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Case Report

PLA2-R positive primary membranous nephropathy: a case report

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ABSTRACT

Membranous nephropathy (MN) is a significant cause of nephrotic syndrome in adults, often linked to the presence of circulating antibodies against phospholipase A2 receptor (PLA2R). This case report details the clinical presentation, diagnostic process, treatment, and outcomes of a patient diagnosed with PLA2R-positive membranous nephropathy. The report highlights the importance of early diagnosis and personalized treatment strategies, demonstrating the evolving landscape of MN management. A brief review of the literature related to the topic is also presented. For this purpose, a search was made in freely accessible sources, selecting those with the most relevant and up-to-date information.

Keywords: Membranous nephropathy, PLA2-R receptor, Nephrotic syndrome, Modified ponticelli, Rituximab

INTRODUCTION

Membranous nephropathy (MN) ranks as the second most common cause of nephrotic syndrome in adults, after diabetic nephropathy. The overall incidence of the disease is estimated to be 8 to 10 cases per million individuals.[1] The key pathological feature of MN consists of the accumulation of subepithelial immunoglobulin (Ig), leading to injury to the glomerular basement membrane (GBM), effacement of the foot processes, and significant proteinuria.[2] In 80% of cases, the specific etiology of MN remains unknown, while the remaining cases are related to medication use or underlying diseases such as systemic lupus erythematosus, hepatitis B virus, or malignancy.[1] The identification of anti-phospholipase A2 receptor (PLA2R) antibodies in 2009 validated the idea of circulating antibodies targeting natural podocyte antigens. PLA2R testing is now available worldwide and is used for diagnosis, prognosis, and treatment evaluation.[2] The availability of clinical testing for autoantibodies against the M-type phospholipase A2 receptor has allowed non-invasive diagnosis of this form of membranous nephropathy and a means to monitor immune activity to guide immunosuppressive therapy. Treatment includes optimal supportive care with renin-angiotensin system blockers, lipid-lowering agents, diuretics, lifestyle changes, and additional immunosuppressive therapy in patients at increased risk for progression to renal failure.[3] In the present case report, we present a patient with PLA2R-positive membranous nephropathy, highlighting her clinical characteristics, histological findings, and response to treatment.

CASE REPORT

A 38-year-old woman, with no history of chronic diseases, only preeclampsia during her last two pregnancies, who denied the consumption of alcohol or tobacco, as well as any drug allergy, hemo-transfusions or important interventions. She denies having previously consumed herbalists or food supplements. Her disease began with edema of the pelvic limbs up to the kneecap, bilateral and

symmetrical, with an insidious appearance, accompanied by general malaise, fatigue, foamy urine, no decrease in urinary volume, no fever and no other symptoms, for which she went to a private doctor, where they detected proteinuria of 1468. 8 mg/24 h, with albuminuria of 1374.51 mg/24 h, serum albumin 2.9 g/dl, renal function preserved with BUN 14.3 mg/dl, urea 30.6 mg/dl and creatinine 0.66 mg/dl.

She started antiproteinuric therapy with atorvastatin 40 mg PO every 24 hours, dapagliflozin 10 mg PO every 24 hours, and enalapril 5 mg PO every 24 hours. She went to the Emergency Department due to the lack of improvement in the symptoms after two months of starting treatment. On physical examination, vital signs were within normal, with adequate hydration of mucous membranes, heart and lungs without compromise, asymptomatic abdomen and edema in the lower extremities up to the knees of grade ++/+++.

Laboratory findings on admission showed unchanged blood counts (Hb 14.46 g/dl, Hto 44.3%, leukocytes 7490 mm^3, platelets 287 200), blood chemistry (urea 19 mg/dl, creatinine 0.7 mg/dl, glucose 84 mg/dl, uric acid 4 mg/dl), serum electrolytes with hypocalcemia (Ca 7.7 mg/dl, K 3.57 mEq/l, Na 142.1 mEq/l, Cl 103.2 mmol/l, P 3.6 mg/dl, Mg 1.7 mg/dl) liver profile with persistence of hypoalbuminemia (albumin 2.4 g/dl), without other alterations; Lipid Profile: triglycerides 144 mg/dl, total cholesterol 180 mg/dl, HDL 116 mg/dl; coagulation tests TP 12.7 s, INR 0.98, TTP 24.5 s.

Urinalysis showed a density of 1.020, pH 6.0, proteins ++++, glucose ++++, negative nitrites, no epithelial cells, crystals and casts, leukocytes 1-3 x field, erythrocytes 1-3 x field and isolated bacteria. Total protein in 24-hour urine was quantified, with a result of 11583 mg/24 hours, so hospital admission was decided.

During the hospitalization, a renal ultrasound is performed; both kidneys of adequate sizes, isoechogenic, smooth borders, adequate differentiation between cortex and medulla, without hydronephrosis. In addition, in studies for rheumatological disease, complement factor 4 (C4): 0.30 g/l (0.10-0.40), complement factor 3 (C3): 1.34 g/L (0.90-1.80), anti-nuclear antibodies (ANA): negative, anti-DNA antibodies: 11.4 IU/ml (negative <27 IU/ml) were reported. Negative ANCAS profile. Negative viral panel.

It was decided to intensify antiproteinuric treatment with dapagliflozin 10 mg PO every 24 hrs, enalapril 5 mg PO every 12 hrs, spironolactone 25 mg PO every 24 hrs, atorvastatin 80 mg PO every 24 hrs at night, furosemide 40 mg IV every 8 hrs, treatment for hypocalcemia was started with calcium 600 mg and vitamin D 400 IU PO every 12 hrs, as well as prednisone 60 mg PO every 24 hrs. A percutaneous renal biopsy was performed and reported stage I membranous nephropathy (Figure 1), and immunohistochemistry results suggested an etiology associated with antibodies to phospholipase A2 (Table 1).

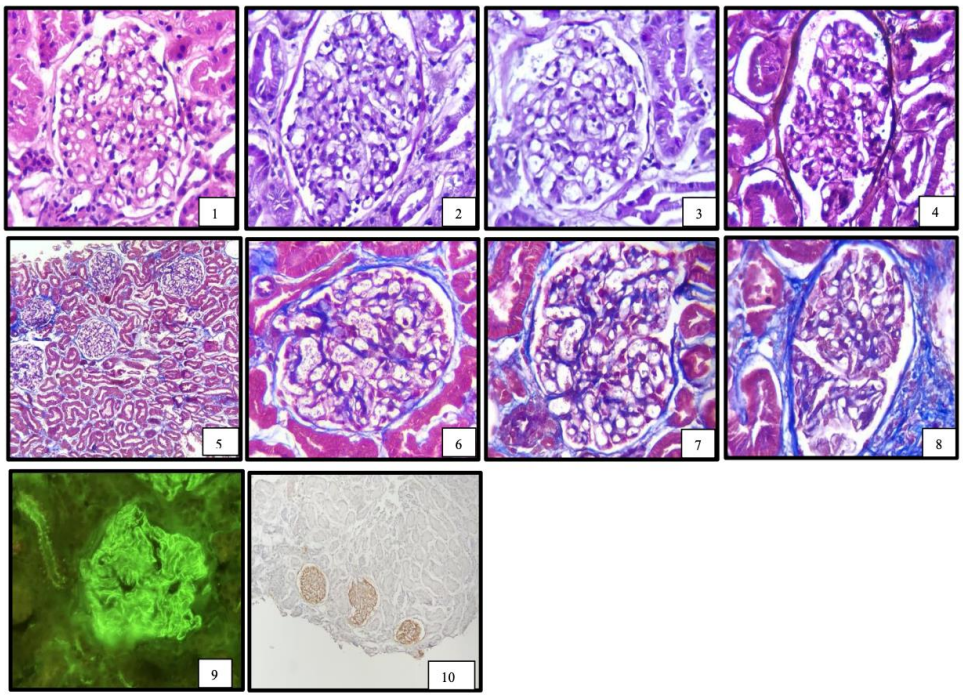

Figure 1: (1-8) Percutaneous kidney biopsy obtained with a cutting needle shows glomerular disease mediated by immune complexes. Light microscopy did not identify reparative morphological changes of the basement membrane, compatible with stage I. FI is observed: positive epimembranous granular positive for IgG C3 (9) and PLA2r: positive granular epimembranous (10).

Table 1: Direct immunofluorescence, five non-sclerosis glomeruli were evaluated.

Antibody	Immunofluorescence result and expression pattern
IgA	Negative
IgG	Positive with fine and granular epimembranous pattern and intensity of 3 (+)
IgM	Negative
C3c	Positive with fine and granular epimembranous pattern and intensity of 3 (+)
C1q	Negative
Kappa	Negative
Lambda	Negative
Fibrinogen	Negative
Albumin	Negative
PLA2r	Positive with fine and granular epimembranous pattern and intensity of 2 (+)

Treatment with the modified Ponticelli regimen was decided, for months 1, 3, and 5: methylprednisolone 500 mg intravenously daily (days 1 to 3), then prednisone 5 mg/day for 27 days (days 4 to 30); for months 2, 4, and 6: oral cyclophosphamide 500 mg every 24 hours for 30 days, and anti-proteinuric and hypocalcemia treatment was continued.[4]

At the end of immunotherapy, she did not present edema and had a partial response of proteinuria. In the latest laboratory tests, 24-hour urine total protein is reported: 2741.3 mg/day; 24-hour urine albumin: 683.17 mg/day. Preserved renal function was maintained: creatinine 0.7 mg/dl, urea 26 mg/dl. Hypocalcemia was improved (Ca 8.1 mg/dl) and hypoalbuminemia was corrected (albumin 4 g/dl).

According to the partial response of proteinuria it was considered initiation of rituximab as a second line of treatment.

DISCUSSION

Membranous nephropathy is the most common cause of nephrotic syndrome in white people with a peak incidence in adults at 30-50 years of age. MN is more common in men than women but with better outcomes in the last ones.[5]

The incidence of primary MN is estimated at 10 to 12 cases per million in North America and 2 to 17 cases per million in Europe.[6] Recent studies suggest an increasing prevalence of MN in regions with high levels of environmental pollutants, particularly fine particulate matter.[7] The pathophysiology of PLA2R-positive MN involves the formation of immune complexes that deposit on the glomerular basement membrane. These deposits trigger an inflammatory response, leading to podocyte injury and subsequent proteinuria. The presence of anti-PLA2R antibodies is a hallmark of this condition, contributing to the immune-mediated damage observed in MN.[8,9,15]

Primary MN is predominantly associated with circulating anti-PLA2R antibodies, found in 70-80% of patients.[8] Secondary MN can occur due to various factors, including infections (e.g., hepatitis B), autoimmune diseases (e.g., lupus), and certain medications (e.g., NSAIDs).[8] The exact etiology of primary MN remains unclear, although genetic predisposition and environmental factors may play a role.[7]

Patients with PLA2R-positive MN typically present with symptoms of nephrotic syndrome: edema, significant proteinuria (>3.5 g/day), hypoalbuminemia and hyperlipidemia. Exist a high risk of thromboembolic events secondary to hypoalbuminemia and alteration in the coagulation cascade. Serum complement levels are normal, but they can be present in the kidney. The clinical course can vary widely; while some patients achieve spontaneous remission, others may progress to end-stage renal disease. As in the previous case, the patient presented with nephrotic syndrome with high-risk proteinuria (11 g/day) and hypoalbuminemia (2.4 mg/dl). She also presented normal levels of serum complement factors C3 and C4.[10]

For the diagnostic process, in accordance with the clinical practice guideline for the management of glomerular diseases a renal biopsy was performed to diagnose glomerular disease because there was no availability of antibody tests against PLA2R in the hospital.[11]

Before deciding on treatment, it is important to consider the risk of progressive loss of renal function. In most patients, it is reasonable to wait 6 months for spontaneous remission while using maximal antiproteinuric therapy. High levels of proteinuria, anti-PLA2R antibodies or low molecular weight proteinuria should lead to reassessment before 6 months. For the case study, the risk of progressive loss of renal function was considered high according to the KDIGO 2021 clinical criteria because of eGFR (113 ml/min/1.73 m2), proteinuria of 11 mg/dl and serum albumin (2.4 mg/dl).[11]

The treatment of MN has evolved over time and there are now several therapeutic options available. The modified Ponticelli protocol is a treatment regimen that combines the administration of corticosteroids and immunosuppressive agents. The protocol consists of the administration of pulse intravenous methylprednisolone 1

g/day for 3 days followed by oral prednisolone (0.4 mg/kg/day) or prednisone (0.5 mg/kg/day) for 27 days in months 1, 3, and 5 and this is alternated with oral cyclophosphamide (2 mg/kg) daily in months 2, 4, and 6.[4,5] This protocol has been shown to be effective in the treatment of MN, with a complete response rate of 60-80%. Rituximab is a monoclonal antibody that targets the CD20 receptor on B cells. It has been shown to be effective in the treatment of MN, particularly in patients with refractory disease or intolerance to other treatments. The usual dose of rituximab is 375 mg/m² every week for 4 weeks.[12,13]

Although both treatments have been shown to be effective, the literature review identified some important differences. In terms of efficacy, the modified Ponticelli protocol has been shown to be more effective in treating MN, with a complete response rate of 60-80%, while rituximab has been shown to have a complete response rate of 40-60%. However, rituximab has been shown to be safer than the modified Ponticelli protocol, with fewer serious side effects. The modified Ponticelli protocol is generally less expensive than rituximab, and the modified Ponticelli protocol requires longer treatment than rituximab.

CONCLUSION

PLA2R-positive membranous nephropathy is a complex condition that requires a thorough understanding of its epidemiology, pathophysiology, clinical manifestations, and treatment options. This case report illustrates the importance of early diagnosis and personalized treatment strategies in improving patient outcomes. Ongoing research into the mechanisms of MN and novel therapeutic approaches will further enhance our ability to manage this challenging condition.

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