CHAPTER

51 Membranous Nephropathy

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Membranous nephropathy (MN) is one of the leading causes of primary nephrotic syndrome in adults. It is recognized by its characteristic subepithelial immune deposits as visualized by immunofluorescence and electron microscopy, in addition to the thickened glomerular basement membrane (GBM) that gives the disease its name. Primary MN is a glomerulus-specific autoimmune disease and accounts for about 75% to 80% of cases of MN. Recent work has found that most patients with primary MN have circulating autoantibodies to the phospholipase A_2 receptor (PLA_2R); the remainder can be considered idiopathic MN. Secondary MN accounts for the remaining 20% to 25% of cases. It may be a feature of systemic autoimmune disease, chronic infections, malignancy, or therapeutic drugs, and is rarely if ever associated with anti-PLA_2R antibodies. The course of primary MN is variable, and may be marked by spontaneous remissions and relapses. Although a proportion of those patients who fail to remit may have persistent proteinuria with maintained renal function, another 30% to 40% will progress to end-stage renal disease (ESRD). MN recurs in the kidney allograft in up to 40% of those cases that are transplanted. When treatment is deemed necessary, often for those with high levels of nephrotic-range proteinuria or worsening renal disease, immunosuppressive agents such as cyclophosphamide and cyclosporine have been shown to be effective. Several other agents have shown promise in small studies and may also turn out to be useful agents for the treatment of MN.

EPIDEMIOLOGY

Primary (or idiopathic) MN has been and remains the leading cause of adult nephrotic syndrome in many Caucasian-predominant populations, and is second only to focal and segmental glomerulosclerosis (FSGS) in others.[1–3] The estimated annual incidence of MN is 1 in 100,000.[4,5] Despite its relatively high incidence in Caucasian populations, it can be found worldwide in all racial groups. It is most common in the fourth through sixth decades, but can also occur in children or adolescents as well as the very elderly.[6,7] The primary form of MN is more common in males, with a male to female ratio of approximately 2:1. Secondary MN, related to autoimmune diseases, infections, malignancy, or drugs may also occur at any age, and is the form most often seen in children (especially hepatitis B-associated[8]). Malignancy-associated MN is more often a disease of older patients.

PRIMARY MEMBRANOUS NEPHROPATHY

As mentioned previously, primary MN is the most common form of this disease, representing 75% to 80% of all cases. It is a glomerulus-specific autoimmune disorder, characterized by the presence of subepithelial immune deposits containing IgG4 and associated in the majority of cases with circulating IgG4 autoantibodies to PLA_2R, a glycoprotein exposed on the podocyte surface (see Pathogenesis). The remainder of cases thought to be primary in nature may reflect a distinct disease with autoantibodies to another podocyte or glomerular protein, patients that remain proteinuric after the disappearance of anti-PLA_2R antibodies, or in fact cases of undiagnosed secondary disease. The primary form may recur after renal transplantation in up to 40% of cases.[9]

SECONDARY MEMBRANOUS NEPHROPATHY

Secondary cases of MN are suspected when the characteristic pathologic findings of MN are found in conjunction with another systemic condition or are associated with the use of a therapeutic agent or toxin. Due to a lack of available serologic markers (e.g., anti-PLA_2R autoantibodies) that could help to rule out primary disease, secondary cases were previously assumed to be present when MN was found in conjunction with one of the well- or lesser-known associations (Table 51.1).[10,11] There are many single case reports of MN occurring in conjunction with rare autoimmune diseases, infections, cancers, or therapeutic agents. It should be kept in mind that many of these may instead represent a coincidental finding of primary MN with these disorders, rather than a

51.1 Causes of Membranous Nephropathy

Primary
- Anti-PLA_2R-associated
- Idiopathic

Secondary
- Autoimmune diseases
  - Systemic lupus erythematosus (class V lupus nephritis)
  - Other: rheumatoid arthritis, autoimmune thyroid disease, IgG4–related systemic disease
- Infection
  - Hepatitis B
  - Other chronic infections: hepatitis C, HIV, syphilis, schistosomiasis
- Alloimmunization
  - Fetomaternal alloimmunization
  - Graft-versus-host disease following hematopoietic stem cell transplantation
  - De novo membranous nephropathy in the renal allograft
- Drugs or toxins
  - Nonsteroidal anti-inflammatory drugs and Cox-2 inhibitors
  - Mercury-containing compounds
  - Other: gold salts, D-penicillamine, bucillamine
- Malignancy
  - Solid tumors (colon, stomach, lung, prostate)
  - Others: non-Hodgkin lymphoma, chronic lymphocytic leukemia, melanoma

disorder that is truly responsible for secondarily causing MN. Evidence for secondary MN comes in situations in which treatment of the underlying process (infection, autoimmune disease, malignancy) or removal of an offending drug is temporally associated with resolution of the nephrotic syndrome, but this still does not guarantee causation because primary MN undergoes spontaneous remission in one third of cases.

Despite these caveats, MN has been repeatedly found to be secondary to lupus and hepatitis B; in addition to being the most common secondary forms, the strength of the association is also the clearest. Malignancy-associated MN is another important secondary cause to be discussed later, but historically the association has been more controversial. In many cases, the pathologic lesion in secondary MN is similar to that of primary MN. However, there are often subtleties in terms of the location of the deposits, type of immunoglobulin deposited, or other additional features that are more supportive of a secondary cause.

Autoimmune Conditions

Various rheumatologic disorders have been described in association with MN (Table 51.1), of which systemic lupus erythematosus (SLE) is the most common. Ten to 20% of patients with lupus nephritis have an International Society of Nephrology/Renal Pathology Society Class V (membranous) lesion with predominantly subepithelial deposits (see Chapter 53). Clinically, the presentation is that of the nephrotic syndrome and is indistinguishable from idiopathic MN. The majority of these patients are young females, and the onset of the nephrotic syndrome may predate the development of other signs and symptoms of SLE. In a substantial proportion of these patients, the antinuclear antibody (ANA) titer may be low or undetectable, and the complement levels are usually normal. Therefore, there should be a high degree of suspicion for SLE in any young female with the nephrotic syndrome who is found to have MN by renal biopsy. With more established disease, ANA and anti–double-stranded DNA antibodies may be present, and complement levels may be slightly depressed. Several pathologic features on biopsy such as the presence of mesangial and/or subendothelial deposits, as well as the precise IgG subclass present in the deposits, may distinguish lupus-associated secondary MN from primary MN (see section on Pathology). Otherwise, the course of lupus-associated MN resembles that of the idiopathic form, with a good long-term prognosis for renal survival as compared to other forms of lupus nephritis.[12,13]

Rheumatoid arthritis is another autoimmune condition that has been historically linked to MN. However, this has usually, but not always, been in the setting of concurrent treatment of the arthritis with agents such as gold salts, D-penicillamine, or bucillamine (which are no longer commonly used), or nonsteroidal anti-inflammatory agents.[14] In these cases, proteinuria develops soon after exposure to the drug and resolves slowly over a period of months after the offending agent is withdrawn. The pathologic lesion is often identical to that of primary MN.

There are other autoimmune and systemic disorders that have been suggested to be rare secondary causes of MN, including autoimmune thyroid disease (Graves disease and Hashimoto thyroiditis),[10,15,16] IgG4–related systemic disease,[17,18] and sarcoidosis.[19,20] Whether or not these are truly causative etiologies or rather coincidental findings (that are likely to be reported in the literature due to this rare association of distinctive diseases) is not known at this point. As a case in point, a recent report described a patient with MN in which the diagnosis of sarcoidosis and the onset of proteinuria were temporally associated; however, the patient tested positive for anti-PLA_2R autoantibodies,[21] which suggests that the MN was in fact primary.

Infectious Diseases

Numerous infectious diseases have been associated with the development of MN (Table 51.1). In all cases, these represent chronic infections with longstanding and persistent antigenemia. The argument for an etiologic role of the

infectious disease is strengthened when the nephrotic syndrome resolves with treatment of the infection, or when antigens produced by the microorganism are consistently found within the immune deposits.

The role of chronic infection with hepatitis B virus (HBV) is particularly strong and was first noted by Combes and colleagues in 1971.[22] HBV infection may account for 30% to 40% of cases of MN in Asia and is particularly prevalent in children in endemic areas, many of whom are asymptomatic carriers with no history of active hepatitis.[8,23–25] It is particularly noteworthy that the incidence of HBV-associated MN declined following the implementation of an active immunization program.[26] The serum transaminases tend to be normal or only mildly elevated, and the serology is positive for surface antigen, anti-core antibody, and usually e antigen. It appears that it is the e antigen and cationic anti-e antibody that are primarily deposited in the glomeruli.[8,25] HBV infection, along with membranous lupus nephritis, is the only other form of MN that may be associated with hypocomplementemia.[24] Although there may be spontaneous resolution of proteinuria in children, successful treatment of the underlying viral infection in adults with antiviral agents such as entecavir or lamivudine is typically necessary to achieve remission of the nephrotic syndrome.

MN has also been associated with many other chronic infectious diseases, although there is less evidence of causality, and MN is often not the predominant histologic lesion. For example, there are a number of case reports of MN in patients with chronic hepatitis C virus (HCV) infection,[27,28] but this agent is much more frequently associated with mixed cryoglobulinemia and the development of a membranoproliferative glomerulonephritis (MPGN) lesion. A membranous pattern has also been reported in patients infected with human immunodeficiency virus (HIV),[29–31] hepatosplenic schistosomiasis,[32] and congenital or acquired syphilis[33–35]; however, other forms of immune complex glomerulonephritis are more usual in these diseases. In several cases, microbial antigens such as those from treponemes in syphilis were found within the immune deposits.[36,37] As in lupus nephritis, the exact nature of the immune complex may determine whether it ultimately forms in a subepithelial versus a mesangial or subendothelial location.

Malignancy

The association of MN with cancer has long been a point of contention, in part due to the implications of screening for malignancy in a patient who has no other potential secondary causes for their MN. Proponents argue that screening a patient for malignancy may reveal an early occult tumor, whereas opponents argue that, because primary MN and malignancy are both diseases that occur with increased frequency in older individuals, the finding of both diseases in the same person is coincidental. The first report of a possible link between carcinoma and MN came in 1966[38] and this association has been reviewed virtually every decade since.[39–44] Although some may argue that detection bias can explain the association (i.e., patients who are found to have MN on biopsy are more likely to be screened for malignancy than their age-matched counterparts), a recent study that restricted the definition of malignancy-associated MN only to those in which the tumor was clinically evident before or at the time of the diagnosis of MN still found a higher than expected incidence of cancer compared to age- and gender-adjusted national cancer rates.[43] Thus, solid tumors, such as those of the gastrointestinal tract (colon and stomach), lung, and prostate, do appear to be detected in patients with MN at a greater frequency than would be expected for an age-matched national cohort. MN may also rarely occur secondary to non-Hodgkin lymphoma or chronic lymphocytic leukemia.[45] The association of MN and malignancy is strengthened by the temporal association, in several reports, of remission of the nephrotic syndrome following removal or treatment of the tumor. Some investigators have found evidence of tumor antigens such as CEA within the subepithelial immune deposits, and have been able to elute glomerular antibodies with reactivity to the tumor.[46,47]

Given evidence that seems to support both sides of the issue, it is likely that malignancy may be etiologically connected to MN in certain cases, but may only be coincidentally present with primary MN in other cases. This is reflected by a recent report that assayed 10 cases of malignancy-associated MN for the presence of anti-PLA_2R antibodies.[48] In 3 of 10 cases, there was evidence of circulating anti-PLA_2R antibodies and the predominant glomerular IgG subclass on examination of the biopsy material was IgG4, suggesting a coincidental occurrence of primary MN with a tumor. In the remaining seven cases, however, the patients were anti-PLA_2R negative, and the immune deposits were not positive for IgG4, suggesting a truly secondary cause of MN.[49] Future studies such as this may clarify the relationship between the two disease processes, and a positive test for autoantibodies may obviate the need for an extensive malignancy workup. For the time being, however, it is worth making sure that an elderly patient who is found to have MN on biopsy has had age- and gender-appropriate cancer screening, such as colonoscopy, prostate examination (and prostate-specific antigen testing), mammography, and chest imaging in patients with a history of past or current smoking.

Drugs and Toxins

Drug-associated MN can occur at any age and typically develops within 6 to 12 months of exposure to the offending agent, but the onset may be delayed for 3 to 4 years.[50] Historically, gold salts, D-penicillamine, and bucillamine used in the treatment of rheumatoid arthritis have been strongly linked to MN, although these agents are no longer in widespread use. The most common therapeutic agents currently implicated are the nonsteroidal anti-inflammatory drugs (NSAIDs), with mercury-containing compounds reflecting the most frequently encountered toxic exposure. The latter can be found as ingredients in certain skin-lightening agents, which have been linked to the development of MN in several reports.[51,52] Discontinuation of the drug leads to resolution of the proteinuria in virtually all cases.[50,53] However, studies with penicillamine,

gold, and bucillamine indicate that protein excretion may continue to rise for several months after the cessation of therapy.[50] The mean time to resolution of the proteinuria is 9 to 12 months, although 2 to 3 years is required in some cases.

Although NSAID-induced nephrotic syndrome is more commonly associated with minimal change disease, it is evident that MN can also occur.[54,55] The association of NSAIDs with MN was illustrated in a study of 125 patients with a biopsy diagnosis of MN[55]; 23% reported regularly using NSAIDs and 13 of them were likely to have had NSAID-associated MN, as they demonstrated resolution of proteinuria within 1 to 36 weeks of discontinuing NSAIDs and had no recurrence of proteinuria at follow-up (5 months to 13 years). Many of the patients who developed MN had been treated with diclofenac, but probably any NSAID can be involved,[55] including cyclooxygenase-2 (Cox-2) inhibitors.[56]

Alloimmunity

MN may develop in situations when the immune system encounters non-self-antigens,[57] such as in renal transplantation or after allogeneic hematopoietic stem cell transplantation (HSCT). Although patients with a previous history of primary MN may develop recurrent disease in their allograft, more common is de novo MN, which may represent an alloimmune reaction to minor histocompatibility antigens on the allograft podocytes. The MN that occurs post-HSCT is likely to be a humoral manifestation of graft-versus-host disease, and is the most common cause of the nephrotic syndrome after HSCT.[58,59] It is of note that, like primary MN, these cases predominate in males, as opposed to the other causes of nephrotic syndrome after HSCT such as minimal change disease. A rare neonatal form of reversible MN due to fetomaternal alloimmunization has been described in babies born to mothers deficient in neutral endopeptidase (NEP), a protein expressed on podocytes (see Pathogenesis).[60,61]

Miscellaneous Conditions

Another form of pediatric MN was recently described in which circulating antibodies were found to be reactive with a cationic form of bovine serum albumin (BSA).[62] BSA, likely derived from cow's milk and absorbed as an undigested or partially digested protein, was detected in the glomerular immune deposits along with IgG. Moreover, specific anti-BSA antibodies could be eluted from the biopsy specimen in one case. MN has also been reported with diabetes, with or without associated diabetic nephropathy.[63] Although this may reflect a coincidental occurrence of MN with another common disease, there was evidence of porcine insulin within the immune deposits by immunostaining, and an improvement in proteinuria after switching from porcine to human insulin in a small case series.[64] There are also several reports of MN co-occurring with ANCA-positive crescentic glomerulonephritis. However, a recent report looking at the frequency of the two conditions in all renal biopsies performed at a single referral center concluded that the association was likely due to coincidence.[65]

PATHOLOGY

The name membranous nephropathy derives from the histopathologic appearance of the glomeruli of advanced cases of the disease in which expansion of the GBM is clearly visible on light microscopy and there is a paucity of inflammatory cells. Earlier in the course of the disease, however, the glomeruli may appear normal by light microscopy and further studies with immunofluorescence and electron microscopy are necessary for diagnosis. Conceptually, it is useful to think of the disease process as beginning with the formation or deposition of immune complexes beneath the podocyte, which then leads to podocyte injury and the deposition of new extracellular matrix between and around the immune deposits, culminating in a morphologically thickened GBM. Whereas several disparate conditions may underlie the development of MN and give rise to the formation of subepithelial immune deposits, as noted previously, the final pattern of injury is strikingly similar with some subtle differences discussed later. Although the histologic hallmarks of this disease—including GBM "spikes" visualized with the use of silver stains, and the fine granular deposition of IgG in a capillary loop pattern on immunofluorescence—were first described by Jones,[66] and Mellors and Ortega,[67] respectively, over 60 years ago, a definitive pathologic diagnosis depends on identifying the immune deposits with electron microscopy.

Light Microscopy

Light microscopy, with either hematoxylin and eosin (H&E) or periodic acid-Schiff (PAS) staining, reveals diffuse and generally uniform thickening of the GBM (Figs. 51.1 and 51.2). The heterogeneous character of the thickened GBM is best

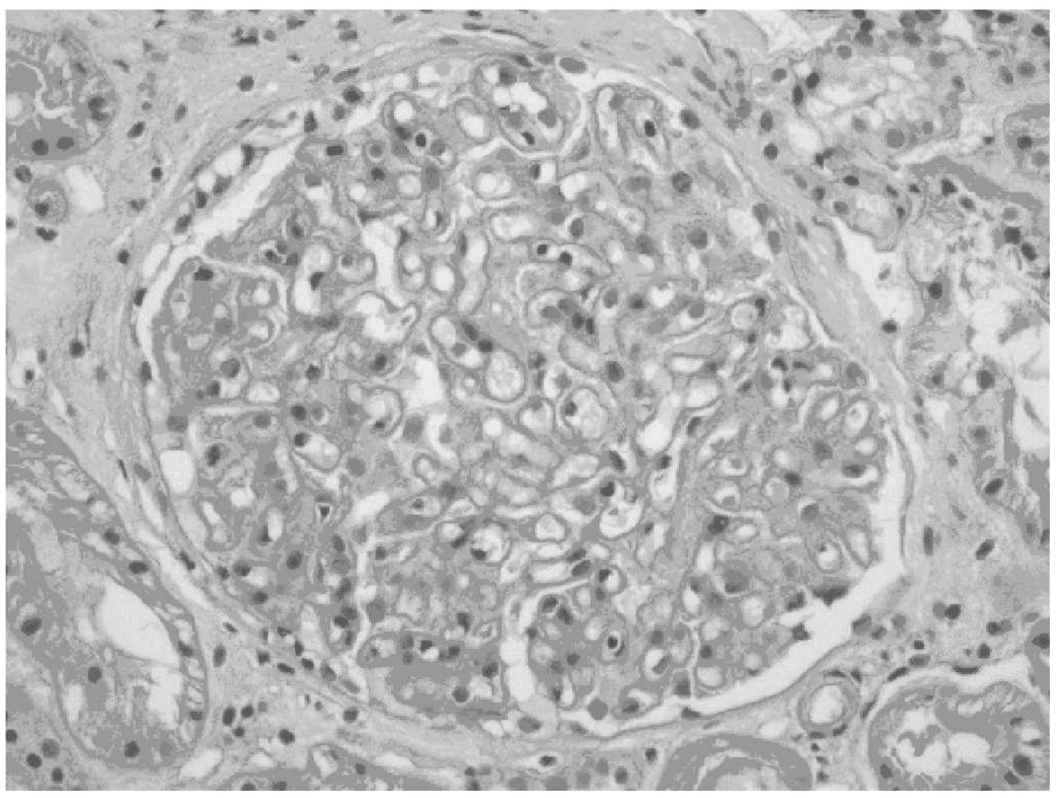

FIGURE 51.1 Hematoxylin and eosin stain (×250) of a glomerulus from a patient with idiopathic membranous nephropathy. There is diffuse thickening of the basement membrane without associated hypercellularity of the glomerular tuft. Inflammatory infiltrates are not seen and the capillary loops are widely patent. (Courtesy of Dr. Helen Cathro.)

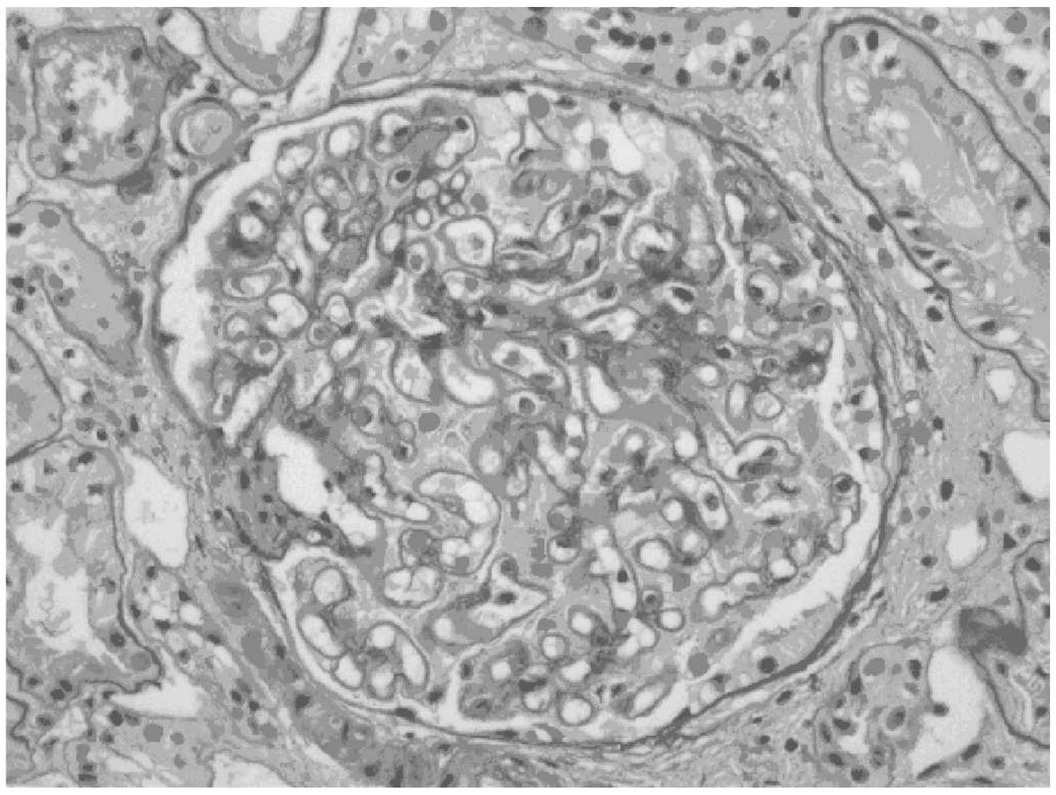

FIGURE 51.2 Periodic acid-Schiff stain of a glomerulus from a patient with idiopathic membranous nephropathy (×250). The basement membrane surrounding the capillary loops is diffusely thickened. (Courtesy of Dr. Helen Cathro.)

seen by silver methenamine (Jones' stain), which binds to basement membrane components but is not taken up by the immune deposits (Fig. 51.3). This staining, in appropriately advanced disease, reveals "spikes" of GBM present between deposits when the GBM is sectioned in cross-section, or "craters" or "pock-marks" caused by the nonsilver stained immune deposits when a tangential section of the GBM is encountered. These findings are pathognomonic for MN. The formation of immune deposits and the basement membrane response proceeds in stages according to the duration of disease (and repair). Ehrenreich and Churg (Table 51.2) classified this progression into four morphologic stages, which are more appropriate for describing the pathologic findings than correlating with clinical findings or prognosis.

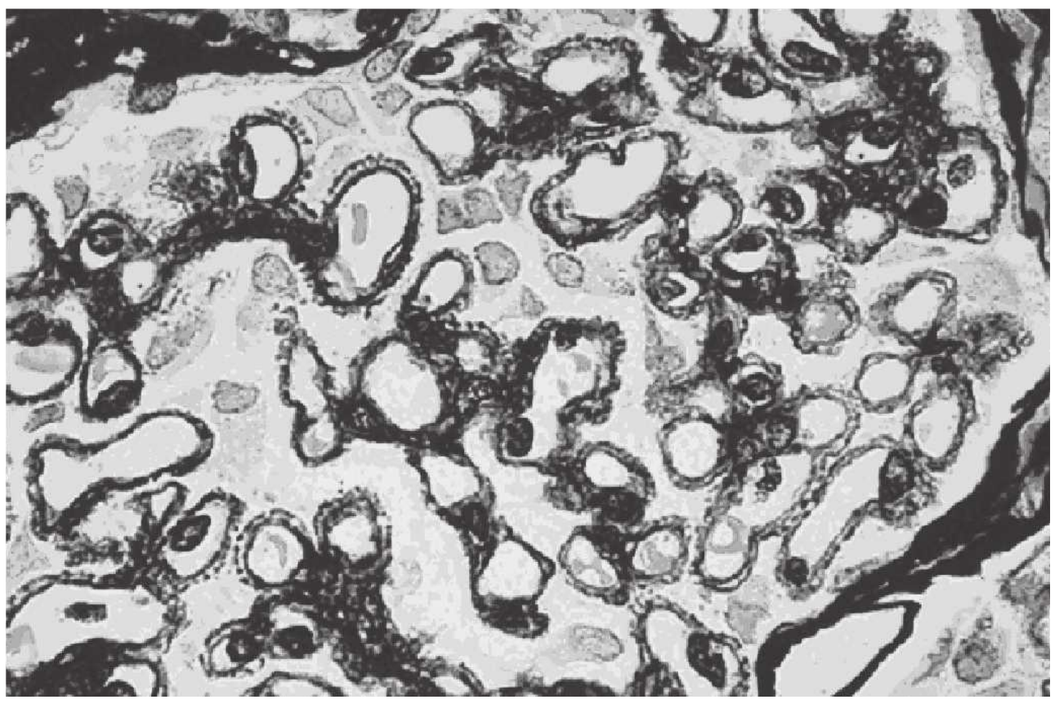

FIGURE 51.3 Jones silver stain (×250) of a glomerulus from a patient with idiopathic membranous nephropathy demonstrating "spikes" corresponding to newly synthesized basement membrane surrounding immune complexes. (Courtesy of Dr. Edward Klatt.)

51.2 Pathologic Staging of Membranous Nephropathy

Stage	Electron Microscopy
I	Subepithelial electron-dense deposits
II	Subepithelial electron-dense deposits with intervening basement membrane ("spikes")
III	Incorporation of subepithelial electron-dense deposits into the basement membrane
IV	Reabsorption of deposits with loss of electron-dense deposits and development of lucent area in the basement membrane
	Remodeling of basement membrane and loss of electron-dense deposits

From Ehreneich T, Churg J. Pathology of membranous nephropathy. Pathol Annu. 1968;3:145.

Other compartments of the glomerulus usually appear normal. There is no evidence of mesangial cell proliferation or expansion except in the setting of SLE and other secondary forms. Importantly, there is typically no evidence of inflammatory cell infiltration (which argues against the continued use of the term "membranous glomerulonephritis"). Experimental studies suggested that this is on account of the subepithelial location of the immune deposits, which are separated from the capillary lumen and thereby unable to recruit inflammatory effector cells, as more readily occurs when immune deposits form in a mesangial or subendothelial location.[68]

With longer duration of disease and/or sustained heavy nephrotic proteinuria, tubulointerstitial damage can occur which is associated with decreased glomerular filtration rate (GFR) and a worsened renal prognosis. Similarly, lesions of secondary FSGS may also develop, also portending a worse prognosis and persistent proteinuria that is likely to be unresponsive to immunosuppression.

Immunofluorescence Microscopy

The finding of granular deposits of IgG in a capillary loop pattern on immunofluorescence is the sine qua non of both primary and secondary MN (Fig. 51.4). With the exception of class V lupus nephritis which may present with a "full house" pattern on immunofluorescence,[69] the deposits are predominantly IgG, with minimal staining for IgA and IgM, and tend to spare the mesangium. The complement component C3 is often seen, with the exception of very early disease. Although not typically performed, the characterization of IgG subclasses often helps to differentiate

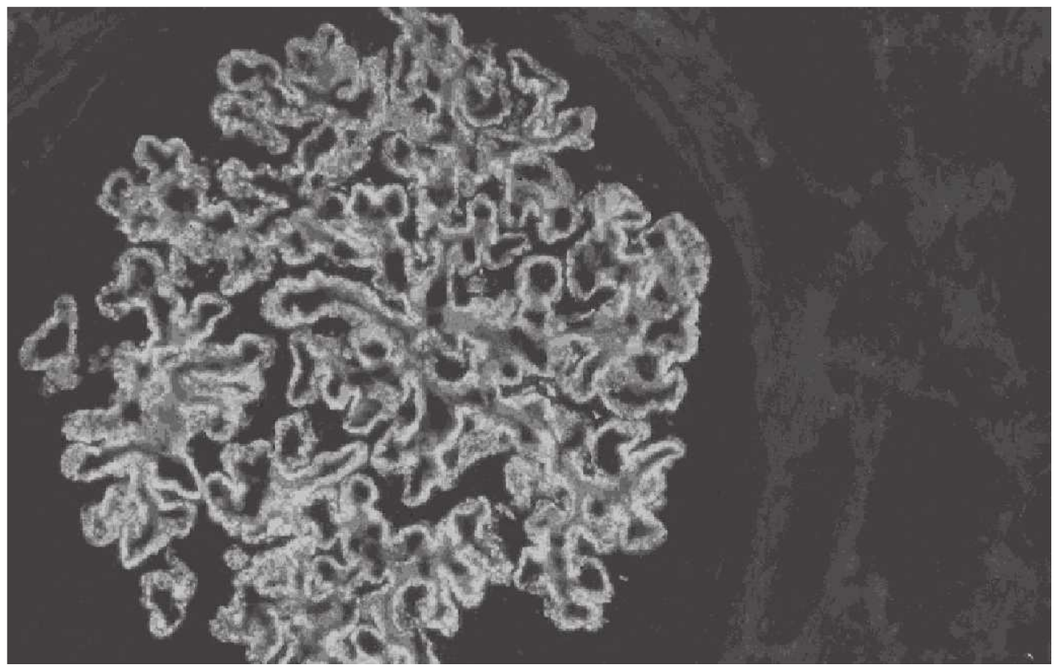

FIGURE 51.4 Immunofluorescence staining (anti-IgG) of a glomerulus from a patient with idiopathic membranous nephropathy (×250). Diffuse granular staining along the basement membrane is evident and corresponds to the deposition of immune complexes. Mesangial areas are free of immune deposits.

primary from secondary disease, as the predominant IgG subclass in primary MN is IgG4. Secondary causes, in most cases, have a predominance of non-IgG4 subclasses, most notably in lupus-associated[69–71] and malignancy-associated MN.[49] The presence of C1q, an early component of the classical complement pathway, may also help distinguish between primary and secondary cases. Strong C1q staining is not typically found in primary MN (less than 20% of cases)[69,72] but is more common in lupus-associated MN.

Electron Microscopy

The hallmark of MN is the presence of subepithelial electron-dense deposits corresponding to the immune complexes (Fig. 51.5). Similar deposits are rare in the mesangium (but may be present in paramesangial areas) in primary MN, but are more common in secondary cases such as lupus- or NSAID-associated MN. These electron-dense deposits are typically homogeneous in nature, without visible substructure. Similar to other causes of the nephrotic syndrome, evidence of podocyte injury is present, with effacement (or "simplification") of the foot processes, microvillous changes, and the presence of protein reabsorption droplets within podocytes and proximal tubular cells. One additional finding on electron microscopy, the presence of tubuloreticular inclusions in the endothelial cells, may be strongly suggestive of lupus- or HIV-associated MN. However, these can be rarely found in primary disease as well.[73]

Variants

The presence of subepithelial electron-dense deposits in a segmental pattern (segmental MN) appears to be different than primary MN, with a childhood predominance and often an association with C1q deposition.[74] The finding of substructure in the deposits by electron microscopy is also atypical. A rare but distinctive form of MN characterized by

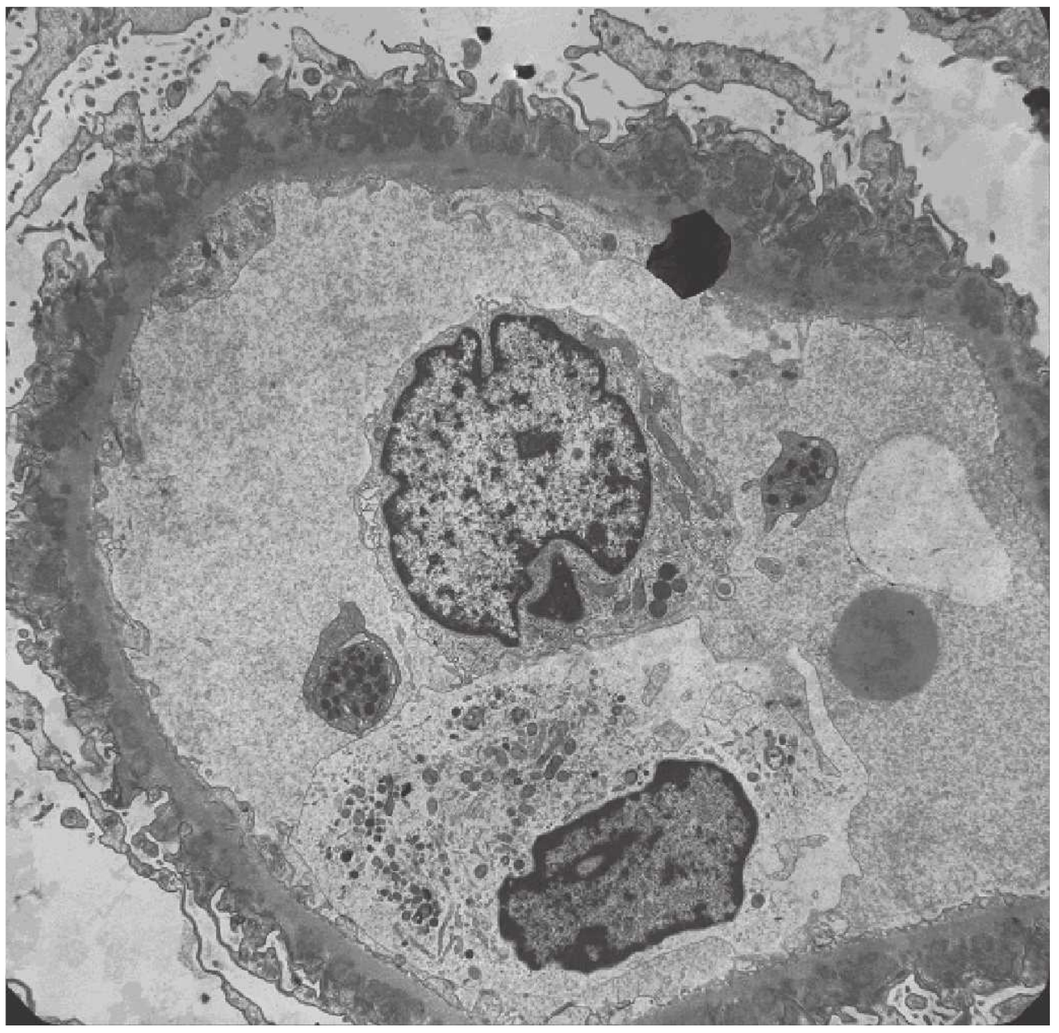

FIGURE 51.5 Electron micrograph of a glomerulus from a patient with idiopathic membranous nephropathy revealing characteristic electron-dense subepithelial deposits (×5,000). In this micrograph, basement membrane can be seen to encircle the deposits forming the spikes seen on Jones' silver staining (stages II and III). (Courtesy of Dr. Helen Cathro.)

"microspherules" within the deposits has been reported[75] and continues to be infrequently seen by pathologists. The nature of these particles and its association with other systemic diseases is unknown. Monoclonal immunoglobulin deposition disease usually gives rise to nodular glomerulosclerosis or a proliferative pattern of glomerular injury[76]; however, a histologic pattern mimicking MN through the presence of subepithelial deposits can also occur.[77–79] This form may be suggested by abnormal findings on serum or urine immunofixation electrophoresis, and is confirmed by demonstrating a kappa or lambda light chain restriction to the deposits on immunofluorescence.

PATHOGENESIS

Much of the proposed pathogenesis of MN has been elucidated from decades of study in the rat model of Heymann nephritis (HN).[80] In the past decade, a better understanding of the disease process in humans has been achieved due to the findings of autoantibodies to human podocyte proteins, especially the phospholipase A_2 receptor. Due to the historical importance of the Heymann nephritis model and the pathophysiologic lessons learned from it, we begin with a synopsis. Further information is available in several comprehensive reviews of the topic.[81–83]

In 1959, Walter Heymann published a description of the experimental rat model of immune deposition disease that

morphologically and clinically mimics human MN and bears his name.[80] Rats actively or passively immunized against a proximal tubular brush border fraction (Fx1a) eventually develop nephrotic levels of proteinuria due to the subepithelial deposition of IgG-containing immune complexes.

Initial assumptions were that circulating immune complexes give rise to the glomerular subepithelial immune deposits. The size, charge, and affinity of the components of the immune complex were thought to determine their distribution into a subepithelial rather than subendothelial location. Using in vitro and ex vivo perfusion of isolated rat kidneys with anti-Fx1a antibodies, two independent research groups clearly demonstrated that the subepithelial deposits in HN form instead by the binding of immunoglobulin in situ to an antigen expressed on the basal surface of the podocyte foot processes.[84,85] The primary antigenic component of Fx1a was subsequently identified as the endocytic tubular brush border receptor megalin.[86–90] In rats, but not in humans, megalin is additionally present on the foot processes of the podocyte where it serves as the target for the circulating anti-Fx1a antibodies. These individual antibody-antigen interactions were shown to coalesce into small immune complexes through a process of "capping and shedding,"[91] and to ultimately aggregate in the GBM into the large electron-dense subepithelial deposits visible by electron microscopy.[92]

Further work in this experimental model unraveled the pathogenesis of the disease process.[81] Local complement activation by the immune complexes leads to the assembly of C5b-9, the membrane attack complex (MAC) that inserts into the plasma membrane of nearby podocyte foot processes. This instigates a series of maladaptive downstream signaling events leading to calcium influx, increased generation of arachidonic acid metabolites, and the production of reactive oxygen species. The resulting cytoskeletal changes lead to simplification or effacement of the foot processes, loss of slit diaphragms, and massive nonselective loss of protein into the urine. As a result of the signaling changes and loss of differentiated cell phenotype, the podocytes began to secrete and deposit extracellular matrix between and around the immune deposits, leading to an expansion of the GBM.[93] Despite the continued generation of C5b-9, the podocyte is not lethally injured as it is able to continually shed the MAC from its plasma membrane into the GBM and urine.

A similar process is presumed to take place in humans, and a role for complement activation in human MN is clear, because both C3 and C5b-9 have been shown to be present in the glomerular immune deposits[94] as well as in the urine.[95] However, the precise arm of the complement cascade responsible for these findings in MN is not clear. The absence of C1q[69,72] and the presence of IgG4 (IgG4 is generally considered to be unable to fix complement[96]) argue against a major role for the classical pathway, at least in primary MN. It is possible that the alternative or mannan-binding lectin pathways of complement activation may play a more important role in the cellular injury in primary MN, given the predominance of IgG4 in the deposits.

Because megalin, the target antigen in HN, is not expressed in the human glomerulus, it has long been hypothesized that an alternative protein expressed on the surface of the podocyte would serve as the target for antibody-mediated cytotoxicity in human disease. In a seminal case report,[60] Debiec and colleagues provided the first demonstration of such circulating antibodies reactive with an endogenous podocyte protein. A mother deficient in neutral endopeptidase (NEP), which is expressed by the podocyte, was immunized to this protein during a prior miscarriage. In a subsequent pregnancy, these anti-NEP alloantibodies crossed the placenta and into the fetal kidney, binding NEP at the surface of the fetal podocyte and causing the formation of subepithelial deposits. The infant was born with an antenatal form of MN, although the disease spontaneously resolved within several months after birth due to the eventual clearance of circulating maternal IgG. Several other cases of fetomaternal alloimmune MN in response to NEP have been described.[61] Importantly, infants were only proteinuric when mothers had both the complement-fixing IgG1 as well as the noncomplement-fixing IgG4 anti-NEP antibodies.

The next major advance in the field of primary MN came recently with the description of circulating autoantibodies to the M-type phospholipase A_2 receptor (PLA_2R) in the majority of patients with primary MN.[97] PLA_2R is a member of the mannose receptor family of transmembrane glycoproteins,[98,99] and is expressed by the human podocyte.[97] At least 70% of patients with primary MN have these autoantibodies when they are initially nephrotic. In contrast, such antibodies are absent in patients with secondary forms of MN, other glomerular diseases, and normal controls. Consistent with the known subclass distribution of IgG within the immune deposits of primary MN, the predominant circulating anti-PLA_2R subclass is IgG4, a marker of a type-2 helper T cell (Th2) response. These anti-PLA_2R autoantibodies have been found in patients with MN worldwide and of all major ethnicities. Antibodies from all anti-PLA_2R positive patients have exhibited reactivity only with the nonreduced protein, suggesting the presence of one or more conformation-dependent epitopes within the molecule, and likely in its N-terminal portion. IgG4 localizes with the PLA_2R antigen within the subepithelial immune deposits in primary (but not secondary) MN biopsy specimens,[97] which suggests that PLA_2R-anti-PLA_2R complexes are shed from the podocyte surface as noted earlier in the Heymann nephritis model. Furthermore, PLA_2R-reactive IgG can be specifically eluted from these biopsies.

A role for anti-PLA_2R autoantibodies in disease pathogenesis is suggested by observations that the presence of such antibodies is closely associated with clinical disease activity. Importantly, the anti-PLA_2R antibodies tend to disappear with a spontaneous- or treatment-induced remission and return with a relapse of the disease.[100] Further supportive of a pathogenic role is the repeated observation that changes in autoantibody precede corresponding changes in proteinuria by months. Indeed, biopsy studies

have shown that residual evidence of the PLA_2R antigen may persist in deposits despite clearance from the circulation.[101] This lag time most likely represents the period of glomerular recovery, during which subepithelial deposits are slowly cleared, and podocyte cytoskeletal structure and the slit diaphragm apparatus returns to its baseline architecture. Final proof of pathogenicity awaits the creation of a suitable animal model.

The presence of anti-PLA_2R antibodies seems to largely be restricted to primary forms of MN; it is not found in lupus-, hepatitis-, or drug-associated MN, and is also not found in normal individuals or patients with other forms of glomerular disease.[48,97] Although not yet commercially available in the United States, it is anticipated that measurement of anti-PLA_2R antibodies may represent a powerful screening and monitoring tool, to be used adjunctively with renal biopsy and measurements of proteinuria.

Recent work has detailed the presence of antibodies against glomerular neoantigens, or podocyte proteins not expressed in the healthy state, but rather induced by disease. These include antibodies to aldose reductase and superoxide dismutase 2, which are normally intracellular proteins that appear to be expressed at the cell surface in MN.[102] The role of these antibodies in the initiation of disease activity is not clear; however, it is possible that they serve as progression factors that can lead to further immune complex formation and thus worsening of disease.

In all forms of MN, a complete clinical remission can occur with a reduction in proteinuria from nephrotic to completely normal levels. This is accompanied by the gradual disappearance of subepithelial and intramembranous deposits, reorganization of the podocyte foot processes, and reestablishment of slit diaphragms. Repeat biopsies performed in several patients who attained a complete remission after having been treated with the anti-B cell agent rituximab found a virtual disappearance of immunofluorescence staining for IgG4 (but not total IgG), a trend toward decreased C3 staining, as well as a complete or partial disappearance of the subepithelial deposits.[103] The structural changes that underlie a partial remission are less clear, but may reflect balanced rates of immune deposit formation and clearance, or incomplete restoration of the normal podocyte architecture due to the disordered GBM. Moderate proteinuria that persists despite the absence of immunologic activity may also be due to tubulointerstitial damage, nephron loss, and secondary FSGS. The transplantation of kidneys from rats with experimental HN into naïve rats revealed that, although a significant amelioration of proteinuria occurred in the absence of circulating antimegalin antibodies, the animals were left with permanent residual proteinuria due to persistent abnormalities of the glomerular capillary wall.[104]

The mechanisms for the formation of subepithelial deposits in secondary MN are not well understood, and may involve planted antigens or low-avidity circulating immune complexes rather than antibodies to native podocyte antigens. The presence of deoxyribonucleic acid (DNA)-histone complexes and the HBV e antigen have been variably demonstrated within the immune deposits of MN secondary to lupus or HBV infection, respectively.[8,105] Circulating immune complexes, which may have a net positive charge, eventually deposit on the outer aspect of the GBM, perhaps after dissociation and reassociation. Several isolated reports have detected various tumor antigens in the deposits in malignancy-associated MN, although it is unclear whether such antigens represent the initiators of disease or are only secondarily trapped within existing deposits. The molecular differences underlying the various locations in which immune complexes may deposit in lupus nephritis are not currently known. Similarly, the mechanisms whereby therapeutic drugs, toxins, or chronic infections lead to secondary MN have not yet been established.

The genetics of primary MN has highlighted both the major antigen PLA_2R and components of the antigen presentation system. Early studies documented an association with specific HLA molecules.[106,107] This was confirmed in a recent genome-wide association study (GWAS) that linked MN in a cohort of 585 European Caucasians with a single nucleotide polymorphism (SNP) in the HLA-DQA1 locus.[5] Remarkably, this study also showed an allelic association with PLA2R1, the gene that encodes PLA_2R. Surprisingly, no other loci were identified in this association study, although it is possible that studies in larger or ethnically different cohorts may identify further gene associations. Although this GWAS study was performed in an exclusively Caucasian population, two smaller studies in a Korean[108] and a Taiwanese[109] cohort have also defined SNPs within the PLA2R1 coding region that are associated with primary MN. The implications of the studies in terms of the precise pathophysiology of the triggering events in primary MN are not yet known, nor are the implications for genetic testing.

Much work remains to be done to understand the early events that underlie the initiation of MN, although the finding of specific HLA molecules and a target antigen may stimulate further research in this vein. B cells are found within the renal interstitium in MN[110] and these or periglomerular or peritubular dendritic cells could serve as local antigen presenting cells.

CLINICAL FEATURES

The onset of clinical disease in MN is typically an insidious process, unlike the more explosive onset of the nephrotic syndrome as seen in minimal change disease or primary FSGS. The majority of patients present with weight gain, edema, proteinuria, and other signs of the nephrotic syndrome that have likely been developing over the course of months. Up to one third of cases may have hypertension at presentation as well. A smaller percentage of patients present with subnephrotic levels of proteinuria, perhaps detected by an abnormal urinalysis performed for an unrelated reason such as screening in pregnancy or for a life insurance examination. The proteinuria tends to be nonselective; that

is, there is increased immunoglobulin as well as albumin excretion, as opposed to mainly albuminuria as seen in minimal change disease. Microscopic hematuria is present in up to 50% of cases despite the absence of frank glomerulonephritis, although red cell casts and macroscopic hematuria are typically not seen. Features of proximal tubular dysfunction such as glycosuria may be seen with especially heavy proteinuria. GFR is usually normal, unless the disease has been present but undetected for years. Other features of the nephrotic syndrome, including hypoalbuminemia, hyperlipidemia, low levels of 25-hydroxyvitamin D, and lipiduria are generally present.

Thromboembolic complications such as deep vein thrombosis, pulmonary embolism, and renal vein thrombosis can be the presenting feature in some patients with MN.[111] These complications are more common in MN than in other nephrotic conditions, even when adjusted for age and the degree of proteinuria, and MN is the most commonly associated condition in patients with renal vein thrombosis. Thromboembolic complications most frequently occur in patients with heavy, persistent proteinuria and serum albumin concentrations below 2 g per dL. Renal vein thrombosis may be asymptomatic and manifest for the first time with pulmonary embolism, or present with flank pain, hematuria, or deterioration in renal function.

LABORATORY FINDINGS

Laboratory findings in patients with MN reflect ongoing proteinuria and the nephrotic syndrome. Thus, hypoalbuminemia, hyperlipidemia, low levels of 25-hydroxyvitamin D and lipiduria (oval fat bodies, fatty casts) are common findings. The results of routine serologic studies, including complement levels, are all normal in primary MN. However, studies should be performed to exclude secondary causes of MN and include ANA, hepatitis B and C profiles, rapid plasmin reagin (RPR), as well as age-appropriate cancer screening. In addition, complement levels may be depressed in HBV- and lupus-associated secondary forms of MN. As in most cases of nephrotic syndrome, the erythrocyte sedimentation rate is typically elevated and is of no value in differentiating primary from secondary causes of MN. Currently, renal biopsy is the exclusive means for diagnosing MN and distinguishing primary disease from secondary etiologies. It is anticipated that circulating autoantibodies to PLA_2R may soon be used to support a diagnosis of primary MN. At this time, however, the test is only available in the research setting.

NATURAL HISTORY AND PROGNOSIS

Predicting the clinical course of an individual patient with MN at disease presentation is impossible given the variable and fluctuating disease course. It is a commonly taught dictum that one third of cases spontaneously remit, another third have persistent proteinuria that does not lead to a significant decline in renal function, and the final third progress inexorably to renal failure; however, these numbers vary considerably among different reports. Those patients that do undergo transplantation for ESRD have up to a 40% risk of recurrence of MN in the renal allograft.

The immunologic factors that trigger primary MN, impact its severity, or ultimately lead to its remission (and relapse) are not understood at this time. There have not been consistent links to any preceding infection; MN most often appears for no apparent reason in otherwise healthy middle-aged adults. Increased severity of proteinuria and longer duration of the nephrotic syndrome are clearly linked to poorer renal outcomes. The amount of time between a biopsy diagnosis of MN and the actual immunologic initiation of the disease (which is virtually never known) may determine in part the degree of proteinuria at presentation, as it may take many months before a patient develops peak proteinuria. In general, 75% of patients with primary MN are fully nephrotic at the time of biopsy diagnosis, whereas the remainder has nonnephrotic levels of proteinuria.[112] Patients who never develop nephrotic syndrome (approximately 40% of those who are nonnephrotic at presentation) have excellent prognosis, with a 10-year renal survival of nearly 100%. Nearly 70% of those who progress from nonnephrotic to nephrotic levels of proteinuria do so in the first year after diagnosis, and yet have a better renal prognosis than those who are nephrotic at presentation.[112]

Baseline demographic differences in natural history studies of MN appear to have blurred the overall prognostic picture, and are partially responsible for differences in opinion on whether or when to treat MN patients with immunosuppressive agents. A widely quoted single-center study involving 100 patients with untreated MN reported a 65% spontaneous remission rate and an 88% 5-year renal survival.[113] However, more than one third of the initial cohort in this study never had nephrotic range proteinuria, clearly biasing toward a more favorable prognostic picture. A more recent analysis that statistically corrected for the percentage of nonnephrotic patients has estimated that up to 50% of nephrotic patients with primary MN may reach ESRD over the course of 10 years.[114]

It is difficult to determine where an individual patient lies in the longitudinal spectrum of disease when relying only on proteinuria as a measure of clinical outcome. Either after a spontaneous remission or in response to treatment, the level of proteinuria may decline at a variable rate, and may or may not reach zero. Due to the severity and duration of structural changes in the glomerulus, or due to secondary changes such as tubulointerstitial damage and glomerular sclerosis, proteinuria may take months to years to normalize, or may remain persistently elevated, all in the absence of ongoing immunologic activity. A recent article by Polanco and colleagues shows that this decline in proteinuria can continue over years, even in those starting with very high levels of initial proteinuria.[115] Thus, a partial (incomplete) remission of proteinuria (typically, a greater than 50% decrease from baseline proteinuria to less than 3.5 g per day) does

not provide an accurate account of the activity of the disease because several factors may cause a reduced but persistent level of proteinuria, including the hemodynamic changes induced by RAS and calcineurin inhibitors or immunologic remission with residual structural abnormalities.

Several prognostic factors have been identified that are associated with an unfavorable course. These include advanced age, male sex, reduced renal function at presentation, high levels of nephrotic-range proteinuria, urinary excretion of low molecular weight proteins such as β_2 microglobulin, hypertension, and tubulointerstitial fibrosis or glomerular sclerosis on renal biopsy. As has been shown in many renal diseases, the histologic presence of glomerular sclerosis, advanced vascular sclerosis, or tubulointerstitial disease generally portends an unfavorable renal prognosis.[116] However, these biopsy findings are also a function of age, the presence of concomitant hypertension, and were not independently predictive of poor prognosis when adjusted for creatinine clearance; nor did they predict severity of proteinuria, rate of progression, or response to treatment.[117] Thus, it appears that patients with these pathologic features merely have reduced renal reserve due to a later diagnosis, rather than an inherently more aggressive disease process. Although not commonly employed in treatment algorithms, this same study also showed that a higher degree of complement deposition was associated with a faster rate of disease progression.[117]

The factors that seem to be most important in predicting both a spontaneous remission and its durability are persistent, low grade (subnephrotic) proteinuria and female gender. Ethnicity may also be a factor, because a natural history study in 941 Japanese patients with MN showed excellent long-term outcomes.[118] Several groups have looked at the excretion of urinary proteins as predictors of prognosis in MN. Branten and colleagues found that the combination of high urinary β_2 microglobulin and high urinary IgG are excellent predictors of worsening renal function.[119]

As mentioned previously, this variable natural history of MN makes individual treatment decisions difficult, and interpretation of trials less than straightforward, as there is often no way to clearly differentiate a treatment response from a spontaneous remission, especially when it occurs very early after the start of treatment. Because only a subset of patients will progress to renal failure over an extended period of time, and due to the uncertainty of whether or not a spontaneous remission will occur, therapy with immunosuppressive agents must be tailored to those patients at greatest risk for a poor outcome. Cattran and colleagues have developed a predictive model using data from 184 patients with MN from the Metro Toronto Glomerulonephritis Registry.[120] Based on this model, it is generally acceptable to observe the patient (with the addition of conservative therapy) for 6 months to assess disease trajectory and to await a spontaneous remission, in the absence of rapidly worsening renal function or other life-threatening manifestations of the nephrotic syndrome such as pulmonary embolism. Those with normal renal function and lower amounts of proteinuria (<4 g per day) over 6 months constitute a group at low risk for developing progressive renal insufficiency from their disease. Intermediate levels of proteinuria (4 to 8 g per day) with stable renal function over 6 months represent an intermediate risk group. Those with persistent high grade nephrotic-range proteinuria (>8 g per day) over the course of 6 months, and/or reduced renal function at the outset or a progressive deterioration over 6 months, are at high risk (>75% likelihood) of having further renal deterioration.

A Dutch group follows a similar strategy, with a "wait-and-see" approach for those with nonnephrotic levels of proteinuria, and immediate immunosuppressive therapy for those with evidence of renal failure.[114] Patients with normal renal function are subjected to a risk assessment through the measurement of urinary markers such as β_2 microglobulin and IgG, which reflect both nonselective proteinuria at the level of the glomerulus as well as secondary tubular dysfunction. Those considered to be at high risk of progression to renal failure based on increased levels of excreted IgG and β_2 microglobulin are treated, whereas the rest are managed under a wait-and-see policy with reassessment at 1 year. Although this strategy is appealing in being able to immediately stratify those patients with normal renal function and nephrotic syndrome into those who should or should not be treated, these urinary indices have not been adopted widely.

The prognosis for renal survival that is associated with a response to treatment is in keeping with the tenet that sustained heavy proteinuria is detrimental to renal function. Patients achieving complete remission fare better than those who attain a partial remission, although both have improved renal survival over those who fail to remit at all.[121] Relapse occurs in nearly 25% of patients who achieve complete remission and nearly 50% of those with a partial remission, and renal survival is best in those that never relapse.[121]

Given that a high proportion of nephrotic patients may ultimately achieve remission spontaneously,[115] and that both spontaneous and treatment-induced remissions may take years to become fully apparent, the reader should interpret clinical therapeutic trials in MN cautiously; there are a large number of small trials with relatively short (1 to 2 years) follow-up, and only a few with long-term follow-up data.

THERAPY

It is important to differentiate primary from secondary causes of MN when establishing a treatment plan. Secondary forms of MN are best treated by focusing on the underlying disease process or therapeutic agent. Remission of proteinuria may gradually occur following successful treatment of underlying infection such as hepatitis B or syphilis, the withdrawal of an offending drug, or removal of an associated malignancy. The management of lupus-associated MN, often managed in conjunction with a rheumatologist, is similar to the approaches listed below for primary MN, using calcineurin inhibitors,

cyclophosphamide, or mycophenolate.[122–127] The reader is also directed to excellent recent reviews on the therapy of primary MN for further details.[114,128]

The goals of therapy for patients with MN are the preservation of renal function, reduction of proteinuria, and minimization of complications from the nephrotic syndrome. These aims must be weighed against the risks associated with therapy, especially in light of the variable and unpredictable natural history of the disease itself. Although there have been a number of clinical trials in MN, small sample sizes due to the rarity of the disease as well as residual questions about the risk-benefit of each treatment option still preclude a consensus about first-line treatment in MN. Historically, the best evidence is for the use of alkylating agents or cyclosporine in conjunction with corticosteroids, but the toxicity of these agents and the emergence of newer agents with fewer side effects has maintained the controversy as to the optimal treatment regimen. Although the treatment of primary MN should largely be dictated by the nephrologist, there is certainly a role for a team care approach, including a pharmacist and dietician.

Conservative Therapy

All patients with MN should be started on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) to reduce proteinuria. This recommendation comes in light of their effectiveness in most other proteinuric disease, although the data in MN does not support a major effect on disease outcome.[112,114,121] Diuretics and dietary salt restriction are necessary to treat the edema, due in part to sodium retention by the nephrotic kidney, and to enhance the antiproteinuric effect of inhibitors of the RAS. Additional antihypertensive agents should be added to achieve a target blood pressure goal of 125/75 mm Hg. Statins should be added and titrated to control hyperlipidemia.

Due to the high risk for thromboembolism in MN, prophylactic anticoagulation should be considered for those with serum albumin levels less than 2 g per dL, or even higher levels if the patient has an additional history of previous venous thromboembolism or has other risk factors, such as hereditary thrombophilia, malignancy, the use of oral contraceptives, or immobility. Anticoagulation is clearly indicated in those who present with or have a thromboembolic event in the course of their disease.

Other considerations for nonspecific treatment of the nephrotic state include supplementation with vitamin D, due to its loss with the vitamin D–binding protein in the urine, as well as careful surveillance for infectious disease, as the nephrotic syndrome is an acquired immunodeficiency state due to urinary losses of innate and adaptive immune factors.

Alkylating Agents: Cyclophosphamide and Chlorambucil

A meta-analysis of trials that investigated the use of corticosteroid monotherapy for the treatment of MN failed to show any evidence of efficacy.[129] Instead, typical immunosuppressive regimens for primary MN combine corticosteroids with alkylating agents for six to 12 months. Treatment with cyclophosphamide or chlorambucil in conjunction with corticosteroids is supported by several randomized controlled trials. Cumulative data suggests that 30% to 40% of those treated will achieve a complete remission from their disease. Another 30% to 50% will achieve a partial remission, with only 10% developing progressive renal disease. Relapse may occur in up to 30% of patients within 5 years of discontinuing the alkylating agent. However, these relapses can often be successfully treated with a repeat course of immunosuppressive therapy.

A series of reports from Italy provided convincing evidence for the efficacy of what has become known as the "Ponticelli regimen." This 6-month protocol alternates months of corticosteroid treatment with months of an alkylating agent.[130–132] Three daily 1-g doses of intravenous methylprednisolone are used to initiate the steroid months, followed by oral prednisone at 0.4 to 0.5 mg/kg/day for the remainder of the month. This regimen was originally alternated monthly with daily doses of oral chlorambucil (0.2 mg/kg/day), but a more recent study showed equivalent efficacy with fewer side effects with oral cyclophosphamide (2.5 mg/kg/day). The remission rate at 5 years was 73% for treated patients versus 40% for those who received only supportive therapy in the original study, in addition to better preservation of renal function. A subsequent report detailing 10 years of follow-up in this cohort demonstrated a 10-year dialysis-free survival of 92% (versus 60%) in the group treated with corticosteroids and chlorambucil.

Recently, Jha and colleagues provided confirmatory evidence from a 10-year follow-up of an Indian population with primary MN.[133] This open-label randomized controlled trial compared a 6-month treatment course consisting of alternating months of corticosteroids (as above) and oral cyclophosphamide (2 mg/kg/day) with supportive therapy alone. There were 34 remissions (15 complete) in the 51 treated patients who were followed for the full 10 years, versus only 16 remissions (5 complete) in the 46 patients treated with conservative therapy. Ten-year dialysis-free survival was higher in the treatment arm (89% versus 65%).

Despite the proven success of such cytotoxic therapy, concerns about adverse effects, such as infertility, hemorrhagic cystitis, and long-term bladder malignancy, limit its use, especially in lower risk patients in whom the risks of treatment may outweigh the benefits. Younger patients who desire to have children in the future should be encouraged to bank sperm or eggs prior to the initiation of therapy with alkylating agents, and all patients should be instructed to stop smoking tobacco to reduce the risk of bladder cancer.

The Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Cyclosporine is an alternative, clinically validated immunosuppressive agent used in the treatment of MN.[134]

In 51 patients with steroid-resistant MN, treatment with cyclosporine plus corticosteroids for 6 months followed by a 4-week taper resulted in a 75% remission (complete and partial) rate, versus only 22% in the steroid-only control arm.[135] A frequently noted issue with the use of calcineurin inhibitors such as cyclosporine is the tendency for patients to relapse soon after discontinuation of therapy. Use of steroids in conjunction with cyclosporine appears to reduce relapse rates, as evidenced by a study investigating the use of cyclosporine, with or without steroids, over a 12-month treatment course. Although both groups achieved a remission rate of approximately 80% at 12 months, the relapse rate was lower in the group receiving the adjunctive corticosteroids.[136]

Longer courses of cyclosporine (1 to 2 years) with a slow taper may be necessary to avoid a high rate of relapse. Other investigators have demonstrated that tacrolimus induced a higher rate of remission than conservative treatment alone in heavily nephrotic patients.[137] However, nearly half of these patients had a nephrotic relapse within several months of tapering tacrolimus. Current trials are investigating the use of maintenance agents such as mycophenolate initiated during the taper of the calcineurin inhibitor, in an attempt to prevent these relapses. Thus far, a clinically validated combination has not been found.

The mechanism of cyclosporine in the reduction of proteinuria may be pleiotropic. There is a known effect on T cell activation as is seen in allograft immunosuppression, and there is also a vasoconstrictor effect that likely plays an additional role in the long-term nephrotoxicity of these agents. More recently, Faul and colleagues have provided intriguing evidence that cyclosporine may have direct effects on the podocyte, by inhibiting cathepsin L-mediated degradation of synaptopodin and maintaining the cytoskeleton in a more differentiated state that limits effacement and proteinuria.[138]

Adverse effects of the calcineurin inhibitors are well known, and may be dose limiting given the extended time periods that patients are required to remain on these agents in order to induce and maintain a clinical effect. Nephrotoxicity is of most concern, but other adverse effects include tremor, neuropathy, hypertension, gingival hyperplasia, and hyperglycemia (with tacrolimus).

Treatment of Advanced Disease

Patients sometimes present to medical attention after the disease has been present but undiagnosed for many months to years, and they may have developed significant renal dysfunction by that time. Several studies have shown that immunosuppressive therapy is still of use in selected patients, even in advanced renal disease. MN patients with heavy baseline proteinuria and progressive renal dysfunction who were randomized to cyclosporine had decreased proteinuria and slower progression of renal disease at 1 year, compared to those treated with supportive therapy alone.[139] Based on the toxicity of currently available therapies and this ability to successfully treat MN despite worsening renal function, Wetzels' group in the Netherlands has recommended a restrictive policy of treatment and has provided data that delaying treatment until there is evidence of renal disease progression does not alter long-term outcome.[140]

Alternative Agents

Due to the often severe adverse or nephrotoxic effects associated with the alkylating agents and calcineurin inhibitors, several newer and potentially less toxic agents are under evaluation for the treatment of MN. These studies tend to be of short duration and lack the benefit of long-term follow-up data.

Mycophenolate

Mycophenolate is another important immunosuppressive agent widely used in renal transplantation and lupus, but thus far has only been studied for the treatment of MN in the form of small trials of limited duration. The results have been varied. Initial studies[141,142] demonstrated that mycophenolate could reduce proteinuria in MN patients who had not responded to other conventional therapies. Although a recent randomized controlled trial demonstrated no effect of mycophenolate monotherapy in patients with normal renal function and nephrotic levels of proteinuria, compared to conservative antiproteinuric therapy alone,[143] its combination with corticosteroids may be more effective. Two randomized controlled trials[144,145] and one nonrandomized study that used a matched historically treated control group[146] all showed a composite remission rate of approximately 65% in response to 6 to 12 months of therapy with mycophenolate and steroids, compared to rates of 67% to 80% in the control groups treated with alkylating agents and steroids. The median lengths of follow-up ranged from 15 to 23 months. One study revealed a relapse rate of nearly 40% in the mycophenolate group.[146] Given these small studies with insufficient long-term follow-up, mycophenolate is not a first-line agent for the treatment of MN but may be considered, with adjunctive corticosteroids, if standard therapies are not effective or cannot be tolerated.

Rituximab

Rituximab is a B cell depleting humanized anti-CD20 antibody that has been widely used in the treatment of B cell lymphomas and a number of rheumatologic diseases. The rationale for its use in MN is plausible, given the role of humoral immunity and the presence of B cells within the kidney.[110] Although rituximab appears to induce remission with an initial efficacy that is similar to that provided by alkylating agents in combination with corticosteroids,[147] long-term data on dialysis-free survival have yet to be reported. In addition, there have not been consistent dosing protocols,[148–150] leaving the optimal treatment regimen still in question. A recent open-label trial that benefited from 24 months of follow-up involved the treatment of 20 high-risk MN patients with four

weekly injections of 375 mg per m^2 body surface area.[151] Of the 18 patients who completed the 24 months (two were discontinued and switched to other agents due to a perceived lack of clinical benefit), there were 4 complete and 12 partial remissions. One other patient achieved a complete remission at 18 months, but had relapsed by the final time point. Patients who have not responded to other immunosuppressive therapies are not precluded from demonstrating a clinical response to rituximab.[152] Potential short-term adverse effects of rituximab seem limited to a mild infusion reaction, but longer term side effects such as the development of progressive multifocal leukoencephalopathy, as has been seen in patients with lupus treated with this agent, await longer term follow-up data.

Adrenocorticotrophic Hormone

Another intriguing agent that may have clinical utility in MN is adrenocorticotrophic hormone (ACTH). In an open-label study, Berg and colleagues treated 14 MN patients subcutaneously with a synthetic form of ACTH over an 8-week period, and achieved short-term results similar to those described previously.[153] Another small trial randomized 32 treatment-naïve patients with primary MN who had preserved renal function to either 1 year of ACTH therapy or 6 months of alternating therapy with alkylating agents and prednisone.[154] At 1 year, 87% in the ACTH group had achieved a complete or partial remission, versus 93% in the standard therapy group. Although not significant, there were twice as many complete remissions in the ACTH group. The synthetic formulation of ACTH used in these European studies differs from the form available in the United States, and there are no long-term follow-up studies that document the efficacy of this agent. Because exogenous corticosteroids given as monotherapy lack therapeutic effect in MN, the effects of synthetic ACTH are likely to extend beyond merely increased adrenal release of endogenous corticosteroids. The 13 N-terminal amino acids of ACTH comprise another small immunomodulatory hormone known as alpha-melanocyte stimulating hormone, and it is possible that some of the effect in MN may be due to these melanocortin peptides.

CONCLUSION

It is clear that a significant proportion of patients with MN will require treatment with immunosuppressive agents to cause remission of disease and to preserve their long-term renal function. A 6-month or longer period of conservative therapy with antiproteinuric therapy and diuretics is often warranted, in the absence of already-impaired or worsening renal function, to identify those who might spontaneously remit. Once the utility of anti-PLA_2R antibodies has been validated in larger studies, there might also be a role for the serologic monitoring of patients to assess immunologic disease activity. Clinically validated treatment protocols for MN include alkylating agents or cyclosporine, both in combination with corticosteroids, although newer agents such as rituximab or mycophenolate may also permanently join the armamentarium if the effects they have shown in small studies of limited duration hold up in the longer term.

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