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Is the Big Imitator Back or Did He Never Leave?

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- CNM: Conception and drafting of the article, and approved the final version of the manuscript
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CLINICAL PRESENTATION

We present a case of a 19-year-old Caucasian male patient without a relevant past medical history, medication or family history of kidney disease. He presented to the emergency department due to rapid sudden lower limb (godet sign +++) and peri- orbital edema that had started three days before. He also referred abdominal pain and diarrhea for 3 days and noticed enlarged cervical, axillary and inguinal lymph nodes for 1 month. He reported that he had no fever, recent infections and neither received new vaccines or took new drugs. No other organ involvement including arthralgias, dysuria, gross hematuria or previous gastrointestinal involvement was reported. No past allergies or malignancies were documented. Blood analysis revealed no alterations in blood counts, kidney, hepatic or electrolyte disfunction (serum creatinine of 1.01 mg/dL; urea of 36 mg/dL). Severe hypoalbuminemia of 18.8 g/L (35 – 52 g/L) and hypercholesterolemia with a total cholesterol of 427 mg/dL (normal range < 190 mg/dL) and LDL 201 mg/dL (normal range < 207 mg/dL) were noticed. Urinalysis showed middle hematuria (46/UL) without leukocyturia and nephrotic range proteinuria with 7300 mg 24-hour urine sample was found. Renal ultrasound showed normal kidneys. He was diagnosed with new onset nephrotic syndrome and admitted in the nephrology ward. A kidney biopsy was performed.

QUESTIONS

1. **What is the most likely diagnosis given the clinical history and presentation?**
2. **What is the diagnosis considering light microscopy and immunofluorescence studies?**
3. **What is the differential diagnosis?**
4. **How should this patient be managed?**
5. **How was the patient treated and how did he evolve?**

ANSWERS

1. **What is the most likely diagnosis given the clinical history and presentation?**

In young adults, one of the most common causes of rapid onset nephrotic syndrome (NS) is minimal change disease (MCD). Although in children idiopathic MCD is the most usual form, in adults there is a serious concern about secondary forms. As our patient presented lymphadenopathies and abdominal complaints, it is mandatory to exclude hematologic malignancies and infections. Given the age of presentation and its rapid development, MCD poses as the most likely diagnosis.

Focal and segmental glomerulosclerosis (FGS) is another very common cause of NS. Viral infections like CMV, HIV, parvovirus B19 and EBV are common secondary causes of FGS. Although, the patient denied family history of renal disease, a genetic form should also be considered if other secondary forms are excluded. When both genetic and secondary forms are excluded, FSGS is considered to be idiopathic.

Differential diagnosis also includes membranous nephropathy. Although its primary form, which is the most common, more commonly presents in middle aged, secondary forms due to infections, malignancies and drugs must be considered.

Other less common etiologies should also be considered: membrano-proliferative glomerulonephritis is a viable possibility if there is any active hematologic or infectious disease. NS as a presentation of IgA nephropathy is very rare but should not be ignored. Given the young age and its rarity, amyloidosis poses the less probable diagnose.

A systemic evaluation is mandatory to exclude secondary forms and in conjunction with a kidney biopsy will give important considerations about the final diagnosis.

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2. What is the diagnosis considering light microscopy and immunofluorescence studies?

The kidney biopsy specimen consisted of two fragments with capsule, cortex, medulla, 28 glomeruli and medium size-artery.

In light microscopy, all glomeruli showed moderate podocyte hypertrophy (Fig. 1). Tubular reabsorption droplets in the cytoplasm of proximal tubular cells are seen (Fig. 2).

Figure 4 (IMF) shows strong and diffuse granular staining deposits of IgG along the glomerular capillary walls and in the mesangium.

Figure 5 (IMF) shows the same pattern of distribution, with less intensity, of granular IgM along the GMB and in the mesangium. Both kappa and lambda light chains also demonstrated a granular staining pattern.

Membranous nephropathy (MN) is the final diagnosis.

MN is the prototype of kidney disease caused by the deposition of sub-epithelial immune complexes that are responsible for structural alterations which result in the typical glomerular pattern of injury of GBM thickening.[1] Once the diagnosis is established, it is necessary to classify MN etiology. Its primary form occurs in the setting of an idiopathic auto-immune disease with in situ glomerular immune complex formation directed to glomerular antigens that are routinely found

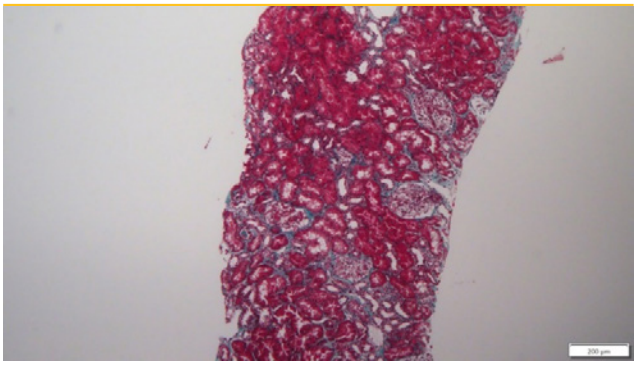

Figure 3

Trichrome stains shows a global picture of the kidney biopsy with normal tubules and preserved interstitium.

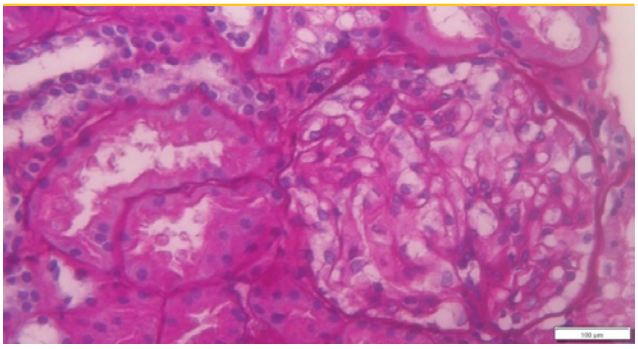

Figure 1

Periodic acid Shiff coloration shows moderate podocyte hypertrophy.

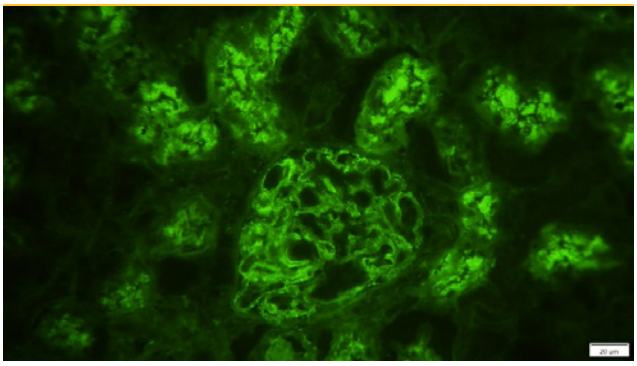

Figure 4

IMF showing a granular pattern of IgG distribution in GBM.

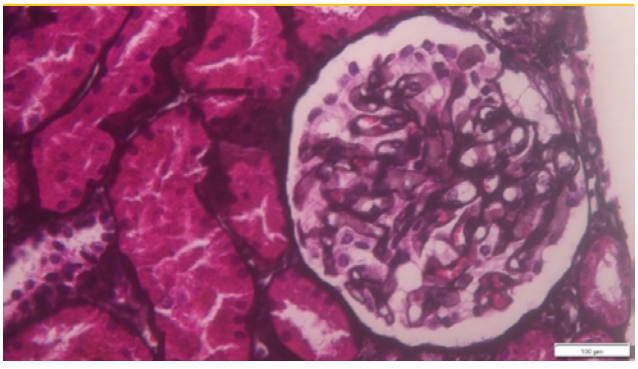

Figure 2

Jones methamine silver stain showing numerous tubular reabsorption protein droplets.

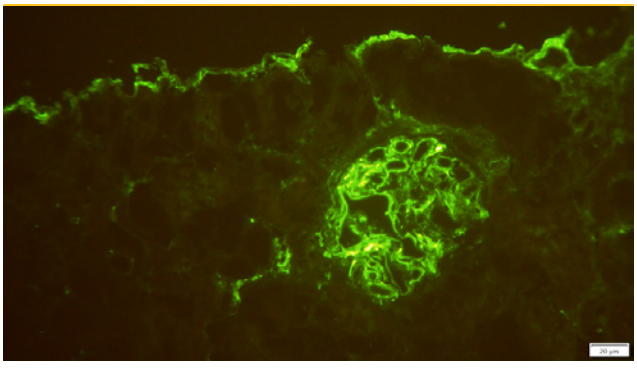

Figure 5

A glomerular and mesangial pattern of IgM staining in IMF.

on podocytes – primary membranous nephropathy. Alternatively, it can occur in association with an underlying disorder such as an autoimmune disease, systemic infections, malignancy or drug toxicity – secondary membranous nephropathy.[1-4]

Primary MN is the most common, amounting to 70% of cases. The most common antigen is the M-type phospholipase A2 receptor 1 (PLA2 R) in the podocytes and represents 80% of primary MN.[3]

In the last decade, multiple other antigens were found to be associated with MN: EXT1/EXT2, NELL1, Sema 3B and PCDH7. All of these can be, in a minority of patients, associate with a secondary disease: NELLL1, Sema 3B and PLA2R more associated with malignancy[5,6] and EXT1/EXT2, THSD7A and PLA2R with autoimmune diseases.[6,7] It is also likely that each specific antigen-associated MN is distinctive about pathophysiology, clinical and disease associations, response to treatment and outcomes.

For this reason, some authors defend that, in the future, a classification based on the antigen detection with or without an associated disease over *"primary versus secondary"* would be more suitable.

When no auto antibody could be found and secondary forms were excluded, the term idiopathic primary MN is used.

3. What is the differential diagnosis?

The main differential diagnosis is to distinguish between primary and secondary MN. Some histologic features can be of help to ascertain the correct etiology.

Glomerular thrombi are sometimes associated with malignancies. In IMF mesangial deposits are more common in secondary forms. The main subtype in primary MN is IgG4 whereas IgG1 and IgG2 subtypes are associated with carcinoma and IgG3 is the dominant subclass in membranous lupus nephritis. Tubular basement membrane Ig deposits are common in lupus as well.[8]

Given the histologic diagnosis, etiologic investigation was performed. Immunological investigation showed a positive anti-nuclear antibody (Ab) with a low title of 1:160 with negative anti double-stranded DNA, extractable nuclear antigens Ab, anti-Smooth muscle, anti-Sjogren's syndrome-related antigen A, rheumatoid factor, anti-Cyclic citrulline peptides and anti-streptolysin O-titer all negative. C3 and C4 presented in the normal level range. Serum electrophoresis showed polyclonal hypergammaglobulinemia and serum and urine IMF were negative for a monoclonal component. Antibodies against PLA2R were negative as well. Thyroid function was normal.

Serological viral testing including anti-Hepatitis C, anti-HIV 1 and 2, Ag HbS, EBV, CMV and herpes virus simplex were all negative. His rapid plasma reagin (RPR VDRL) test was found to be strongly positive with a title 1/8.

A diagnosis of membranous nephropathy secondary to syphilis was assumed.

4. How should this patient be managed?

There are two sets of complementary therapeutic arms that should be implemented for the treatment of MN secondary to syphilis: general measures to manage nephrotic syndrome complications and disease-specific therapy directed to the etiology.[9]

General management:

- Intravenous loop diuretics and dietary sodium intake should be restricted to 2.0 g/d.
- Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in order to reduce proteinuria.
- ACEI and ARB are first line therapy to target systolic blood pressure < 120 mmHg.
- Lipid-lowering agents may be indicated in persistent nephrotic syndrome.
- Prophylactic full-dose anticoagulation especially with serum albumin below 2 g/dL
- Lifestyle modifications with a healthy diet, increased physical activity, weight reduction and smoking cessation are recommended.

Penicillin G benzathine remains the antibiotic of choice in treating a syphilis owing to remarkable susceptibility of *Treponema pallidum* to this drug being intramuscular injection (2.4 million units) the ideal choice of administration.[10]

5. How was the patient treated and how did he evolve?

Our patient was treated with penicilin G benzatine 2.4 million units IM once weekly for three weeks and with the general management described above. One month after the last dose of penicilin, the patient showed total resolution of complaints of malaise and lower limb and peri-orbitary edema. Two months later, blood analysis revealed that he maintained normal renal function and serum albumin levels had returned to normal range without dyslipidemia. Urinalysis showed no alterations and PCR was of 648 mg/g. So, it was assumed that the patient had been cured.

In the developed countries, syphilis infections were reported to be in decline until the 1990s.[11] In recent years, the rise in syphilis cases have been primarily attributable to the recent increase in the use of pre-exposure prophylaxis for HIV and consequently reduced use of barrier protection particularly between men who have sex with men.[12]

MN secondary to syphilis is more prevalent in man with a mean age of 22 years old. Most cases reported in the literature suggest that is readily reversible with penicillin therapy alone.[13] Despite its resurgence, syphilis is not routinely included in the differential diagnosis of MN. Our case illustrates the importance of considering syphilis as a reversible cause of nephrotic syndrome due to its impact in the therapeutic management and kidney outcome.

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