Title

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CLINICAL VIGNETTE

Anti-Phospholipase A2 Receptor Antibody Positive Primary Membranous Glomerulonephritis with Partial Remission of Proteinuria and Complete Disappearance of Antibody Marker with Rituximab Therapy

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Introduction

Membranous glomerulonephritis (MGN) can be caused by a primary process due to autoantibodies or as a secondary process most typically associated with malignancy, but also sometimes with hepatitis b infections and autoimmune disease. Primary membranous is usually distinguished from secondary membranous clinically, as well as by presence of one autoantibody markers. These markers include anti-phospholipase A2 receptor antibody (anti PLA2R),[1] anti-neutral endopeptidase (NEP) antibodies,[2] and anti-Thrombospondin type I domain containing 7A (THSD7A).[3] The anti PLA2R is the predominant etiologic agent for primary membranous glomerulopathy, with 70% of patients with primary MGN having positivity in serum and biopsy.

Other distinguishing features include Immunoglobulin G (IgG 1) predominating in patients with secondary membranous due to malignancy, IgG2 in both primary and secondary cases, and IgG4 predominating in patients with primary MGN.[4] The finding of mesangial deposits also points pathologically towards secondary disease. Electron micrographic and light microscopic findings of both primary and secondary disease are nearly identical.[5]

Clinically, MGN particularly which is not clearly a primary process, is not readily apparent on biopsy, should spark a search for a concomitant malignant, infectious, or autoimmune diagnosis. This can be accomplished with the customary serological labs for associated viruses and age appropriate cancer screening.[6]

We report a classic case of primary membranous glomerulopathy initially treated with cyclophosphamide on protocol by an outside nephrologist. After the Ponticelli protocol as previously reported by an outside nephrologist.[7] This resulted in a short partial remission with 6 grams proteinuria and improved renal function. The MGM flared immediately after immunesuppression was removed. We report a more durable partial remission with drop in proteinuria from a peak of 12 grams down to 4.4 grams as well as complete disappearance of serum anti PLA2R antibody with rituximab, cyclosporine and low dose maintenance steroids.

Case Report

A 53-year-old generally healthy male with hyperlipidemia developed increased leg edema. He underwent a renal biopsy, showing primary membranous glomerulonephritis. It also included a positive anti PLA2R stain consistent with primary MGN diagnosis.

He was initially treated with cyclophosphamide and high dose steroids on the Ponticelli protocol and presented for another opinion. He was completing his induction regimen of oral cyclophosphamide, and was advised to consider additional treatment with intravenous rituximab as the response to the Ponticelli protocol was not sufficient. He was informed of the risks of alkylating agents including bone marrow toxicity, infertility, and infection as well as the increased risk of oral cyclophosphamide over intravenous treatment. He returned to his primary nephrologist who finished the protocol with six months of cyclophosphamide, but relapsed shortly after completion and returned for re-evaluation.

Total urine protein to creatinine ratio increased from a nadir of 6 grams on alkylating therapy to 14.2 grams on a spot specimen. Serum creatinine increased from a nadir during the Ponticelli protocol of 0.9 mg/dL to 1.69 mg/dL. The patient and care team jointly agreed to start rituximab therapy and he switched his care to UCLA. He was started on Rituximab 0.375g/m every 2 week for four doses and responded quickly with reduction in serum creatinine and improvement in proteinuria, as well as a commensurate decline in measured anti PLA2R levels. Please see Figure 1 for graphical trends of renal function improvement, proteinuria amelioration, and anti PLA2R level reduction.

The renal biopsy (Figure 2) was consistent with Ehrenreich and Churg stage II primary membranous glomerulonephritis.[8] Four glomeruli were seen on light microscopy without sclerosis, but with an enlarged mesangial matrix and globally thickened glomerular basement membranes with spikes. Cortical loss was mild at about 10% or less. Immunofluorescence on 17 glomeruli was strongly positive for IgG, C3, and kappa and lambda chains consistent with a MGN pattern. Anti PLA2R, stain was again strongly positive showing likely primary MGN with IgG4, as well as anti PLA2R antibodies typically for IgG4 subclass. Electron micrographs on 11 glomeruli showed charac-

teristic spike and dome pattern of sub epithelial electron dense deposits.

The patient had a durable improvement with rituximab and was maintained on cyclosporine, 3-5 mg/kg dosing with a trough goal of 100-200 ng/ml. He had to leave the state and transferred his care to an east coast academic institution.

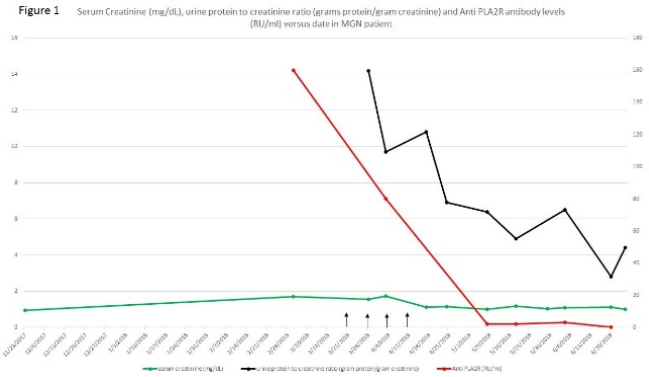

Figure 1: Graph of trends of serum creatinine (mg/dL), urine protein to creatinine ratio (gram protein/gram creatinine), and anti PLA2R levels (RU /mL) versus date. Black arrows, rituximab therapy. Anti PLA2R=anti phospholipase A2 receptor antibody levels, RU=reference units.

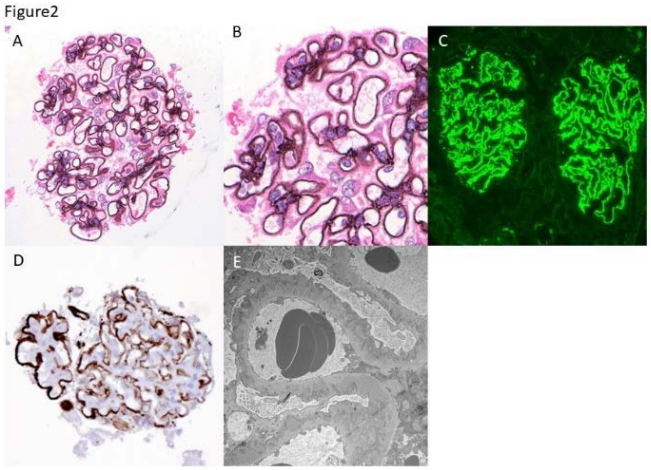

Figure 2: Renal biopsy demonstrating primary membranous glomerulonephritis with positive anti PLA2R
a) Light micrograph 20-x magnification, thickened glomerular basement membrane indicative of membranous glomerulonephritis view 1
b) Light micrograph 40-x magnification, thickened glomerular basement membrane indicative of membranous glomerulonephritis view 2
c) IgG + granular pattern on Immunofluorescence consistent with membranous glomerulonephritis
d) Anti Phospholipase A2 receptor antibody positive stain (this marker is usually IgG4) confirming primary membranous glomerulonephritis
e) Spike and dome pattern sub epithelial deposits seen on electron micrograph suggesting membranous glomerulonephritis

Discussion

Primary Membranous glomerulonephritis, once labeled idiopathic, has benefited from the discovery of the underlying antiPLA2R, anti NEP, and anti THSD7A antibodies.[9] There is an improved understanding of diagnosis, treatment tracking, and pathophysiology. The declining antiPLA2R levels predicted clinical remission as has been previously published.[10] Figure 1 indeed shows that the drop in anti PLA2R levels precedes decline in proteinuria and predicts response to therapy.

This case also illustrates the importance the newer approaches to treatment, years of following the Ponticelli protocol, better understanding of risks of alkylating agents and the relatively low success rate spurred evaluation of other treatments. Rituximab is a relatively new, less toxic, treatment to reduce proteinuria in patients with MGN who are severely nephrotic and rarely have spontaneous remissions.[11] With rituximab almost 75% of cases experience a partial or complete remission.[12] Care must be taken to prevent serious infections and to monitor patients for development of John Cunningham virus (JC virus) induced progressive multifocal leukoencephalopathy.[13] Calcineurins have typically been used for maintenance once remission has been induced,[14] but rituximab has shown efficacy in maintaining remission in a small trial.[15] Less conventional treatments like ACTH gel have also been used with some success in treatment of primary MGN.[16]

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