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Teaching Point
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A 34-year-old man with membranous nephropathy, a rash, meningitis and ocular involvement

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A previously healthy 34-year-old Caucasian man was referred to our outpatient clinic, due to an accidental finding of nephrotic range proteinuria (11.5 g/24 h). His urinalysis had been completely normal 1 year earlier. He reported having had a 'sore throat' ∼6 weeks earlier, treated with amoxicillin for 5 days. He denied any recent travel and sexual activity. On examination the patient appeared well, with 1 + ankle oedema, small inguinal lymph nodes were palpable bilaterally, physical exam was otherwise unremarkable; his blood pressure (BP) was 134/88 mmHg, with 76/bpm heart rate, BMI 25.1 kg/m^2. Laboratory investigation confirmed the presence of heavy proteinuria (6.4 g/24 h, albumin 3.2 g/l); urinary sediment showed only 2–5 leukocytes per high power field. His blood count, including WBC and platelets, was normal, as well as liver and renal function (creatinine clearance 103 ml/min ×1.73 m^2). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and C3 and C4 levels were normal. Serum total proteins were 6.2 g/dl with albumin 3.6 g/dl. No monoclonal components were detected either in the serum or the urine. The search for anti-nuclear (ANA) and anti-glomerular basement membrane antibodies was negative, as well as that for ANCA and rheumatoid factor. A borderline positivity to anticardiolipin IgG was detected, which was considered of no clinical significance at the time. A chest X-ray and an ultrasound scan of the abdomen were also normal; in particular, no abnormalities were detected regarding the kidneys, ureters, bladder and prostate gland. Tests for HBsAg, HCV-ab and HIV serology were also negative. Tuberculin skin testing (PPD 5 U) was non-reactive. At this point, a renal biopsy was deemed necessary, and performed. By light microscopy a diffuse thickening of the glomerular capillary basement membrane was present, with slight expansion of the mesangial matrix. Blood vessels were intact, as well as the tubules, which contained proteinaceous material. Immunofluorescence showed diffuse, granular deposition of IgG^{2+}, IgA^{1+} and C3^{1+}. Unfortunately, electron microscopy examination was not possible, as the fragment of tissue sampled contained no glomeruli. Based on these findings, primary membranous glomerulonephritis was diagnosed, and treatment started with methylprednisolone iv (1 g daily for three consecutive days), followed by oral prednisone 75 mg qd and irbesartan 300 mg qd. We considered cyclophosphamide as first line treatment, but the patient refused for fear of side effects; therefore we decided to try a course of steroids alone, to later add a cytotoxic agent, if no response were to be observed. A prompt remission of proteinuria to 800 mg/24 h was observed after 3 weeks. Nebivolol (5 mg qd) was added because of raised BP (160/90 mmHg). A few days later the patient was seen by a dermatologist due to the appearance of a rash involving the palms and soles, which was interpreted as a 'scaly rash, probably drug induced'; the nebivolol was withdrawn, and the rash resolved. Approximately 20 days later, the patient presented to our outpatient clinic complaining of persistent headache, arthralgias and low-grade fever, for which he had taken paracetamol, with transient benefit. The patient was again admitted to the hospital. His physical exam was unremarkable, but for the presence of 1 + ankle oedema. BP was 140/90 mmHg, heart rate 92 b/min, body temperature 37.6°C. Lab tests on admission showed mild normocytic anaemia (Ht 33.2%, Hb 10.7 g/dl), raised CRP (78.0 mg/l) and ESR (70 mm/h), polyclonal hypergammaglobulinaemia (22.3%, IgG 1379 mg/dl) and a moderate recurrence of proteinuria (1600 mg/24 h). Renal and liver functions were normal, as well as C3 and C4 levels. Again, the search for ANA, rheumatoid factor, cryoglobulins and ANCA was negative. Cultures of blood and urine were also negative, as well as tests for B and C hepatitis and HIV. Tuberculin skin testing was again non-reactive. Serology for CMV, HSV, Chlamydia pneumonia and Mycoplasma pneumonia was also negative, except a slight positivity to M. pneumonia IgM(+–). A chest X-ray showed a small infiltrate in the retrocardiac region, whereas an ultrasound scan of the abdomen showed multiple lesions of the liver, which, after a contrast CT-scan, were identified as angiomata, with a pattern typical of peliosis hepatis. On the 6th day after admission, the

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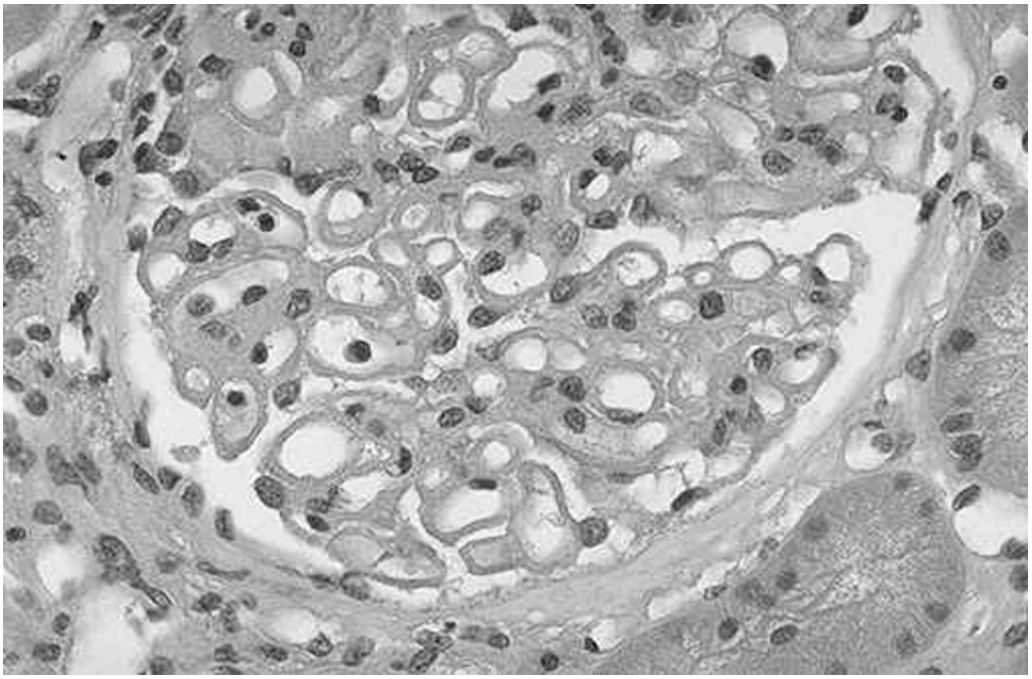

Fig. 1. Light microscopy image of a representative glomerulus (haematoxylin eosin).

patient complained of persistent headache and scotomas. An ophthalmology consultant found bilateral oedema of the papilla and signs of diffuse retinal vasculitis. A CT and an NMR scan of the encephalon were unrevealing. A retinal fluorescein angiography confirmed the presence of severe diffuse vasculitis consistent with the 'retinal necrosis syndrome'. A lumbar puncture was performed which yielded clear, colourless fluid, total protein 49.9 mg/dl (albumin 31.5 mg/dl, IgG 6.5 mg/dl, link index 0.42), leukocytes 29/mm^3 (100% lymphocytes), glucose 2.7 mmol/l (plasma 4.4 mmol/l). No bacteria or acid-fast bacilli were identified.

Thus, we are confronted with a patient who has membranous nephropathy (Figure 1), a rash, meningitis, ocular involvement and peliosis hepatis. Can a single disease explain all these clinical findings?

At this point the following results of lue screening were received: VDRL 1:256, TPHA 1:20480 and a positive qualitative test for both anti-treponemal IgG and IgM. The same tests were performed on the CSF: VDRL 1:128, TPHA 1:1280, positivity for specific IgG and IgM. On further questioning, the patient admitted having had unprotected homosexual intercourses, and having noted, a few months earlier, a painless ulcerative lesion on his penis, which had healed spontaneously after ~10 days. A diagnosis of secondary syphilis with involvement of the central nervous system was established, and treatment with ceftriaxone (2 g iv, qd, for 14 days) was promptly started. The administration of oral prednisone (50 mg/day) was continued. After completion of the treatment cycle, all the clinical symptoms, including fever, headache and scotomas, resolved; a repeat scan of the abdomen showed complete resolution of peliosis hepatis, CRP was 0.3 mg/dl, ESR 12 mm/h, proteinuria 350 mg/24 h. Retinal fluorescein angiography showed incomplete resolution of the vasculitis. The patient was discharged on tapering steroids, and irbesartan 300 mg qd. After 3 months a lumbar puncture was repeated, which showed clear, colourless fluid, no proteins, no leukocytes, and tested negative for VDRL, TPHA and specific IgG and IgM. In the serum VDRL was 1:8 and TPHA 1:5120, specific IgG tested positive, IgM negative; proteinuria was 220 mg/24 h, GFR 103 ml/min* 1.73 m^2. One year later serum VDRL titre was 1:4, TPHA 1:1280, GFR 98 ml/min* 1.73 m^2, mild proteinuria (174 mg/24 h) persisted, the retinal lesions had cleared completely. The patient declined a repeat renal biopsy.

Discussion

The association between syphilis and 'dropsy' was reported as early as 1813 by Blackall [1]. Renal involvement (the presenting manifestation in this case) in syphilis is uncommon, accounting for <0.3% of cases in the acquired form, and between 5 and 8% in the congenital form [2,3]. It becomes apparent during the secondary phase of the disease, and, by far, its most frequent clinical presentation involves isolated proteinuria and/or the nephrotic syndrome (Table 1), and, although rarely, acute glomerulonephritis, IgA nephropathy and even salt losing nephropathy have been described [2–6], whereas, the most frequent histological lesion (Table 2) is represented by membranous nephropathy [1,3], with subepithelial deposition of IgG, C3 and C1q [2,3]. The glomerular lesion is thought to be immunologically mediated [3,4,6–8]: in fact, treponemal antigens have been detected within the glomerular capillary wall deposits [4,8] and antitreponemal antibodies have been identified by elution studies [3,4]. Penicillin (benzathine penicillin 2.4 million units, weekly in two to three doses, in the absence of CNS involvement) is the treatment of choice [9],

Table 1. Clinical manifestations of renal syphilis

Isolated proteinuria (most common)
Nephrotic syndrome
Acute nephritic syndrome
Rapidly progressive glomerulonephritis
Nephrotic syndrome with acute renal failure
Renal gumma
Salt losing nephropathy

Table 2. Pathologic findings in renal syphilis

Membranous nephropathy (most common)
Mesangial prolipherative glomerulonephritis
Postinfectious endocapillary glomerulonephritis
Minimal change + interstitial oedema
Rapidly progressive glomerulonephritis with crescents
Renal gumma
IgA nephropathy
Amyloid renal disease

although ceftriaxone is also effective [10], and it generally leads to resolution of proteinuria in 2–6 weeks and to the recovery of the glomerular lesion in most patients, though follow-up biopsies have demonstrated the presence of a significant proportion of hyalinized glomeruli [7].

To our knowledge, peliosis hepatis, a rare condition associated to anabolic steroid use or Bartonella henselae infection [11], has not been reported previously in association to syphilis; in our patient, it might have been caused by the prolonged use of steroids; nonetheless, its prompt resolution after antibiotic treatment supports a causative role for the treponemal infection.

Ocular syphilis is manifested at times by retinal vascular involvement [12]: it is vaso-occlusive in nature, and may lead to serious retinal damage, if left untreated.

We chose to treat our patient with a ceftriaxone based regimen, due to the extensive involvement of the eyes and central nervous system, since such a therapy has been shown to be effective in neurosyphilis [13]. We achieved a complete response, as shown by the complete remission of symptoms and by the greater than fourfold reduction of VDRL and TPHA titres.

In conclusion, syphilis, an almost forgotten disease in western countries till a few years ago, is undergoing a dramatic resurgence, and must be kept in mind when evaluating cases of unexplained proteinuria and/or nephrotic syndrome.

Teaching points

1. Whenever confronted with a case of membranous nephropathy, the search for a systemic disease, amenable to specific treatment, must be thorough.
2. Syphilis must be considered in the differential diagnosis of otherwise unexplained nephrotic syndrome, or isolated proteinuria.
3. The rash of secondary syphilis typically involves the palms and soles.
4. Ocular involvement in syphilis also implies involvement of the central nervous system.

Conflict of interest statement. None declared.

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