MEMBRANOUS NEPHROPATHY

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  - Research focus: membranous nephropathy
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Learning Objectives

• Distinguish primary membranous nephropathy from secondary forms of disease

• Describe how the immunological course of disease is related to the clinical course

• Know how to judge when immunosuppression is indicated to treat membranous nephropathy
Representative case:

52 y/o male presents to his PCP with several months of weight gain and lower extremity edema

BP 148/92  HR 80
Lungs clear, heart sounds normal, 3+ bilateral pitting edema up to knees

Lab tests: Cr 1.08, Alb 2.9, Cholesterol 386
UA: 4+ protein, trace blood, no leuk esterase
Case, continued

Due to the unexplained nephrotic syndrome and a 24 hr urine proteinuria value of 13 g, the patient is referred to a nephrologist, who schedules a kidney biopsy

The biopsy is read as **membranous nephropathy**, with IgG and C3 present as fine granular deposits in a capillary loop pattern

There is minimal glomerular scarring, tubular atrophy, or interstitial fibrosis
Which of the following statements about primary membranous nephropathy (PMN) is *incorrect*?

a) PMN affects males more often than females

b) PMN only affects Caucasians

c) The median age of onset is in the mid 50s

d) 30-40% of patients may undergo spontaneous remission, given enough time
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What is Membranous Nephropathy?

• A leading cause of nephrotic syndrome in adults
• Antibody-mediated kidney disease

• **Primary MN**
  • may still be called ‘idiopathic’ in older texts or on Boards
  • can be sub-typed by antigen
  • organ-specific autoimmune disease
  • variable course – remission, persistent nephrotic syndrome, ESRD, recurrence post-transplant

• **Secondary MN** – lupus, HBV, cancer, drugs

• **Alloimmune** – neonatal MN (anti-NEP), de novo post-transplant MN
Natural history of MN

• Insidious onset (compare with MCD or primary FSGS)
• Patients often report weight gain, leg edema that has increased over course of months
• 75% nephrotic at presentation; 25% subnephrotic, but half of these will progress to full nephrotic syndrome
• “Rule of thirds”
  • 1/3 will undergo spontaneous remission
  • 1/3 remain proteinuric with stable renal function
  • 1/3 will progress towards ESKD (esp. with heavy proteinuria)
• Resolution is slow (again, as compared to MCD)
Phospholipase A2 Receptor (PLA2R) was identified as the major target antigen for PMN in 2009:

Why was this finding so important?

• Clinicians previously had only proteinuria and serum albumin to follow

• Clinical remissions occur **SLOWLY**

• Now we can additionally follow a serological marker of disease activity

• Serology **precedes and predicts** clinical course

• More rapid treatment decisions!
Based on a simple but key concept:

"Immunological (or serological) remission"

There are two disease courses that are separated by a predictable lag time.
It takes time for the deposits to form in early disease, and to clear in late disease.
The anti-PLA2R / PLA2R system in MN

• PLA2R is a normal protein in podocytes
• 70-80% prevalence of circulating anti-PLA2R in primary MN
• In disease, the PLA2R antigen co-localizes with IgG within the subepithelial immune deposits
• Genetic association of MN with PLA2R1 and with class II MHC alleles
• Circulating anti-PLA2R and/or tissue PLA2R is highly specific for MN
• Strong association of anti-PLA2R with clinical disease activity
Primary MN can be sub-classified by immunofluorescence staining of biopsy

PLA2R-associated MN  
80-85%

Non-PLA2R-associated MN  
15-20%
Possible test results in PLA2R-associated MN

Clinical manifestationsLAG BEHIND the immunological course of MN

Detectable anti-PLA2R in circulation

Proteinuria

neg? Low High Anti-PLA2R High Low neg neg

POS? POS POS Tissue PLA2R POS POS POS POS
Primary MN can be sub-classified by immunofluorescence staining of biopsy

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WHAT OTHER ANTIGENS ARE THERE?
THSD7A is another podocyte antigen targeted in membranous nephropathy

Which of the following findings on renal biopsy most strongly favors the diagnosis of *primary* rather than secondary membranous nephropathy?

a) Positive staining for C1q within deposits

b) Predominance of the IgG4 subclass

c) Presence of subendothelial and mesangial deposits

d) Endothelial tubuloreticular inclusions
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<table>
<thead>
<tr>
<th></th>
<th>Primary (Idiopathic) MN</th>
<th>Secondary MN</th>
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</thead>
<tbody>
<tr>
<td><strong>Caused by:</strong></td>
<td>AutoAb to intrinsic podocyte Ag</td>
<td>Deposition of planted Ag, immune complexes, or alloantibodies</td>
</tr>
<tr>
<td><strong>Examples:</strong></td>
<td>PLA(_2)R, THSD7A</td>
<td>HBV, SLE, drugs, tumors</td>
</tr>
<tr>
<td><strong>Histopathology:</strong></td>
<td>Predominant IgG, C3</td>
<td>May also have IgA, IgM, C1q (&quot;full house&quot; pattern)</td>
</tr>
<tr>
<td></td>
<td><strong>Typically IgG4 predominant</strong></td>
<td>Other IgG subclasses</td>
</tr>
<tr>
<td><strong>Subepithelial deposits</strong></td>
<td>Often stains for PLA(_2)R or THSD7A</td>
<td>Often with mesangial and/or subendothelial deposits as well</td>
</tr>
<tr>
<td><strong>Often stains for PLA(_2)R or THSD7A</strong></td>
<td></td>
<td>No specific staining for autoAg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have infiltrating glomerular immune cells</td>
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<tr>
<td></td>
<td></td>
<td>Tubuloreticular inclusions</td>
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Proposed categorization of membranous nephropathy

Membranous nephropathy and malignancy:

• **Always consider the possibility!**
• Association may be causal or coincidental
• A closer temporal relation between malignancy and diagnosis of MN may be more suggestive of a true secondary process
• Consider searching for malignancy if:
  • no PLA₂R staining within immune deposits (THSD7A, NELL1)
  • lack of IgG4 dominance or co-dominance
  • presence of other secondary features on biopsy
What does the clinician need to know?

**THSD7A, NELL1**: need to rule out malignancy

**SEMA-3B**: childhood MN cases

**EXT1/EXT2; NCAM1; TGFBR3**: biomarkers/antigens in lupus MN

Many of these assays for circulating autoantibodies or the staining of biopsy tissue are not yet widely available, and are only done by specialized centers.
Suggested treatment algorithm

- **Low risk**
  - Normal eGFR
  - Proteinuria < 3.5
  - **WATCH & WAIT**
    - ACEI/ARB, diuretics
    - Statin

- **Moderate Risk**
  - Normal eGFR
  - Proteinuria > 4 with no decrease by 6 mo
  - **WATCH & WAIT**
    - Anti-PLA2R present?
      - "Low" anti-PLA2R
      - "High" anti-PLA2R

- **High Risk**
  - eGFR < 60
  - Proteinuria > 8 after 6 mo supportive Rx
  - **IMMUNOSUPPRESSION**
    - "Low" anti-PLA2R
    - Cytotoxics / prednisone
    - Rituximab (+ CNI?)

- **Very High Risk**
  - Life-threatening nephrotic syndrome
  - Rapid drop in eGFR
  - **IMMUNOSUPPRESSION**
    - "High" anti-PLA2R
    - Cytotoxics / prednisone
Which patients with MN should be anticoagulated?

- Risk of VTE is 10-40% and increases with serum albumin <2.8 g/dL
- Personalized prophylactic anticoagulation decision analysis based on 539 patients with MN
- Benefit-to-risk ratios were predicted according to bleeding risk and serum albumin:
  
  **Low bleeding risk**
  - Ratio increases with worsening hypoalbuminemia
  - 4.5 : 1 for albumin < 3 g/dl
  - 13.1 : 1 for albumin < 2 g/dl

  **Intermediate bleeding risk**
  - 5 : 1 for albumin < 2 g/dl

  **High bleeding risk**
  - Unlikely to benefit regardless of albumin level

Lee et al. Kidney Int 85: 1412-1420, 2014

https://www.med.unc.edu/gntools
The (modified) Ponticelli regimen:

**Months 1, 3, 5:** 1 g i.v. methylprednisolone daily x 3, then oral methylprednisolone (0.5 mg/kg/d) x 27 days

**Months 2, 4, 6:** Oral chlorambucil at 0.15-0.2 mg/kg/d (or oral cyclophosphamide at 2 mg/kg/d) x 30 days

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Remissions occur late following completion of treatment.
ALKYLATING AGENTS remain the only agents proven effective in preventing ESKD or death in MN

- Should be restricted to patients with high risk of progression
- Should be avoided if possible in smokers, patients of child-bearing age

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Factors associated with the risk of progressive loss of kidney function in patients with membranous nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Proteinuria $&lt;3.5$ g/d</td>
<td>Serum creatinine $&gt;1.5$ mg/dl (133 μmol/l)</td>
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<td>Decrease in eGFR by $\geq 20%$ over any time period during the preceding 12 months not explained otherwise$^a$</td>
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<tr>
<td></td>
<td>Proteinuria $&gt;8$ g/d for $&gt;6$ mo</td>
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<td></td>
<td>Presence of low-molecular-weight proteinuria</td>
</tr>
<tr>
<td></td>
<td>Urine IgG $&gt;250$ mg/24 h</td>
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<tr>
<td></td>
<td>PLA2R antibody levels and evolution$^b$</td>
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</table>

25 patients received tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper; 23 patients were in the control group

Limitations of these therapeutic agents

**Calcineurin inhibitors:**
- Aggravate severe HTN, impaired GFR and interstitial fibrosis
- Diabetogenic
- Relatively high relapse rate on discontinuation

**Alkylating agents and prednisone:**
- Cytopenias
- Cancer risk (bladder and lung) in smokers
- Infertility
- Diabetogenic
Anti-CD20 therapy
Rituximab

Lack of suppression of anti-PLA2R is associated with failure to induce remission


(Despite effective depletion of B cells)
Many relapses after cyclosporine was tapered off.
MN in native kidneys

PLA2R+ MN

Development of ESKD

Anti-PLA2R

Circulating anti-PLA2R at time of transplant

Recurrent Membranous Nephropathy

Assessment of anti-PLA2R pre- and post-transplant can be helpful in guiding management
Recurrent membranous nephropathy

- Incidence of recurrence in allograft: **10 to 45%**

- Centers performing protocol biopsy report higher incidence and earlier recurrence

- The mean time for *overt* clinical recurrence is 13-15 months

- Persistent nephrotic range proteinuria increases risk of graft failure

- Anti-PLA2R can be found in association with recurrent (but not *de novo*) MN

- **Positive anti-PLA2R serology at transplantation should not affect decision to transplant**

- Heightened surveillance for proteinuria is warranted if patient is seropositive pre-transplant
PLA₂R and THSD7A are the major and minor autoantigens in primary MN; others such as NELL1, Sema-3B, HTRA1 have recently been identified.

Circulating autoantibodies to these podocyte proteins, and/or enrichment of these antigens within subepithelial deposits, is highly suggestive of primary MN.

A consistent relationship exists between the immunologic and clinical courses of disease.

Due to the slow onset and time to remission, monitoring autoAb levels has emerged as an adjunctive and more rapid method to follow disease course and monitor response to treatment.
Summary/Take Home Points

- **Alkylating agents** *(e.g. the modified Ponticelli regimen)* have the best long-term outcomes for inducing a durable remission and preserving renal function; however side effects are significant.

- **Calcineurin inhibitors** are a widely-used alternative agent, but often require a lengthy duration of treatment to fully suppress autoAb levels. Relapse is common with shorter treatments.

- The anti-B cell agent **rituximab** has emerged as a very effective agent for treating primary MN, as demonstrated in observational trials, GEMRITUX, and most recently, MENTOR.

- A serological approach (titer, trajectory of autoantibodies) can be very useful for treatment decisions about starting, stopping, or changing immunosuppression.
Brief References:


