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Case Report

Nephrotic syndrome with minimal change disease due to syphilis: a report of two cases

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Abstract: Nephrotic syndrome, a rare complication of secondary syphilis and syphilitic minimal change disease, has only been fully documented in one case thus far. The current study describes two cases of nephrotic syndrome with minimal change disease due to syphilis infection. One case was of a 15-year-old boy while the other was a 47-year-old male. Both patients showed renal pathologic characteristics of minimal change disease and both were positive for the rapid plasma reagin (RPR). Prolonged antibiotic therapy with penicillin or ceftezole resulted in full remission in the two cases. In conclusion, it is important to recognize that syphilis is a reversible cause of nephrotic syndrome with minimal change disease. Antibiotic therapy can result in complete remission.

Keywords: Syphilis, nephrotic syndrome, minimal change disease, renal biopsy, prolonged antibiotic therapy

Introduction

Nephrotic syndrome is characterized by heavy proteinuria (> 3.5 g/24 hours), accompanied by hypoalbuminemia (< 30 g/L), hyperlipidemia, and edema, often resulting in hospitalization, end-stage renal disease (ESRD) requiring renal replacement therapy, or death [1]. Secondary syphilis is a systemic disease characterized by maculopapular rashes and lymphadenopathy with liver and kidney involvement. Nephrotic syndrome is a rare complication of secondary syphilis. Given the re-emergence of syphilis as a worldwide health problem in recent years [2, 3], syphilis infections should be given due consideration as a cause of nephrotic syndrome in patients at risk.

Minimal change disease (MCD) represents key pathohistological findings that accompany primary or idiopathic nephrotic syndrome. Though MCD may develop consequent to autoimmune disorders and infections, it has been rarely reported as a complication of syphilis. Krane et al. described a case of nephrotic syndrome in a 74-year-old latent syphilis male patient with renal pathologies compatible with MCD [4]. Adhikari et al. reported two cases of endemic syphilis with MCD in African children. No other documented cases of MCD secondary to syphilis are available [5].

The current report describes two cases of nephrotic syndrome with MCD due to syphilis.

Case reports

Case No. 1

A 15-year-old boy presented on June 13, 2012, with intermittent swelling of both limbs and reduced urine volume for one month. The patient denied fever or adenopathies, tick bites, and non-steroidal anti-inflammatory drug intake. He also denied any sexual contact history and signs and symptoms of sexually transmitted diseases (STDs), urinary tract infection (UTI), and connective tissue diseases. He reported a penicillin allergy history.

During the physical examination, both legs showed pitting edema. Laboratory tests (**Table 1**) showed a 24-hour urinary protein of 4.03 g (normal reference < 0.3 g/24 hour) and a urine output of 550 mL. Serum albumin was 17.3 g/L (normal reference 35.0-55.0 g/L) and serum total cholesterol was 9.57 mmol/L (normal reference 2.90-5.17 mmol/L). Hepatic [ALT: 21 U/L (normal reference 5-40 U/L); AST: 21 U/L

Table 1. Patient demographic and baseline data upon admission

Patient No	Sex	Age, years	24-h urinary protein, g	Urine output, mL	Scr, μmol/L	Serum albumin, g/L	ALT/AST, U/L	HBsAg	RPR titer
1	Male	15	4.03	550	36.6	17.3	21/21	-	1:128
2	Male	47	6.66	2200	62.0	16.8	21/18	-	1:64
3	Male	56	9.9	2900	92.0	24.4	17/16	-	1:16

Scr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B-surface antigen; RPR, rapid plasmin reagin.

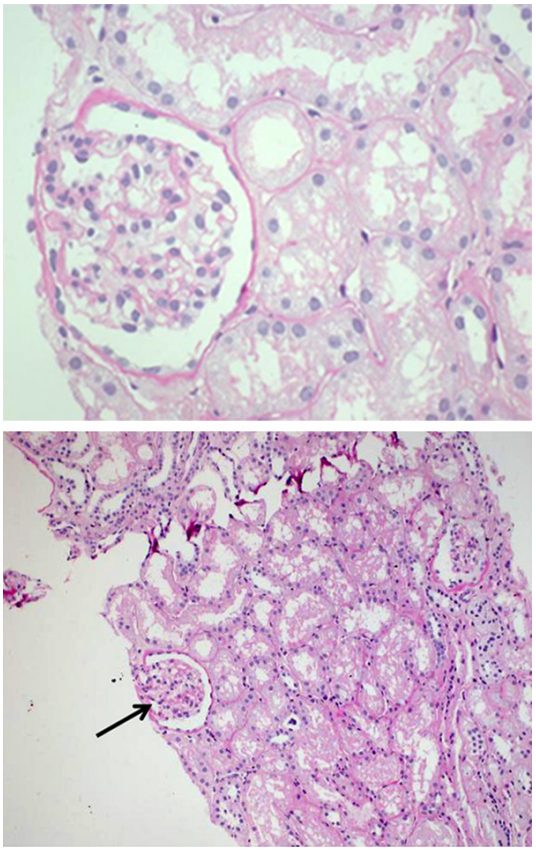

Figure 1. Light microscopy reveals minimal change disease in a 15-year-old boy with nephrotic syndrome secondary to syphilis. Typical lesions of minimal change disease are indicated by an arrow. H&E, ×200.

(normal reference 8-40 U/L)] and renal function (serum creatine: 36.6 μmol/L; normal reference 44.0-106 μmol/L) were normal. Hepatitis serology testing for HBsAg was negative. HIV and hepatitis C testing were negative. RPR titer during syphilis serology testing was 1:128.

Ultrasound examinations revealed a normal kidney size. The renal biopsy showed typical lesions of MCD (**Figure 1**). Immunofluorescence staining for IgG, IgA, IgM, and C3 was negative. Light microscopy showed unremarkable changes with a regular thin basement membrane and no mesangial hypercellularity or increases in the mesangial matrix. Electron microscopy was not performed because no glomerulus was detected in the tissue sample. A diagnosis of nephrotic syndrome with MCD secondary to syphilis was made. Intravenous ceftezole (2 g) was administered twice a day. Three months after antibiotic treatment, serum albumin returned to the normal range and the 24-hour urine protein excretion decreased to 0.15 g. At the 5-month follow up visit, RPR testing was negative (**Table 2**).

Case No. 2

A 47-year-old male presented on October 14, 2015, with intermittent edema of bilateral legs for two months. He exhibited no symptoms and signs of UTI or STD. Clinical examinations on admission showed moderate edema on his bilateral legs. Laboratory investigations revealed a 24-hour urinary protein of 6.66 g and a urine output of 2200 mL. Serum albumin was 16.8 g/L. Serum total cholesterol (9.63 mmol/L) and triglycerides (6.04 mmol/L) were elevated. Kidney (serum creatine: 62 μmol/L) and liver function (ALT 21 U/L; AST: 18 U/L) were normal. RPR testing was positive with a titter of 1:64 (**Table 1**).

Renal biopsy showed pathological changes compatible with MCD (**Figure 2A**). Immunofluorescence staining for IgG, IgA, IgM, and C3 was negative. Electron microscopy revealed diffuse foot-process effacement of podocytes and unremarkable changes in the glomerular basement membrane (**Figure 2B**). A diagnosis of nephrotic syndrome with MCD due to syphilis was made. Penicillin G benzathine (2.4 million units/w) was administered. Two months after antibiotic therapy, serum albumin recovered and proteinuria disappeared. At the 6-month follow up visit, RPR testing was negative (**Table 2**).

Table 2. Diagnosis, therapy, and outcomes of patients

Patient No	Clinical diagnosis	Pathological diagnosis	Immunological influence	Antibiotics	Antibiotic course, months	Recovery time, months
1	Nephrotic syndrome	MCD	IgG (-), IgA (-), IgM (-), C3 (-)	Ceftezole	3	RPR (-): 5UP < 0.3 g: 3
2	Nephrotic syndrome	MCD	IgG (-), IgA (-), IgM (-), C3 (-)	Benzathine penicillin	2	RPR (-): 6UP < 0.3 g: 2
3	Nephrotic syndrome	MN	IgG (++), IgA (-), IgM (-), C3 (++)	Benzathine penicillin	6	RPR (-): 9UP < 0.3 g: not yet

MCD, minimal change disease; MN, membranous nephropathy; RPR, rapid plasmin reagin.

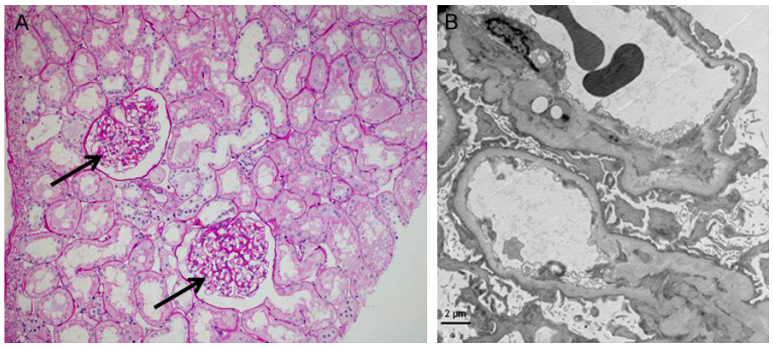

Figure 2. Pathological changes in a patient with minimal change disease. A. Light microscopy reveals minimal change disease in a 47-year-old male with nephrotic syndrome secondary to syphilis. Typical lesions of minimal change disease are indicated by arrows, ×200. B. Electron microscopy shows diffuse foot-process effacement of podocytes and unremarkable changes in the glomerular basement membrane are seen. Lead citrate and uranyl acetate, ×6000.

Discussion

Syphilis is a systemic STD caused by *Treponema pallidum*, affecting diverse organ systems, such as the skin, heart and blood vessels, nervous system, eyes, bones, stomach, and kidneys [6-9]. Nephrotic syndrome due to secondary syphilis has been reported, but these cases are mostly membranous nephropathy. Nephrotic syndrome with MCD has only been described in three cases [4, 5]. The current study reported two cases of nephrotic syndrome with MCD due to syphilis. These were successfully managed with appropriate antibiotic therapy.

MCD is most commonly seen in children and is the cause of nephrotic syndrome in about 90% of children younger than ten years of age. It is less commonly seen in adults, with MCD as the cause of nephrotic syndrome in 10 to 15% of cases [10]. One patient in the present report was 15 years of age when nephrotic syndrome with MCD was diagnosed. The other patient was an adult. The two cases had normal appearing glomeruli. Electronic microscopy revealed diffuse foot-process effacement of podocytes, typical of MCD, in the adult case.

It is not very difficult to establish a true causal relationship between nephrotic syndrome and secondary syphilis [11]. A precise diagnosis relies on detailed clinical, morphological, and immunostaining studies, and excludes underlying causes, such as lupus nephritis, hepatitis B virus infection, and malignancy, suggesting that extensive examinations are necessary for diagnosis. Most cases of MCD are idiopathic and typically respond to corticosteroid therapy. The two cases in the current report and the case by Krane et al. [4] responded to antibiotic therapy. Syphilitic nephrotic syndrome and other renal pathologies, such as membranous glomerulonephritis, respond well to antibiotic therapy [12]. One case of syphilitic nephrotic syndrome with membranous nephropathy was treated. The patient reacted well to penicillin therapy (**Tables 1** and **2**; Supplementary Figure 1). These patients showed significant improvement without the intervention of corticosteroids and immunosuppressive agents. The average course of antibiotics was reported to be four weeks. In the present patients, the antibiotic course was prolonged (two to six months). Prolonged antibiotic therapy reduced proteinuria significantly. It seems to be more helpful than the average course treatment in the remission of proteinuria and RPR titer.

The current prevalence of syphilitic nephrotic syndrome is unknown. An early report showed a prevalence of 0.28% for syphilitic nephrotic syndrome [13]. Ishiwatari et al. reviewed 16 publications on cases of syphilitic nephrotic syndrome from 1991 to 2013. None of these

patients had nephrotic syndrome with MCD [12]. Heavy proteinuria in the nephrotic range (> 3.5 g/24 hours in adults) was present in the two cases in the present report. Hyperlipidemia is a common laboratory finding in MCD, also seen in both of the present cases. In the literature, syphilitic nephrotic syndrome with MCD has only been fully documented in one case [4] while the other two cases were only mentioned in a clinical series of nephrotic syndrome [5]. The present report describes the first two cases of syphilitic nephrotic syndrome with MCD in Chinese patients. These cases indicate that MCD due to syphilis should be considered as an underlying cause of nephrotic syndrome.

In summary, the present study reported the first two cases of syphilitic nephrotic syndrome with MCD in Chinese patients, suggesting that MCD due to syphilis should be considered as an underlying cause of nephrotic syndrome. Prolonged antibiotic therapy is effective for recovery from syphilitic nephrotic syndrome with MCD. Therefore, it is important to recognize that syphilis is a reversible cause of nephrotic syndrome. Antibiotic therapy can result in complete remission.

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Disclosure of conflict of interest

None.

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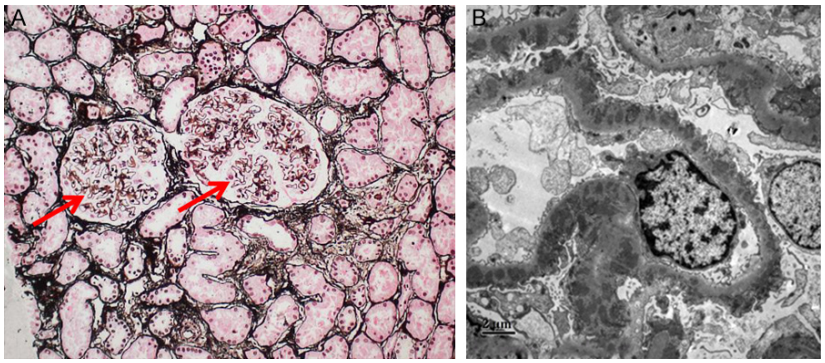

Supplementary Figure 1. Pathological changes in a patient with membranous nephropathy. Light microscopy reveals membranous nephropathy in a 56-year-old male with nephrotic syndrome secondary to syphilis (A, PASM, ×200). Glomeruli with uniform and diffuse thickening of the basement membrane are seen (arrows), along with segmental spikes on the subepithelial side of the membranes. Electron microscopy shows extensive foot-process effacement of podocytes and scattered subepithelial electron dense deposits (B). Lead citrate and uranyl acetate, ×4000.