89
Membranous Nephropathy

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Abstract Membranous nephropathy (MN) is a glomerular disease characterized by nephrotic syndrome and typical changes on renal biopsy. MN could be idiopathic or secondary to other conditions. Both idiopathic form and secondary forms are mediated by autoantibodies supporting the autoimmunity base of this disease. The underlying pathogenesis of the idiopathic form is still obscure, but diagnostic criteria based on clinical presentation and renal biopsy are suggested in this chapter, provide us diagnostic and therapeutic tool and help us to assess one prognosis.

Keywords Membranous nephropathy · nephrotic syndrome · renal biopsy · subepithelial deposits · in situ autoantibodies

Membranous nephropathy (MN) is one of the glomerular diseases; as in other glomerular diseases, the name arises from the histopathological appearance in biopsy.

MN is accounting for one-third of biopsy results taken from adult patients present with nephrotic syndrome (1).

On light microscopy, one can see a glomerular basement membrane thickening with no proliferation or infiltration (2).

MN is mediated by different autoantibodies and immune complexes deposition with subsequent complement system activation.

MN could be secondary to different conditions (Table 89.1), but it is most often idiopathic; the scope of this chapter is to define diagnostic criteria for idiopathic MN.

TABLE 89.1. Major secondary causes of membranous nephropathy (MN).

SLE (WHO class V)
Hepatitis B virus
Hepatitis C virus
Malignancy (commonly solid tumors: lung and GI)
Renal transplantation
Bone marrow transplantation
Sarcoidosis
Sjögren's syndrome
Tertiary syphilis
Malaria
Schistosomiasis
In association of other glomerular diseases
Drugs
Gold salts
Penicillamine
NSAIDS (diclofenac is most commonly associated)
Anti-TNF therapy (infliximab, etanercept, adalimumab)
Bucillamine
Tiopronin
Captopril

Epidemiology

In the past, the majority of adult patients with nephrotic syndrome had the biopsy diagnosis of MN. Presently only one-third of patients with nephrotic syndrome are diagnosed with MN with increase diagnosis of focal segmental glomerulosclerosis especially in the black population (1).

MN distributes evenly in all races and in both sexes; the idiopathic type is more common in white male over the age of 40 years. When a young woman is diagnosed with MN, we have to suspect lupus as the underlying cause.

When the disease is diagnosed in children (represent less then 5% of nephrotic syndrome in this population), one should look for hepatitis B infection (3). Still the majority of MN cases are idiopathic (75%).

Pathology

The classical appearance on light microscopy is diffusely distributed glomerular basement membrane thickening without significant cellularity (2). In early stage, the

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glomeruli may appear normal, but in late stages, one will see diffuse sclerosis associated with tubulointerstitial changes. There are different classifications and staging systems of MN biopsy results, which have no effect on patient management and prognosis.

Diffuse granular pattern of IgG and C3 along the glomerular basement membrane (GBM) is seen in immunofluorescence microscopy. In electron microscopy, characteristic findings are subepithelial dense deposits located on the outer aspect of the GBM, effacement of podocytes foot processes and deposition of extracellular matrix between deposits (spikes).

The pathological findings described above are common both to idiopathic and secondary MN, but there are subtle differences that help to differentiate between idiopathic and secondary forms of GN.

In idiopathic MN, the deposits seen in EM are located subepithelial compared with secondary forms, where the deposits could be seen also in the mesangium and subendothelium.

In the idiopathic form there are no tubuloreticular structures inside the glomerular endothelium, characteristic findings of lupus MN.

Pathogenesis

In the past, MN was thought to be a presentation of chronic serum sickness. With research evolvement, MN like other glomerular diseases is now thought to be an autoimmune disease (4).

Heymann and colleague (5) described the first model of MN in rats called Heymann nephritis; this model is the base of our understanding of MN pathogenesis.

In immune complex-mediated process, one expect to see deposits in the mesangium or subendothelium (like in lupus MN), but in the idiopathic form of MN, there are isolated deposits in the subepithelial area.

Couser et al. (6) showed that subepithelial deposits result from direct in situ binding of IgG antibodies against self-antigens presented on podocytes foot processes.

The IgG deposits are IgG4 in the idiopathic form compared with other immunoglobulins and different complement deposits seen in the secondary forms; IgG4 is produced in type 2 immune response of Th2 lymphocytes (7). The antigen that involved in the idiopathic form of MN needs to be found. But there is a single report (8) on antibodies developed against podocyte neutral endopeptidase that lead to MN. In the secondary forms of MN, there are several known antigens described by Ronco et al. (9).

The glomerular injury is mediated by complement activation (10). C5b-9 stimulates podocytes to produce catalytic enzymes and to secrete different cytokines leading to podocytes dysfunction and barrier insufficiency with subsequent massive proteinuria.

Clinical Manifestations

Most patients present with a nephrotic syndrome (80%). In 70% of patients, the blood pressure is normal and there are no signs of renal failure unless there is an associated glomerular disease or one of the secondary causes of MN that can lead to a renal failure in different mechanism, keeping in mind that nephrotic syndrome by itself is a hypercoagulable state that can lead to a renal vein thrombosis with a further insult to renal function.

Urinary Findings (Table 89.2)

Proteinuria can range from a non-nephrotic range (<3 g/24 h urine collection) to a dozen of grams per day. The proteinuria is non-selective. In urine microscopy one can see fatty casts, oval fat bodies and lipid droplets. RBC casts are rare, but microscopic hematuria is seen in 50% of cases. Sometimes glycosuria is seen in normoglycemic patients.

Biochemical Findings (Table 89.2)

Hypoalbuminemia and severe hyperlipidemia are seen in most cases.

Diagnostic Criteria (Table 89.3)

The diagnosis of idiopathic form of MN is based on three criteria: renal biopsy (Table 89.4), appropriate clinical presentation (Table 89.2) and excluding an alternative diagnosis. In every patient with MN or nephrotic range

TABLE 89.2. Urinalysis and blood biochemistry in idiopathic membranous nephropathy (MN).

Non-selective proteinuria	100%
Nephrotic range proteinuria	80%
Microscopic hematuria	50%
Glycosuria	>50%
Urine microscopy	
Fatty casts	up to 90%
RBC casts	rare (consider other diagnosis)
Blood biochemistry	
Hypoalbuminemia	>90%
Hyperlipidemia	>90%
Azotemia	rarely

TABLE 89.3. Diagnostic criteria for idiopathic MN.

1. A nephrotic syndrome
2. The classic pathological picture in renal biopsy (Table 89.4)
3. Exclusion of other possible etiologies (Tables 89.1 and 89.5)

All criteria must be met.

TABLE 89.4. Renal biopsy findings in idiopathic membranous nephropathy (MN).

Light microscopy: Basement membrane thickening without a significant cellularity.
Immunofluorescence: Diffuse granular pattern of IgG 4 and C3 along the GBM.
Electron microscopy: Isolated subepithelial deposits.
No tubuloreticular structures inside the glomerular endothelium.
No subendothelial or mesangial deposits.

TABLE 89.5. Laboratory tests ordered in membranous nephropathy (MN).

ANA
Complement levels
Hepatitis B serology
Hepatitis C serology
Routine screening for malignancy (e.g., colonoscopy in patients over the age of 50 years) unless there are directing signs and symptoms.

proteinuria, different laboratory tests are ordered (Table 89.5) to rule in or out other diagnosis. Even though the autoimmunity nature of MN is well established by biopsy findings, immunohistochemistry studies and significant response to an immunosuppressive therapy, the underlying mediating antibodies need to be found and specific autoantibodies are not considered part of MN diagnosis.

Prognosis

MN has a benign course; spontaneous remission occurs in 30% of patients. It happens mostly in the first 2 years but can occur at any time along the course of the disease. Schieppati et al. (11) studied the natural history of the idiopathic form of MN. In this study, 37 patients with MN were followed for 5 years and 65% had a complete or partial remission without the use of steroids or other immunosuppressive drugs. The prognosis in this study was related to the level of proteinuria, with a worse prognosis in cases present with massive proteinuria.

Louis et al. (12) reviewed the literature, listing the prognostic factors that can help to identify the patients at risk of an end-stage kidney disease, who can benefit from an early immunosuppressive intervention. Their review concluded that age, glomerular stage on biopsy and hypertension are not useful as predictors. In contrast, young females with normal plasma creatinine, without tubulointerstitial changes or sclerosis, and without nephrotic syndrome or massive proteinuria (the most important prognostic factor) have very good prognosis. Cumulative prognostic factors that are sensitive and specific enough and help to direct the treatment and to assess disease activity are urinary levels of C3dg, C5b-9, IgG and B2 microglobulin. These tests are not available in most clinical laboratories.

Treatment

To treat or not to treat is a significant question asked in every patient with idiopathic MN, especially when considering the possibility of spontaneous remission in 30% of patients and the significant adverse effects of the immunosuppressive therapy (13).

The questions need to be asked are: When to treat? and with what to treat? Obviously patient with several risk factors for an end stage kidney disease will benefit from the therapy but for most patients the decision is complicated and depends mostly on the knowledge and experience of the treating physician.

In the secondary forms of MN, the therapy is directed to the underlying cause.

In any patient with a nephrotic syndrome including those with MN, our goals are to treat the edema, control blood pressure, to lower blood cholesterol and to employ angiotensin-converting enzyme inhibitors to reduce proteinuria.

The risk for progression to an end-stage kidney disease is assessed and patients are assigned to different risk groups. The low-risk group (normal plasma creatinine, proteinuria <4 g) is treated conservatively.

Two therapeutic approaches are considered beneficial in the medium risk group (normal plasma creatinine, proteinuria between 4 and 8 g on a maximal conservative treatment). Monthly cycling of corticosteroids and cyclophosphamide on alternate months over 6 months period is one accepted approach (14); the other alternative is using cyclosporine as a single drug for 6 months period (15). The high-risk group (deteriorating renal function and or proteinuria more then 8 g) will benefit from a combined therapy with steroids and cytotoxic drugs. Few cytotoxic drugs are suggested in this indication, including chlorambucil, cyclosporine and cyclophosphamide.

New therapies have been used with a great success in resistant cases, including mycophenolate mofetil (16) and rituximab (17).

The conditions of 30% of the patients deteriorate on therapy and few of them depend on dialysis or undergo kidney transplantation. The advances in understanding of autoimmunity will provide us better understanding of this disease and help us to help these patients.

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