Membranous Nephropathy- over the counter? NELL yes!

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Case Report

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Abstract

In adults, membranous Nephropathy (MN) is a common cause of idiopathic nephrotic syndrome. Primary MN is caused by antibodies directed against podocyte antigens, while secondary MN with the deposition of circulating immune complexes in the same area of glomeruli. Most of the primary membranous are positive for PLA2R- and THSD7A- antibodies associated with the progression of the disease. Some of the novel antibodies like NELL 1 are primarily secondary causes, including malignancy but sometimes may present as a primary disease with no underlying reason or ingestion of lipoic acid. Our patient presented to the hospital with a rash and swelling of lower limbs, which was sudden in onset. With a history of diabetes mellitus with comorbidities, he used multiple medications, including over-the-counter supplements (lipoic acid). Renal biopsy revealed NELL 1 positivity likely secondary to over-the-counter supplement usage.

INTRODUCTION

Membranous Nephropathy (MN) is the most common cause of nephrotic syndrome in predominantly white male adults. The disease's main components include high protein levels in urine, edema, hypoalbuminemia, and elevated serum lipids.¹ MN is a chronic disease that may course to spontaneous remissions (usually within the first two years) or frequent relapses. Those patients the severe disease typically progress to end-stage renal disease.¹

MN is caused by the deposition of immune complexes in a glomerular distribution which may be primary with deposits against podocyte antigens or secondary with circulating immune complexes deposits.² MN can also be divided into primary (idiopathic) and secondary due to autoimmune diseases (membranous lupus nephritis), NSAIDs, infections (such as viral hepatitis), graft-versus-host disease, allergic responses (such as against bovine serum albumin) and medications.²

An autoimmune response was first recognized in 1959, with the discovery of M-type phospholipase A2 receptor 1 (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A). These were present in approximately 70% and 1–5% of patients with primary MN, respectively.³ Although these antigens are mostly related to primary MN. Sometimes MN antigens may be associated with a secondary disease, such as Neural-epidermal-growth-factor–like 1 (NELL1)-associated MN linked with a malignancy, and EXT1/ EXT2-, Sema3B-, or even PLA2R associated MN linked with an autoimmune disease. Identifying an association with these antigens may help treat the disease, such as EXT1/EXT2-associated MN with class V lupus nephritis and NELL1-associated MN with malignancy or undetermined antigen associated with hepatitis or no steroidal anti-inflammatory drug use.³ Here, we will discuss a case that increased the curiosity to determine the antigen responsible for MN and its association with proper management.

CASE PRESENTATION
Mr. YZ, a 65-year-old man, presented to the hospital emergency department with sudden onset of the lower limb and scrotal swelling (1 week) associated with a pruritic rash on both legs. His medical history was significant for diabetes, hypertension, chronic kidney disease stage 2, schizophrenia, BPH (since 2017), and prior suicidal ideations.

His medications were lisinopril, amlodipine, insulin, furosemide. He has been using NSAIDs for several months. He was also using over-the-counter multivitamins. There was no history of malignancy, though his family history was positive for colorectal carcinoma.

Examination revealed bilateral pedal edema with a rash and multiple excoriations showing moderate to severe pruritus. The systemic examination was unremarkable. At presentation, lab work revealed blood sugar of 168 mg/dl, HbA1c of 12.3%, serum albumin of creatinine of 2.4 mg/dl, and electrolytes (sodium of 138 mEq/L and potassium of 4.0 mEq/L). His baseline creatinine of 1.4 mg/dl. Urinalysis showed protein of +3 and RBC of +1. Workup for glomerulonephritis (ANA, ANCA, HIV, Hep B, C, C3, C4 complement) was negative. The patient had a 24-hour urine protein of 21gm. A skin biopsy was done, showing lipo-dermatosclerosis. Following this, a renal biopsy was done. The report was significant for MN. Immunotyping was negative for PLAR2 and TALPD7 negative. Further fixation revealed NELL1 positivity.

The biopsy results are shown in Figure A-D.

Extensive workup for malignancy, including CT chest abdomen, PSA, and colonoscopy, was negative. NSAIDs were stopped along with over-the-counter medication. We found lipoic acid supplements on detailed medication reconciliation. The patient was treated with furosemide, lisinopril, insulin, atorvastatin, diltiazem, and plasma apheresis (PLEX) therapy with additional steroids. We initially considered cyclophosphamide with a steroid taper plan. However, we treated with rituximab and tacrolimus regimen due to poorly controlled hyperglycemia. Repeat 24hr urine protein before discharge decreased to 11gm and creatinine of 1.7mg/dl.

On follow-up, he improved clinically, and the pedal edema subsided. The proteinuria further decreased to 6.0 gm.

**DISCUSSION**

Nephrotic syndrome is one of the most prevalent disorders with several causes. MN is the most common glomerular disease, which may occur coincidently with neoplasms, NSAIDS, medications, paraproteinemia, and infections. First reported by Lee et al. in 1966, 11% of patients with nephrotic syndrome had an underlying carcinoma. Ro et al. showed that 22% of patients with MN aged 60 years and above had chances of malignancy 10-fold higher than that in age-matched controls. Other characteristics of malignancy-associated MN include phospholipase A2 receptor (PLA2R) negativity and IgG1-and IgG2- restricted subclass predominance. Because of this close association, our patient underwent an extensive search for malignancy with age-appropriate screening tests.
Moreover, we also found PLA2R and THSD7A negative on biopsy staining. A connection between NELL1-MN and male predominance was also observed by Caza et al., especially in cancer patients. Wang et al. found more female patients without malignancy. However, a detailed association between supplements was not studied in any of the studies.

MN can be related to supplement ingestion by having lipoic acid (LA), considered an antioxidant and insulin-mimetic supplement, works by acting on superoxide radicals and is proven to be beneficial in ischemic reperfusion injury and complications related to diabetes. Spain et al. report the development of unexpected proteinuria in 3 patients with multiple sclerosis (MS) who were receiving LA for MS. The critical finding on the kidney biopsies of these patients had a histologic pattern of membranous Nephropathy (MN) and stained positive for neural epidermal growth factor-like 1 (NELL1).

In our case, the patient was also on antioxidants having lipoic acid, and chronic use of NSAIDs. MN got reversed when supplements were stopped and were not started on immunosuppression. Still, in our case, as the patient had multiple comorbidities, we started him on immunosuppression.

For most of these with NELL1 positivity, no significant extra glomerular staining was demonstrated along tubular basement membranes, Bowman's capsule, or vessels. Electron microscopy shows severe podocyte foot process effacement (> 50%) in NELL1-associated MN and a higher incidence of mesangial deposits with no sub-endothelial deposits. These findings were found in our case as well.

Regarding the treatment of MN, patients should be treated for hypertension, edema, cardiovascular events, and thromboembolism risks. Angiotensin-converting enzyme inhibitors are recommended for controlling blood pressure and proteinuria. But a decrease in proteinuria may not exceed 30% compared to pre-treatment values, particularly in patients with proteinuria > 10 g/24 hr. We started our patient on ACEIs, statins for hypercholesteremia, and apixaban as an anticoagulant.

Another critical part of the treatment is immunosuppressive therapy, including Alkylating Agents (Cyclophosphamide or Chlorambucil), Corticosteroids, and other agents. Ponticelli et al. demonstrated the benefit of a 6-month regimen of alternating alkylating agents (cyclophosphamide or chlorambucil) with intravenous corticosteroids for achieving remission in MN patients. But it comes with the price of increased risk of opportunistic infection, reactivation of viral hepatitis, alopecia, gonadal damage, hemorrhagic cystitis, neoplasia, and toxic hepatitis.

A combination of corticosteroids with an alkylating agent has been the most commonly used therapy to preserve kidney function long-term, anti-CD20 biotherapy, particularly with Rituximab, has been becoming popular as first-line therapy because of its safety profile. Rituximab causes the depletion of B cells by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis. One of the studies on using Rituximab in MN evaluated the effects of an infusion (375 mg/m2) every four weeks in 8 patients on primary MN, causing a decrease in
urinary protein from 8.6 g/day at baseline to 3.7 g/day at 20 weeks. Complete remission was achieved in 3 patients and partial remission in the other.

The KDIGO Guidelines recommend treatment according to the risk score. Treatment depends on patient characteristics, drug availability, and physician preferences in high-risk patients. Immunosuppressive agents are not needed for low-risk. The recommendations accept two essential changes with Rituximab on the same level as cyclophosphamide in moderate to high-risk patients. The second change concerns CNIs. The MENTOR trial has confirmed the high relapse rate in patients treated with cyclosporine. It should not be used as monotherapy in higher-risk patients but in combination with Rituximab. Still, there is insufficient evidence regarding rituximab use to prevent ESRD in high-risk patients.

CONCLUSION

MN is one of the most important causes of nephrotic syndrome. It is vital to distinguish between primary and secondary MN to manage the patient properly. It’s essential to look for antibodies against antigens like NELL 1 if PLAR and TLAD7. Lipoic acid supplements, frequently prescribed in diabetic populations, may cause MN. Close monitoring for proteinuria must be done to detect the disease in its early phases. Moreover, in moderate-risk cases, Rituximab and cyclophosphamide may be equally effective, and Rituximab with tacrolimus may allow a steroid-sparing regimen.

Declarations

Ethical Approval and Consent to participate: Not applicable. Institutional policy does not require ethics approval for anonymized case report.

Consent for publication: Informed consent was obtained from the patient for their anonymized information to be published in this article. This is available in the patients chart.

Availability of data and materials: Available In chart.

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Authors' contributions: Dr Umair Ali wrote the first draft. Dr N Gokden provided the pathology section images and write up. Dr J Arthur and M Singh reviewed and did final edits including discussion. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

References


Figures
Figure 1

A. Glomerulus with global capillary loop thickening and mild mesangial matrix expansion, PAS stain, 10X.

B. Segmental subepithelial electron-dense deposits with extensive foot process effacement.

D. Positive NELL1 staining in capillary loops

C. Segmental capillary loop staining, IGG, 400X.