CLINICAL VIGNETTE

A Rare Case of PLA2R- and THSD7A-positive Membranous Nephropathy

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Introduction

Primary MN is medicated by circulating auto-antibodies against podocyte membrane antigens which is mainly M-type phospholipase A2 receptor (PLA2R 70%) or thrombospondin type 1 domain containing 7A (THSD7A, 5-10%).[1]

Autoantibodies directed against podocyte membrane antigens cause deposition of immune complex in subepithelial associated with podocyte effacement and proteinuria.[2,3]

Although PLA2R and THSD7A are the two main antigens identified in primary MN, simultaneous presence of autoantibodies against both antigens is rare.[4,5] However, cases of patients with both positive PLA2R-and THSD7A have been reported more recently.[6]

We present a rare case of PLA2R and THSD7A positive primary MN and its associated clinical and histopathology findings.

Case Report

An 86-year-old male was referred to nephrology for recent onset of worsening lower extremities edema. Symptoms started 3 weeks prior and were associated with fatigue and frothy urine. Past Medical History included hyperlipidemia and there was no history of chronic Nonsteroidal anti-inflammatory drugs (NSAIDs) usage. Physical examination was positive for elevated blood pressure (BP 140/85 mmHg) and lower extremities edema. Labs revealed reduced renal function with serum creatinine: 1.5 mg/dL with the baseline creatinine of 0.80 mg/dL, without any electrolyte abnormalities. Uric analysis showed 3+ urinary protein with no hematuria. The 24-hour urine collection showed 10.0 g of urinary protein over 24 hours. Albumin was decreased 3.0 mg/dL, and total cholesterol was 227 mg/dL. Serology tests including, ANA, ANCA, RF, HIV, hepatitis B and C and VDRL were all negative. C3 and C4 were within normal limits. Venous Doppler ultrasound of lower extremities did not show any deep venous thrombosis and Echo showed normal ejection fraction of 60-65%. Serum anti-PLA2R antibody was sent to outside lab, and he underwent a kidney biopsy given high chance of glomerular disease. The biopsy showed glomeruli with diffuse and global capillary loop thickening with spike/pinhole formations, occasional segmental double contour formation of glomerular capillary loops is present (Figure 1). Immunofluorescence showed glomerular capillary walls witht global granular staining for IgG (4+), IgA (1+), IgM (2+), C1q (trace), C3 (1+), kappa (3+) and lambda (3+) light chains. Mesangial regions exhibit similar but segmental staining with the same reagents. Immunohistochemistry showed a focal weak granular pattern staining along the basement membrane for THSD7A, and negative for PLA2R (Figure 1-A to 1-C). Electron microscopy showed extensive electron dense immune complex deposits globally in subepithelial spaces associated with variable interposition of new basement membrane material. Overlying podocytes exhibit patchy but extensive foot process effacement (Figure 1-D). Interestingly while immunohistochemistry was negative for PLA2R the serum for anti-PLA2R antibody was positive (37.8 RU/mL, reference 0.0-19.9). These findings were consistent with PLA2R and THSD7A positive primary membranous stage I-II of IV. In addition, all testing for secondary causes were negative, including upper gastrointestinal endoscopy, colonoscopy, and head-chest-abdomen and pelvic computed tomography scans. Patient was put on RAAS blockade and started on Rituximab 1 gm IV x 2 doses. He responded to treatment with decreasing proteinuria from 10 to 3.5 grams/24 hours after 8 weeks of the 2nd dose of rituximab and renal function improved from Creatinine 1.5 to 1.2 mg/dL, and GFR 39 to 51.

Discussion

Primary MN may have different clinical outcomes, ranging from spontaneous remission to end stage renal disease.[7] Patients with primary MN are classified into 4 different risk categories low, moderate, high and very high risk, determined by degree of proteinuria, level of glomerular filtration rate (GFR) and level of serum anti-PLA2R antibody.[8] Generally Immunosuppressive therapy is recommended for patients with high or very high risk of progression unless contraindicated.[8,9] Our patient was categorized as high risk case for progression based on persistent of nephrotic syndrome with massive proteinuria (10 grams/24 hours) and decreased in eGFR >25 % (creatinine :> 1.5 mg/dL). Therefore, immunosuppressive treatment with rituximab was initiated. Rituximab is the first line immunosuppressive agent in high or very high-risk patients who have stable kidney function like this case.[10,11]

Patients with membranous nephropathy must be investigated for secondary causes of MN. Despite improvements in laboratories testing and immunohistochemistry, excluding secondary

MN is still challenging.[12] Our patient underwent extensive evaluation for secondary causes of MN which were negative.

Kidney biopsy exhibited diffuse and global capillary loop thickening with spike-pinhole formations. Electron microscopy revealed extensive electron dense immune complex deposits globally in subepithelial spaces associated with extensive foot process effacement. Immunohistochemistry showed a focal weak granular staining pattern along the basement membrane for THSD7A, and negative for PLA2R, confirming the diagnosis of primary MN stage I-II of IV.

As shown by Francis et al,[13] the glomerular PLA2R deposition may precede the appearance of circulating anti-PLA2R antibody, but interestingly in our case the immunohisto-chemistry was positive for THSD7A and negative for PLA2R staining while the serum was positive for circulating anti-PLA2R antibody, which did not follow the usual pattern of glomerular involvement in PLA2R positive PMN.

Generally, presence of one autoantibody against podocyte's antigen was believed to exclude the presence of other antibodies.[4,5] The first cases of PLA2R and THSD7A positive was published in 2016[6] and a meta-analysis in 2018 reported 6 cases of PLA2R and THSD7A positive patients.[14] Our case is another rare report of PLA2R and THSD7A positive GN.

The diagnosis of primary MN has significantly changed due to new immunohistochemistry analysis and identification of new autoantibodies against podocyte's antigens. This report shows the use of PLA2R, and THSD7A to establish the diagnosis of primary MN and documents a rare case of simultaneous PLA2R and THSD7A positivity. We also recommend screening for malignancies in THSD7A positive patients as association between THSD7A and malignancy has been reported in recent studies.[14]

Figures

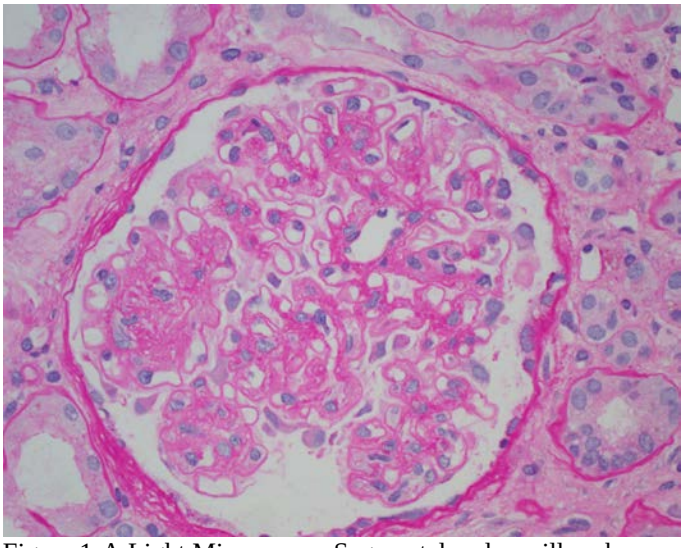

Figure 1-A Light Microscopy, Segmental endocapillary hyper-cellularity

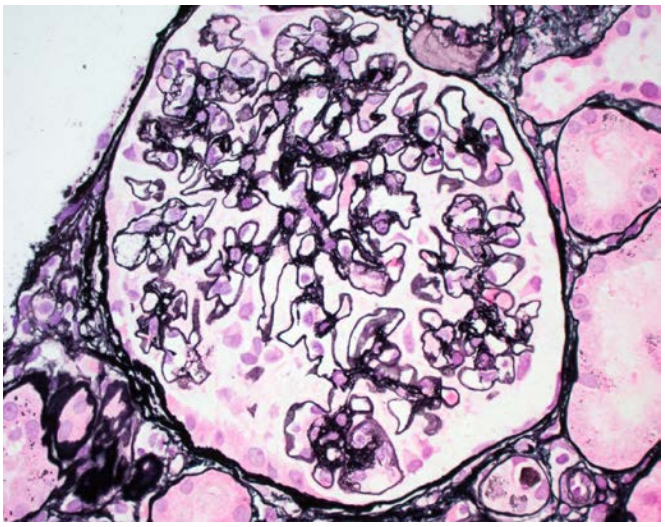

Figure 1-B Silver stain, Capillary loop spikes and double contour formation

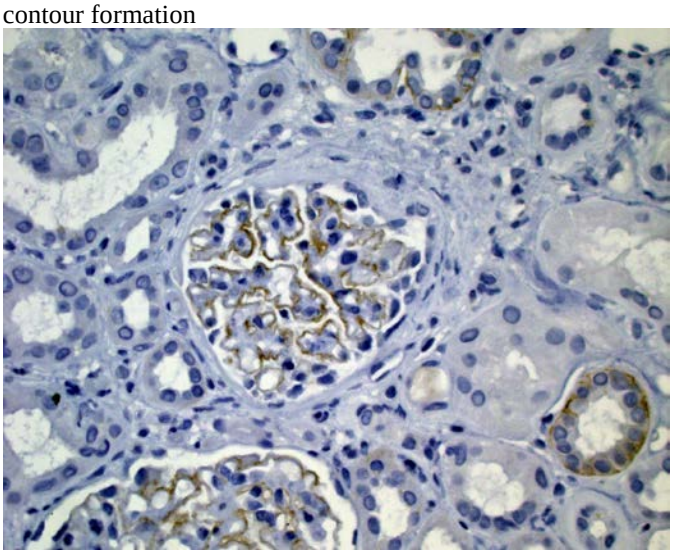

Figure 1-C. THSD7A staining, focal weak granular pattern along the basement membrane

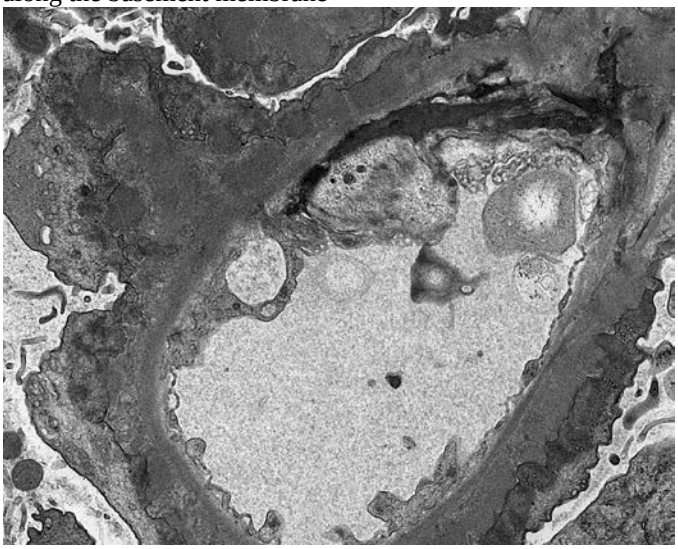

Figure 1-D. Electron microscopy, sub-epithelial deposits & extensive foot process effacement

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