The Role of Complement in Membranous Nephropathy

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Summary: Membranous nephropathy (MN) describes a histopathologic pattern of injury marked by glomerular subepithelial immune deposits and collectively represents one of the most common causes of adult nephrotic syndrome. Studies in Heymann nephritis, an experimental model of MN, have established a paradigm in which these deposits locally activate complement to cause podocyte injury, culminating in cytoskeletal reorganization, loss of slit diaphragms, and proteinuria. There is much circumstantial evidence for a prominent role of complement in human MN because C3 and C5b-9 are found consistently within immune deposits. Secondary MN often shows the additional presence of C1q, implicating the classic pathway of complement activation. Primary MN, however, is IgG4-predominant and IgG4 is considered incapable of binding C1q and activating the complement pathway. Recent studies have identified the M-type phospholipase A_2 receptor (PLA_2R) as the major target antigen in primary MN. Early evidence hints that IgG4 anti-PLA_2R autoantibodies can bind mannan-binding lectin and activate the lectin complement pathway. The identification of anti-PLA_2R antibodies as likely participants in the pathogenesis of disease will allow focused investigation into the role of complement in MN. Definitive therapy for MN is immunosuppression, although future therapeutic agents that specifically target complement activation may represent an effective temporizing measure to forestall further glomerular injury.

Keywords: Membranous nephropathy, phospholipase A_2 receptor, PLA_2R, complement, IgG4

Membranous nephropathy (MN) is an immune-mediated glomerular disease and one of the most common causes of the nephrotic syndrome in adults. The term *membranous nephropathy* does not refer to a single disease, but rather to a histologic pattern shared by a number of separate etiologies. Biopsy features characteristic of MN include the triad of capillary wall thickening visualized by light microscopy, often with spikes and pits shown by Jones silver stain,[1] electron-dense subepithelial immune deposits by electron microscopy (EM),[2] and a fine granular, peripheral capillary loop staining for IgG by immunofluorescence (IF).[3] Of particular relevance to this article, IgG nearly always is accompanied by the complement component C3 in the same fine granular pattern by IF.

MN is a rare disease; its incidence in the Western world is estimated at 1.2 per 100,000 persons per year.[4] It commonly presents as the nephrotic syndrome, often with a more insidious onset than minimal change disease or primary focal and segmental glomerulosclerosis, which tend to have a more explosive onset. Approximately 20% of the MN cases present with non-nephrotic proteinuria. MN also exists in pediatric populations, but it is a much less frequent cause of the nephrotic syndrome.[5] Initial manifestations of the disease are related to the nephrotic syndrome: proteinuria, hypoalbuminemia, hyperlipidemia, and edema. MN is more likely than other causes of the nephrotic syndrome to lead to venous thromboembolic events such as deep vein or renal vein thrombosis, and pulmonary embolism.[6] Although MN may remit spontaneously without treatment, as many as one third of patients have progressive loss of kidney function and may progress to end-stage renal disease at a median of 5 years after diagnosis. In patients who have undergone transplantation after having reached end-stage renal disease because of MN in their native kidneys, the disease can recur, either in a subclinical or overt form, in up to 40% of patients.[7]

PRIMARY AND SECONDARY MN

Approximately 25% of MN cases, collectively referred to as *secondary MN*, are associated with a variety of systemic diseases, infections, medications, or exposures (Table 1). The most common secondary causes in the United States include systemic lupus erythematosus, hepatitis B infection, nonsteroidal anti-inflammatory drugs, and malignancy. The remaining 75% of MN cases traditionally have been designated as primary or idiopathic MN. Recent investigations from our laboratory have shown that more than 70% of primary MN cases are associated with circulating autoantibodies directed against the M-type phospholipase A^2 receptor (PLA_2R1), a 180-kDa transmembrane glycoprotein expressed on glomerular podocytes (see later).[8]

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Table 1. Causes of Secondary MN

Autoimmune diseases
Systemic lupus erythematosus (class V lupus nephritis)
Rheumatoid arthritis
Autoimmune thyroid disease
Sjögren syndrome
IgG4-related systemic disease
Infectious agents
Viral: hepatitis B, human immunodeficiency virus
Bacterial: syphilis
Parasitic: schistosomiasis, malaria
Iatrogenic
Nonsteroidal anti-inflammatory agents
Antirheumatic drugs: D-penicillamine, gold salts
Mercury-containing skin-lightening creams
Malignancy
Solid tumors (colon, stomach, lung, prostate)
Non-Hodgkin lymphoma
Chronic lymphocytic leukemia

Anti-PLA_2R antibodies as well as the presence of the PLA_2R antigen within subepithelial deposits on biopsy specimens are quickly becoming established biomarkers of primary disease. There remains a significant minority of cases of apparent primary MN in which the target antigen remains unidentified.

Distinguishing primary from secondary MN is not always straightforward. The finding of histopathologic features typical of MN with a well-established secondary cause such as lupus or hepatitis B infection is often enough to label that particular case secondary MN. When MN is found in association with other, less-common diseases, it is not unusual for the association to be reported in the medical literature, which has led to long tables of secondary associations found in many nephrology textbooks and reviews (eg, see the recent Kidney Disease: Improving Global Outcomes Clinical Practice Guideline on Glomerulonephritis[9]). However, a true causal relationship is not often established and the possibility of two separate but coincidental diseases cannot be easily ruled out.

Despite similar clinical features, the distinction between primary and secondary MN sometimes can be suggested by histopathology, with atypical lesions more frequent in secondary forms. The immune deposits in primary MN tend to be subepithelial and paramesangial exclusively, whereas additional subendothelial and mesangial deposits are more likely to be found in secondary MN. Lupus- and human immunodeficiency virus–associated MN additionally may be associated with tubuloreticular inclusions in endothelial cells, a histologic signature of the interferon response.[10]

There are also differences between primary and secondary MN in terms of the immunoglobulins found within the immune deposits as assayed by IF, which is important for the subsequent discussions in this article. IgG is the predominant immunoglobulin found within immune deposits in primary MN. Secondary forms, especially lupus MN, may show IgG, IgA, and IgM by IF. IgG subclasses also can help to distinguish primary from secondary MN, although most renal pathology services do not routinely characterize the IgG subclasses. Primary MN is characterized by IgG4-rich deposits, at times including IgG1, especially very early in the disease process.[11,12] In contrast, IgG1, IgG2, and IgG3 are the predominant forms in secondary MN deposits.[13,14] Consistent with the inability of the IgG4 subclass to bind and activate the classic complement pathway, C1q usually is absent or found at very low levels in primary MN, whereas it more typically is present in secondary disease. The finding of a full house pattern by IF (ie, the presence of IgG, IgM, IgA, C3, and C1q) is very specific for secondary MN.[15]

MECHANISMS OF IMMUNE DEPOSIT FORMATION

There are several potential mechanisms by which subepithelial immune deposits might form in MN. An intrinsic glomerular antigen located on the foot process of the podocyte can serve as the target antigen for circulating antibodies and lead to in situ deposition of immune deposits. This appears to be the main mechanism of deposit formation both in primary human MN and the rat experimental model of Heymann nephritis (see later). In secondary MN, the target antigen typically is extrinsic to the glomerulus. Circulating antigens from a variety of sources may accumulate in the subepithelial space as so-called planted antigens.[16] In an experimental model of MN, rabbits injected with cationized bovine serum albumin (cBSA) subsequently developed subepithelial deposits and proteinuria.[16,17] Because cBSA has low immunogenicity in rabbits and stimulates formation of low-affinity antibodies, uncomplexed cBSA can traverse the GBM as a result of electrostatic interactions.[18,19] Subepithelial immune deposits form later, resulting from antibodies binding this exogenous antigen that have been planted in the subepithelial space. Observational studies have uncovered a similar form of cBSA-induced MN in infants who are exposed to this modified dietary antigen.[20] Similar electrostatic interactions have been hypothesized for the subepithelial deposition of histone-rich nucleosomes in lupus-associated MN.[21]

A third potential mechanism involves deposition of preformed circulating immune complexes (CICs) in a subepithelial position. In MN secondary to hepatitis,[22] immune complexes are observed both in the blood and in GBM. There are also CICs in systemic lupus erythematosus and lupus nephritis; however, it is not clear why the majority of lupus nephritis involves proliferative glomerulonephritis with primarily mesangial and subendothelial immune complex deposition, whereas class V