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CASE REPORT

Simultaneous nephrotic syndrome and hepatitis in secondary syphilis: case report and review of the literature

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Abstract A 66-year-old man presented with a penile ulcer, an acute clinical onset of nephrotic syndrome and hepatitis. Secondary syphilis was diagnosed on the basis of the history of rash and the result of strongly positive serological test for syphilis. A renal biopsy demonstrated membranous glomerulonephritis with subepithelial electron-dense deposits. After treatment with amoxicillin for 2 weeks, he achieved clinical recovery. It is important to recognize syphilis as a reversible cause of nephrotic syndrome and acute hepatitis because antibiotic therapy can result in complete remission.

Keywords Nephrotic syndrome · Hepatitis · Membranous glomerulonephritis · Syphilis

Introduction

Syphilis has been called "the great imitator" because it is associated with various clinical presentations. Despite the existence of inexpensive and effective antibiotic treatment regimens, more than 10 million new syphilis cases occur annually throughout the world. Nephrotic syndrome and acute hepatitis are known as complications of secondary syphilis [1], but they rarely occur simultaneously. In this case, we describe a patient with syphilitic nephrotic syndrome and hepatitis who achieved complete remission after treatment with amoxicillin.

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Case report

A 66-year-old man with no prior history of systemic disease was admitted to our hospital because of peripheral edema lasting for 1 week and increasing general fatigue for 1 month.

The patient noticed penile swelling and induration 2 months before admission, followed by a sore throat and general fatigue. A non-pruritic eruption gradually spread over the arms and back. 2 weeks before admission, he went to our hospital for sore throat and decreased appetite and was administered cefcapene pivoxil hydrochloride for 5 days; however, he developed bilateral lower extremity edema. He had no fever, chills, nausea, vomiting, arthralgia, history of renal disease, alcohol abuse, or illicit drug use. His sexual history included sexual contact 4 months before with a female other than his wife.

On physical examination, his height was 158.9 cm, body weight was 55.2 kg, blood pressure was 149/76 mmHg, pulse was 63 beats per minute and regular, and body temperature was 36.2 °C. There was pitting edema of lower extremities bilaterally. External genitalia revealed penile swelling and an almost resolved penile ulcer with erythematous macules. There was a minimal residual rash in the upper extremities. His liver and spleen were not palpable. There was no sign of meningeal irritation or any other neurological abnormalities. Examination of the head and neck, lungs, heart, and abdomen was normal. Uveitis was not evident on ophthalmic examination.

Laboratory findings showed white cell count of 6450/μl, serum protein of 5.3 g/dl, albumin of 2.0 g/dl, cholesterol of 243 mg/dl, triglyceride of 250 mg/dl, blood urea nitrogen of 32.8 mg/dl, serum creatinine of 2.15 mg/dl, alanine aminotransferase of 76 IU/l, aspartate amino transferase of 51 IU/l, total bilirubin of 0.5 mg/dl, and alkaline phosphatase of

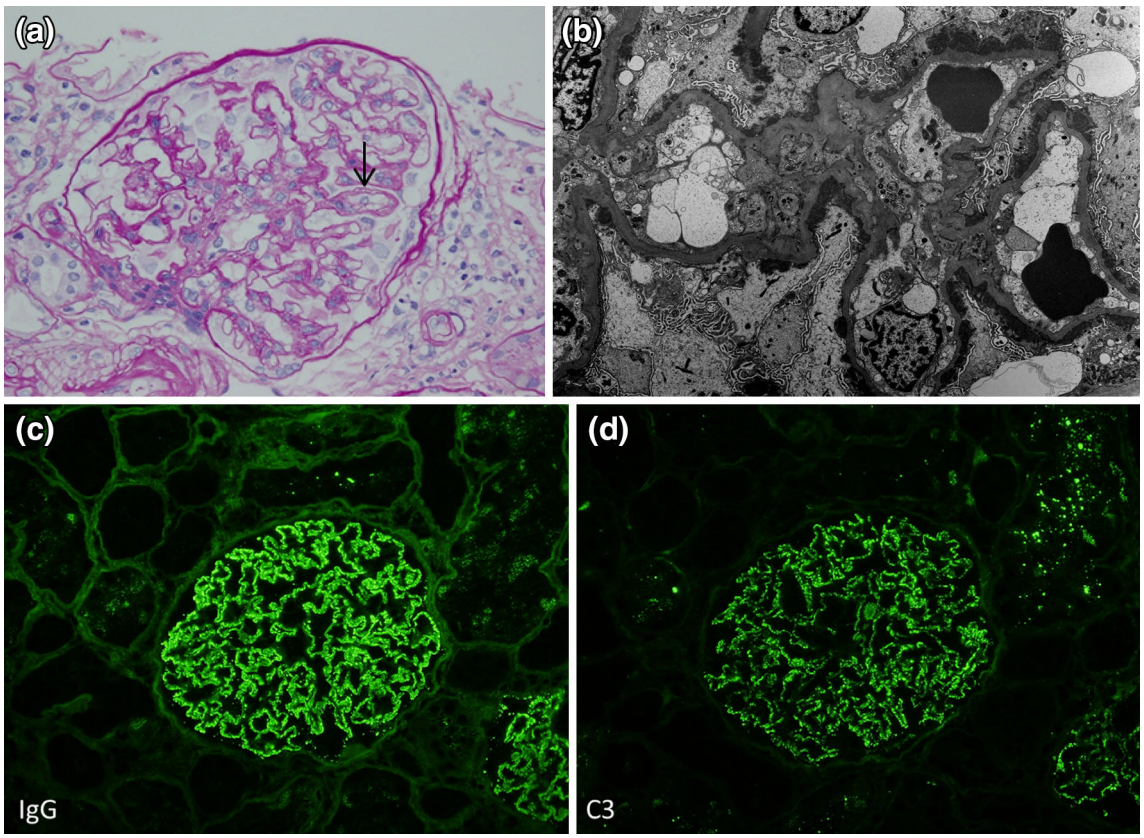

Fig. 1 **a** Hematoxylin and eosin (H&E)-stained slides of kidney biopsy: essentially normal except a double contour of glomerular basement membrane (*black arrow*). **b** Subepithelial and intramembranous electron-dense immune-type deposits with differences in size and density (Ehrenreich and Churg glomerular stage I). **c**, **d** Direct immunofluorescence (DIF) showed bright diffuse granular glomerular capillary wall staining for IgG and C3

3793 IU/l. A work up including antimitochondrial antibody, antinucleolar antibody, and hepatitis A, B, C, CMV, and EBV serology were unremarkable. The initial spot urine protein-to-creatinine ratio increased to 19 g/gCre. The rapid plasma reagent (RPR) test was markedly reactive at 1:128 and a treponema pallidum hemagglutination (TPHA) test was positive at 1:41.2. Human immunodeficiency virus antibody test was negative. Serum complement C3 level was 137 mg/dl (normal range 65–135 mg/dl), and C4 was 28 mg/dl (normal range 13–35 mg/dl). Serum immunoglobulin (Ig) G level was 1646 mg/dl (870–1700 mg/dl), IgA was 314 mg/dl (110–410 mg/dl), and IgM was 335 mg/dl (33–190 mg/dl). Ultrasonography indicated a dull liver edge, kidneys of normal size, and a celiac lymph node swelling (11.0 × 6.8 mm).

Nephrotic syndrome was diagnosed and secondary syphilis was strongly suspected. Besides he might have hepatitis.

A kidney biopsy was performed on the eighth day of hospital stay, which revealed renal cortex and medulla with a total of 18 well-perfused glomeruli and five with glomerulosclerosis. Glomeruli were essentially normal except a double contour of the glomerular basement membrane in some glomeruli on staining with hematoxylin and eosin (H&E), periodic acid–Schiff (PAS), and Jones methenamine silver (Fig. 1a). There was evidence of mild interstitial fibrosis and atrophy and severe tubular injury. Direct immunofluorescence (DIF) showed bright diffuse granular glomerular capillary wall staining for IgG, C1q, and C3 (Fig. 1c, d). DIF staining with antibodies to IgG subtypes showed moderate IgG1, IgG2, and IgG3; however, IgG4 was trace to negative. Electron microscopy showed subepithelial and intramembranous electron-dense immune-type deposits varying in size and density (Ehrenreich and Churg glomerular stage I; Fig. 1b).

On the basis of the history of rash and the results of serology and kidney biopsy, the patient was diagnosed as secondary syphilis with syphilitic membranous nephritis and hepatitis.

He received amoxicillin for 14 days and a low-protein diet for edema, and was hydrated with intravenous fluids. He was responsive to the treatment. It seems urinary protein levels and serum creatinine began to decrease and liver

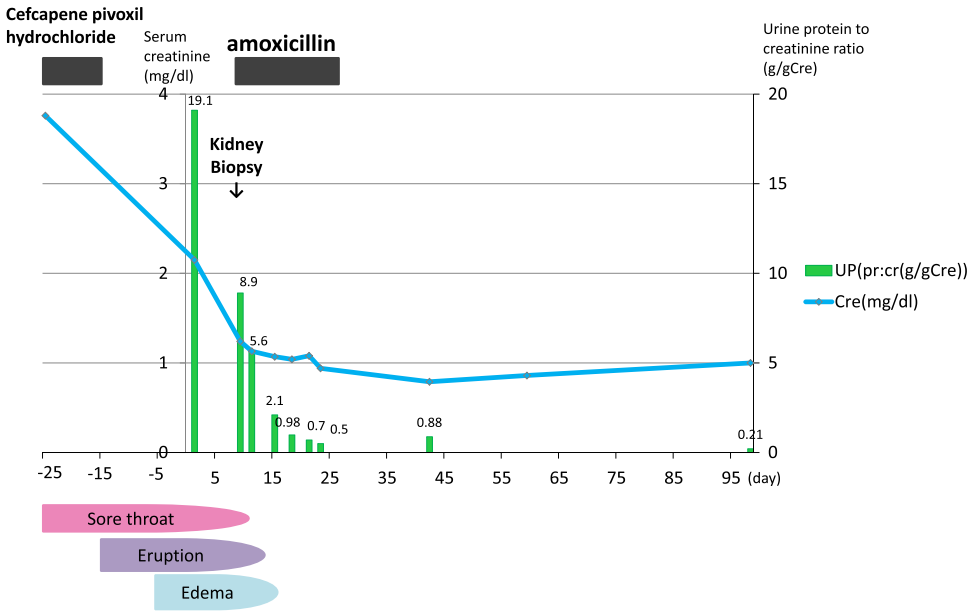

Fig. 2 Clinical course

Table 1 Renal biopsy and treatment of syphilitic nephropathy

Year	Author	Renal biopsy	Treatment
1991	Balikocioglu	MGN	Unknown
1991	David J. Kusner	No biopsy	Penicillin
1992	Hruby	MGN	No treatment
1992	Hruby	MGN, vasculitis	Penicillin
1992	Hruby	RPGN	Penicillin, hemodialysis
1992	Magarian G. J.	No biopsy	Penicillin
1993	Hunte	MGN, mesangial proliferation	Penicillin
2005	Yung-Chih Chen	Interstitial nephritis	Penicillin
2006	Z. Soehardy	MGN	Penicillin
2008	Y.-C. Tsai	Mesangial proliferation	Penicillin
2010	K. Boslooper	MGN	Penicillin
2010	Anjali A. Satoskar	MGN	Penicillin
2011	John P. Havil	MGN	Penicillin
2011	M. T. Mora Mora	MGN	Penicillin
2012	Lisa M. Scheid	MGN, mesangial proliferation	Unknown
2013	M. Louis Handoko	MGN	Penicillin

MGN membranous glomerulonephritis, *RPGN* rapidly progressive glomerulonephritis

and biliary enzymes returned to normal soon after amoxicillin treatment. Nephrotic syndrome had completely resolved with normalization of urinary protein excretion (Fig. 2). He has remained in complete remission for 1 year after treatment.

Discussion

Nephrotic syndrome is a well-recognized but rare complication of secondary syphilis. The association between syphilis and renal disease was first reported in the 1900s. The prevalence of nephrotic syndrome in early syphilis was reported to be 0.28 % [2].

The manifestations of syphilitic renal disease include albuminuria, nephrotic syndrome, acute nephritis, and rapidly progressive nephritis (Table 1). Membranous glomerulonephritis (MGN), as seen in this case, is the most commonly observed histopathological lesion, and is thought to be mediated by immune complex deposition within the capillary walls [3–9]. Renal function is normal in most cases, but this case is reported to involve acute kidney injury (AKI). Volume depletion due to anorexia and tubular injury was associated with infection, and

Table 2 Simultaneous nephrotic syndrome and hepatitis in six patients with syphilis

Ref No.	Presentations	Clinical features		Pathology	
		Kidney	Liver	Kidney	Liver
[1]	Edema, rash	Nephrotic syndrome	Elevated ALP, AST and ALT	MGN, IgA nephropathy	No biopsy
[10]	Edema	Nephrotic syndrome	None	No biopsy	Active hepatitis
[11]	Fever, rash, edema	Nephrotic syndrome	Hepatosplenomegaly, elevated ALP	MGN	Granulomatous hepatitis
[12]	Jaundice, rash, dyspnea	Nephrotic syndrome	Elevated ALP and bilirubin	MGN	No biopsy
[13]	Edema, general fatigue	Nephrotic syndrome	Elevated AST and ALT	Mild increase of mesangial matrix	No biopsy
[14]	Rash, edema	Nephrotic syndrome	Elevated AST and ALT	MGN	Granulomatous hepatitis

ALP alkaline phosphatase, *AST* aspartate transaminase, *ALT* alanine transaminase, *MGN* membranous glomerulonephritis

cephalosporin may cause AKI. Syphilitic nephritis can be resolved with penicillin in most cases, but hemodialysis, plasmapheresis, and methylprednisolone are required in some cases with rapidly progressive glomerulonephritis [20].

It is interesting that in our patient, the proteinuria seemed to have essentially abated before specific treatment for syphilis with amoxicillin. Cephalosporin administered early in the course for presumptive upper respiratory infection might be partially efficacious against syphilis.

To our knowledge, there have been six reports in the literature describing a similar case where nephrotic syndrome and acute hepatitis occurred simultaneously (Table 2) [1, 10–14]. Clinically apparent syphilitic hepatitis has a similar incidence as nephrotic syndrome (0.24 %) as reported by a large retrospective study [15]. Although the exact pathogenesis of the liver and kidney damage is uncertain in syphilis infection, glomerular injury via deposition of antigen–antibody complexes might be a contributory factor.

Most reports agree that in syphilitic hepatitis, alkaline phosphatase is disproportionately elevated in comparison with serum bilirubin and transaminases. Key historical findings include a nonspecific periportal hepatocyte necrosis and pericholangiolar inflammation [16–19]. Some reports have attributed cholestasis and elevation of serum alkaline phosphatase levels to a pericholangiolar inflammation. We did not perform liver biopsy and cannot exclude the possibility of coincidental viral hepatitis or liver dysfunction due to cefcapene pivoxil hydrochloride, but the clinical course and time of occurrence would not contradict syphilitic hepatitis.

Our case illustrates that it is important to recognize syphilis as an underlying cause of MGN, because appropriate antibiotic treatment can lead to complete remission [3, 20–23]. In addition, syphilis should always be considered in the differential diagnosis of nephrotic syndrome.

Conflict of interest The authors have declared that no conflict of interest exists.

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