INTRODUCTION

Membranous nephropathy (MN) is among the most common causes of the nephrotic syndrome in non-diabetic adults, accounting for up to one-third of biopsied cases of nephrotic syndrome.

The term MN reflects the primary histologic change noted on light microscopy: Glomerular basement membrane (GBM) thickening with little or no cellular proliferation or infiltration. MN is most often primary (previously called idiopathic), although it has been associated with hepatitis B antigen, autoimmune diseases, thyroiditis, malignancies (1,2).

This case has been reported as its rarely encountered in our clinical practice. Its progression is worsened despite immunosuppressive treatment. The case of male patients with primary membranous nephropathy is presented. He was three years. Still, the nephrosis recurred with massive proteinuria (19180 mg/day) in treated corticosteroid and cyclosporine after conservative therapy had failed and went into remission for addition to weight loss without.

Keywords: Membranous Glomerulonephritis, Therapies, Prognosis, Malignancy, Positive serum PLA2R antibodies

Case Report

Membranous glomerulonephritis with positive serum PLA2R antibodies: A case report of replacing membranous nephropathy, massive proteinuria despite immunosuppressive therapies

Abstract

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INTRODUCTION

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Pathogenesis: Animal and experimental models of MN suggest that the glomerular basement membrane’s (GBM) immune deposits develop in situ due to the circulating immunoglobulin G (IgG) antibodies movement across GBM. The immunoglobulin G (IgG) antibodies expressed on or near the podocyte foot processes are directed against endogenous antigens such as circulating cationic or low-molecular-weight antigens that have crossed the anionic charge barrier in the GBM [3,4].

Genetic: The major antigen was identified as the PLA2R (phospholipase A2 receptor) [5].

Malignancy: Up to %5-%20 of adults, particularly those over the age of 65 years, with MN, have been reported to have a malignancy, most commonly a solid tumor (principally carcinoma of the prostate, lung, breast, bladder, or gastrointestinal tract) [2,6,7]. MN diagnosis preceding that of malignancy is more likely in older adults with weight loss.

We present a case of the male patient, showing features of membranous nephropathy, such as global glomerulosclerosis, fibrosis, mononuclear infiltration, thick basement membrane, and deposition of immunoglobulin IgG on immunofluorescence positive, PLA2R antibodies, weight loss without malignancy,
and massive proteinuria, approximately 20 gr/day.

**CASE REPORT**

The patient who applied to the outpatient clinic on 28.02.2022 with complaints of nocturia and swelling in the legs since 2017 and was diagnosed with membranous glomerulonephritis after renal biopsy. He was admitted to the nephrology service due to swelling in the legs and 19180 mg/day proteinuria in his examinations during his routine controls, and a recent involuntary weight loss.

**Known diseases:**


**Drugs used:**

- Olmesartan + Amlodipine 40/5/12.5 gr 1x1
- Cyclosporine 25 mg 1x1
- Carvedilol 12.5 mg 1x1
- Vitamin D 10000 IU uses every other day
- Duloxetine 30 mg 1x1

**Physical Examination:**

- **Head and Neck:** No lymphadenopathy, normal
- **Cardiovascular System:** S1+ S2+ no additional sound/murmur
- **Respiratory System:** No ral/rhonchi, respiratory rate normal
- **Abdomen:** Normal inspection, percutaneous, liver palpation normal. No guarding/rebound, no painful focus.
- **Lower Extremity:** Peripheral pulses on, pretibial edema -/

The hospital information of the patient dated 02.03.2017 was reached. The patient had complaints of itching, redness, and edema in the legs, starting from the distal feet and arms and spreading to the chest and head; it has been around for 30 days. The patient applied to the dermatology department several times due to these complaints. After the physical examination in the internal medicine outpatient clinic revealed stage 3 hypertension and pretibial edema, albumin: 2 gr/dl, complete urinalysis: protein 3 positive (+). LDL: 340 mg/dl, the patient was referred to nephrology outpatient clinic, considering nephrotic syndrome. The results were urea: 43 mg/dl complete urinalysis: protein 3 positive (+), spot urine protein: 700 mg/dl. The patient was hospitalized in terms of proteinuria etiology.

Abdomen ultrasonography report; both kidneys were normal in size and localization, contours were regular, bilateral parenchyma thickness was normal, and grade I increased in echoes. The bilateral pelvicalyceal system was in normal shape and width, and there was no cystic or solid mass lesion or stone echo in both kidneys.

Protein electrophoresis was within normal limits, immunofixation monoclonal gammopathy not detected, kappa normal, lambda normal, antinuclear antibodies (ANA) negative, antibodies to double-stranded (AntiDs DNA) negative, serum complement 3 (C3) and complement 4 (C4) were within normal limits. Protein in 24-hour urine from the patient: 1007 mg/day. In 2017 biopsy was planned for the etiology of proteinuria, but when the patient did not accept the biopsy, ramipril 2.5 mg was added in terms of proteinuria. Later, he agreed on the procedure of renal biopsy. Biopsy resulted as membranous nephropathy.

On 26.04.2017 proteinuria in 24-hour urine result; 6885 mg/day; cyclosporine 2*100 mg, methylprednisolone 64 mg was started.

On 28.02.2022 proteinuria in 24-hour urine result; 19180 mg/day; Rituximab was started. cyclosporine 2x50 mg, methylprednisolone 40 mg treatment was continued.

By the time of his routine outpatient controls, see the results of the proteinuria under the immunosuppressive treatment (Table 1).

<table>
<thead>
<tr>
<th>Date</th>
<th>Creatine mg/dl</th>
<th>eGFR ml/minute</th>
<th>Proteinuria mg/day</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.04.2017</td>
<td>1.1</td>
<td>71</td>
<td>6885</td>
<td>Cyclosporine 2x100 mg, methylprednisolone morning: 48 mg night: 16 mg</td>
</tr>
<tr>
<td>25.11.2018</td>
<td>1.22</td>
<td>46</td>
<td>3680</td>
<td>Cyclosporine 2x125 mg, Methylprednisolone morning: 32 mg night: 16 mg</td>
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<tr>
<td>09.04.2019</td>
<td>1.13</td>
<td>40</td>
<td>1404</td>
<td>Cyclosporine 2x50 mg, methylprednisolone morning: 8 mg night: 4 mg</td>
</tr>
<tr>
<td>07.11.2019</td>
<td>1.16</td>
<td>68</td>
<td>875</td>
<td>Methylprednisolone morning: 8 mg night: 4 mg</td>
</tr>
<tr>
<td>02.01.2020</td>
<td>1.12</td>
<td>71</td>
<td>1885</td>
<td>Cyclosporine morning: 75 mg night: 50 mg, methylprednisolone 1x4 mg</td>
</tr>
<tr>
<td>20.02.2020</td>
<td>1.05</td>
<td>77</td>
<td>762</td>
<td>Cyclosporine morning: 50 mg night: 25 mg, methylprednisolone 2x4 mg</td>
</tr>
<tr>
<td>10.08.2021</td>
<td>1.34</td>
<td>58</td>
<td>262</td>
<td>Cyclosporine morning: 50 mg night: 25 mg, methylprednisolone 2x4 mg</td>
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<tr>
<td>28.02.2022</td>
<td>1.76</td>
<td>40</td>
<td>19180</td>
<td>cyclosporine 2x50 mg, methylprednisolone morning: 24 mg night: 16 mg, rituximab</td>
</tr>
</tbody>
</table>
Abdomen ultrasonography result (30.12.2021); no solid mass lesions were detected (including liver, gall bladder, pancreas, spleen, and kidneys).

Laboratory results; total prostate-specific antigen (PSA), cancer antigen-15.5, cancer antigen-125, alpha-fetoprotein (AFP), carcinoembryonic antigen, cancer antigen-19.9 were in normal ranges.

<table>
<thead>
<tr>
<th>Date</th>
<th>Transaction name</th>
<th>Result</th>
<th>Result Unit</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>03.03.2022</td>
<td>PLA2R AB</td>
<td>774,95 (positive)</td>
<td>RU/ml</td>
<td>negative &lt;14 positive &gt;=20</td>
</tr>
</tbody>
</table>

Table 2. PLA2R Antibodies (AB) serum levels of patient

Colonoscopy result (08/03/2022); colon and rectum are normal; Peripheral grade-1 hemorrhoids were observed in the anal canal.

No thoracoabdominal mass or pathology detected in the thoracic and abdominal scanning of the patient on 08/03/2022.

Discontinuation

Membranous nephropathy occurs when the small blood vessels in the kidney (glomeruli), which filter wastes from the blood, become damaged and thickened.

As a result, proteins leak from the damaged blood vessels into the urine (proteinuria). For many, loss of these proteins eventually causes signs and symptoms known as nephrotic syndrome. Typically, loss of protein from the blood causes swelling in the legs and ankles and weight gain due to the extravasation of fluid. Many patients have much swelling from the onset of the disease, but some may not have any severe symptoms until they have advanced kidney disease.

In mild cases, membranous nephropathy may get better on its own, without any treatment. As protein leakage increases, the risk of long-term kidney damage increases, and the disease ultimately leads to kidney failure.

There is no absolute cure for membranous nephropathy, but successful treatment can lead to remission of proteinuria and a good long-term outlook [8-10].

Up to 5%-20 of adults, particularly those over the age of 65 years, with MN, have been reported to have a malignancy, most commonly a solid tumor (principally carcinoma of the prostate, lung, breast, bladder, or gastrointestinal tract) [2,6,7]. MN diagnosis preceding that of malignancy is more likely in older adults with weight loss.

Conclusion

In our case, the trigger factor of the disease is unknown, and the patient's altered response to therapy and the weight loss without accompanying malignancy is also unknown. The answers to these questions remain unknown as well. It is certainly possible that there were several different stimuli to the patient's immune system that caused the disease and different responses to therapy.

Future research may determine the nature of the stimuli that induce the response (development of antibodies to the known antigens and perhaps to more ). Until then, patients with MN will continue to be treated with powerful, frequently effective but
non-specific treatments.

Univariate analysis of the comparisons has shown that the low ejection fraction in the pre-operative period (P-value 0.010) and cardiogenic shock requiring the IABP installation (P-value 0.031) are the risk factors that determine surgical mortality. Having analyzed both these risk factors, it was found out that only cardiogenic shock was an independent risk factor for operative mortality with an odds ratio of 2.17. As to the low ejection fraction, it turned out a concomitant factor for operative mortality. Additional revascularization of coronary arteries had no impact on the survival rate.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Informed Consent
Written consent was obtained from the patient and his parents.

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3. Quigg RJ. Why study membranous nephropathy in rats?