Concurrent PLA2R-Associated Membranous Nephropathy and Antiglomerular Basement Membrane Disease

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INTRODUCTION

Membranous nephropathy (MN) is etiologically associated with circulating autoantibodies against M-type phospholipase A2 receptor (PLA2R) in approximately 80% of cases (when secondary etiologies are excluded).1 Whereas a kidney biopsy may be unnecessary to diagnose MN in patients with detectable serum anti-PLA2R antibody and preserved estimated glomerular filtration rate, a biopsy may reveal findings that alter therapy in patients with reduced estimated glomerular filtration rate.2,3 In this report, we describe a patient with PLA2R-associated MN who developed acute kidney injury with renal biopsy findings of concurrent anti-glomerular basement membrane (GBM) disease, and discuss diagnostic considerations for patients with MN and crescents.

CASE PRESENTATION

A 69-year-old Hispanic male with well-controlled hypertension, diabetes mellitus, and rheumatoid arthritis presented with nephrotic syndrome and preserved estimated glomerular filtration rate. Serologic evaluation revealed positive anti-PLA2R antibody (43.8 RU/ml), and a kidney biopsy confirmed the diagnosis of PLA2R-associated MN. The patient was receiving rituximab for rheumatoid arthritis, received treatment 3 months prior to biopsy, and was not due for another treatment for 3 months. Therefore, no additional immunosuppression was administered at that time. Three months later, the patient presented to the emergency department with anuric acute kidney injury, requiring renal replacement therapy. Physical examination revealed blood pressure of 136/76 mmHg and edema. Laboratory testing revealed serum creatinine 6.0 mg/dl. Complement levels of C3 and C4 were normal. A full panel of serologies was ordered and repeat kidney biopsy was performed.

Kidney Biopsy

Light microscopy revealed 20 glomeruli, none of which were globally sclerotic. Sixteen of the 20 glomeruli contained circumferential cellular crescents associated with extensive fibrinoid necrosis and rupture of the GBM. (Figure 1a). The remaining 4 glomeruli appeared normocellular. GBMs were thickened with short spikes highlighted by periodic acid-Schiff and Jones methenamine silver stains. There was diffuse acute tubular injury, moderate interstitial inflammation, and mild tubulointerstitial scarring. Vessels exhibited mild arteriosclerosis, without evidence of vasculitis.

Conventional immunofluorescence revealed 3+ linear staining for IgG, C3, K and λ along the GBMs (Figure 1b). Closer inspection additionally revealed 2+ granular staining for IgG, C3, K and λ on the outer aspect of the GBMs (Figure 1b). Immunofluorescence staining for PLA2R was positive in the distribution of the subepithelial deposits (Figure 1c).

Ultrastructural examination confirmed the presence of subepithelial electron dense deposits with intervening GBM spikes (Ehrenreich and Churg stage 1-2; Figure 1d). No mesangial or subendothelial electron dense deposits or endothelial tubuloreticular inclusions were seen. Podocytes displayed 100% foot process effacement. The findings were diagnostic of anti-GBM disease and PLA2R-associated MN.

Follow-up

The patient was found to have positive antinuclear antibody and anti-GBM antibody (65.9 AU/ml).
Antineutrophil cytoplasmic antibody (ANCA), anti-dsDNA antibody, hepatitis B surface antigen, and hepatitis C antibody were undetectable. The patient had no signs or symptoms of systemic lupus erythematosus. The patient was treated with intravenous pulse methylprednisone (500 mg), oral cyclophosphamide (2 mg/kg/day), 5 cycles of plasmapheresis, and was maintained on prednisone (60 mg/day). Five months later, the patient remains dialysis-dependent, without evidence of pulmonary involvement.

**DISCUSSION**

MN is a common cause of nephrotic syndrome in adults. Antibodies against podocyte antigen PLA2R are implicated in approximately 80% of cases of presumed “primary” MN. Due to the availability of sensitive and reliable assays for anti-PLA2R antibodies, kidney biopsies may be unnecessary for the diagnosis of PLA2R-associated MN in patients with normal kidney function. Nevertheless, a rapid decline in kidney function and/or active urine sediment with red blood cell casts should prompt further evaluation for a superimposed disease with serological testing and possibly kidney biopsy. Differential diagnosis for kidney function decline in patients with MN includes renal vein thrombosis, tubulointerstitial nephritis, acute tubular injury, and, rarely, superimposed glomerulonephritis with crescents.

Crescents are identified in less than 3% of kidney biopsies with MN from patients who lack evidence of systemic lupus erythematosus or an alternative secondary etiology of disease. In such cases, the available medical literature suggests that the crescents are due to superimposed ANCA-associated vasculitis in approximately 46% to 60% of cases (most commonly anti-MPO ANCA) and anti-GBM disease in approximately 13% to 33%. Rarely, patients with MN and crescents exhibit negative ANCA and anti-GBM serologies and no evidence of systemic lupus erythematosus. Therefore, serologic testing for ANCA, ANA, and anti-GBM antibody can be informative in patients with MN and acute kidney injury and/or active urine sediment and should be routinely evaluated in patients with MN and crescents. Most cases of MN with crescents are not associated with anti-PLA2R antibodies. In our experience with 4 additional cases of PLA2R-negative MN with anti-GBM disease, none were associated with THSD7A, EXT2, or NELL1.
MN with anti-GBM disease manifests with features of both diseases (Table 1). Patients present with nephrotic-range proteinuria and rapidly progressive glomerulonephritis, often requiring hemodialysis.7,8 Though both diseases are often diagnosed simultaneously, either disease may temporally precede the other.4 Pulmonary-renal syndrome occurs in a minority of patients.7,8 The typical histologic changes are diffuse necrotizing and crescentic glomerulonephritis, which may obscure the more subtle light microscopic changes of MN. Immunofluorescence reveals linear staining of the GBM, characteristic of anti-GBM disease. Therapy is primarily focused on anti-GBM disease, and includes a combination of prednisone, cyclophosphamide, rituximab, and plasmapheresis. The disease severity of concurrent MN and anti-GBM disease is often intermediate between isolated MN and isolated anti-GBM disease, but the overall kidney prognosis is poor, and many patients eventually require renal replacement therapy.7,8,52 MN with concurrent ANCA-associated GN is characterized by fewer crescents than MN with concurrent anti-GBM disease but has a similarly poor prognosis.9,53

Animal models provide insight into the pathophysiological link between concurrent MN and anti-GBM disease. Experimental toxic exposure of brown Norway rats to mercuric chloride produces antibodies against components of the GBM, resulting in initial linear GBM staining, followed by granular subepithelial immune complex deposition over time.54 Experimental immunization of DBA/1 mice with recombinant human noncollagenous domain 1 of the α3 chain of type IV collagen (α3(IV)NC1), the target antigen in anti-GBM disease, results in the formation of

Table 2. Teaching points

- In patients with MN and a rapid decline in renal function, clinical considerations include renal vein thrombosis, acute tubular injury, tubulointerstitial nephritis, and rarely, superimposed crescentic glomerulonephritis.
- MN with crescents should lead to prompt serologic testing for ANCA, ANA, and anti-GBM antibodies.
- MN with anti-GBM disease is characterized clinically by rapidly progressive glomerulonephritis, nephrotic range proteinuria, and in some cases pulmonary involvement. The findings of anti-GBM disease may obscure the findings of MN.
- Treatment and outcomes are more typical of anti-GBM disease, and PLA2R serologies are usually negative.

**Table 1.** Clinical and laboratory data at presentation of patients with concurrent anti-GBM and MN from recent case series

| Reference | No. of pts | Mean age (Yrs, range) | Sex | Race | Mean proteinuria (g/d) | Mean albumin (g/d) | Mean sCr (mg/dl) | Pts with AKI-D at presentation (%) | Pts with pulmonary signs or symptoms (%) | PLA2R positivity (%) | Biopsies with > 50% crescents (% of pts biopsied) | Pts with kidney failure requiring long-term HD (%) |
|-----------|------------|-----------------------|-----|------|-----------------------|-------------------|-----------------|-----------------------------------|------------------------------------------|-------------------|---------------------------------------------|---------------------------------------------|
| Jia et al.7 | 8 | 32 | 8 | 32 | 7 | 7.9 | 5.9 | 5.9 | 5.9 | 60 (4/8) | 100 (2/2) | 0.5 | 1/5 |
| Nikolopoulou et al.5 | 5 | 55 | 55 | 55 | 22.0 | 2.5 | 7.6 | 60 (3/5) | 20 (1/5) | 0.4 | 0.2 | 1/5 |
| Alawieh et al.6 | 2 | 24 | 2 | 24 | 1.5 | 7.3 | 12.8 | 16.8 | 16.8 | 100 (2/2) | 0.2 | 0.2 |
| Ahmad et al.8 | 12 | 55 | 55 | 55 | 5.1 | 5.1 | 5.1 | 5.1 | 5.1 | 100 (1/12) | 0.1 | 0.1 |
| Zuo et al.9 | 2 | 67 | 67 | 67 | 5.6 | 5.6 | 11.4 | 11.4 | 11.4 | 100 (2/2) | 0.2 | 0.2 |

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor.
α3(IV)NC1-specific antibodies that cause concurrent linear and subepithelial granular GBM staining for IgG. Mice initially exhibit an MN phenotype with proteinuria and later develop crescentic glomerulonephritis in a dose dependent manner.53,54 Epitope mapping studies have further narrowed down specific linear peptides on α3(IV)NC1 that induce either disease phenotype.55 Interestingly, MN and anti-GBM are linked to HLA-DRB1 alleles, suggesting an overlapping genetic proclivity for the development of both diseases.56

Declining kidney function in MN can rarely be due to crescent formation in the setting of superimposed glomerulonephritis such as anti-GBM disease (Table 2). Serological testing and kidney biopsies are critical to the diagnosis and management of this rare complication. The kidney outcome in these patients is generally poor with patients often requiring plasmapheresis, immunosuppression, and renal replacement therapy. Most cases of MN with crescents are not associated with anti-PLA2R antibodies.

**DISCLOSURE**

All the authors declared no competing interests.

**PATIENT CONSENT**

The authors declare that they have obtained consent from the patient discussed in the report.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)
Supplementary References.

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