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Membranous nephropathy with collapse in a HIV negative patient; a case report with a 34-month follow-up

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ABSTRACT

Membranous nephropathy (MN) is a common cause of nephrotic syndrome (NS) in nondiabetic adults. Collapsing nephropathy (CN) is a morphological pattern that is usually classified as a variant of focal segmental glomerulosclerosis (cFSGS). The simultaneous presence of both MN and CN is rare and their combination usually foresees an unfavorable outcome. Herein, we describe a case report of a patient with PLA₂R-associated MN with collapse, its treatment and clinical course.

Keywords: Membranous nephropathy, Collapsing variant, Nephrology, Podocytopathy, Immunosuppressive therapy, Rituximab

Implication for health policy/practice/research/medical education:

The coexistence of CN and MN is a rare finding. This case highlights its difficult management and the potential benefit of rituximab administration in this rare entity of kidney disease.

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Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome (NS) in nondiabetic adults. It is mediated by immune complexes and it is characterized by subepithelial granular deposition of IgG and complement leading to podocyte injury (1). Collapsing variant of focal segmental glomerulosclerosis (cFSGS) is diagnosed in light microscopy by the presence of at least one glomerulus tuft with segmental or global collapse and podocyte hypertrophy or hyperplasia (2). Although both entities present with NS, unlike MN, cFSGS has worse prognosis and usually fails to respond to therapy, evolves with rapid deterioration of kidney function and progresses to end stage kidney disease (3). Herein, we report a case of a patient with PLA₂R-associated MN with collapse.

Case Report

A 64-year-old woman, with past medical history of non-toxic multinodular goiter and depression, medicated with sertraline 100 mg and lorazepam 1 mg once a day, went to the emergency department with anasarca, asthenia and

orthopnea that lasted for six weeks. Physical examination showed normal blood pressure and peri-orbital, abdominal and lower limbs edema. Auscultation revealed decreased breath sounds at the right lung base. Blood laboratory analysis showed a creatinine of 0.7 mg/dL and urea of 30 mg/dL, an hemoglobin of 13.0 g/dL with normal white blood cell count and normal platelets, normal electrolytes and low total proteins and albumin (3.9 g/dL and 2.1 g/dL, respectively), high total and low-density lipoprotein cholesterol, negative B-type natriuretic peptide and normal thyroid function. Urine examination showed proteinuria in the nephrotic range (3.70 g/24 h) and urinalysis showed erythrocyturia (40/μL). The autoimmune screening was negative and complement levels were normal.

Serum and urinary proteins electrophoresis had no monoclonal component. IgG was diminished (446 mg/dL), IgA and IgM were normal. Human immunodeficiency virus, hepatitis B and C virus serology tests were negative.

Tumor markers as Cyfra 21.1, neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), cancer antigen 19.9 (CA 19.9) and CA 15.3 were normal, but CA 125

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was elevated. Abdominal and renal ultrasound, chest X-ray, electrocardiogram and echocardiogram were normal. Since the patient had a NS of unknown etiology, a renal biopsy was conducted and then the patient was discharged with angiotensin-converting enzyme inhibitor (ACEi), aspirin and diuretic. Three days later, she was re-admitted for pulmonary embolism, therapeutic anti-coagulation was started.

Kidney biopsy results showed global thickening of the glomerular wall in light microscopy (Figure 1). Some of the glomeruli also had marked podocyte hyperplasia, leading to the collapse of the tuft (Figure 2). Immunofluorescence staining was positive for IgG, C3, kappa and lambda with a granular parietal pattern while immunohistochemistry was positive for glomerular M-type phospholipase A₂ receptor (PLA₂R) (Figure 3). A final diagnosis of PLA₂R-associated MN and collapsing nephropathy (CN) was suggested. Serum antibodies against PLA₂R (anti-PLA₂R) were also positive by indirect immunofluorescence with a titer of 20 (reference value: negative if titer <10).

Most frequent neoplasms were excluded by upper endoscopy, colonoscopy, thyroid sonography, mammography, breast ultrasound, ultrasound-guided hysteroscopy and abdominal pelvic and thoracic computed tomography. Screening for parvovirus B19, Epstein-Barr virus and cytomegalovirus was negative as it was negative on Interferon Gamma Release Assay (IGRA) for *Mycobacterium tuberculosis*.

We started modified Ponticelli regimen for patient's treatment. At the start of this regimen, the patient had a serum creatinine of 0.8 mg/dL, serum albumin of 2.4 mg/dL and proteinuria of 6.96 g/d. Three months after the initiation of immunosuppression, she presented with worsening proteinuria to 23 g/d and anasarca. Serum creatinine remained stable. At that point, treatment was changed to cyclosporine targeted to trough levels of 100-175 ng/mL and prednisolone 15 mg/d. One month later, a partial clinical response was attained with proteinuria reduction to 2 g/d. The patient maintained this therapy for 12 months reaching a proteinuria nadir of 0.41 g/d. For the next 12 months, prednisolone was tapered until suspension and cyclosporine was progressively reduced to 50 mg bid. During this follow-up period, our case evolved with intermittent worsening of proteinuria without recurrence of NS. After two years of cyclosporine treatment, she had proteinuria of 4.7 g/d, serum albumin of 3.8 mg/dL, serum creatinine of 1.1 mg/dL and anti-PLA₂R was positive with titer of 40. Since the patient remained cyclosporine dependent, it was decided to treat the patient by rituximab (1 g intravenous, twice within two weeks). At the last evaluation, six months after the last rituximab administration and 34 months of total follow-up, the patient had proteinuria of 3.31 g/d, serum

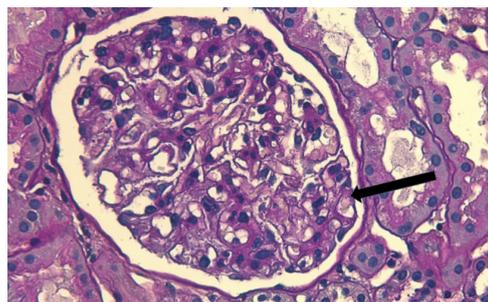


Figure 1. Light microscopy, PAS stain (400×) showing global thickening of the glomerular wall (arrow).

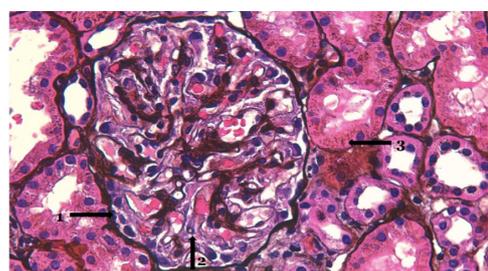


Figure 2. Light microscopy, Silver stain (400×) showing a glomeruli with marked podocyte hyperplasia (1) leading to the collapse of the glomerular tuft (2) and protein droplets in tubular epithelial cells (3).

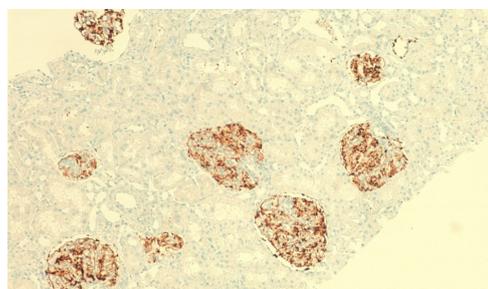


Figure 3. Immunohistochemistry showing positivity for glomerular M-type phospholipase A₂ receptor (200×).

albumin of 3.9 mg/dL and serum creatinine of 1.1 mg/dL. Anti-PLA₂R decreased to borderline value of 10.

Discussion

MN is an immune-mediated disease, caused by auto-antibodies that target the glomerulus, especially the specific antigens on the podocyte surface, resulting in sub-epithelial deposition of immunocomplexes with complement activation and damage of glomerular capillary wall (4,5).

We described a PLA₂R associated MN, which is the most common antigen in MN accounting for 70%–80% of cases (6). Thrombospondin type-1 domain-containing 7A neural epidermal growth factor-like 1 protein and Semaphorin 3B can also be associated with primary forms

of MN (7-9). Secondary causes, namely malignancy, drugs, autoimmune diseases and infections (10) were excluded in our patient.

CN morphological pattern was first described in 1986 by Weiss et al (11). It is far more common in people with African ancestry and was initially associated with HIV infection. Nowadays, other causes are acknowledged, such as other infectious micro-organisms, autoimmune diseases, drugs or genetic disorders (3,12). Although it is increasingly considered a different entity due to its unique features, it is usually classified as a variant of FSGS (12). The pathogenesis of CN is still largely unknown, although it has been postulated that it is caused by podocyte de-differentiation and gain of a proliferative phenotype (3).

Clinical course of MN and CN differ: while the first usually grants good prognosis, with 30% spontaneous remission (13), the latter has low-rates of remission (3). The simultaneous presence of both MN and CN is rare and their combination usually foresees an unfavorable outcome. Furthermore, optimal therapeutic regimens are still unknown. Al-Shamari et al and Bharati et al described eight HIV seronegative patients that presented with NS and were diagnosed with coexistent primary MN and CN (14,15). In those reports, all patients were treated with immunosuppression and therapeutic options included prednisone plus cyclophosphamide, mycophenolate mofetil or azathioprine. All evolved with rapid deterioration of kidney function (14,15). Two patients received rituximab for relapse and resistant disease, both showing no response in proteinuria, although one had improvement in his renal function (15).

In our patient, therapeutic choices have also been challenging. The thrombotic event due to NS, plus the coexistence of MN and CN, motivated the prompt initiation of immunosuppressive treatment. Initial regimen consisted in cyclical corticosteroid and cyclophosphamide administration as recommended in KDIGO 2021 guidelines for very high risk MN (16). Nevertheless, after three months of modified Ponticelli regimen starting, the patient had three admissions due to anasarca and presented a raise in 24 hour proteinuria to 23 g. As a result, immunosuppressive treatment was switched to cyclosporine with prednisone, a regimen approved for both MN and FSGS. Although the patient evolved with partial remission, she became cyclosporine dependent. In light of the new recommendations for MN and the favorable reports of rituximab use in cFSGS unresponsive to other immunosuppressive treatments (17), we decided to maintain a low-dose of cyclosporine and start a trial of rituximab (two doses of 1 g, two weeks apart). At six months, she maintained partial remission and a positive PLA₂R but at a lower titer of 10.

Conclusion

We present a rare case of co-existing CN and MN with a more favorable outcome than that described in previous reports. Although we did not witness a further reduction in proteinuria with the association of rituximab, the reduction in anti-PLA₂R titers may anticipate clinical remission and potentially allow for further reduction or suspension of cyclosporine. That is not surprising as rituximab maximal effect has been shown to sometimes be delayed in other glomerulopathies. Also, we believe that complete remission may not be achievable due to persistency of proteinuria related to chronic damage. This case highlights the difficult management of the patients with MN with collapse and the lack of literature on its clinical course and treatment. We further illustrate the potential benefit of rituximab administration in this rare entity of kidney disease.

Authors' contribution

LLC is the first author, she made substantial contributions to the conception and drafting of the article, acquisition and interpretation of data for the work, writing of the manuscript, revision of the manuscript and critical evaluation of the intellectual contents. AIR made substantial contributions to the writing of the manuscript, critical revision of the article and critical evaluation of the intellectual contents. CF made substantial contributions to the writing of the manuscript. CPL, TCS and SSL made contributions to critical revision of the article and final approval of the version to be published. HV and MG had made substantial contributions for the acquisition and interpretation of data for the work.

Conflicts of interest

The authors declare that they have no competing interest.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. This case report was conducted in accord with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this report.

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