Membranous Nephropathy in a Patient With Common Variable Immune Deficiency

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INTRODUCTION

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in white adults. Approximately 70% of MN cases are considered primary; the remaining 30% of cases are considered secondary to systemic conditions, such as lupus, hepatitis B, and solid tumors. In the last decade, target antigens and their associated autoantibodies, which are responsible for the development of primary MN cases, have been identified. The M-type phospholipase A2 receptor (PLA_2R) is the specific podocyte antigen responsible for eliciting immune complex formation with circulating autoantibodies in most ($\sim 75\% - 80\%$) primary MN cases.[1] In addition, alternative podocyte autoantigens—mitochondrial superoxide dismutase 2, aldose reductase, α-enolase, neutral endopeptidase, and thrombospondin type-1 domain-containing 7A (THSD7A)—have subsequently been reported in patients with primary MN,[2,3] potentially filling in the missing gaps in PLA_2R antibody negative disease. Testing for antibodies directed at these target antigens, via either serologic assays or immunofluorescence staining of kidney biopsy tissue, is increasingly being used to help distinguish primary from secondary forms of disease.[4] Such a distinction is crucial because secondary forms of MN are expected to remit if the underlying systemic disease responsible for the MN lesion is successfully treated.

However, even in the era of antibody testing, a number of cases have arisen that pose a challenge in distinguishing primary from secondary forms of MN. We present the first reported case of MN in an adult patient with common variable immune deficiency (CVID), a disorder associated with hypogammaglobulinemia and recurrent infection, and discuss whether the clinical course of the patient suggests that CVID should be considered an ultra-rare etiology of secondary MN.

CASE REPORT

A 36-year-old Hispanic female, with a history of asthma and CVID, presented with nephrotic syndrome. At age 22, she experienced chronic bruising for approximately 4 months, which was initially attributed to an allergic reaction to an asthma medication. After referral to hematology, she was diagnosed with hemophilia and treated with prednisone and cyclophosphamide for 6 months. While on these medications and after cessation of immunosuppression, she experienced recurrent upper respiratory infections, prompting referral to an immunologist. She was diagnosed with CVID, and the diagnosis of hemophilia was repositioned as a CVID-associated hematologic manifestation. She began monthly infusions of i.v. Ig that were eventually replaced with weekly subcutaneous IgG therapy.

Approximately 13 years after her diagnosis of CVID, at age 36, she was admitted to the hospital after presenting with sudden onset of lower extremity edema and abdominal distention. Her laboratory results were consistent with nephrotic syndrome, including serum creatinine 0.6 mg/dl, serum albumin 2.0 g/dl, and 8.0 g/d proteinuria on 24-hour collection. Other laboratory workups showed negative or normal antinuclear antibodies, antidouble stranded DNA antibodies, hepatitis B and C serologies, and C3 and C4 complement levels.

Renal biopsy (Figure 1) revealed findings of stage 1 MN. Specifically, light microscopy demonstrated glomerular basement membranes (GBMs) of normal
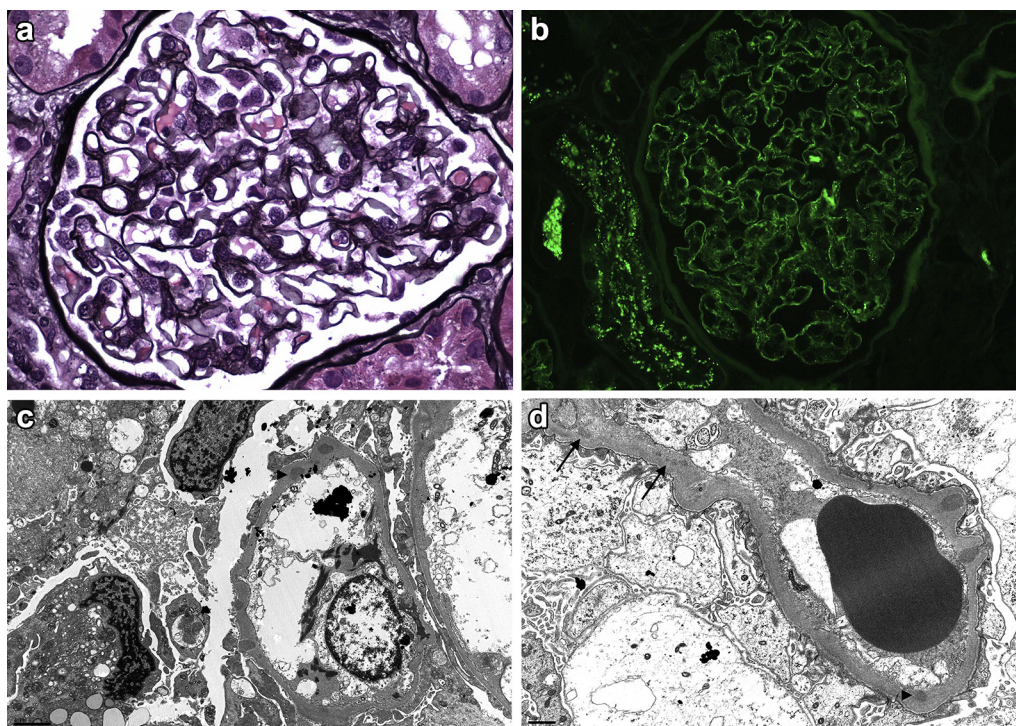
Figure 1. Initial renal biopsy showing membranous nephropathy, stage 1. The glomerular basement membrane is of normal thickness with rare crater-like depressions (Jones methenamine silver, original magnification ×400) (a). Immunofluorescence, performed on pronase-digested tissue, reveals 1+ glomerular basement membrane positivity for IgG (original magnification ×300) (b). Electron microscopy reveals segmental to global small subepithelial deposits, rare segmental mesangial (arrows) and subendothelial (arrowheads) deposits, and 95% foot process effacement (c,d) (original magnification: c, ×3000; d, ×6000).

thickness containing scattered, rare, crater-like indentations, seen best with the Jones methenamine silver (JMS) stain. Immunofluorescence, performed on pronase-digested tissue (due to the absence of frozen tissue containing glomeruli), showed trace to 1+ GBM positivity for IgG, κ, and λ staining in the absence of staining for IgM, IgA, C3, C1q, or the PLA$_2$R antigen. Electron microscopy revealed segmental to global small subepithelial deposits, segmental mesangial and subendothelial deposits, and 95% foot process effacement. No endothelial tubuloreticular inclusions were apparent. Due to the negative PLA$_2$R staining, coupled with mesangial and subendothelial deposits, a secondary form of MN was favored.

The patient was initially treated conservatively with losartan and furosemide. Within 2 weeks, she was admitted for worsening lower extremity edema, abdominal pain, and nausea. Her creatinine had risen to 2.0 mg/dl by admission, and within the first 72 hours of her hospital stay, she progressed to oliguric renal failure with a peak creatinine of 5.8 mg/dl. Renal ultrasound showed no evidence of renal vein thrombosis. Serologic testing for anti-PLA$_2$R antibodies and anti-THSD7A antibodies were negative. She was initiated on dialysis and a repeat renal biopsy was performed in an effort to better explain the abrupt worsening of renal function.

Repeat renal biopsy (Figure 2), performed 4 weeks after her initial biopsy, revealed stage 1 to 2 membranous changes with mild GBM thickening and short GBM spikes visible with periodic acid Schiff and JMS stains. Of note, 18 glomeruli were sampled for light microscopy, and none were globally sclerotic. Proximal tubules displayed patchy to diffuse degenerative changes characterized by luminal ectasia, cytoplasmic simplification, irregular luminal contours, and prominent nucleoli. There was minimal tubular atrophy and interstitial fibrosis involving <5% of the cortex sampled. Immunofluorescence revealed granular global subepithelial and segmental mesangial deposits that stained 2+ for IgG, 1+ for C3, 2+ for κ, and 1+ for λ. As in the first biopsy, staining for C1q was negative, and PLA$_2$R staining remained negative. Electron microscopy was not performed. The findings of acute tubular injury correlated with the development of acute kidney injury that required hemodialysis, which has been reported for severe forms of nephrotic syndrome.[5]

The patient was treated with 6 sessions of hemodialysis and started on a course of immunosuppression using 3 days of pulse corticosteroids, followed by a prednisone taper, and 2 doses of i.v. rituximab (1 g) spaced 2 weeks apart. After the pulse steroid infusions, but before the first dose of rituximab, she was able to discontinue hemodialysis, and her creatinine ranged
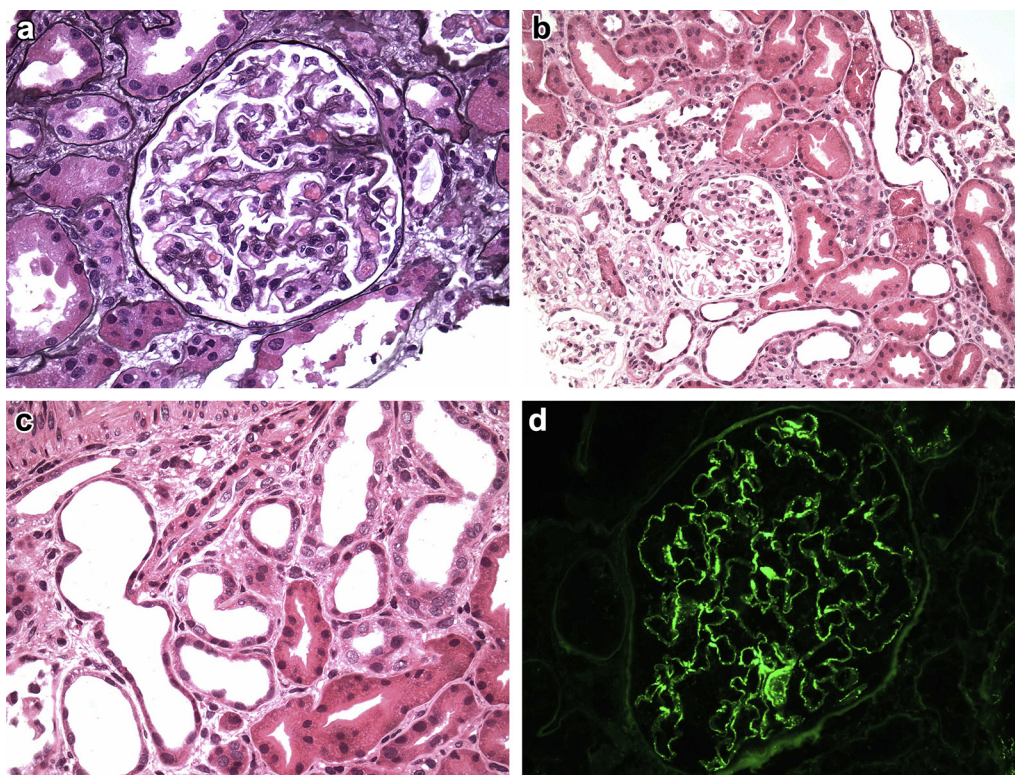
Figure 2. Repeat renal biopsy in the setting of oliguric renal failure. Light microscopy shows glomeruli that appear normal in size and cellularity with minimal thickening of the glomerular basement membrane (Jones methenamine silver, original magnification ×250) (a). Proximal tubules display acute degenerative changes characterized by luminal ectasia, cytoplasmic simplification, irregular luminal contours, and the attenutation of the brush border (b,c) (hematoxylin and eosin, original magnification: c, ×100; d, ×400). Immunofluorescence displays granular global subepithelial and segmental mesangial deposits that stain 2+ for IgG (original magnification ×300) (d).

from 0.6 to 0.8 mg/dl through the remainder of her hospital course. Her albumin remained depressed (2.0 g/dl) at the time of hospital discharge.

Two months after starting immunosuppressive treatment, at her first clinic follow-up, her creatinine remained at 0.6 mg/dl, her urine protein/creatinine ratio (UPCR) was 345 mg/g, and her serum albumin was 3.4 g/dl. By 4 months, her creatinine was 0.6 mg/dl, her UPCR was 154 mg/g, and her serum albumin had risen to 4.0 g/dl. She completed treatment with steroids at 6 months and did not receive additional treatment with rituximab. Because she had no detectable proteinuria and baseline low blood pressure, losartan was also discontinued. Eighteen months later, and approximately 2 years after her hospitalization, her most recent laboratory reports were notable for creatinine 0.7 mg/dl, UPCR 95 mg/g, and serum albumin 4.2 g/dl.

DISCUSSION

CVID is frequently associated with other autoimmune diseases,[6] including autoimmune hemolytic anemia, immune thrombocytopenia, rheumatoid arthritis, pernicious anemia, autoimmune thyroiditis, and vitiligo. We reported on a 36-year-old woman with CVID who presented with nephrotic syndrome and MN, with negative testing for PLA$_2$R and THSD7A antibodies, together with a negative workup for common secondary etiologies of MN. This case, which is the first report of CVID-associated MN in an adult patient, complements the only other reported case of this entity, a 13-year-old Korean patient with CVID in whom known secondary causes of MN were ruled out and who eventually achieved remission with immunosuppressive therapy.[7] These 2 cases suggest that CVID, a rare disease, might be an even rarer etiology of secondary MN that nonetheless appears to respond to immunosuppressive therapy.

The initial management of a patient newly diagnosed with MN is to determine whether the lesion should be considered primary or secondary, as such a distinction will guide subsequent therapeutic decisions. The advent of antibody testing—primarily for anti-PLA$_2$R antibodies but which now also increasingly includes anti-THSD7A antibodies—has aided this differentiation process. In addition, there are hallmark morphological features on renal biopsy that favor a secondary form of disease, including mesangial and subendothelial deposits, as seen in this case, and immunofluorescence staining of C1q antibodies, which was not seen in this

case. The negative testing for MN-associated antibodies and the location of deposits on electron microscopy favored a secondary etiology of MN in the case reported herein, presumably due to CVID. Autoimmunity is a manifestation of the immune dysregulation inherent in CVID, although the specific mechanisms for this susceptibility have not been delineated. Renal involvement is rare, with granulomatous interstitial nephritis, immune complex—mediated glomerulonephritis, and membranoproliferative glomerulonephritis previously reported in patients with CVID.[8,9]

Primary MN occurs when circulating antibodies permeate the GBM, and in the subepithelial space, form immune complexes with epitopes on podocyte membranes. This *in situ* antigen—antibody interaction leads to activation of complement; the ensuing formation of the membrane attack complex (MAC, or C5b-9) inflicts sublytic damage to the podocyte and induces synthesis by the damaged podocyte of an extracellular matrix that further expands the GBM. In secondary forms of MN (e.g., class V lupus nephritis), immune complexes formed in the circulation deposit in the subepithelial space and activate complement but only locally. The injury is limited to the glomerular epithelial cells, the primary clinical manifestation is proteinuria, and the histologic pattern on light microscopy is similar to primary MN. However, in many instances, these systemically formed immune complexes can also deposit in the mesangial and subendothelial spaces. Treatment of secondary forms of MN is typically directed at the underlying condition (e.g., lupus, hepatitis, malignancy) that drives the formation of immune complexes.

Because in secondary forms of MN the lesion is believed to be the sequelae of circulating, rather than *in situ*, immune complex formation, in theory, the exogenously Ig administered to the patient could have served as the inciting antibody for her disease, reacting with polymorphic autoantigens to form circulating immune complexes that, in turn, deposited in the subepithelial space. This pathophysiology was recently proposed but eventually rejected in a case report of MN in a patient with X-linked agammaglobulinemia who received i.v. Ig therapy.[10] IgG subtyping was not performed on the biopsy of our patient, but this would not be expected to help solve this question because her medication was a polyvalent IgG formulation. Importantly, her treatment history argued against a medication-induced secondary form of MN, because (i) she had been on Ig therapy for many years before her MN diagnosis, (ii) she never discontinued the medication during the period in which she went into a rapid and complete remission, and (iii) she continued on therapy for >18 months since remission without any evidence of relapse.

In our patient, and in the 13-year-old CVID patient previously reported,[7] although a secondary form of MN was suspected, immunosuppression was used to counter a presumed autoimmune response that included the production of autoantibodies and subsequent formation of circulating immune complexes. The pediatric patient was successfully treated with corticosteroids and cyclosporine. Because our patient required dialysis for acute kidney injury, we opted to avoid a calcineurin inhibitor and instead treated her with rituximab and steroids. We felt that rituximab, a monoclonal antibody that targets the CD20 antigen of the B lymphocyte and a viable treatment option for primary MN,[11] would reduce the production of an unidentified autoantibody being produced as part of her CVID-associated autoimmunity. The efficacy of rituximab in MN has been interpreted in 2 ways: first, by depleting B-cell production of pathogenic antibodies[12] and, second, by direct binding to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) in the podocyte, which can stabilize the actin cytoskeleton of the podocyte and prevent podocyte apoptosis.[13] This latter mechanism of podocyte stabilization has previously been proposed as the route for efficacy of cyclosporine in nephrotic syndrome[14] and might explain why the previously reported patient with CVID-associated MN responded to cyclosporine and our patient likewise responded to rituximab. The rapid response of our patient to rituximab, with complete remission of proteinuria and normalization of serum albumin within 4 months, is not typical of remission courses in primary MN treated with rituximab, which typically occurs 6 to 9 months postinfusion.[15]

DISCLOSURE

ACKNOWLEDGMENTS

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