Membranous Nephropathy: Core Curriculum 2021

Loulwa Alsharhan and Laurence H. Beck Jr

The understanding and management of membranous nephropathy, a common cause of nephrotic syndrome that is more frequently encountered in adults than in children, has rapidly evolved over the past decade. Identification of target antigens has allowed for more precise molecular diagnoses, and the ability to monitor circulating autoantibodies has added a new vantage point in terms of disease monitoring and decisions about immunosuppression. Although immunosuppression with alkylating agents combined with corticosteroids, or with calcineurin inhibitor–based regimens, has been the historical mainstay of treatment, observational and now randomized controlled trials with the B-cell–depleting agent rituximab have moved this agent to the forefront of therapy for primary membranous nephropathy. In this Core Curriculum, we discuss the typical features of primary and secondary disease; highlight the target antigens such as the phospholipase A_2 receptor, thrombospondin type 1 domain-containing 7A, neural epidermal growth factor-like 1, and semaphorin-3B; describe the relationship between the immunologic and clinical courses of disease; and review modern management with supportive care or immunosuppressive treatment based on these composite parameters.

Complete author and article information provided at end of article.

Am J Kidney Dis. XX(XX):1-14. Published online month xx, xxxx.

doi: 10.1053/j.ajkd.2020.10.009

Introduction

Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome and is seen less commonly in children. The field has advanced significantly and rapidly in the past decade, with the introduction of new tools to diagnose, classify, and monitor disease activity. This Core Curriculum is intended to update the reader on the recent progress in the field and provide a general guide for the clinical management of disease.

Classification

Case: *A 46-year-old Asian woman is referred for a gradual 10-pound weight gain and new-onset leg edema, as well as protein (3+) and trace blood on urine analysis. She denies recent infections, joint pains, or new rashes. Physical examination is significant for blood pressure 145/85 mm Hg, normal findings of heart and lung examinations, but pitting edema (2+). Laboratory testing shows a serum creatinine level of 1.03 mg/dL, serum albumin level of 3.1 g/dL, total cholesterol level of 278 mg/dL, and total urinary protein-creatinine ratio of 6.7 g/g. She is up to date on her age-appropriate cancer screening, and antinuclear antibody, hepatitis serologic findings, and complement levels are within the normal ranges. You initiate supportive care for her nephrotic syndrome with renin-angiotensin system inhibition, diuretics and sodium restriction, and a statin.*

Question 1: Which additional test would be most helpful at this point?

a) Kidney biopsy
b) Duplex ultrasonography of her renal vessels
c) Titer of phospholipase A_2 receptor (PLA_2R) antibodies
d) Antiphospholipid antibody test

For the answer to the question, see the following text.

MN represents a spectrum of diseases sharing a common histopathologic pattern, namely the presence of immunoglobulin and complement-containing immune deposits in a subepithelial position (see *Kidney Pathology*). Historically, MN has been classified as idiopathic or secondary MN on the basis of clinical and pathologic clues. The identification of target autoantigens in adult idiopathic MN, starting with the description in 2009 of antibodies against the M-type PLA_2R, was a turning point in our understanding of this disease and rapidly led to new methods for diagnosis and monitoring.

The nomenclature and classification of MN is rapidly evolving as an increasing number of target antigens are being identified and new phenotypes of disease become apparent. We will use the term "primary" to describe those subtypes of disease in which there is a humoral autoimmune response to a normal podocyte antigen in the absence of secondary features or etiologies of disease. "Secondary" MN refers to cases that arise in the setting of systemic processes such as infection, malignancy, or drug exposure in which treatment of the underlying disorder is expected to lead to the resolution of the MN. The subtype of MN should be specified by underlying antigen

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Box 1. Common Causes of Primary, Secondary, or Alloimmune MN

Primary MN[a]
- PLA_2R-associated
- THSD7A-associated
- NELL-1–associated
- Sema3B-associated
- Uncharacterized

Secondary MN
- Autoimmune/collagen-vascular disease: SLE and mixed connective tissue disease (includes EXT1/EXT2-associated), Sjogren's, thyroiditis, sarcoidosis, dermatitis herpetiformis
- Infection: HBV and HCV, malaria, secondary or congenital syphilis, leprosy
- Drugs, toxins, other adulterants: NSAIDs, gold salts, penicillamine, mercury, cationic bovine serum albumin (infant formula)
- Malignancy: more commonly solid-organ carcinomas (lung, breast, colon, and kidney), NHL, leukemia; rarely associated with THSD7A expression in tumor; NELL-1–associated MN linked to underlying malignancy

Alloimmune MN
- Antenatal alloimmune MN caused by anti-NEP antibodies
- De novo MN in kidney allograft
- Graft-vs-host disease

Abbreviations: EXT1/EXT2, Exostosin 1/Exostosin 2; HBV, hepatitis B virus; HCV, hepatitis C virus; MN, membranous nephropathy; NELL-1, neural epidermal growth factor-like 1; NEP, neutral endopeptidase; NHL, non-Hodgkin lymphoma; NSAID, nonsteroidal anti-inflammatory drug; PLA_2R, phospholipase A_2 receptor; Sema3B, semaphorin-3B; SLE, systemic lupus erythematosus; THSD7A, thrombospondin type 1 domain-containing 7A.
[a]Primary MN reflects an autoimmune process that targets an intrinsic podocyte protein (see text). NELL-1–associated MN is included here even though the source of the antigen is not yet clear. Several more target antigens are under investigation but are listed here as uncharacterized.

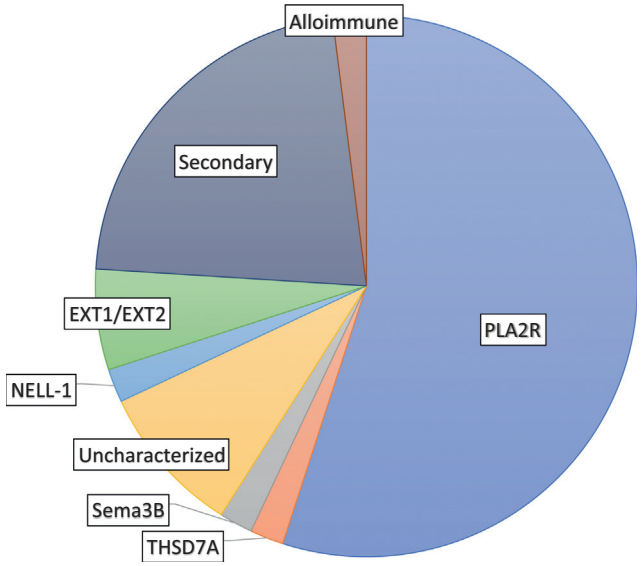

Figure 1. Spectrum of disease within the larger pathologic classification of MN according to the observation that secondary entities represent approximately 30% of all MN. The percentages of MN associated with the newer antigens NELL-1, Sema3B, and EXT1/EXT2 are estimates, and larger cohorts are needed to determine the true prevalence of these subtypes of MN. The uncharacterized group reflects those cases of presumed primary MN in which the target antigen has yet to be described.

(eg, PLA_2R-associated MN) when feasible, as we are learning that certain MN subtypes may have features that blur the distinction between primary and secondary disease (Box 1; Fig 1).

Antigens Implicated in Primary MN

PLA_2R

PLA_2R is a 180-kDa transmembrane glycoprotein expressed by the human podocyte, where its precise function is not clear. Autoantibodies to PLA_2R may be responsible for primary MN in as many as 80% of patients (reflecting approximately 55% of all MN cases found on biopsy). The discovery of this antibody has allowed a serologic assay for diagnosis, obviating kidney biopsy in certain situations. Data are highly suggestive of a causal relationship between anti-PLA_2R antibody (henceforth simply anti-PLA_2R) and MN pathogenesis, but further studies are needed to ascertain this relationship.

THSD7A

Thrombospondin type 1 domain-containing 7A (THSD7A) was the next podocyte protein identified as a target antigen in adult primary MN. THSD7A is a 250-kDa multidomain protein expressed at the basal surface of the podocyte immediately beneath the slit diaphragm. Autoantibodies against THSD7A account for 1%-3% of MN cases in Western countries. THSD7A is also overexpressed by certain malignancies and may incite a humoral reaction against tumor and glomerular THSD7A, leading to MN. Although the exact mechanism of how anti-THSD7A antibodies lead to the nephrotic state of MN is not known, in a mouse model, human and rabbit anti-THSD7A antibodies have been observed to cause disease.

Neural Epidermal Growth Factor-Like-1

Autoantibodies to the 90-kDa secreted protein neural epidermal growth factor-like 1 (NELL-1) are a recent addition to the MN disease spectrum and may be more prevalent than anti-THSD7A antibodies. NELL-1 was identified through a mass spectrometric approach that identified the enrichment of peptides from candidate antigens within laser-capture microdissected glomeruli from patients with uncharacterized MN. The evidence for NELL-1 being a podocyte protein is not as strong as that for PLA_2R and THSD7A. NELL-1–associated MN was identified in approximately 16% of PLA_2R-negative MN cases without any identifiable secondary associations, representing an approximate 2.5% prevalence across the entire spectrum of MN (Fig 1). Unlike PLA_2R- and THSD7A-associated MN, autoantibodies in NELL-1–associated MN are immunoglobulin (Ig) G1-predominant. The current

literature suggests a connection between NELL-1–associated MN and malignancy.

Semaphorin-3B

Further study of uncharacterized MN cases by laser-capture microdissection mass spectrometry (LCM-MS) revealed another MN antigen, semaphorin-3B (Sema3B), with associated circulating autoantibodies. Anti-Sema3B autoantibodies were found to be predominantly IgG1 and detected the protein on immunoblot only under reducing conditions, suggesting the existence of a potentially cryptic epitope. Of note, most cases were identified in infants or children, and the deposits were present in a segmental pattern in the glomerular tuft and occasionally in the tubular basement membrane as well.

Exostosin 1/Exostosin 2

Detection of this protein complex within immune deposits is associated with systemic autoimmune diseases such as lupus (class V lupus nephritis; see *Secondary MN*). Circulating autoantibodies to Exostosin 1/Exostosin 2 (EXT1/EXT2) have not been identified, but histopathologic staining for this complex may be helpful to identify certain cases of MN in the setting of these autoimmune disorders.

Secondary MN

As many as 30% of all biopsy diagnoses of MN represent disease that is most likely secondary to autoimmune/collagen vascular disease; infections; drugs, toxins, or other adulterants; or malignancy (Box 1). The precise pathologic mechanisms and target antigens responsible for disease are less well defined in secondary MN. It is commonly assumed that circulating antigens (endogenous or exogenous), immune complexes, or even monoclonal immunoglobulins may become "planted" on the subepithelial side of the glomerular basement membrane (GBM) by virtue of size and/or charge and thereby initiate immune complex formation in the subepithelial position.

Alloimmune MN

Finally, there are alloimmune etiologies of MN (antenatal and de novo posttransplantation MN) in which inconsistencies between host and donor antigens and humoral immune systems lead to the phenotype of MN.

Laboratory Testing for Circulating Autoantibodies

The identification of the target antigen PLA_2R and the ability to detect and monitor circulating anti-PLA_2R autoantibodies has established a paradigm by which to approach MN for clinical purposes and to conceptualize its pathophysiology. It is expected that the same principles will apply for the more recently discovered autoantibodies.

There are currently 2 tests approved by the US Food and Drug Administration for clinical use to detect anti-PLA_2R to assess the presence and amount of circulating autoantibodies. The enzyme-linked immunosorbent assay reports the titer of anti-PLA_2R IgG and is useful for initial detection of anti-PLA_2R as well as monitoring the change in titer over time. Values <14 RU/mL are considered negative by the manufacturer, but some studies have shown that levels in the 2-14 RU/mL range may represent very low titers of anti-PLA_2R that can be verified in other assays. The indirect immunofluorescence (IF) test uses cells transfected with recombinant human PLA_2R to assay for the antibodies. Although more sensitive than the enzyme-linked immunosorbent assay for low-titer anti-PLA_2R, the indirect IF test yields only semiquantitative titers (eg, 1:10, 1:100, 1:300). These tests for circulating antibodies complement the histopathologic stains for the accumulated antigen within the immune deposits on biopsy (see *Kidney Pathology*).

The answer to question 1 is (c), as it represents a noninvasive test that can establish the diagnosis of PLA_2R-associated MN and provide a baseline titer. Kidney biopsy (a) should be considered if the anti-PLA_2R test result is negative. There are no clinical signs to warrant immediate testing for antiphospholipid antibodies (d) or the need for duplex ultrasonography (b) to look for a renal vein thrombosis.

Additional Readings

- Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med.* 2009;361(1):11-21. ★ESSENTIAL READING
- Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. *N Engl J Med.* 2014;371(24):2277-2287.
- Sethi S, Madden BJ, Debiec H, et al. Exostosin 1/exostosin 2-associated membranous nephropathy. *J Am Soc Nephrol.* 2019;30(6):1123-1136.
- Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int.* 2020;97(1):163-174.
- Sethi S, Debiec H, Madden B, et al. Semaphorin 3B-associated membranous nephropathy is a distinct type of disease predominantly present in pediatric patients. *Kidney Int.* 2020;98(5):1253-1264.

Epidemiology, Clinical Features, and Natural History

Epidemiology

MN is one of the most common causes of nephrotic syndrome in White, nondiabetic adults. Despite this generalization, it can be found in all races and ethnicities. MN has an incidence of approximately 1 case per 100,000 persons per year. PLA_2R-associated MN is typically more common in male patients, although some of the more recently described subtypes such as THSD7A- or NELL-1–associated MN may have less of a male predominance.

The median age of onset is in the early 50s, although there is a wide distribution of age at presentation ranging

from children to the very elderly. In the pediatric population, primary MN is quite rare, and secondary forms such as those associated with hepatitis B virus (HBV) infection or lupus should be considered. In very young children, Sema3B- or cationic bovine serum albumin–associated MN should also be considered.

Clinical Features

The clinical presentations of MN from a renal standpoint are similar in primary and secondary forms of disease and often involve features of the nephrotic syndrome: heavy proteinuria, hypoalbuminemia, edema or anasarca, hyperlipidemia, and lipiduria. These features tend to develop slowly and can be overlooked for months, unlike other more explosive causes of nephrotic syndrome such as minimal change disease. In its earliest stages, MN can have an indolent course. Conceptually, this is due to the gradual but progressive growth of immune deposits and resultant podocyte injury (see *Pathophysiology*). Proteinuria has typically been ongoing for months to even years at a subclinical level before diagnosis. The degree of proteinuria at presentation is variable, ranging from subnephrotic to more than 20 g/d.

Eighty percent of patients present with nephrotic syndrome, and the remainder are diagnosed earlier in the disease course after an incidental finding of proteinuria. Urinary sediment usually shows evidence of lipiduria with oval fat bodies and fatty casts (Fig 2). Microscopic hematuria is not uncommon but is usually trace or 1+ (unless renal vein thrombosis is present, in which case it can be more significant). Red blood cell casts are not seen, although fatty casts, with their pleiomorphic circular fat droplets, can sometimes be mistaken for such casts.

Blood pressure is normal at presentation in 70% of patients, and glomerular filtration rate (GFR) is preserved in most patients. If GFR is or becomes reduced, one should consider a coexisting diagnosis such as renal vein thrombosis, concomitant interstitial nephritis or crescentic glomerulonephritis, or an iatrogenic effect of therapy caused by overdiuresis or introduction of inhibitors of the renin angiotensin system or the calcineurin pathway. Hyperlipidemia is common in the presence of nephrotic-range proteinuria. Venous thromboembolic events may be the initial reason why a patient presents for clinical attention (see *Anticoagulation*).

Clinical clues to help distinguish primary from secondary causes of MN can often be obtained with a careful history, laboratory studies, and histologic features on biopsy. In some cases, the offending agent or the underlying disease can predate the diagnosis of MN by months to

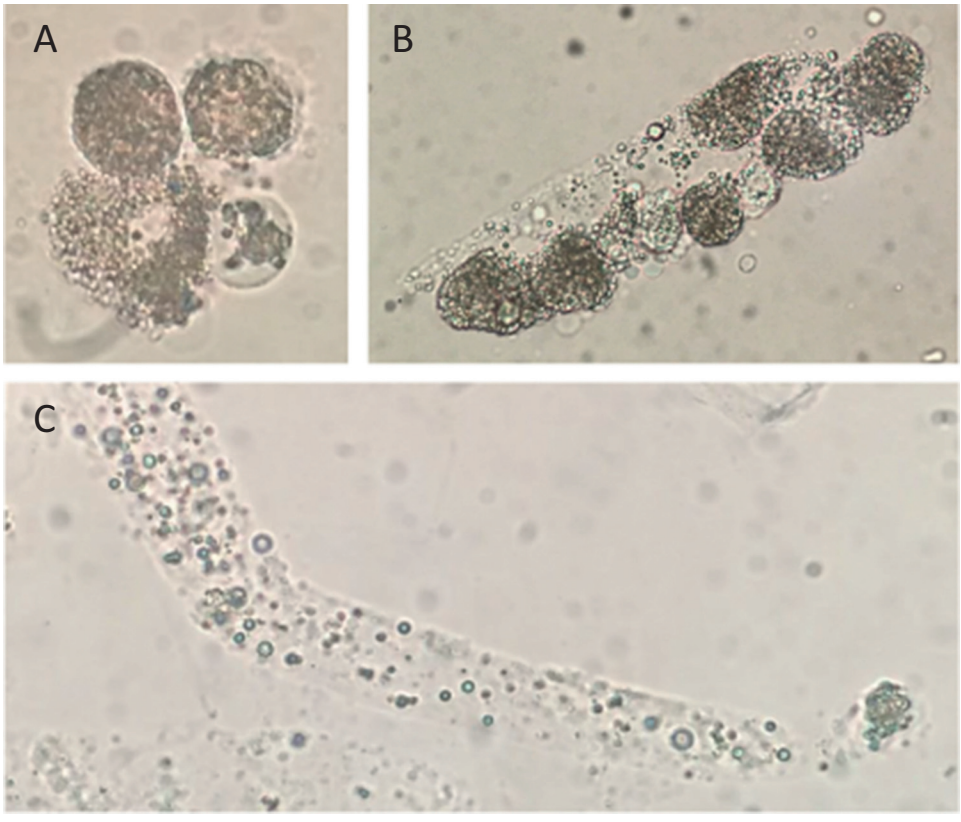

Figure 2. Examples of lipiduria from a patient with MN. Oval fat bodies in a cluster (A) or embedded within a cast (B). (C) Fatty cast with a single oval fat body at the tip. Note that the lipid droplets are of unequal size, which can distinguish a fatty cast from a red blood cell cast, in which the cells are more similar in size.

years, whereas, in other cases (malignancy or lupus), the nephrotic state induced by MN may be the presenting clinical feature of the underlying disease.

Natural History

One of the most vexing issues with MN is its highly variable clinical course and the few baseline parameters that can predict its ultimate course. Even patients in a highly nephrotic state have the potential to undergo spontaneous remission, but are often treated with immunosuppression to avoid the adverse consequences of the prolonged nephrotic state. On average, one third of patients will exhibit spontaneous remission (slightly more when baseline proteinuria level is <8 g/d), but it may take 15-20 months to achieve a partial remission and 25-40 months to reach a complete remission. Any type of remission, whether spontaneous or induced by immunosuppressive therapy, is beneficial in terms of kidney survival. In contrast, cases that remain nephrotic typically progress to advanced kidney disease or kidney failure. Ten-year follow-up data from 2 independent trials demonstrate a 35%-40% rate of reaching kidney failure in patients treated conservatively, compared with an 8%-11% rate in patients treated with an alkylating agent/corticosteroid regimen.

Because of the slow time frame in which MN resolves, patients often experience a partial remission (>50% decrease in proteinuria from baseline to <3.5 g/d) well before they experience a complete remission (<0.3 g/d). Therefore, long-term follow-up (≥5 years) is needed in any given trial to determine the full rate of complete remissions. Relapses of MN occur in approximately 25%-30% of cases, often years after a complete remission. Rates of relapse are higher after partial clinical remission and may reflect incompletely-suppressed immunologic activity at the time immunosuppression is withdrawn.

In secondary MN, treatment of the underlying disease or cessation of the offending agent should result in eventual remission, with the understanding that it will take months for the proteinuria to dissipate. In class V ("membranous") lupus nephritis, prognosis depends on whether it is found alone or in combination with another class of lupus nephritis. In general, isolated class V lupus nephritis has an excellent prognosis, with reported 10-year kidney survival rates of 72%-98%.

Additional Readings

- Donadio JV Jr, Torres VE, Velosa JA, et al. Idiopathic membranous nephropathy: the natural history of untreated patients. *Kidney Int.* 1988;33(3):708-715.
- Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. *N Engl J Med.* 1993;329(2):85-89.
- Hladunewich MA, Troyanov S, Calafati J, et al. The natural history of the non-nephrotic membranous nephropathy patient. *Clin J Am Soc Nephrol.* 2009;4(9):1417-1322.
- Polanco N, Gutiérrez E, Covarsí A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol.* 2010;21(4):697-704. ★ESSENTIAL READING
- van den Brand JA, van Dijk PR, et al. Long-term outcomes in idiopathic membranous nephropathy using a restrictive treatment strategy. *J Am Soc Nephrol.* 2014;25(1):150-158.

Kidney Pathology

The characteristic histopathologic features of MN seen by light microscopy, IF, and electron microscopy are shown in Fig 3. These changes are due to the immune complexes of antigen, immunoglobulin, and complement components that form beneath the podocyte (ie, are subepithelial) or to the reaction of the podocyte to injury, which includes simplification, loss of slit diaphragms and foot processes, and production of new matrix material between and around the deposits. These features may be more or less pronounced depending on when during the course of the disease the biopsy was performed. Keep in mind that "membranous nephropathy" is merely a descriptor for a particular lesion as detected by histopathology and does not by itself refer to a single disease or common pathophysiology.

Light Microscopy

Early in the course of the disease, the only change noted may be rigid-appearing capillary walls without evidence of deposits. The Jones silver stain highlights extracellular matrix elements of the GBM but does not stain the immune deposits. With very close observation, areas of translucency ("craters") representing the deposits might be observed early in the course of the disease. As the deposits persist and grow in size, increased matrix is deposited by the injured podocyte between the deposits and results in spike-like projections seen by silver stain. As the reaction progresses, the matrix encircles the deposits, resulting in a lace-like splitting or laddering appearance of the GBM.

In longstanding disease, signs of chronic damage including glomerular sclerosis, interstitial fibrosis, and tubular atrophy can be found. These features are associated with an inferior kidney prognosis. Coexisting conditions such as glomerular crescent formation or tubulointerstitial nephritis may be noted and may require additional serologic testing.

IF and Immunohistochemistry

IF is generally more sensitive than light or electron microscopy in detecting early deposits. For routine cases, the renal pathologist will stain frozen kidney biopsy tissue sections for IgG, IgA, IgM, C3, and C1q. In primary MN, IgG and C3 are nearly always positive, appearing in a fine granular, peripheral capillary loop pattern. The ability to stain for PLA_2R and THSD7A by IF or, on fixed tissues, with immunohistochemistry has become an important adjunctive test to aid in the classification of MN. Less frequent and emerging antigens such as NELL-1 or Sema3B can be assayed in a similar manner. The target antigens, which accumulate over time with immunoglobulin within the immune deposits, exhibit a staining pattern identical to

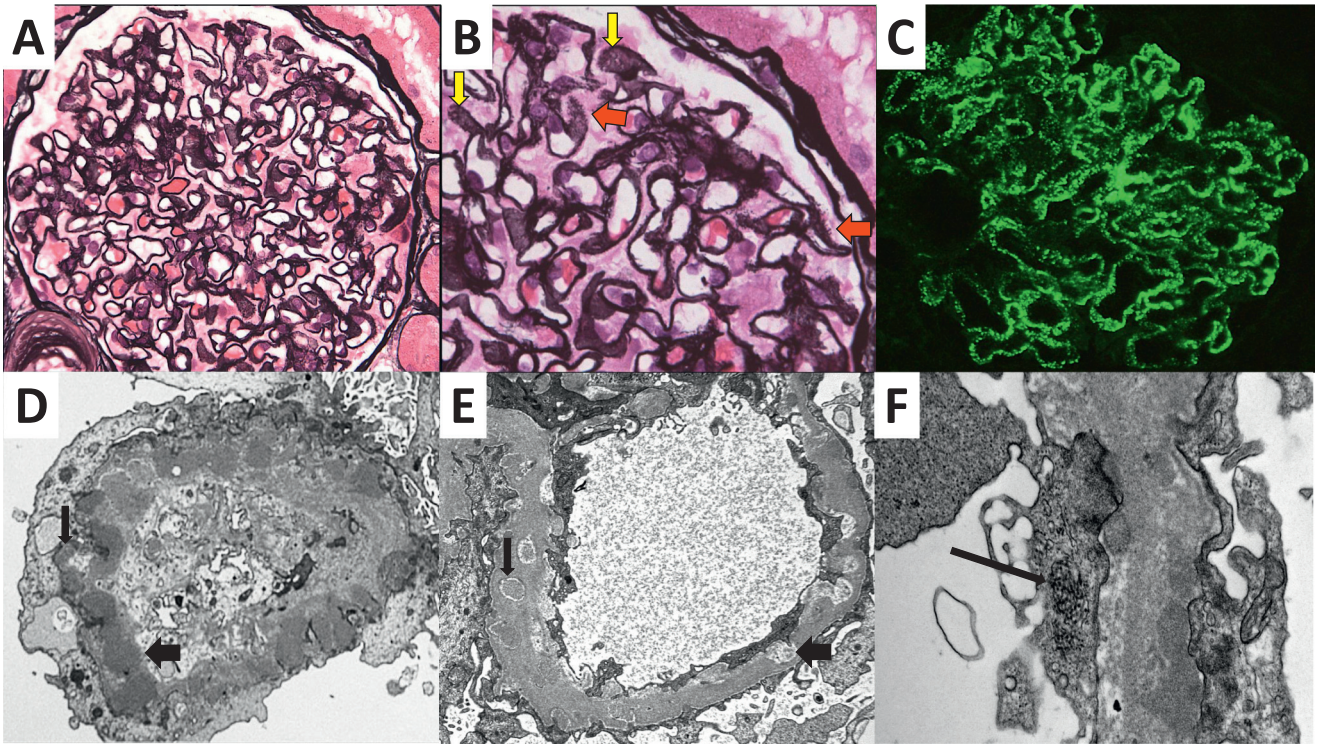

Figure 3. Kidney pathology of MN. Jones silver stain (A and B) reveals thickening of the GBM in A. A higher-resolution image (B) reveals "spikes" of positively staining basement membrane reaction (red arrows) and craters (yellow arrows) representing the negatively staining immune complexes. (C) Immunofluorescence staining for IgG with granular subepithelial and intramembranous immune deposits. Representative electron microscopy images are shown in D–F. (D) Mixed stage 1 (thin arrow) and 2 (thick arrow) deposits abutting an effaced podocyte. (E) Mixed intramembranous stage 3 (thin arrow) and electron-lucent stage 4 (thick arrows). (F) Tubuloreticular inclusion (arrow) in an endothelial cell, characteristic of interferon-mediated processes such as systemic lupus erythematosus.

those of IgG and C3. Although most MN lesions are global and affect all portions of the glomerular tuft, some subtypes (such as NELL-1-associated MN) may exhibit segmental lesions.

Features suggestive of a secondary etiology of MN include a moderate to strong presence of IF reactants beyond C3 and IgG, such as the "full-house" pattern (IgG/IgA/IgM and C3/C1q) often seen in class V lupus nephritis. The presence of EXT1/EXT2 staining in a fine granular capillary-loop pattern can be seen in class V lupus or similar systemic autoimmune conditions. Another recently described entity is membranous-like glomerulopathy with masked IgGκ light-chain deposits for which pronase digestion is required to expose the IgG deposits. Many of these cases were associated with systemic autoimmune diseases.

Staining for IgG subclasses can assist in the determination of etiology. Although there is usually a mixture of IgG subclasses in any type of MN, IgG4 tends to be predominant or codominant in primary forms of MN. In contrast, in secondary causes such as lupus or malignancy, IgG1, IgG2, or IgG3 may predominate. It is not yet clear why MN associated with NELL-1 or Sema3B are IgG1-predominant diseases, although a significant proportion of NELL-1–associated cases are associated with malignancy.

Electron Microscopy

The Ehrenreich-Churg stage of the electron-dense immune deposits is assessed by electron microscopy. It is not uncommon to find mixed stages of deposits: stage 1 (small and discrete deposits immediately beneath the podocyte), stage 2 (deposits separated from each other by newly formed matrix material), stage 3 (deposits completely encircled by matrix), and stage 4 (electron-lucent; reflect resorption of the immune complexes).

Podocyte foot processes will show effacement and loss of slit diaphragms, and the apical surface will typically show significant microvillous change. The presence of subendothelial or significant mesangial deposits, as well as the presence of tubuloreticular structures in the endothelium, is suggestive of secondary disease.

Additional Readings

➢ Larsen CP, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. *Mod Pathol.* 2013;26(5):709-715.

➢ Huang CC, Lehman A, Albawardi A, et al. IgG subclass staining in renal biopsies with membranous glomerulonephritis indicates subclass switch during disease progression. *Mod Pathol.* 2013;26(6):799-805.
➢ Fogo AB, Lusco MA, Najafian B, Alpers CE. AJKD atlas of renal pathology: membranous nephropathy. *Am J Kidney Dis.* 2015;66(3):E15-E17.

Genetics

Like many autoimmune diseases, there is a heritable component of MN and a very strong link to the human leukocyte antigen (HLA) locus on chromosome 6, with associations with certain HLA class II phenotypes common in the White population such as DR3. A European genome-wide association study of 556 cases of idiopathic MN indeed demonstrated a significant association of disease with a single-nucleotide variation in the class II HLA-DQA1 locus. A second peak of association mapped to an intronic region of *PLA2R1*. Homozygosity for both risk alleles conferred an odds ratio for disease of nearly 80, showing strong interaction between the alleles.

Larger cohorts from international populations, especially China, have shown associations at other HLA class II loci such as DRB1 and DRB3. The allelic risk variants have been mapped to positions within the peptide-binding groove of the class II HLA molecule. It is suggested that genetic risk at the HLA class II locus can enhance or discourage presentation of antigenic peptides derived from PLA_2R to the immune system.

A recent very large international genome-wide association study has confirmed previous findings about a genetic interaction with the *PLA2R1* locus and class II HLA genes, with risk alleles in both East Asian and European populations mapping to the peptide-binding region of HLA DRB1. The intronic single-nucleotide variation within *PLA2R1* is closely linked to an enhancer region that seems to direct increased expression of the gene in kidney tissue. Important for further insights into the immunologic pathogenesis of MN, 2 new highly significant peaks of association were identified within *NFKB1* and *IRF4*, genes with important roles in the regulation of immune responses.

Additional Readings

➢ Stanescu HC, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med.* 2011;364(7):616-626.
➢ Cui Z, Xie LJ, Chen FJ, et al. MHC Class II risk alleles and amino acid residues in idiopathic membranous nephropathy. *J Am Soc Nephrol.* 2017;28(5):1651-1664.
➢ Le WB, Shi JS, Zhang T, et al. HLA-DRB1*15:01 and HLA-DRB3*02:02 in PLA2R-related membranous nephropathy. *J Am Soc Nephrol.* 2017;28(5):1642-1650.
➢ Xie J, Liu L, Mladkova N, Li Y, et al. The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis. *Nature Comm.* 2020;11:1600.

Pathophysiology of Primary MN

Overview

Decades ago, studies in the Heymann nephritis rat model of MN established a paradigm for the underlying pathophysiology of MN. Rats express megalin (LRP2) both in the proximal tubular brush border and (unlike humans) in podocytes. When anti-megalin antibodies were introduced actively or passively, there was aggregation of immune complexes at the basal surface of the podocyte. Complement activation led to assembly and insertion of the terminal complement components C5b-9 into the podocyte cell membrane, resulting in sublethal injury, proteinuria, and eventually elaboration of new basement membrane material.

Observations that megalin is not expressed by the human podocyte led to a decades-long search culminating in the identification of neutral endopeptidase in a rare form of alloimmune antenatal MN in 2002 (see below) and PLA_2R as the major antigen in adult MN in 2009. In keeping with what we have learned from the Heymann nephritis model, antibodies targeting these and other subsequently identified podocyte antigens bind these proteins in situ, leading to the formation and accumulation of subepithelial immune deposits.

The main target antigens identified to date in primary MN are PLA_2R, THSD7A, NELL-1, and Sema3B, with even more in the pipeline. Although PLA_2R, THSD7A, and Sema3B are clearly proteins expressed by the human podocyte, NELL-1 is less convincingly so in the native state but could potentially be induced as a "neoantigen." Circulating antibodies to other intracellular antigens such as aldose reductase, superoxide dismutase, and α-enolase have been detected in primary MN and may also represent neoantigens that secondarily become targeted after cellular injury. What remains a mystery is how tolerance to these normal proteins is broken. Possible triggers that have been proposed include molecular mimicry due to exposure to microbial antigens or environmental exposures such as air pollution with high concentrations of particles smaller than 2.5 μm.

We know from Heymann nephritis that epitope spreading from amino-terminal portions of the antigen to more distal regions is necessary for development of disease. Similar evidence exists for PLA_2R and THSD7A. The immunodominant epitope (recognized in every PLA_2R-associated case of MN with circulating antibodies) lies within the amino-terminal cysteine-rich domain. However, patients often have additional autoantibody reactivity with epitopes in the C-type lectin-like domains 1, 7, and 8. Both epitope spreading and high titers of anti-PLA_2R have been associated with fewer remissions and more adverse kidney outcomes; however, there is controversy whether these 2 risk factors are independent of each other.

Role of Complement

An apparent paradox for subtypes of primary MN like PLA_2R-associated MN is that the predominant IgG4 subclass does not activate the classical complement pathway. Although C3 is typically strong on IF staining of the biopsy, C1q is usually weak or absent, suggesting a minor role for the classical pathway. There is experimental evidence that IgG4 may activate the lectin pathway of complement activation. MN subtypes with more predominant IgG1 (such as EXT1/EXT2-, NELL-1–, and Sema3B-associated MN) may have more activation of the classical pathway. No matter which pathway initiates the complement cascade, the alternative pathway is most likely the main maintenance pathway that amplifies complement activation and results in formation of the podocytopathic membrane attack complex C5b-9.

Animal models in which relevant antigens such as PLA_2R (which is not normally expressed by the mouse podocyte) and THSD7A were used have not yet convincingly supported a major role for complement in these systems. However, understanding the precise role of complement in the initiation and maintenance of the disease will be important as more therapeutic agents become available to target these pathways. Although controlling the process of autoantibody production will be paramount in any treatment scheme, being able to halt glomerular damage through inhibition of the complement system may help stop disease progression while other therapies have time to work.

Additional Readings

- Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient's care. *Lancet.* 2015;385(9981):1983-1992.
- Seitz-Polski B, Dolla G, Payré C, et al. Epitope spreading of autoantibody response to PLA2R associates with poor prognosis in membranous nephropathy. *J Am Soc Nephrol.* 2016;27(5):1517-1533. ★ESSENTIAL READING
- Tomas NM, Hoxha E, Reinicke AT, et al. Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. *J Clin Invest.* 2016;126(7):2519-2532. ★ESSENTIAL READING
- Meyer-Schwesinger C, Tomas NM, Dehde S, et al. A novel mouse model of phospholipase A2 receptor 1-associated membranous nephropathy mimics podocyte injury in patients. *Kidney Int.* 2020;97(5):913-919.
- Ma H, Sandor DG, Beck LH Jr. The role of complement in membranous nephropathy. *Semin Nephrol.* 2013;33(6):531-542.

Pathophysiology of Secondary and Alloimmune MN

The pathophysiology of secondary and alloimmune forms of MN shares basic features with primary MN, such as the presence of complement-activating subepithelial deposits, but, as a whole, we know less about precise mechanisms.

Secondary MN

Nonrenal (exogenous) antigens have been associated with specific forms of secondary MN. These include antigens derived from infectious causes (hepatitis B virus, treponemes in syphilis), inflamed or malignant tissues (thyroglobulin in thyroiditis, tumor antigens), and even ingested substances such as cationic bovine serum albumin that may become derivatized in the manufacture of infant formula. It seems likely that free antigen becomes localized beneath the podocyte, where it can serve as a nidus for immune complex formation, although there may also be circulating immune complexes. The pathogenesis of HBV-associated MN has been attributed to subepithelial deposition of immune complexes of hepatitis B e antigen and anti–hepatitis B e antibodies. The EXT1/EXT2 complex was recently identified as a biomarker and potential antigen in a form of PLA_2R-negative MN associated with systemic autoimmunity such as lupus. The contribution of these proteins to pathogenesis has not been established.

The link between MN and malignancy has long been controversial. In some cases, there could merely be coincidence of 2 disease processes in an older demographic group. In other circumstances, a humoral immune response to tumor antigens or another etiologic relationship may exist. Tumoral overexpression of THSD7A has been demonstrated as a possible link between certain cancers and THSD7A-associated MN. In an instructive case, Hoxha et al demonstrated localized polysomy in a gallbladder cancer leading to THSD7A overexpression and a local lymph-node reaction to THSD7A. They speculate that this sequence of events led to the development of a humoral response to THSD7A that consequently led to the in situ glomerular immune deposits causing MN. A significant proportion of NELL-1 MN cases are also associated with malignancy.

Alloimmune MN

Alloimmunity develops when there is a discrepancy between host and recipient antigens and is characterized by an immune response to a previously unfamiliar antigen. This is common in the setting of organ transplantation and likely reflects the late development of de novo MN in kidney transplants (see below). The first evidence of circulating antibodies to a distinct human podocyte protein is also an example of alloimmunity. Antenatal alloimmune MN has been described in mothers genetically deficient in neutral endopeptidase who are immunized against this protein from a previous pregnancy and miscarriage. The circulating anti–neutral endopeptidase alloantibodies cross the placenta and target neutral endopeptidase on the fetal podocytes such that the neonate is born with MN. The infant typically recovers quickly when the maternal antibodies have cleared.

Additional Readings

➢ Vivarelli M, Emma F, Pellé T, et al. Genetic homogeneity but IgG subclass-dependent clinical variability of alloimmune membranous nephropathy with anti-neutral endopeptidase antibodies. *Kidney Int.* 2015;87(3):602-609.
➢ Debiec H, Lefeu F, Kemper MJ, et al. Early-childhood membranous nephropathy due to cationic bovine serum albumin. *N Engl J Med.* 2011;364(22):2101-2110.
➢ Hoxha E, Wiech T, Stahl PR, et al. A mechanism for cancer-associated membranous nephropathy. *N Engl J Med.* 2016;374(20):1995-1996. ★ESSENTIAL READING

Relationship Between Immunologic and Clinical Course of Disease

Case, continued: *The anti-PLA_2R titer for your patient is 185 RU/mL. After discussing with her the likely diagnosis, she still would like to confirm the diagnosis by kidney biopsy in case you and she decide on immunosuppressive treatment in the future. The biopsy is uncomplicated and shows stage 2 MN with strong staining of the deposits for PLA_2R. At her return visit in 3 months, repeat testing reveals a serum creatinine level of 1.1 mg/dL, serum albumin level of 2.9 g/dL, and urinary protein-creatinine ratio of 7.6 g/g despite 100 mg losartan. Her blood pressure is better controlled at 132/78 mm Hg, and her leg edema has resolved with diuretic treatment. A repeat anti-PLA_2R measurement is 312 RU/mL.*

Question 2: What do you now recommend?

a. Watchful waiting with 6-month follow-up to see if her urinary protein-creatinine ratio has decreased to <4 g/g
b. Initiation of immunosuppression because spontaneous remission is unlikely with increasing anti-PLA_2R titers
c. Repeat kidney biopsy to assess for progression to MN with stage 3 deposits

The ability to measure specific autoantibodies in MN in clinical practice has opened a new window onto the immunologic course of disease. Understanding this relationship is crucial for the clinical management of MN. Figure 4 describes the 2 courses of disease (immunologic/serologic and clinical) and highlights the temporal lag between changes in autoantibody and clinical manifestations. Although this conceptual model is based on anti-PLA_2R, it will likely hold true for the more recently identified autoantibodies in MN.

Irrespective of the exact mechanism by which tolerance is broken, low levels of anti-PLA_2R are produced, begin to circulate, and soon find abundant antigen in the glomerulus, where they start to form tiny subepithelial deposits. The affinity of anti-PLA_2R for the amino-terminal epitope of PLA_2R is quite strong, and much of the low-level antibody is likely cleared from the circulation, making it nearly impossible to detect circulating autoantibody at this time point (the "kidney-as-a-sink" hypothesis). A kidney biopsy would show these very early deposits of IgG and PLA_2R but is virtually never performed because patients are asymptomatic at this point.

As the humoral response to PLA_2R grows and more antibody-antigen complexes are formed, 2 things occur: anti-PLA_2R becomes detectable in increasing amounts in the circulation and sufficient damage to the podocyte has occurred that proteinuria appears. The speculation that autoantibodies and nascent deposits predate clinically significant proteinuria is based on observations with recurrent MN in the kidney allograft (see below). As immune deposits grow and glomerular damage worsens, patients ultimately come to clinical attention as a result of the nephrotic syndrome. Significant immunologic disease activity (as measured by anti-PLA_2R) can be found in the majority of patients at the time of clinical presentation. Podocyte foot processes are typically fully effaced, and the immune deposits and resulting membrane reaction markedly distort the GBM. These structural changes to the GBM are likely the features that cause such a slow clinical resolution of the disease, even after the production of anti-PLA_2R has ceased and the antibodies decrease and disappear from the circulation.

In the process of spontaneous or treatment-induced remission, anti-PLA_2R levels will decrease in a manner that precedes and predicts the clinical response. In those patients in whom anti-PLA_2R ultimately disappears, the

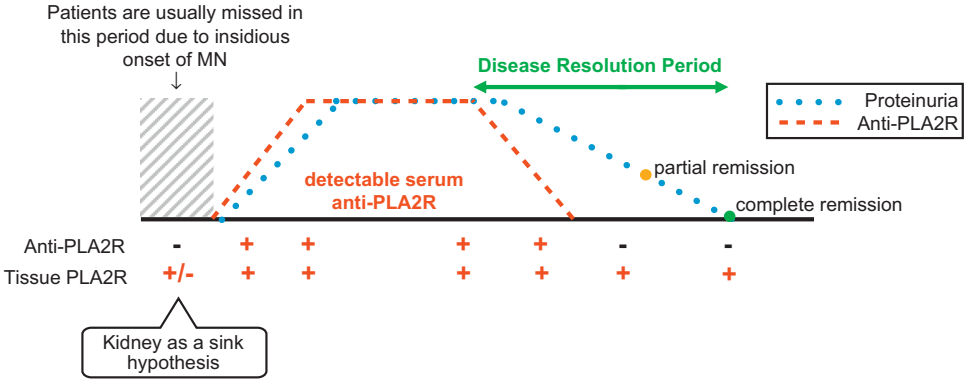

Figure 4. Schematic representation of the immunologic and clinical courses of disease in PLA_2R-associated MN.

proteinuria continues to decrease to a point of a partial remission, followed later by a complete remission in the absence any permanent structural changes to the glomerulus or tubulointerstitium from chronic damage. Those patients in whom circulating autoantibody has not been eliminated by the end of treatment are at risk for a rapid resurgence of immunologic and clinical disease activity. This is the rationale for monitoring anti-PLA_2R every few months during and after the intended course of therapy is complete. It may take years before the GBM architecture has normalized to a sufficient level to allow a complete remission of proteinuria.

Understanding that autoantibody levels must decrease and disappear before any significant clinical remission can occur is the reason why high anti-PLA_2R titers are associated with increased severity of disease, adverse kidney outcomes, and decreased likelihood of remission. The longer proteinuria continues, the higher the chance of developing decreased GFR. In contrast, low or undetectable anti-PLA_2R (in a patient known to have PLA_2R-associated disease by virtue of biopsy staining) is a good prognostic sign, reflective of a higher chance of remission and improved kidney outcomes. These patients are nearly always at the end of their disease course (Fig 4, right), as early-stage disease is usually clinically silent.

The answer to the question is (b), as the patient's anti-PLA_2R titer, serum albumin, and urine protein levels are all worsening. Spontaneous remission with significant reduction of proteinuria to less than 4 g/g (a) is unlikely in the near future. A repeat biopsy (c) is unnecessary because increasing anti-PLA_2R already indicates ongoing immunologic activity.

Additional Readings

- Beck LH Jr, Fervenza FC, Beck DM et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. *J Am Soc Nephrol.* 2011;22(8):1543-1550.
- Hoxha E, Thiele I, Zahner G, et al. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. *J Am Soc Nephrol.* 2014;25(6):1357-1366.
- Ruggenenti P, Debiec H, Ruggiero B, et al. Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. *J Am Soc Nephrol.* 2015;26(10):2545-2558.
- De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. *J Am Soc Nephrol.* 2017;28(2):421-430. ★ESSENTIAL READING

Treatment and Response

Case, continued: *You and your patient agree to starting immunosuppressive treatment, but, as a result of fears about the adverse effects, she would like to avoid cyclophosphamide.*

Question 3: Which therapy is most likely to achieve a complete remission at 24 months in this patient?

a) Prednisone
b) Cyclosporine
c) Mycophenolate
d) Rituximab

For the answer to the question, see the following text.

Overview

All patients with MN should receive supportive management with antiproteinuric measures including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, optimal blood pressure control, dietary sodium restriction, and diuretic therapy as needed (oral vs intravenous depending on the severity of the nephrotic syndrome). Cholesterol-lowering therapies are often necessary as a result of hyperlipidemia. Prophylactic anticoagulation to prevent venous and arterial thromboembolisms will be discussed below.

Decisions regarding the initiation of immunosuppressive therapy should be made in consideration of the risks of treatment versus those of disease progression, taking into consideration baseline GFR, degree of proteinuria, and autoantibody titer. An updated algorithm based on the upcoming revision of the KDIGO (Kidney Disease: Improving Global Outcomes) guideline for glomerulonephritis is shown in Fig 5. Patients are first classified as being at low, moderate, high, or very high risk for disease progression. Based on that classification, a clinical decision can be made about watchful waiting versus immediate treatment with immunosuppression. The trajectory of anti-PLA_2R, followed every 1-3 months according to clinical context, is important as well: patients in a nephrotic state with increasing autoantibody titers would be expected to worsen clinically and might warrant more rapid initiation of immunosuppressive treatment, whereas decreasing titers or disappearance of anti-PLA_2R could justify further watchful waiting for a spontaneous remission. In patients who start immunosuppression, decreasing titers indicate response to treatment, and unchanged or increasing titers are indicative of treatment failure and warrant modification of therapy. Several studies have shown that stopping immunosuppression before the anti-PLA_2R has completely disappeared can lead to an early relapse of disease as autoantibody titers rebound. Evidence is lacking for THSD7A, but similar principles likely apply.

Before discussing the main treatment options for adult primary MN, we should emphasize that corticosteroid monotherapy has been shown to be ineffective as immunosuppression and should be avoided. The possible exception is in the pediatric patient, who tends to have a more benign disease course, exhibits a higher rate of spontaneous remission, and is often empirically treated with steroids from the outset. If steroids do not achieve

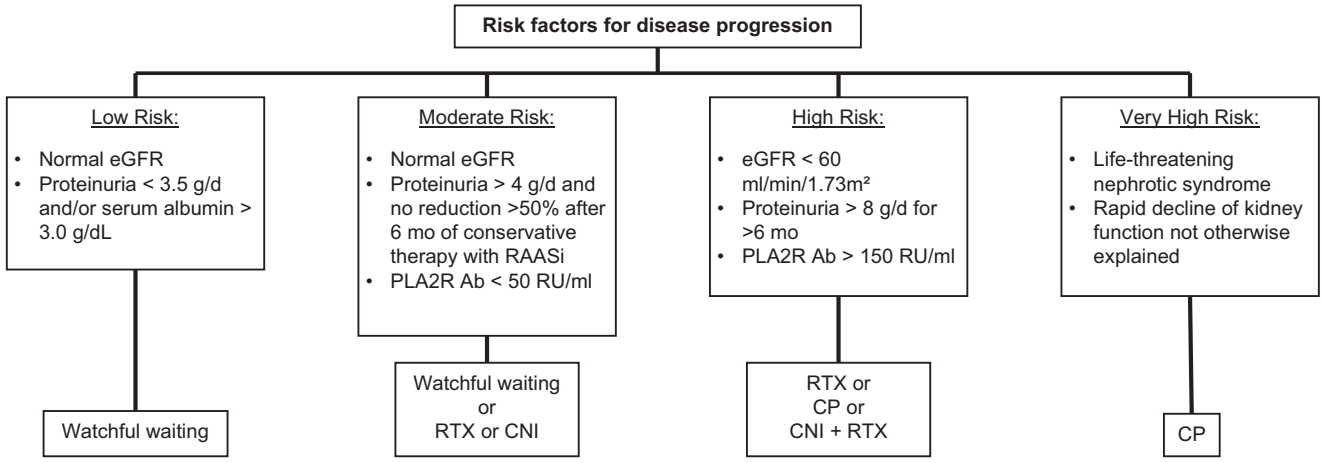

Figure 5. This algorithm classifies patients into 4 different risk groups with the subsequent recommended therapy plan. The thresholds for anti-PLA_2R titer are somewhat arbitrary. Consideration should also be given to anti-PLA_2R trajectory, as a decreasing titer over time might warrant continued monitoring with antiproteinuric therapy alone, whereas increasing titer might increase the level of risk. Abbreviations: CP, cyclophosphamide-based protocol; eGFR, estimated glomerular filtration rate; Ab, antibody; RAASi, renin-angiotensin-aldosterone system inhibition; RTX, rituximab.

remission for pediatric MN, the B-cell–depleting agent or calcineurin inhibitors (CNIs) should be tried.

Cyclophosphamide and Corticosteroids

The best long-term follow-up data for the treatment of primary MN come from 2 studies comparing a regimen of alternating corticosteroids and alkylating agents with supportive therapy. This high-level evidence supports the recommendation to strongly consider their use for patients at very high risk of disease progression.

The original Ponticelli protocol used alternating months of corticosteroids and chlorambucil for a period of 6 months, which proved to be very effective in terms of inducing remission of proteinuria while preserving GFR. This regimen was later compared with a similar regimen that substituted the alternative alkylating agent cyclophosphamide alternating with corticosteroids for a 6-month period (the modified Ponticelli protocol) and resulted in comparable efficacy with less toxicity. A regimen known as the Dutch protocol used daily cyclophosphamide for as long as 1 year with 6 months of daily or alternate-day prednisone followed by a tapering steroid dose. This protocol also achieved a good clinical response, but with significant adverse events that were associated with a higher cumulative dose of cyclophosphamide.

In terms of treatment-specific adverse events, cyclophosphamide is associated with cytopenias, in particular leukopenia, which predisposes patients to infections. It is also known to increase the risk of bladder cancer in smokers. A more concerning toxicity for young patients is oligospermia in male patients and premature ovarian failure in female patients. These risks tend to be associated with higher cumulative doses used in cancer chemotherapy, but nonetheless need to enter into the risk/benefit analysis for each individual patient.

Rituximab

Pioneering pilot studies from Bergamo, Italy, and the Mayo Clinic/University of Toronto demonstrated the utility of the anti–B-cell agent rituximab for the treatment of primary MN. The Bergamo group assembled a large observational cohort of patients with MN effectively treated with rituximab as first- or second-line therapy, and much of our knowledge about long-term remission rates, relapses, and effects on anti-PLA_2R come from this important cohort.

There are 3 randomized controlled trials comparing rituximab with supportive care or other immunosuppressive treatment. An initial study (GEMRITUX) did not show better efficacy of rituximab versus conservative antiproteinuric therapy at the 6-month end point, but long-term follow-up for a median of 17 months showed higher remission rates in the rituximab arm. The MENTOR trial, designed as a noninferiority trial that compared the use of rituximab and cyclosporine in primary MN, demonstrated not only equal efficacy at 12 months, but superiority of rituximab at achieving and maintaining remission at 24 months. This trial lends strong support for the use of rituximab as first-line treatment for primary MN. The recently-published STARMEN trial (ClinicalTrials.gov identifier NCT01955187) compares 24-month remission rate after sequential therapy with tacrolimus and rituximab versus the modified Ponticelli regimen in primary MN. The rationale for dual therapy is to administer rituximab prior to tapering the tacrolimus in an attempt to reduce the rate of relapse that is otherwise common in this setting.

Because of the more limited adverse effects of rituximab, it may be considered in patients with advanced chronic kidney disease and immunologically active MN, as successful treatment of the MN may help to preserve

remaining GFR. It is also important to mention that second-generation anti-CD20 agents such as ofatumumab have been used successfully in cases in which MN becomes refractory to rituximab.

In terms of adverse events, infusion-related reactions are very common and can range from a mild skin rash to anaphylaxis. Pretreatment with dexamethasone and diphenhydramine is standard and can decrease the risk of these reactions. Because rituximab results in prolonged B-cell depletion, there is an increased risk of reactivation of HBV and tuberculosis, and prophylactic treatment of both conditions during the B-cell depletion period should be considered in previously exposed patients. Other serious infections have also been reported. Very rarely, rituximab can cause progressive multifocal leukoencephalopathy.

CNIs

CNIs have immunosuppressive and antiproteinuric effects and can be effective in achieving remission in primary MN. Trials with cyclosporine and low-dose prednisone or with tacrolimus monotherapy have shown increased remission rates compared with supportive therapy alone. The major issue with the use of CNIs is the very high rate and rapidity of relapses when the agents have been tapered and discontinued. If these agents are to be used for therapy for primary MN, serum autoantibodies should be followed every 3-6 months and therapy continued until there is a decrease and disappearance of autoantibodies before the CNIs are tapered and stopped.

In terms of adverse events, the doses used for the treatment of MN are typically much lower than those used in prevention of solid-organ transplant rejection, and therefore acute CNI toxicities are rare. Clinicians should monitor patients for the development of a decrease in estimated GFR and development of hypertension or neurologic changes with prolonged therapy.

Other Therapies

Limited data suggest a utility of adrenocorticotropic hormone for the treatment of MN, as adrenocorticotropic hormone–related melanocortin peptides have immunomodulatory effects as well as direct podocyte effects that can limit proteinuria. Mycophenolate monotherapy is not effective for the treatment of MN, although mycophenolate may have a role as an alternative therapy when combined with corticosteroids or a CNI.

Future Therapies: Antigen-Specific Therapies

As we are learning more about the antigens and epitopes targeted in primary MN, there has been discussion about tolerance induction or specific depletion of B cells producing the pathogenic autoantibodies. No antigen-specific therapy is currently available, although the field is hopeful that such agents can be developed to limit adverse effects of more generalized immunosuppression.

The answer to question 3 is (d): rituximab is the best choice of therapy to achieve complete remission at 24 months for the patient. As shown by the MENTOR study, incomplete remissions and relapses make cyclosporine (b) an incorrect choice. Prednisone monotherapy (a) is not indicated for MN, and mycophenolate (c) has had inferior and inconsistent results in primary MN.

Treatment of Secondary MN

In treatment of secondary MN, the general rule is to treat the underlying disease or stop the offending agent. In cases of malignancy-associated MN, treatment of the malignancy should be paramount, and MN can initially be treated supportively. If the patient subsequently does not show evidence of a remission of proteinuria, a trial of immunosuppression following the algorithm for primary MN is recommended.

The treatment of class V lupus nephritis will vary depending on whether it exists as a solitary lesion or in combination with a proliferative form (class III/IV lupus nephritis). In the latter case, treatment should be focused on the proliferative classes. However, if membranous lupus nephritis is the primary lesion, treatment with immunosuppression can be started if there is nephrotic-range proteinuria with or without nephrotic syndrome and/or progressive decrease in GFR. All patients should be taking antimalarial agents in the absence of contraindications, as there is evidence that they reduce risk of flares, delay progression to kidney failure, and improve 12-month renal response rates. The optimal treatment for membranous lupus nephritis is not known, as published trials are not well powered, but it is well established that patients require immunosuppression. Agents commonly used are cyclophosphamide, mycophenolate, and CNIs combined with corticosteroids. Mycophenolate mofetil has been found to be comparable to cyclophosphamide in 2 prospective studies and is therefore now used as first-line therapy.

Treatment of MN due to chronic HBV infection requires agents directed against the infection, such as pegylated interferon, entecavir, or tenofovir.

Additional Readings

- Ponticelli C, Zucchelli P, Passerini P et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int.* 1995;48(5):1600-1604.
- Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol.* 2007;18(6):1899-1904.
- Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol.* 2012;23(8):1416-1425.
- Fervenza FC, Appel GB, Barbour SJ et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med.* 2019;381(1):36-46. ★ESSENTIAL READING
- Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol.* 2017;28(1):348-358.
- Bomback AS, Fervenza FC. Membranous nephropathy: approaches to treatment. *Am J Nephrol.* 2018;47(suppl 1):30–42.

Table 1. Clinical and Pathologic Features That Distinguish Recurrent from De Novo MN

Category	Recurrent MN	De Novo MN
Epidemiology	• 10%-45% recurrence rate (higher rates in centers with protocol biopsies) • Clinically apparent by 13-15 mo, but proteinuria can begin within months of transplantation	• 1%-2% posttransplant with increasing incidence with time; reported as ~5.3% at 8 y • Higher incidence in pediatric population, reaching ~9%
Pathogenesis	• Anti-PLA_2R at time of transplantation is a risk factor • Can appear years later with reemergence of autoantibodies when transplant immunosuppression decreased	• Not fully known • Has been associated with chronic and/or antibody-mediated rejection
Clinical presentation	• Similar to primary MN • May be detected earlier with lower amounts of proteinuria due to heightened surveillance (especially with protocol biopsy)	• Can be asymptomatic or with various degrees of proteinuria many years after transplantation
Diagnosis	• MN present on biopsy of native kidney • Presence of anti-PLA_2R can support recurrent MN if native diagnosis not known • Positive PLA_2R staining within deposits in 70%-80% • IgG4 is the dominant or codominant IgG subclass	• Diagnosis other than MN in biopsy of native kidney • Typically not associated with anti-PLA_2R antibody or PLA_2R staining of deposits • Evidence of chronic and/or antibody-mediated rejection • IgG1 is predominant IgG subclass
Treatment	• Can closely follow if low titer anti-PLA_2R, subnephrotic proteinuria, stable kidney function • Transplant immunosuppression may cause decrease and disappearance of autoantibodies • Heightened concern warranted as process already resulted in loss of native kidneys • Rituximab for worsening disease in setting of transplant immunosuppression	• Unknown natural history but 50% graft loss has been reported • Treat underlying rejection and implement antiproteinuric therapy • Increase maintenance immunosuppression, consider plasmapheresis if chronic rejection is present • Consider rituximab or cyclophosphamide if kidney function is rapidly declining

IgG, immunoglobulin G; MN, membranous nephropathy; PLA_2R, phospholipase A_2 receptor.

➢ Radhakrishnan J, Moutzouris DA, Ginzler EM, et al. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kidney Int.* 2010;77(2):152-160.

Anticoagulation

The nephrotic syndrome represents a hypercoagulable state with increased risk of venous thromboembolism (VTE) such as deep vein or renal vein thrombosis and pulmonary embolism. There is a lower, but still increased, risk for arterial thromboembolic events. The risk of VTE is particularly high in MN for unclear reasons. The best evidence supporting the use of prophylactic anticoagulation in MN comes from a cohort study of 2 large glomerulonephritis registries that demonstrated that the VTE risk starts to increase at a serum albumin level lower than 2.8 g/dL and increases further with lower values. However, the risk of bleeding due to anticoagulation needs to be weighed against the benefit of preventing a major thromboembolic event. A risk/benefit analysis equation has been developed to guide decisions about anticoagulation based on serum albumin and bleeding risk. Warfarin and low-molecular-weight heparin can be used for VTE prophylaxis, and the dosing and target International Normalized Ratio are identical for the general treatment of VTE; the use of direct oral anticoagulant agents such as apixaban for prophylaxis needs further study.

Additional Readings

- Lionaki S, Derebail VK, Hogan SL, et al. Venous thromboembolism in patients with membranous nephropathy. *Clin J Am Soc Nephrol.* 2012;7(1):43-51.
- Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol.* 2012;7(3):513-520.
- Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. *Kidney Int.* 2014;85(6):1412-1420. ★**ESSENTIAL READING**
- Lee T, Derebail VK, Kshirsagar AV, et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. *Kidney Int.* 2016;89(5):1111-1118.

Kidney Transplantation

Case, continued: *Your patient, despite exhibiting initial remission of her MN with rituximab, has several relapses over the next decade and is ultimately diagnosed with stage 5 chronic kidney disease with no evidence of the nephrotic syndrome. She is deemed an acceptable candidate for preemptive kidney transplantation, and her healthy daughter would like to donate a kidney. As part of the*

peritransplantation process, your patient is found to have an anti-PLA_2R titer of 43 RU/mL.

Question 4: How should you proceed in terms of transplantation?

a) Treat with rituximab and await disappearance of anti-PLA_2R before proceeding with transplantation
b) Insist on another donor, as a living-related donor is highly likely to lead to recurrence of MN in the allograft
c) Proceed with transplantation and monitor anti-PLA_2R and proteinuria closely
d) Perform plasmapheresis in the peritransplantation period

For the answer to the question, see the following text.

MN, when it occurs in the kidney allograft, can represent a recurrence of the same disease that occurred in the native kidneys (ie, recurrent MN) or as de novo disease in a recipient who experienced kidney failure due to other causes. The features of these two forms are quite different (Table 1).

Recurrent MN

The development of recurrent MN likely recapitulates the earliest stages of MN in the native kidney, when circulating autoantibodies have started to target intrinsic podocyte proteins (eg, PLA_2R) in the donor kidney and form immune deposits of increasing size. Although the humoral response is typically quite mature by the time someone has progressed to kidney failure and requires transplantation, transplant immunosuppression itself can mitigate the humoral response and is sometimes able to cause decrease and disappearance of circulating antibodies. Knowledge of autoantibody status in the peritransplantation period is critical. In those with low antibody titers, transplantation can often proceed, with careful monitoring of autoantibody titer after transplantation; the answer to question 4 is therefore (c). In those with high titers, it is less likely that transplant immunosuppression alone will fully treat the autoimmune process before clinically significant recurrent disease can occur and potentially threaten the allograft. In this case, consideration should be given to treatment before transplantation.

De Novo MN

It has been proposed that de novo MN occurs as a result of multiple triggers that all lead to formation of antigen-antibody complexes in the subepithelial space of the GBM, resulting in podocyte injury and MN. These antigens are exposed as a result of a prior episode of rejection or planted in the subepithelium as a result of an infection in an immunocompromised host. It has also been proposed that episodes of rejection can lead to disturbance in the GBM architecture, rendering it susceptible to formation of subepithelial deposits.

Additional Readings

- Rodriguez EF, Cosio FG, Nasr SH, et al. The pathology and clinical features of early recurrent membranous glomerulonephritis. *Am J Transplant.* 2012;12(4):1029-1038.
- Debiec H, Hanoy M, Francois A, et al. Recurrent membranous nephropathy in an allograft caused by IgG3κ targeting the PLA2 receptor. *J Am Soc Nephrol.* 2012;23(12):1949-1954.
- Grupper A, Cornell LD, Fervenza FC, et al. Recurrent membranous nephropathy after kidney transplantation: treatment and long-term implications. *Transplantation.* 2016;100(12):2710-2716.
- Leon J, Pérez-Sáez MJ, Batal I, et al. Membranous nephropathy posttransplantation: an update of the pathophysiology and management. *Transplantation.* 2019;103(10):1990-2002. ★ESSENTIAL READING
- Batal I, Vasilescu ER, Dadhania DM, et al. Association of HLA typing and alloimmunity with posttransplantation membranous nephropathy: a multicenter case series. *Am J Kidney Dis.* 2020;76(3):374-383.

Conclusion

The progress made in the field of MN has been substantial as a result of the identification of multiple target antigens, the ability to monitor disease course with circulating autoantibodies, advances in the genetics of this disease, and therapeutic trials identifying effective treatments with fewer adverse effects, such as rituximab. We expect that this progress will continue in the next decade and urge the readers of this Core Curriculum to stay abreast of the new studies in this fascinating disease.

Article Information

Authors' Full Names and Academic Degrees: Loulwa Alsharhan, MD, and Laurence H. Beck Jr, MD, PhD.

Authors' Affiliations: Section of Nephrology, Department of Medicine, Boston Medical Center, Boston, MA (LA, LHB) and Section of Nephrology, Department of Medicine, Boston University School of Medicine, Boston, MA (LHB).

Address for Correspondence: Laurence H. Beck Jr, MD, PhD, Section of Nephrology, Department of Medicine, Boston University School of Medicine and Boston Medical Center, 650 Albany St, X-536, Boston, MA 02118. E-mail: lhbeckjr@bu.edu

Support: The preparation of this work was supported by institutional funding from Boston Medical Center and the Department of Medicine's Glomerular Disease Center.

Financial Disclosure: Dr Beck reports being a coinventor on the US patent "Diagnostics for Membranous Nephropathy" with royalties from Boston University; Dr Beck has served on advisory boards for Visterra, Ionis, and Genentech; has received research support in the area of MN from Sanofi Genzyme and Pfizer; and receives royalties from UpToDate for topics related to MN. Dr Alsharhan declares that he has no relevant financial interests.

Peer Review: Received May 29, 2020, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form October 1, 2020.