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REVIEW ARTICLE

Membranous nephropathy: A review on the pathogenesis, diagnosis, and treatment

Wei Ling Lai [a], Ting Hao Yeh [a], Ping Min Chen, Chieh Kai Chan, Wen Chih Chiang*, Yung Ming Chen, Kwan Dun Wu, Tun Jun Tsai [a]

Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

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In adults, membranous nephropathy (MN) is a major cause of nephrotic syndrome. However, the etiology of approximately 75% of MN cases is idiopathic. Secondary causes of MN are autoimmune diseases, infection, drugs, and malignancy. The pathogenesis of MN involves formation of immune complex in subepithelial sites, but the definite mechanism is still unknown. There are three hypotheses about the formation of immune complex, including preformed immune complex, *in situ* immune-complex formation, and autoantibody against podocyte membrane antigen. The formation of immune complex initiates complement activation, which subsequently leads to glomerular damage. Recently, the antiphospholipase A_2 receptor antibody was found to be associated with idiopathic MN. This finding may be useful in the diagnosis and prognosis of MN. The current treatment includes best supportive care, which consists of the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, lipid-lowering agents, and optimal control of blood pressure. Immunosuppressive agents should be used for patients who suffer from refractory proteinuria or complications associated with nephrotic syndrome. Existing evidence supports the use of a combination of steroid and alkylating agents. This article reviews the epidemiology, pathogenesis, diagnosis, and the treatment of MN.

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* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail address: wcchiang@ntu.edu.tw (W.C. Chiang).
[a] These two authors contributed equally to this paper.

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Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults.[1] Patients with MN usually present with severe proteinuria, edema, hypoalbuminemia, and hyperlipidemia. MN is a glomerulopathy with characteristic histopathological features of subepithelial immune-complex deposit and subsequent thickening of glomerular basement membrane. The etiology of approximately 75% of MN cases is idiopathic. During the past decade, several studies have led to the identification of possible pathogenesis. Although spontaneous remission occurs in approximately one third of MN patients, 30—40% of the patients progress toward end-stage renal disease within 5—15 years. All patients with MN should receive excellent supportive care. Immunosuppressive agents are central to the treatment of MN. Risk and benefit for prescription should be individualized, and patient-dependent factors, such as age and comorbidities, should be considered. The purpose of this review is to highlight these considerable progresses and discuss their implications in clinical practice.

Epidemiology

The incidence of primary MN is 10 per million populations per year.[2–4] The peak incidence of MN is in the fourth to fifth decade of life.[5] A pooled analysis of studies of patients with idiopathic MN found a 2:1 predominance of men.[6]

Approximately 75% of the MN cases occur as an idiopathic (primary) disease.[7] The remainder, as secondary MN, is associated with autoimmune diseases (e.g., systemic lupus erythematosus), infection (e.g., hepatitis B or hepatitis C), drugs (e.g., penicillamine, gold), and malignancies (e.g., colon or lung cancer).

In patients older than the age of 60 years, MN is associated with malignancy in 20—30% of cases. In a cohort study in France, the incidence of cancer was significantly higher in these patients than in the general population (standardized incidence ratio = 9.8 for men and 12.3 for women). The most common malignancies were lung cancer and prostate cancer. The frequency of malignancy increased with age.[1] In another large cohort study in Norway, the incidence of cancer was significantly higher in patients with MN than in the age- and sex-adjusted general population (standardized incidence ratio, 2.25). The median time from diagnosis of MN to cancer was 60 months. Patients with MN who developed cancer were older (65 years vs. 52 years, $p < 0.001$).[8] Although spontaneous remission of the nephrotic syndrome occurs in approximately one third of patients, 30—40% of the patients progress toward end-stage renal disease within 5—15 years.[1]

Pathogenesis

The formation of immune complex in subepithelial sites is central to MN. However, the mechanisms of deposit formation remain elusive. Three major putative mechanisms are proposed so far.

The first hypothesis stresses the passive entrapment of preformed immune complexes (Fig. 1A). Most protein might be forced across the glomerular capillary wall due to higher intraglomerular pressure and negatively charged capillary wall. Lupus nephritis is an excellent example of immune-complexes-related human kidney disease. Preformed immune complexes, containing antibodies to double-stranded DNA, histone, ribonucleoproteins, and others, are found in patients with systemic lupus erythematous.[9] In addition, levels of circulating immune complexes were found to correlate with disease activity.[10] Anti-DNA and DNA immune complexes were detected in glomerular elutes from lupus patients.[11] Therefore, it was proposed that immune-complex deposits in the glomeruli of lupus patients reflect entrapment of preformed immune complexes.

The second hypothesis is that the pathogenic circulating antigens are localized, or planted, in the subepithelial sites, and these antibodies subsequently form *in situ* immune-complex deposits with antibodies (Fig. 1B). The hepatitis B virus (HBV) was found to be strongly associated with glomerulonephritis, especially MN. With regard to pathologic findings in patients with HBV-related glomerulonephritis, HBeAg is found to be distributed along the glomerular capillary wall. Clusters of viral-like particles were detected within immune deposits. It is proposed that the HBV antigen might serve as the circulating antigens, which are localized in the glomerulus. Further interaction with antibodies forms immune-complex deposits in HBV-related glomerulonephritis patients.[12–14] In addition, hepatitis C virus antigens,[15–17] *Helicobacter pylori* antigens,[18,19] tumor antigens,[20–24] and thyroid antigens[25–28] were found in immune deposits in patients with secondary MN.

In a small group of children with MN, cationic bovine serum albumin (BSA) acts, through binding to the anionic glomerular capillary wall, as an externally planted antigen. Antibodies then bind to the planted antigen to form the immune complex [immunoglobulin (Ig)G4 and IgG1]. Cow's milk is the major source of BSA, which is processed by the intestine and modified by intestinal microbiota. In comparison with normal individuals, the immature intestinal wall of these patients may be more permeable to cationic BSA and allow for the entry of BSA antigen into circulation. Elimination of BSA from the diet might be beneficial in BSA-related MN. The titer of circulating BSA and anti-BSA antibodies strongly correlates with the clinical condition and decreases substantially during remission.[29] It is noteworthy that the *in situ* mechanism also contributes to pathogenesis of lupus nephritis. DNA, nucleosomes, histone, and other antigens can bind to glomeruli, and serve as planted antigen.[30]

The third mechanism focuses on the effect of autoantibodies that bind to podocyte membrane antigens, thereby causing subepithelial deposition of immune complex (Fig. 1C). The Heymann nephritis model has been extensively studied as a model of MN. It was first described in 1959 and played a vital role in the identification of a culprit antigen.[31] In 1978, Couser et al[32] reported the formation of subepithelial immune complex following the direct perfusion of bloodless kidneys with the pathogenic IgG antibody. This study established a novel mechanism, *in situ* immune-complex formation, in the development of MN.

Several possible culprit antigens were identified in experiments. Kerjaschki and Farquhar in the early 1980s