Therapy of Membranous Nephropathy Associated With Malignancy and Secondary Causes

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Membranous nephropathy (MN) most commonly is idiopathic, but secondary causes are common in children and in older adults. The most common secondary causes of MN in industrialized countries include malignancy and systemic lupus erythematosis. Infectious causes (hepatitis B, quartan malaria, schistosomiasis) remain the most common etiologies in endemic areas. In this article we describe the clinical approach to patients with MN associated with malignancy and other common secondary causes. Treatment of secondary MN generally targets the primary disease rather than the renal lesion.

MEMBRANOUS nephropathy (MN) is the most common cause of adult nephrotic syndrome worldwide,[1] and is idiopathic in the majority of cases. However, a secondary cause may be detected in up to 20% of adult cases (see Table 1). The most common secondary causes of MN in industrialized countries include malignancy and systemic lupus erythematosis. Infectious causes (hepatitis B, quartan malaria, schistosomiasis) remain the most common etiologies in endemic areas. The incidence of secondary causes varies with age, with older adults having an increased incidence of MN secondary to malignancy.[2] Idiopathic MN is also uncommon in children who have an increased incidence of associated infections.

MN ASSOCIATED WITH MALIGNANCY

An association between MN and malignancy was first noted in the 1960s,[3] most commonly with tumors of the lung and gastrointestinal tract.[4] A wide range of other tumors also have been associated, although these are not sufficiently common to establish any causal relationship (Table 1).

The incidence of malignancy in patients with MN has been reported to range from 1.4% to 11%, with most studies reporting an incidence of 7% to 8%.[2,3,5-10] In older age groups (age $>$ 60 y) the incidence of malignancy has been reported to be as high as 22%.[8] Despite this, autopsy series of patients with cancer, although often showing minor glomerular immunoglobulin deposition, rarely show subepithelial deposits, and clinical renal disease is uncommon.[11,12] It also should be recognized that the incidence of cancer in the older general population is increased, and it has been suggested that the relationship between malignancy and MN may be overstated.[13]

Pathophysiology of MN

Idiopathic MN is characterized by thickening of the glomerular basement membrane seen on light microscopy caused by the formation of subepithelial immune deposits and the deposition of new basement membrane material. In secondary forms of MN the immunopathologic appearance is similar.[4] The presence of certain features, however, may suggest a secondary cause including mesangial cell proliferation, mesangial or subendothelial deposits by electron microscopy, and immunoglobulin A or C1q deposition by immunofluorescence.

Insights into the pathogenesis of idiopathic MN have been gained from investigation of the Heymann nephritis models in rats that closely mimic the human disease. In this model antibodies to a glomerular epithelial cell (podocyte) antigen (Heymann nephritis antigenic complex consisting of megalin and the receptor-associated protein) bind in situ on the podocyte foot process membranes and produce local complement activation. The insertion of C5b-9 into the glomerular epithelial cell (GEC) membrane leads to sublytic podocyte injury, cell activation, and the release of mediators (reactive oxygen species, proteases, and inflammatory cytokines) that injure the underlying glomerular basement membrane (GBM) and lead to loss of glomerular barrier function and proteinuria.[14] In humans, megalin is not expressed in the podo-

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Table 1. Secondary Causes of MN

Tumors	Carcinoma (lung, colon, rectum, stomach, breast, kidney), melanoma, leukemia, non-Hodgkin's lymphoma
Infections	Hepatitis B, hepatitis C, syphilis, quartan malaria, schistosomiasis, filariasis, hydatid disease, leprosy, scabies, tuberculosis
Drugs and toxins	Gold, penicillamine, bucillamine, captopril, probenecid, nonsteroidal anti-inflammatory drugs (NSAIDs), tiopronin, lithium, mercury, formaldehyde, hydrocarbons
Autoimmune diseases	Systemic lupus erythematosis, rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, Graves disease, Hashimoto's thyroiditis, dermatomyositis, primary biliary cirrhosis, bullous pemphigoid, dermatitis herpetiformis, ankylosing spondylitis, Guillain Barre syndrome, myasthenia gravis
Miscellaneous	Diabetes mellitus, sarcoidosis, sickle cell anemia, Kimura disease, sclerosing cholangitis, systemic mastocytosis, Gardner-Diamond syndrome

cyte,[15] and the nature of the intrinsic glomerular antigen in human disease remains elusive, although a recent case report has established that typical human MN may be caused by antibody to another podocyte antigen, in this case neutral endopeptidase.[16]

In malignancy-associated MN, it has been postulated that the disease is mediated by subepithelial immune complexes composed of tumor antigen and antibody. The subepithelial immune complexes in MN are believed to represent in situ immune complex formation rather than passive trapping of circulating preformed complexes. Tumor antigens alone may be deposited in the subepithelial space (planted antigen) accompanied by activation of an antibody response, leading to in situ immune complex formation and complement activation at the site where the antigen initially localized—in this case the subepithelial space. Such antigens are likely to be small and positively charged to allow passage across the GBM. In some patients, tumor-specific antigens have been detected in glomerular deposits and serum antibody from a patient with cancer and MN was shown to react with an antigen deposited on the GBM.[17] In patients with MN and colon cancer, carcinoembryonic antigen has been detected in the glomeruli of some patients,[18,19] but not in others.[10,17] Furthermore, antibodies to lung tumor antigens have been eluted from postmortem kidneys in patients with lung cancer and MN.[20,21] However, the presence of tumor antigens or antibody in the damaged glomeruli does not necessarily imply causation because there is a high prevalence of circulating immune complexes in cancer patients,[22] and the increased glomerular permeability may facilitate nonspecific trapping of tumor antigen or immune complexes in the glomerulus.

Alternative mechanisms to explain the association between MN and malignancy have been postulated including the presence of shared epitopes between tumor and podocyte antigens, and impaired immune function secondary to malignancy, allowing the development of autoantibodies to normal GEC antigens.

Clinical Features

Minor urinary abnormalities are common in patients with malignancy and minor glomerular abnormalities frequently are noted at autopsy.[23] Patients with MN associated with malignancy typically present with edema and nephrotic range proteinuria with a benign urine sediment. Renal function often is well preserved. The tumor usually is overt at the time of disease presentation. However, in up to 40% of patients, nephrotic syndrome may present before the diagnosis of malignancy. The tumor typically is detected readily at this time by history and physical examination and simple investigations. Occult tumors usually become apparent within 12 months.[2,4]

Supporters of a causative role for malignancy in MN have cited cases in which the nephrotic syndrome apparently is cured by resection or treatment of the tumor,[4,9,24] and relapse of MN has been reported in a patient after relapse of gastric cancer[25] and Hodgkin's disease.[26] However, it should be noted that up to one third of patients with idiopathic MN undergo spontaneous remission, and chemotherapy for the tumor may be effective therapy for the MN. In addition, there are cases reported of patients in whom MN did not resolve

despite apparently successful treatment of the tumor.[10,17]

Management

With regard to the focus of this issue on therapy, it is a general fact that when membranous nephropathy is diagnosed in the setting of malignancy the primary treatment is directed at the cancer. Nonspecific treatment of nephrotic syndrome with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, HMG-CoA reductase inhibitors, and aspirin should be used in nephrotic patients. Immunosuppression for MN generally should be avoided because this may exacerbate the malignancy. The tumor prognosis determines patient outcome, but the malignant disease often is advanced when detected in this setting. A 75% mortality 12 months after the diagnosis of MN and 3 months after the diagnosis of malignancy has been reported.[4] It should be recognized that the time to remission in MN after successful therapy often is slow (months to years) and that successful treatment of a malignancy may not result in resolution of the proteinuria for 6 to 18 months.

Tumor Screening in MN

A more difficult question is the investigation of the patient with MN who is not known to have a malignancy. In general, the risk for malignancy is greatest in men and increases with age. It is unusual to find a malignant cause in those younger than 40 years of age. The most common tumors are those of the lung and gastrointestinal tract. The extent of investigation required has been debated because most tumors are obvious or present within a short period of time of the presentation with proteinuria. In older patients (age $>$ 50 y), we recommend a limited tumor work-up consisting of a thorough history (including risk factors and family history) and physical examination. Investigations should include stool guaics, colonoscopy, chest radiography, mammography, and carcinoembryonic antigen and prostate-specific antigen measurements. It should be noted that these recommendations are similar to the recommended cancer screening investigations for the general population. Occult malignancy after initial investigation is uncommon, but patients should be followed-up carefully.[2]

A second question is the role of renal biopsy examination in patients with malignancy. In patients with a poor tumor prognosis a renal biopsy examination may not be indicated. Additionally, in patients with solid tumors and nephrotic syndrome the underlying glomerular disease is MN in 60% to 80% of patients, similar to the incidence of minimal change disease in children in whom diagnostic biopsy examinations are not performed routinely.[3,13] However, nephrotic syndrome occasionally may be found with malignancy owing to other glomerular diseases including minimal change in Hodgkin's disease, membranoproliferative disease secondary to chronic lymphatic leukemia and amyloidosis secondary to renal cell carcinoma, multiple myeloma, or lymphoproliferative diseases. In view of the possibility of finding a potentially reversible glomerular lesion, a renal biopsy examination should be considered if warranted by clinical circumstances.

MN ASSOCIATED WITH INFECTION

Hepatitis B

Hepatitis B virus (HBV) infection is associated with a variety of renal diseases including MN, polyarteritis nodosa, membranoproliferative glomerulonephritis (MPGN), and a serum sickness-like syndrome. MN is the most common renal manifestation and develops in the chronic carrier state (hepatitis B e antigen [HBeAg] positive [+ve]; hepatitis B surface antigen [HBsAg] +ve). In adults, HBV accounts for less than 1% of MN in the United States, but accounts for 30% to 40% in endemic regions.[27] In children idiopathic MN is uncommon and HBV accounts for approximately 20% of MN in children in the United States.[27]

In patients with HBV associated with MN, the pathogenesis is considered to be owing to the formation of immune complexes of HBeAg and HBeAb in the subepithelial space. Immunostaining reveals predominantly HBeAg deposition along glomerular capillary walls, but HBsAg and HBcAg also may be detected.[28] The deposits presumably form in situ as previously discussed under idiopathic MN. The possibility that the disease results from autoimmune mechanisms involving podocyte antigens, as discussed earlier for idiopathic MN, and that the glomerular deposition of HBV antigens is secondary, has not been excluded because many patients with chronic liver disease exhibit a variety of autoantibodies.

Clinical Features

HBV associated with MN usually presents with proteinuria and edema with normal blood pressure. Renal insufficiency is rare, particularly in children. Most patients will have abnormal liver function tests. Children (typically boys aged 2-12 y) usually have a mild transaminitis, but not chronic liver disease, whereas adults typically have chronic active hepatitis.

Hepatitis serology reveals the presence of HBsAg and anti-HBc antibody in most patients. The majority of patients also have circulating HBeAg (60% to 80%). Circulating HBeAg correlates with clinical activity and loss of antigen and conversion to antibody to the hepatitis B e antigen (HBeAb) status correlates with recovery of nephrotic syndrome. This is followed by seroconversion to antibody to the hepatitis B surface antigen.[29] Complement studies commonly reveal a low C3 and C4 (15% to 64%) and circulating immune complexes (80%),[27] which rarely are found in idiopathic MN.

Renal biopsy examination reveals features similar to idiopathic MN with subepithelial deposits, although minor subendothelial and mesangial deposits frequently are present as well. Electron microscopy may reveal viral-like particles in subepithelial and subendothelial spaces and within glomerular cells.[27]

It should be recognized that proteinuria in patients with HBV may not be exclusively the result of HBV infection. A high incidence of proteinuria in non–HBV-infected family members has been reported, suggesting that other environmental or infectious agents may be contributing.[30]

Treatment

The treatment of HBV-associated MN with steroids and alkylating agents as is performed in idiopathic MN may cause more harm than good by enhancing viral replication and impairing seroconversion. Many children with HBV-associated MN undergo spontaneous resolution with a cumulative remission rate of 64% at 4 years.[29, 31] Initial observation of these children is appropriate with general supportive measures. Antiviral therapy can be considered in those who remain HBeAg positive and have persistent disease (> 1 year) or in those who are likely to progress (older children with focal sclerosis on biopsy examination). Interferon alfa therapy was shown to be effective in an open randomized study of children (age < 14 y).[32] Treated patients were free of proteinuria by 3 months, with HBeAg seroconversion by 5 to 6 months. The interferon alfa therapy was surprisingly well tolerated in this study.

Unlike children, adults typically develop a progressive disease and may sometimes warrant antiviral therapy.[33] Although data are not available to document this, renal indications for starting such therapy likely would be similar to those in idiopathic MN and relate to the amount and duration of proteinuria or evidence of loss of renal function.[34] Current options for antiviral treatment include interferon alfa and lamivudine. In HBV-positive patients without renal disease both agents have been shown to have similar efficacy (30% to 40% clearance HBeAg with 10% to 30% seroconversion to HBeAb), and both are more efficacious with low levels of circulating HBV DNA and in patients with elevated transaminase levels.[35] Case reports and small series show successful therapy with interferon alfa in patients with HBV-associated MN with roughly 50% to 75% showing a sustained response.[36-38] Lamivudine therapy has not been reported in patients with HBV-associated MN, but a serologic response has been described in hemodialysis patients.[39] Lamivudine therapy is cheaper with fewer side effects, but requires a longer duration of therapy that may produce resistant mutant strains.

Hepatitis C

Although hepatitis C virus (HCV) typically causes a MPGN related to mixed cryoglobulinemia, there are several reports of MN associated with HCV.[40-42] De novo MN in HCV-positive renal transplant patients also has been described.[43] One case has reported HCV core protein deposits in glomeruli by immunofluorescence,[44] but this could simply represent coincidental disease because both MN and HCV infection are relatively common. If HCV infection is causal in the glomerular lesion, the reason for the development of MN in HCV-infected patients is unclear. Possibilities include: (1) the deposits represent in situ formation of immune complexes containing rheumatoid factor and cryoglobulin containing immune aggregates, a process that likely accounts for the more typical subendothelial deposits; (2) the subepithelial deposits represent relocation of previous subendothelial deposits that have dissociated to cross the GBM and reform in the subepithelial space; or

(3) the deposits, similar to those in idiopathic MN, represent formation of autoantibodies reactive with podocyte membrane antigens. It is well recognized that patients with chronic inflammatory hepatic disorders have a high incidence of autoantibody formation.[45]

Unlike patients with the more common HCV-associated MPGN, in the reported cases of HCV-associated MN, patients presented with heavy proteinuria with normal serum complement levels and negative cryoglobulins and rheumatoid factor. In most cases, liver biopsy examination showed evidence of chronic active hepatitis.[40]

There are limited data on the treatment of this condition, but in addition to nonspecific antiproteinuric treatments, antiviral therapy with interferon alfa and ribavirin should be considered as in HCV-associated MPGN.[46] Therapy with interferon alfa alone has been followed by improvement in proteinuria in 2 patients with MN, however, relapse is common on discontinuing therapy.[40] A few cases of co-infection with HBV and HCV have been reported with a similar clinical presentation and course to HBV-associated disease alone.[47]

Other Infections

MN has been reported with a number of other infections although some of these associations remain debatable (Table 1). Glomerular disease and nephrotic syndrome occur much more commonly in tropical countries than in industrialized countries.[48] Nephrotic syndrome accounts for 2% to 5% of all hospital admissions in Nigeria and Uganda. Most tropical glomerulonephritides are caused by chronic parasitic infection. MN has been reported with quartan malaria and hepatosplenic schistosomiasis, although a steroid-resistant membranoproliferative lesion is much more typical with these infections. In general, these chronic immune complex glomerulonephritides respond poorly to therapy of the underlying infection.

MN ASSOCIATED WITH DRUGS

MN has been associated with a number of drugs and toxins but most notably gold and penicillamine in the treatment of rheumatoid arthritis[49] and nonsteroidal anti-inflammatory drugs.[50] Most cases of MN secondary to gold or penicillamine develop within the first 6 to 12 months of treatment. Discontinuing the drug leads to resolution of the proteinuria, usually within 12 months, although this may take up to 3 years.[49] The subepithelial location of the immune complexes and separation of these from phagocytic cells in the circulation may be responsible for the delayed recovery. Progressive chronic renal failure is very uncommon.

The course of MN secondary to other drugs and toxins has not been well described, but the majority resolve without chronic sequelae once the antigenic stimulus has been removed.[50]

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