a very promising role for rituximab in HCV associated cryoglobulinemia. This monoclonal antibody targets B cells, which are chronically stimulated by HCV thus producing cryoglobulins and other autoantibodies. A small randomized controlled trial[63] and multiple small series have shown often dramatic responses in the clinical features of cryoglobulinemic vasculitis (purpura, arthralgias, peripheral neuropathy), which correlate with a decrease in serum cryoglobulins (RF) and rising serum C4 levels.[64–68] The exact role is still being clarified, however, as increased viremia,[69] and systemic drug reactions similar to serum sickness[70] have now been reported.

### Cryoglobulinemic Glomerulonephritis (Not Associated with Hepatitis C)

It is important to recognize that cryoglobulinemic MPGN may occur in the absence of HCV infection.[62,71,72] In geographic regions where HCV infection is less prevalent—for example, Northern Europe—the majority of mixed cryoglobulinemia (MC) is the result of causes other than HCV infection.[73,74] Cryoglobulinemia is well described in patients with other infections, but the most common etiologies in several series are primary Sjögren syndrome and B cell lymphomas (Table 50.8). The term essential mixed cryoglobulinemia describes cases in which a secondary cause is not identified. Characteristic clinical features of MC include asthenia, arthralgia, purpura, and peripheral neuropathy. Notably, renal involvement typically occurs in the context of type II cryoglobulinemia.[72,73]

In one study from France, 20 patients with mixed cryoglobulinemia unrelated to HCV and MPGN were described. [72] Nine patients had primary Sjögren syndrome, one patient had a B cell lymphoma, and the remaining 10 patients were diagnosed with essential mixed cryoglobulinemia. The majority presented with nephrotic range proteinuria and microscopic hematuria, and investigations revealed a low or undetectable C4 with relatively normal C3 serum levels. All patients had type II cryoglobulins composed of polyclonal IgG and monoclonal IgMκ, similar to patients with HCV associated cryoglobulinemia. Renal biopsy showed MPGN with features of cryoglobulinemic glomerulonephritis including microtubular substructure of the deposits. Seven out of the 20 patients also had interstitial lymphocytic nodules, mostly composed of B cells. The patients were treated with a variety of therapies, including immunosuppression, and overall the renal outlook was favorable, but there was a 40% mortality from nonrenal causes. Notably, four out of 20 (20%) developed a B cell lymphoma during follow-up, and this group of patients requires close monitoring.

## OTHER SECONDARY FORMS OF MPGN

### MPGN Associated with Monoclonal Gammopathy

In a large biopsy series, a monoclonal gammopathy occurred in 22% of patients with a pathologic diagnosis of MPGN.[75] The majority (57%) of these were subsequently classified as a monoclonal gammopathy of uncertain significance (MGUS). Renal biopsy showed typical features of MPGN on light microscopy, with monoclonal deposition of IgG or IgM and either κ or λ light chain restriction. Clinical presentations were similar to other forms of MPGN, but the subsequent course was heavily determined by the etiology of the monoclonal protein (MGUS versus multiple myeloma). Notably, patients with an MGUS had a very high rate (66.7%) of recurrence post kidney transplantation, compared to MPGN patients without MGUS (30%).[76]

Notably, most forms of light and heavy chain deposition disease can present with patterns on light microscopy mimicking MPGN[77,78] (Table 50.4). A differential subgroup for this pattern of injury has been called proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID).[79] This frequently presents with an MPGN pattern, with immunofluorescence demonstrating a single light and heavy chain subtype (most commonly IgG3κ).

### MPGN Secondary to Chronic Infections

Although hepatitis C is the most common infectious cause of MPGN, many other chronic infections have been implicated (Table 50.1). Infective endocarditis,[80] shunt nephritis,[81] and chronic bacterial abscesses[82] are examples of chronic bacterial infections that are associated with MPGN. Persistent antigenemia resulting in the glomerular deposition of antigen-antibody immune complexes is the presumed pathogenesis.

Clinical features are variable, but hypocomplementemia is commonly seen, in keeping with activation of the classical pathway of complement (low C3, low C4). Treatment is directed at the underlying infectious etiology.

## DENSE DEPOSIT DISEASE

The term DDD is derived from the finding of distinctive ribbonlike electron-dense deposits within the GBM that are revealed by electron microscopy. It was formerly considered a subtype of MPGN, and the clinical presentation is similar, but it is now clear that only a minority of cases of DDD present with an MPGN pattern on renal biopsy,[83] and DDD is now widely considered a separate glomerular disorder.

### Epidemiology

DDD is primarily a disease that affects children and young adults, with a mean age of onset of 10–14 years.[84] It affects males and females equally, and may be more common in Caucasians. The finding of DDD in older patients suggests the presence of a monoclonal gammopathy, in which the MGUS protein may directly activate the alternate pathway of complement.[85] Familial DDD is rare, but a few cases have been reported, mostly secondary to inherited complement disorders.[86]

### Pathogenesis

DDD is mediated by a persistent overactivation of the alternate pathway of complement. In health, the alternate pathway is in a state of balance. Spontaneous low level C3 activation due to a process called "tick-over" leads to the formation of the C3 convertase (C3Bb) (Fig. 50.1). This further cleaves C3 generating more C3Bb in a positive feedback process called the C3 amplification loop.[87] This process is controlled by a series of both fluid phase and surface bound proteins known as regulators of complement activation (RCA).[88] Factor H is the predominant RCA of the alternate pathway. It inhibits the C3 convertase of the alternate pathway (C3Bb) by cleaving Bb, and also serves as a cofactor for factor I which cleaves membrane bound C3b. Other RCA regulating the alternate pathway C3 convertase include factor I, MCP, DAF, CR1, and factor H related proteins. Enhanced progression through the complement pathway may occur due to increased early activation (e.g., by microbial pathogens in MPGN type I) or by failure of AP complement regulation due to mutations in, or antibodies to, the various RCA.

Animal models have helped to elucidate the role of factor H in DDD.[89,90] In a spontaneous porcine model of DDD, mutations in the factor H (CFH) gene led to structural changes which impaired protein secretion, leading to an absence of factor H in plasma.[91] Similarly, mice deficient in factor H develop a form of MPGN with subendothelial deposits, but without deposition of IgG.[92] Notably, double knockout mice (Cfh-/- Cfb -/-), deficient in both factor H and factor B, do not develop complement mediated renal disease confirming the need for alternate pathway activation.[92] Surprisingly, the Cfh-/- Cfi -/- double knockout mice did not show enhanced disease despite evidence of complement activation (low C3 and Cfb levels).[93] Indeed, they were protected from GBM abnormalities, suggesting that factor I is required for the generation of this model. It is suggested that it is the factor I dependent C3 fragment (iC3b) that targets the GBM as a component of the dense deposits, whereas excess plasma C3b may preferentially deposit in the mesangium.[94]

In human DDD, dysregulation of the AP leading to unregulated activation in the fluid phase may occur by several mechanisms.

#### C3 Nephritic Factor (C3NeF)

C3NeF is a heterogeneous group of antibodies which are found in about 80% of cases of DDD.[95,96] C3NeF binds to neoepitopes on Bb only when bound to C3b,[97] and stabilizes the nascent C3 convertase (C3Bb) making it resistant to inactivation by factor H, and other RCAs, thus amplifying the cleavage of C3. Notably, C3Nef may be found in some normal individuals, but is commonly seen in patients with partial lipodystrophy.[98] Adipsin, a surface protein on adipocytes, is identical to factor D of the alternate pathway and promotes complement activation on the adipocyte surface leading to cell lysis.[99] C3NeF has also been described in some patients with MPGN type 1, where it may amplify the classical pathway by enhancing the amplification loop of the alternate pathway. A nephritic factor of the classical pathway has also been described (C4NeF) which stabilizes the classical pathway C3 convertase (C4b2a) and may be found in 20% of cases of MPGN type 1.[100] A nephritic factor of the terminal pathway (NFt) is also described. This stabilizes the C5 convertase (C3bBbP).[101] Stabilization of the C3 convertase (C3Bb) has also been described in DDD due to autoantibodies to Factor B and C3b.[102,103]

#### Role of Factor H

Factor H is the most important regulator of complement activation (RCA) in the fluid phase. Impaired factor H function leads to uncontrolled activation of the complement pathway and has been associated with a number of renal diseases including DDD, atypical hemolytic syndrome, and C3 glomerulopathy.[19] Mutations in the CFH gene, both homozygous and heterozygous, have been associated with the development of DDD.[104–106] The majority of these mutations alter protein structure which impairs the secretion of factor H into the circulation.[107] Notably, even in cases of DDD secondary to C3NeF, a permissive genetic background is often found.[108] The His402 polymorphism in the CFH gene, which impairs the heparin and endothelial cell binding properties of factor H protein, has been described in 85% of patients with DDD.[109,110] This polymorphism is also common in age-related macular degeneration and retinal drusen, both conditions in

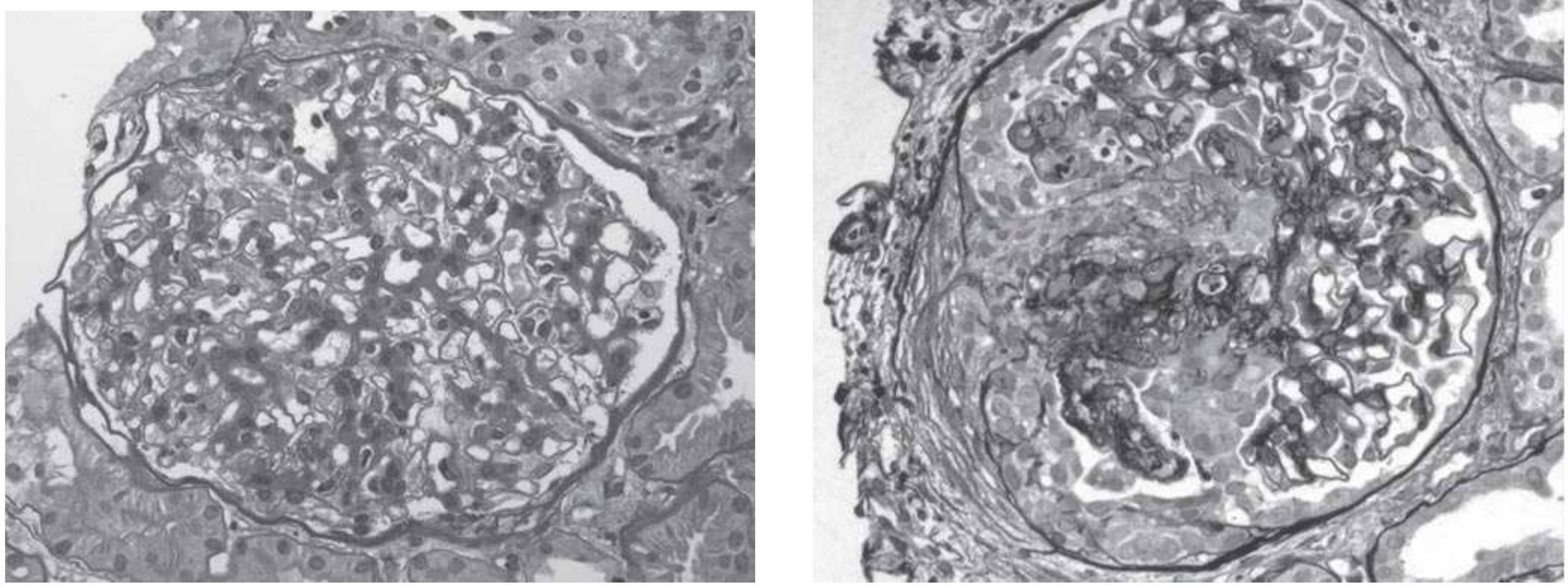



**FIGURE 50.11** Dense deposit disease. **A:** Dense deposit disease can have histologic features indistinguishable from membranoproliferative glomerulonephritis type I, but many cases are characterized by a mesangial proliferative glomerulopathy, of varying severity, which in this case is only of minimal to mild severity. Periodic acid-Schiff stain. **B:** Dense deposit disease can also manifest as an acute crescentic injury with extracapillary proliferation of cells. Jones' silver methenamine stain.

which alternate pathway upregulation occurs.[111] Factor H mutations have also been described in atypical hemolytic uremic syndrome (aHUS), and it remains unclear why some patients develop aHUS versus DDD.[112,113] Interestingly, the mutations in aHUS typically map to the c-terminal end of the CFH gene, often do not reduce factor H levels, but inhibit the binding of factor H to membrane-bound C3b, whereas in DDD, the mutations are typically found in the n-terminal region with reduced circulating factor H levels.[106,114,115] Factor H activity may also be impaired by an autoantibody to factor H, which in some cases may be a monoclonal gammopathy.[85] Alternate pathway activation in DDD has also been described secondary to a mutation in the C3 gene, which produces a protein that upon cleaving to C3b, constructs a C3 convertase resistant to inactivation by fH.[116]

## Pathology

Although initially described as a subtype of MPGN, it is now recognized that a variety of pathologic appearances by light microscopy may be encountered. In one study of 81 cases of DDD, the most common histologic pattern was a mesangial proliferative glomerulonephritis (43%), followed by MPGN (25%), crescentic glomerulonephritis (17%), acute proliferative and exudative glomerulonephritis (12%), and a few cases that could not be classified (3%).[83] Notably, subepithelial humps may be seen in some cases, and in others the mesangial proliferative pattern may be very mild and resemble minimal change disease by light microscopy (Fig. 50.11). The crescentic pattern usually occurs on a background of MPGN or mesangial proliferative disease (Fig. 50.11). Immunofluorescence shows intense C3 staining of the glomerular capillary walls and also the mesangium, but in the absence of immunoglobulin or C1q staining (Fig. 50.12). The morphologic hallmark of DDD is seen on electron microscopy which reveals dense, wavy, ribbonlike linear deposits within glomerular and tubular basement membranes (Fig. 50.13). Bowman's basement membrane may show similar deposits. The exact chemical composition of these dense deposits remains unclear, but they contain C3b and its breakdown products iC3b, C3dg, or C3c, and the terminal complement complex.[83,117]

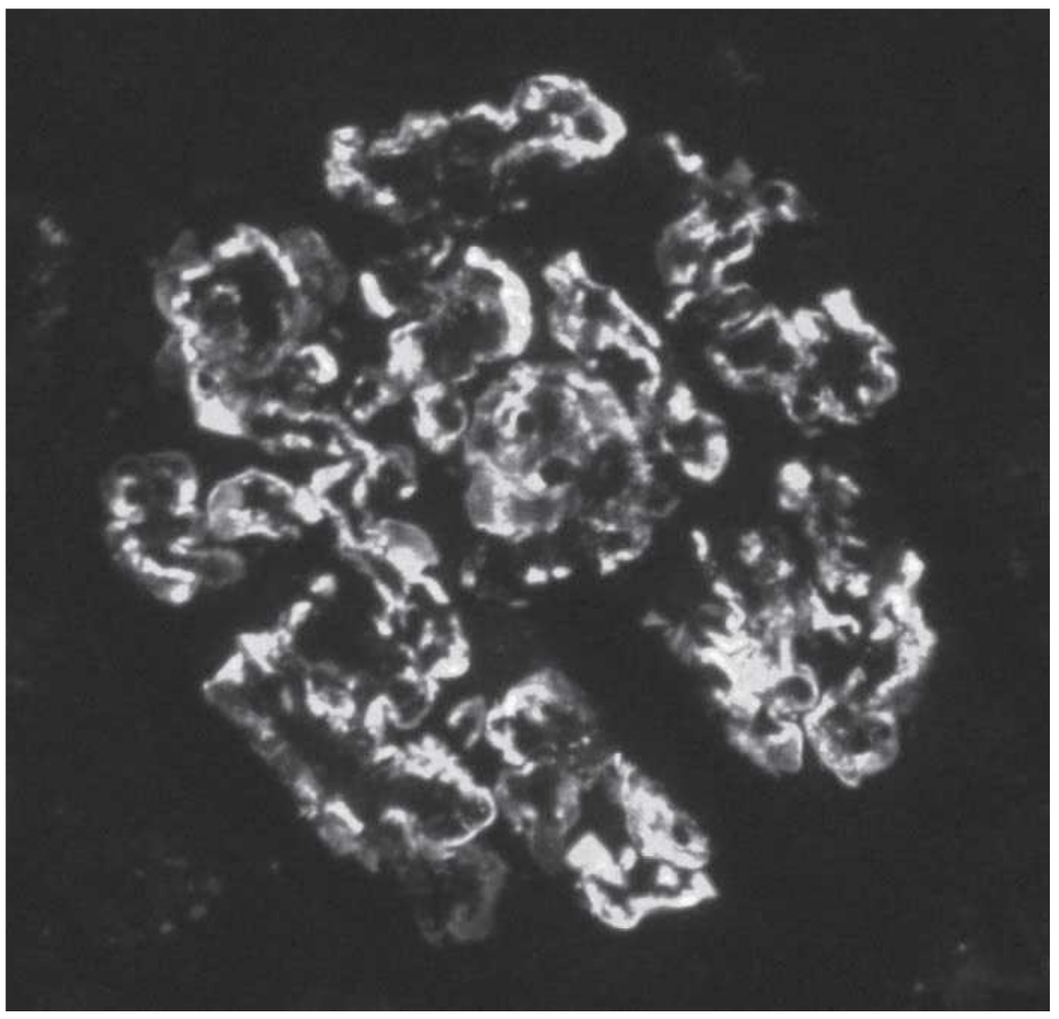


**FIGURE 50.12** The typical immunofluorescence finding in dense deposit disease is strong, clumpy to confluent C3 deposition in mesangial regions and glomerular peripheral capillary walls.

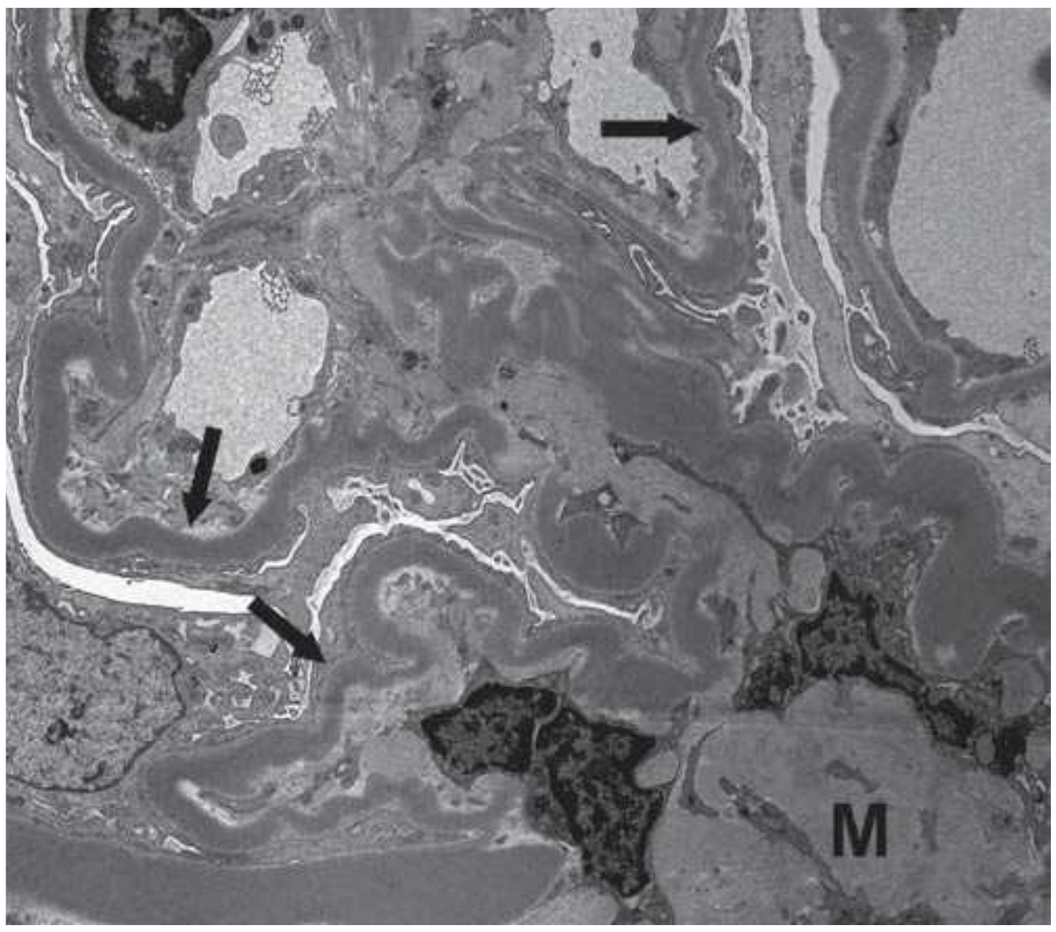



**FIGURE 50.13** Pathognomonic of dense deposit disease is the presence of ribbonlike, confluent deposits with high electron density, extensively involving peripheral capillary walls (*arrows*) and mesangial regions (*M*) where such deposits may also be present in a more interrupted and less widespread distribution, and can involve other renal structures such as Bowman's capsules and tubular basement membranes.

## Clinical Features

This is typically a disease of children who present with hematuria (may be macroscopic), proteinuria, and an acute nephritic or nephrotic syndrome, clinically indistinguishable from other forms of MPGN. Worsening proteinuria and hypertension predict a worse course. Laboratory testing reveals activation of the AP of complement with low C3 levels (805 to 100% children, 50% adults), normal C4 levels, and C3Nef (<80%). In some it may be associated with partial lipodystrophy or drusen in Bruch's membrane of the retina. An increased incidence of type I diabetes has been described.[118] The development of DDD in adults should prompt a search for a plasma cell dyscrasia.[119]

The long-term prognosis of DDD is often poor with ~50% of patients progressing to ESRD. Notably, neither the presence of C3NeF nor the serum C3 levels predict the clinical course.[120] Recurrent disease following kidney transplantation is common (affecting 50% to 100% of patients) and may occur as early as 12 days posttransplantation with 5-year graft loss around 50%.[121]

## Treatment

The condition is diagnosed on biopsy, but a thorough investigation of the complement AP is required to determine the underlying disorder. This includes measures of complement activity (CH50, AP50), measurement of serum levels (C3, C4, factor H), mutation analysis of CFH, and testing for C3NeF. Further complement studies including factor B and factor I may be required.

The best treatment for this disease is unclear, and due to the rarity of the condition will not be guided by randomized controlled trials. The traditional therapy consists of high dose alternate day steroid therapy.[122] We advocate for additional treatment of DDD based on the individual pathogenesis.[123] In patients with C3NeF, one should consider the use of plasma exchange (to remove autoantibody) and therapy with mycophenolate or rituximab to try and eliminate autoantibody production. Plasmapheresis may also be considered in factor H deficiency to supply factor H with fresh frozen plasma. Recombinant active factor H may soon be available.[124] Eculizumab, a monoclonal antibody directed against complement C5 which inhibits the formation of the membrane attack complex, has been used successfully in the therapy of atypical hemolytic uremic syndrome,[125,126] and in a few cases of DDD.[127–129] In the future, the development of specific complement inhibitors may revolutionize the treatment of this condition.

# C3 GLOMERULOPATHY

This term has been used to describe a range of disorders characterized by isolated deposition of C3, without the presence of immunoglobulin, due to uncontrolled activation of the alternate pathway of complement.[19] This group includes DDD, but also several other disorders with variable glomerular pathology. A consensus classification for these disorders does not yet exist, and the terms and groupings may change as better understanding of the genetic mutations and acquired abnormalities in the complement system is achieved.

## C3 Glomerulonephritis

This subgroup has been defined by the presence of glomerular C3 deposition, in the absence of immunoglobulin, with electron-dense deposits, indistinguishable from immune complexes by electron microscopy, predominantly in a subendothelial and mesangial distribution, but also including subepithelial "hump-like" deposits.[115,130,131] It is synonymous with the prior description of MPGN type 1 with isolated C3 deposits but also includes cases formerly classified as MPGN III and cases of purely mesangial proliferative glomerolunephritis. There are many features analogous to DDD, but the characteristic intramembranous dense deposits of DDD are not seen. The majority of patients (75%) have an MPGN pattern on renal biopsy, whereas others had mesangial immune deposits, but without mesangial cell proliferation (Fig. 50.14). The clinical course is very variable (heterogeneous) with approximately 50% maintaining normal renal function, whereas 15% progressed to ESRD.

The absence of immunoglobulin and low serum levels of C3, but normal C4, are compatible with dysregulation of the alternate pathway of complement leading to isolated C3 deposition in the glomerulus. Both autoantibodies (C3NeF[~50%], anti-factor H[132]) and mutations in complement regulatory proteins (factor H, factor I, membrane cofactor protein) have been described in C3 glomerulonephritis.[19,90,95,115] However, the clinical experience with cases defined by this pathologic pattern is not yet sufficient to ascertain the proportion of such patients in which complement abnormalities can be identi-

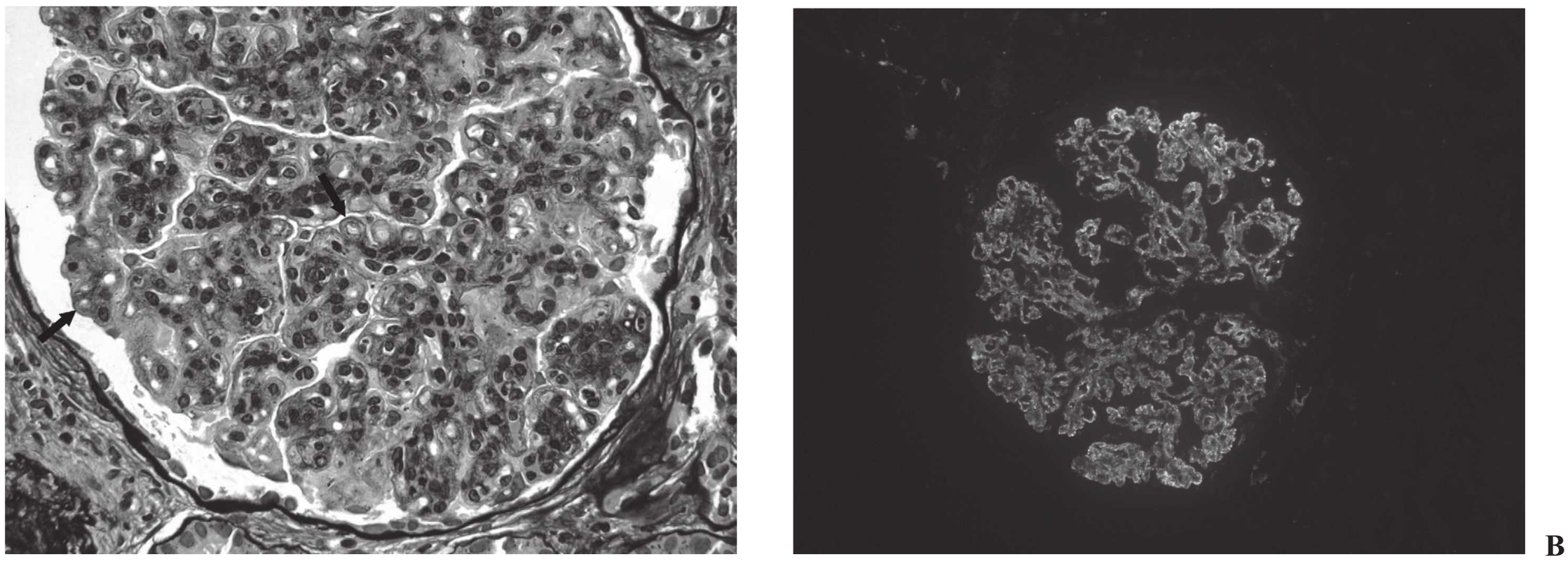



**FIGURE 50.14** C3 glomerulonephritis. **A:** This case has a histologic appearance indistinguishable from membranoproliferative glomerulonephritis type I, with mesangial hypercellularity, leukocyte influx, and split/duplicated glomerular basement membranes (*arrows*). Jones' silver methenamine stain. **B:** Immunofluorescence microscopy demonstrates capillary wall and mesangial deposits of C3, but notably the absence of immunoglobulin heavy or light chains.

fied and implicated in causation, and the proportion of cases that may be due to other etiologies. C3GN has also been associated with a monoclonal gammopathy, which may present as a proliferative glomerulonephritis with isolated C3 deposits and large subepithelial humps that may be confused with a postinfectious glomerulonephritis.[133]

The identification of isolated glomerular C3 deposits should prompt an extensive evaluation of the complement system and the regulators of complement activation. Therapy for this condition is mostly supportive. With progressive disease, immunosuppression may be considered, but similar to DDD, the identification of specific complement abnormalities may result in focused treatments such as plasmapheresis, rituximab, or specific complement inhibitors (e.g., eculizumab).

## Complement Factor H-related Protein 5 Nephropathy

There are five complement factor H-related proteins (CFHR1-5), encoded by genes within the RCA gene cluster on chromosome 1, which share some complement regulatory functions with factor H. In a Cypriot family, an inherited form of C3 glomerulopathy with autosomal dominant transmission has been described that was due to mutations in CFHR5.[134] Notably, the disease recurred posttransplant in one family member.[135] Isolated C3 deposition in the absence of immunoglobulin has also been described in familial MPGN3 linked to the same region.[136]

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