Lumbar tuberculosis associated with membranous nephropathy and interstitial nephritis

Yuan Quan¹, Sun Li², Feng Jiangmin², Liu Nan³, Jiang Yi³, Ma Jianfei², Wang Lining²

1 Department of Osteology, Shengjing Hospital of China Medical University, Shenyang 110003, PR China.
2 Department of Nephrology, the First Affiliated Hospital of China Medical University, Shenyang 110001, PR China.
3 Department of Pathology, the First Affiliated Hospital of China Medical University, Shenyang 110001, PR China.

Corresponding author: Dr. Yuan Quan

Department of Osteology, Shengjing Hospital of China Medical University, Shenyang 110003, PR China.

Tel: 86-24-83956411

E-mail: yuanquan1973@yahoo.cn
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Tuberculosis is a common disease worldwide. However, it now is clear that tuberculosis can affect the kidney more insidiously. We describe a case of lumbar tuberculosis associated with simultaneous membranous nephropathy and interstitial nephritis, in which recovery of renal function occurred after treatment with steroids in addition to antituberculosis agents.

CASE REPORT

A 50-year-old woman was admitted to the hospital with a two week history of hematuria, proteinuria, and renal failure. She was diagnosed with lumbar tuberculosis six weeks ago because of mild fever, fatigue, night sweating, weight loss and low-back pain. Her tuberculin skin test was strongly positive. A colloidal gold-based serological assay with Mycobacterium tuberculosis (MTB) antibody assay kit (MP Biomedicals Asia Pacific Pte. Ltd. Singapore), ASSURE™ TB Rapid Test, was used to detect MTB antibody. The result was positive. Lumbar X-ray examination showed that L3-L4 disc space was narrow and destroyed(Figure1). She had been treated with rifampicin, isoniazid, ethambutol, and pyrazinamide for four weeks before the admission. Her temperature normalized and the low-back pain disappeared. However, two weeks before the admission, she developed hematuria and proteinuria. Her serum creatinine, which had been 63 µmol/L one month prior to presentation, rose to 183 µmol/L. She reported no urinary frequency, dysuria or flank pain. Her remaining medical history, travel history and family history were unremarkable. Physical examination showed a body temperature of 36.8°C, a regular
pulse rate of 85/min, respiratory rate of 18/min, and blood pressure of 140/85 mmHg. Laboratory findings included a hemoglobin level of 9.3g/dl, a platelet count of 320×10⁹/L, and a white cell count of 11.7×10⁹/L. The erythrocyte sedimentation rate was 24mm/h, and C-reactive protein was 5.45 mg/dl. The blood urea nitrogen was 7.34 mmol/L, and serum creatinine was 183umol/L. Serum complement levels were normal. Urinalysis revealed 2+ protein, with 12-15 red blood cells and 16-20 white blood cells per high-power field in the urinary sediment. Daily urinary protein excretion was 2.6g. C3 and C4 concentrations were normal. Serology for antinuclear antibody, human immunodeficiency virus and syphilis were negative, and the patient was not otherwise immunocompromised. Sputum smears for acid-fast stain were negative. Chest X-ray examination was normal. Renal ultrasonography showed normal-sized kidneys without any abnormality. PCR analysis using specific primers for MTB was performed on early morning urine samples of three consecutive days. DNA was extracted from the urine samples with QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. The primers targeted to the specific insertion element insertion sequence (IS)6110 of MTB were synthesised by Takara Bio Inc (Dalian, China). The amplicon size was 156bp. The results were positive (Figure 3).

Morning urine sample was collected from the patient for MTB culture. The urine sample was pre-treated by decontamination with 4% (w/v) sodium hydroxide and centrifugation at 1500 g for 10 min. The sediment was used for MTB culture, which was performed using in-house Löwenstein-Jensen (LJ) solid medium, with a maximum incubation period of eight weeks. The result was read and reported weekly.

The patient had been treated with antituberculosis therapy for four weeks when she was
admitted to the hospital. However, her renal function had deteriorated. To evaluate this, renal biopsy was performed a few days after admission. Pathological evaluation of the biopsied renal tissue showed membranous nephropathy with massive infiltration of inflammatory cells in the interstitium (Figure 2a, 2b). Immunofluorescent studies showed granular staining for IgG (++) and C3 (+) in the mesangium.

Approximately eight weeks later, urine culture for *Mycobacterium tuberculosis* was negative.

Because of the inflammatory pathological changes, a small dose of prednisone (30mg/d) was added to the treatment, as well as the same antituberculosis agents as mentioned above.

One month after beginning treatment with prednisone, the patient’s serum creatinine decreased to 143 µmol/L, and 24 hour urinary protein excretion was 1.6g. Two months after the prednisone treatment, the serum creatinine decreased to 80 µmol/L, and the 24 hour urinary protein excretion was 0.4g. At that point, the daily dosage of prednisone was tapered by 5mg per week. Six months later, her renal function remained normal and the urinalysis returned to normal (negative for protein, red blood cells 0-2/HPF, white blood cells 0-5/HPF). Both PCR analysis of MTB on urine samples and urine MTB culture were repeated one month, two months and six months respectively after steroid and antituberculosis medication during follow-up. The results were negative.

Tuberculosis (TB) is still a common disease worldwide. The World Health Organization estimates that one-third of the world’s population is infected with *Mycobacterium tuberculosis* (MTB), which is responsible for 8.7 million new TB cases and
approximately 3 million deaths annually (4). Most often, the lung is affected, but after tuberculosis lymphadenopathy, the next most common form of nonpulmonary tuberculosis is genitourinary disease, accounting for 27% of nonpulmonary TB cases in several surveys in the United States, Canada, and United Kingdom (5).

Renal TB is easily overlooked. Many patients present with lower urinary symptoms typical of “conventional” bacterial cystitis, and suspicion of TB is aroused only when there is no response to the usual antibacterial agents, or when urine examination reveals pyuria in the absence of a positive culture on routine culture media.

However, it now is clear that TB can affect the kidney more insidiously. Some patients present with glomerular disease, sometimes with advanced renal failure instead of the features of classical renal TB (2, 3, 6, 8, 12).

This case clearly documents that TB infection can result in glomerulonephritis and interstitial nephritis simultaneously. It is well known that interstitial nephritis can be resulted from many factors such as some antibiotics, nonsteroidal antiinflammatory drugs, infection, idiopathic interstitial nephritis and so on. In this case, no other susceptible drugs were used except the antituberculosis agents which were not withdrawn during the prednisone therapy. And the patient’s condition improved. This may indicate that interstitial nephritis are related to MTB infection instead of other reasons.

Moreover, primary membranous nephropathy is usually insensitive to steroid therapy. In this case, after the treatment of antituberculosis agents and small dose of steroid, the 24 hour urine protein excretion and serum creatinine improved significantly. Meanwhile, repeated PCR analysis on urine samples returned to negative during the follow-up.

Therefore, the medical history and histopathological findings, along with the therapeutic
outcome demonstrated that the glomerular and tubulointerstitial lesions of this case was associated with MTB infection.

The medical history and histopathological findings, along with the therapeutic outcome, leave no doubt as to this association.

MTB can induce both cellular immune and humoral immune responses when the bacilli invade the body. Studies have shown that MTB infection can lead to disturbances of Th1/Th2 cells, which may give rise to nephritis(10).

On the other hand, type III allergic reactions induced by immune complexes can cause tissue injury, and may be involved in the pathogenesis of TB. The role of disseminated tuberculosis in the pathogenesis of glomerulonephritis has been presumed to be dependent on humoral immunity, and immune complexes have been reported as detectable at high levels in the active phase of disseminated tuberculosis (1, 13).

As a result, some patients have shown clinical features of chronic nephritis, such as hematuria, proteinuria, edema, and hypertension.

Meanwhile, TB infection can result in interstitial nephritis which can lead to renal failure (7,11). In some patients with pulmonary or disseminated tuberculosis, there is evidence of renal failure without typical miliary involvement or localized genitourinary lesions. In these cases, biopsy has shown interstitial nephritis, usually, but not always with granulomata, and renal function has improved after antituberculosis treatment.

This case also demonstrates the value of renal biopsy in patients with glomerulonephritis or interstitial nephritis due to TB in the absence of radiological and urine findings.

Diagnosis of renal TB remains difficult, especially in the early stage, due to the vagueness of chronic, intermittent, and non-specific urinary symptoms. As a result, many
patients are not diagnosed, or are misdiagnosed, and lose the chance for early treatment, and progress to end-stage renal disease, a life-threatening condition. In our case, three urine cultures, considered “the gold standard for diagnosis of renal TB” (9), failed to show positive results. It may be because MTB was intermittently evacuated which made it difficult to detect MTB in urine samples. Also, in the early stage of renal TB, renal radiologic examination usually does not show any abnormalities. Therefore, renal biopsy was performed in this patient. Although it did not show any typical granulomas, massive inflammatory cell infiltration of the glomeruli and nephric tubules was seen. When combined with the knowledge of the patient’s clinical course and urine PCR result, these pathological changes suggested, and gave us potent support for the diagnosis of TB-associated renal disease.

Finally, this case suggested the therapeutic option of using immunosuppressive agents in the treatment of renal tuberculosis. In most circumstances, TB-associated renal disease might respond to antimicrobial therapy alone and immunosuppressive agents would be unnecessary. However, in this case, there had been no improvement after one-month of antituberculosis therapy with rifampicin, isoniazid, ethambutol, and pyrazinamide. Therefore, 30mg/day of prednisone was given to this patient because of the pathological changes showing massive inflammatory cell infiltration. One month after the beginning of antituberculosis agents and steroid treatment, improvement in renal function was noted, and daily urinary protein excretion was decreased. This case indicates that steroids may be used as an adjunctive treatment of renal tuberculosis, particularly during the acute phase, based on the pathological results.

In conclusion, this case showed that glomerulonephritis and interstitial nephritis could
simultaneously be associated with TB infection, and that renal biopsy plays an important role on the diagnosis and treatment of renal tuberculosis. Although in most circumstances, antituberculosis therapy alone will give satisfactory results; steroid treatment is still useful, and perhaps necessary, in some cases for improvement of renal disease.
REFERENCES


9. OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE


Figures

Figure 1. Lumbar plain radiographs showing L3-L4 disc space was narrow and destroyed
Figure 2a. Light microscopy finding of interstitium showing massive inflammatory cell infiltration (HE X100)

Figure 2b. Light microscopy finding of a glomerulus showing GBM thickening and small cystic spaces in the GBM (PAS MX400)
Figure 3. Agarose gel electrophoresis of PCR reaction for TB DNA. M: DNA Marker; lane 1: positive control; lane 2: negative control; lane 3-5: urine samples of three consecutive days.