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A 54-year-old man with new-onset nephrotic syndrome

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CLINICAL PRESENTATION

A 54-year-old Caucasian airplane technician presented in outpatient evaluation with slow-onset lower extremity oedema, foamy urine and hypercholesterolemia on routine blood tests. He had a history of malaria in his infancy and hypertension. He had no family history of renal disease. His medication consisted of atorvastatin, telmisartan, hydrochlorothiazide and nifedipine, and he denied taking NSAIDs. On physical examination his blood pressure was 150/100mmHg and he had severe symmetrical lower extremity oedema. Laboratory testing showed a serum creatinine of 1.52mg/dL (eGFR 51mL/min), a serum albumin of 2.36 mg/dL, a urinary protein to creatinine ratio of 7.9g/g, a serum total cholesterol of 433mg/dL and a urinary sediment with microhematuria and leukocyturia. C3 and C4 were normal, ANA, ANCA and anti-GBM antibodies were negative and there was no monoclonal gammopathy. The titer of PLA2R Ab was determined to be 528 RU/mL. A renal biopsy was performed. On light microscopy, thickening of the capillary wall and severe diffuse hypertrophy of podocytes with collapse of the glomerular tuft was noted (Figure 1; Figure 2; Figure 3), as well as moderate interstitial fibrosis and tubular atrophy. Immunofluorescence showed coarse granular capillary wall deposits of IgG, C3, kappa and lambda light chains (Figure 4). An additional, confirmatory, immunohistochemistry test was performed (Figure 5).HIV, HCV, HBV, CMV, EBV and Parvovirus B19 were ruled out by serologic and molecular biology blood tests.

QUESTIONS

1. **What is the most likely diagnosis, considering light microscopy, immunofluorescence and serologic testing?**
2. **What are the main morphologic features of this disease and what is the target of the positive immunohistochemistry test?**
3. **What treatment options do we have in this case? Should we start treatment? When is the appropriate time to do so?**
4. **Should this patient be put on anticoagulation, and if so, what kind?**

Figure 1

Light microscopy (methenamine silver stain; original magnification, x400)

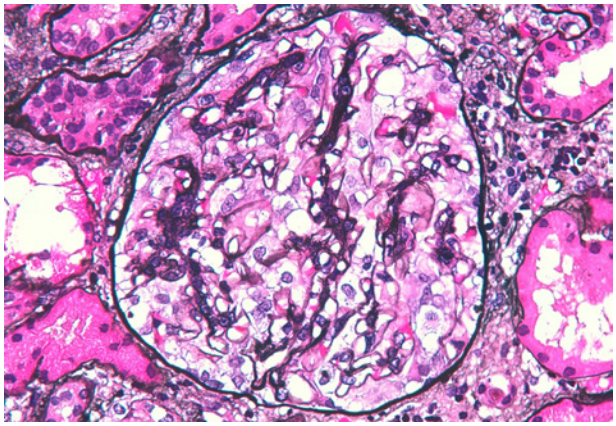


Figure 2

Light microscopy (Masson's Trichome stain; original magnification, x400)

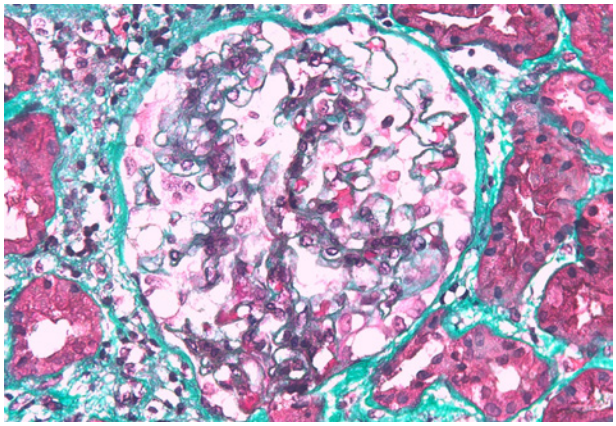


Figure 3

Light microscopy (hematoxylin and eosin stain; original magnification, x400)

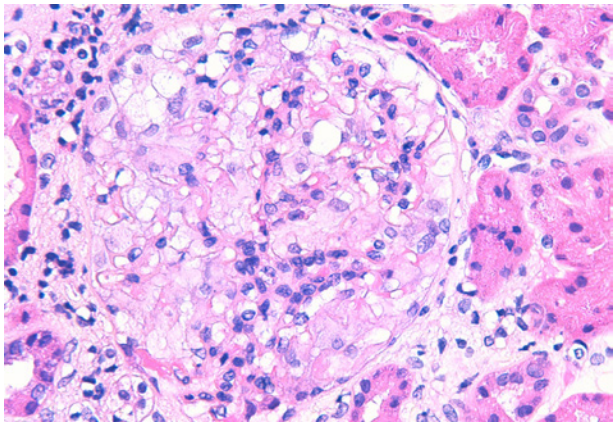


Figure 4

Immunofluorescence, anti-IgG (original magnification, x400)

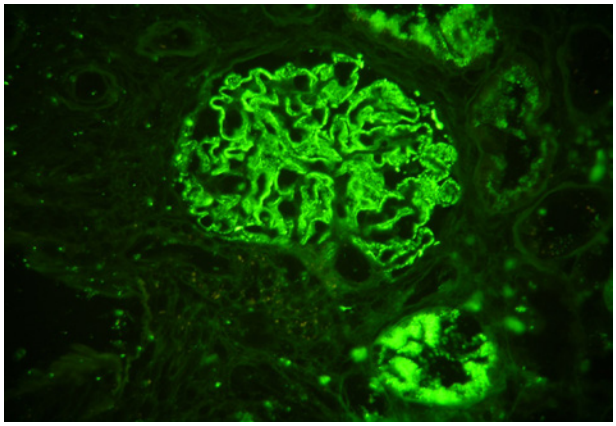
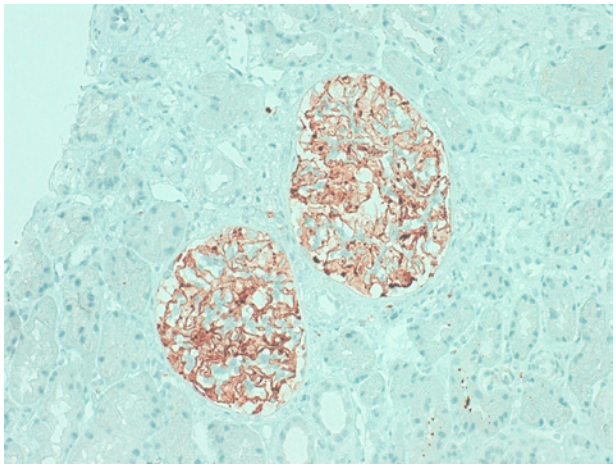


Figure 5

PLA2R Immunohistochemistry (×400)



ANSWERS

1. What is the most likely diagnosis, considering light microscopy, immunofluorescence and serologic testing?

Collapsing glomerulopathy is currently regarded as an uncommon subtype of focal segmental glomerulosclerosis, usually associated with HIV and other viral infections, or drugs, but it may also occur in other clinical settings. It is characterized by focal glomerular tuft collapse caused by severe hypertrophy of visceral epithelial cells.[1] Membranous nephropathy (MN), on the other hand, accounts for over 20% of nephrotic syndromes in adults, surpassed only by diabetic nephropathy and focal segmental glomerulosclerosis in some ethnicities. It presents as nephrotic syndrome in 60-80% of patients, and as asymptomatic proteinuria in the remaining. Microscopic hematuria occurs in up to 50% of cases. The disease is caused by the formation of complement-activating immune deposits in the subepithelial side of the glomerular basement membrane (GBM), against either podocyte antigens or deposited circulating antigens.[2] It can be primary (80% of cases), or secondary due to auto-immune disease (usually systemic lupus erythematosus), cancer, infections (for example hepatitis B), or drugs (such as gold and penicillamine). In this case serologic testing and immunofluorescence were essential for diagnosis, as they demonstrated the existence of highly specific circulating auto-antibodies, as well as glomerular immune deposits and complement, confirming the diagnosis of **primary membranous nephropathy**.

2. What are the main morphologic features of this disease and what is the target of the positive immunohistochemistry test?

Membranous nephropathy characteristically shows **diffuse capillary wall thickening on light microscopy** (best seen in PAS stain), **with or without spikes**. Spikes are protrusions of expanding GBM around immune deposits, which are best seen in silver methenamine stain at high magnification. Some podocyte activation may be observed, but the severe podocyte hypertrophy with partial collapse of the capillary tuft in our case was very misleading. This pattern of glomerular injury associated with MN is quite rare, but has previously been reported.[1] Immunofluorescence shows a characteristic **granular parietal staining of IgG** (IgG4 in primary MN), C3, C4, kappa and lambda. On electron microscopy, the subepithelial electron-dense deposits, expanding glomerular basement membrane and overlying foot process effacement are clearly visible and the disease can be staged (stages I–IV of the Ehrenreich and Churg classification). In 2009 primary membranous nephropathy in adults was shown to be caused by **anti-phospholipase A2 receptor antibodies** in 70-80% of cases.[3] This was an important breakthrough and serologic testing, which is highly specific (almost 100%) and sensitive (up to 70%) is now done routinely. Biopsy samples are now also routinely stained for PLA2R antigen by immunoperoxidase, as was done for our patient. Thrombospondin type-1 domain-containing 7A (THSD7A) was later recognized as a second possible autoantigen in primary MN in a minority of patients, but commercial tests are still not widely available.

3. What treatment options do we have in this case? Should we start treatment? When is the appropriate time to do so?

Membranous nephropathy is the third leading cause of ESRD in patients with primary glomerulopathy. It is a chronic disease with remission and relapse cycles, and spontaneous remission can occur in around 30% of patients. It usually occurs during the first 2 years after presentation, and the predictors for it are younger age, lower proteinuria, preserved renal function and female sex. The other 2 thirds of patients are divided equally between those who maintain chronic proteinuria and preserved renal function and those who quickly evolve to ESRD. It has been found that in primary MN, high PLA2R Ab titers at presentation are associated with a lower chance of spontaneous remission, and a higher chance of progressive renal disease. It has also been shown that therapeutically induced drops in titer predict clinical response.

Because of the unpredictable course of the disease, it has been traditionally recommended to use supportive treatment (ACEi±ARB) and clinically **monitor the patient for 6 months** before deciding whether to start immunosuppression (IS) or not. Conversely, the diagnostic and prognostic value of the PLA2R Ab has led some centers to base the decision to start IS on the titer and its early trends.[4] Steroids alone were shown to have no place in the treatment of MN. The 2 main options are **the Ponticelli regimen**, a 6-month alternating course of pulse and oral steroids and oral cyclophosphamide, **or calcineurin inhibitors**, cyclosporine or tacrolimus, usually in combination with steroids. Both these options have significant adverse effects, namely oncogenic and gonadotoxic effects, and

nephrotoxic effects, respectively. **Rituximab**, on the other hand, which used to be seen as a rescue therapy, has recently been emerging as a promising first line drug in primary MN, due to its more selective action on the pathogenic process. Other less established options include MMF, and ACTH.

Because of our patient's relatively young age, the high titers of PLA2R Ab, and some degree of established renal disfunction, we decided to promptly start him on Rituximab 1g (2 administrations, 15 days apart). We also chose to start prednisolone 60mg because of the collapsing features and active urinary sediment. Four weeks after treatment his PLA2R Ab titer was surprisingly negative, his protein to creatinine ratio had decreased to 1.8g/g, his serum albumin had increased to 3.36 g/dL and his urinary sediment was inactive. He was weaned off steroids. At 3 months follow-up his PLAR Ab titer is still negative but there is still subnephrotic proteinuria. This is an unusually quick response, especially when considering the initial high titter, and it is unclear whether it was due to the IS or if it was a spontaneous remission.

4. Should this patient be put on anticoagulation, and if so, what kind?

Primary membranous nephropathy is associated with an increased risk of venous thrombotic events such as deep vein thrombosis, renal vein thrombosis, and pulmonary embolism, which are inversely correlated with serum albumin levels, especially with albumin levels under 2.8 g/dL.[5] There are currently no evidence-based guidelines on primary or secondary prophylaxis of thrombotic events in MN. A documented thrombotic event is widely accepted as an indication to start anticoagulation. Primary prophylaxis should be based on a risk/benefit analysis. Patients with a high risk of a major bleeding event should not be put on primary prophylaxis, regardless of albumin level. It is suggested that patients with an intermediate or low bleeding risk should be assessed on a case-by-case approach, using risk calculating tools such as the one provided in www.unckidneycenter.org/gntools/bleedrisk.html.[6] It is important to note that current experience and risk calculating tools were made based on oral anticoagulation with coumarin agents, and that there is little experience with novel oral anticoagulants (NOACs). In our case though, for the sake of compliance, since renal impairment was mild and bleeding risk was determined to be low, we started the patient on edoxaban 30mg id. The drug was discontinued once albumin rose above 2.8g/dL.

Disclosure of potential conflicts of interest: none declared.

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