Membranous Nephropathy Associated with Tuberculosis

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To the Editor: Glomerulonephritis (GN) due to Mycobacterium tuberculosis (M. tuberculosis) is rare,1,2 and membranous nephropathy (MN) associated with tuberculosis is seldom reported.2 Because of atypical and nonspecific manifestations, tuberculosis-associated GN (TB-GN) is difficult to diagnose. Patients usually present with hematuria, proteinuria, edema, and varying degrees of hypertension or renal insufficiency, which are similar to symptoms of primary GN. Thus, patients may be misdiagnosed as having primary GN rather than TB-GN. Treatment with glucocorticoids or immunosuppressive agents may lead to the spread of TB and deterioration of renal function, a potentially life-threatening condition.

Here, we report a case of a 15-year-old girl with MN secondary to pulmonary tuberculosis [Figure 1a and 1b].

The girl was presented with a 2-week history of soy urine and lower extremity edema. Before admission, she presented 3+ protein, 3+ red blood cells and 1–3 white blood cells per high-power field by urinalysis in a local hospital. She was then diagnosed with acute GN. After treatment with an intravenous injection of penicillin for 10 days, urinalysis remained abnormal, and she was transferred to Shanghai First People’s Hospital for further treatment. She had no complaints of fever, cough, expectoration, anorexia, or weight loss. She admitted to have suffered from anemia for the last 2–3 years. Her menstrual cycles were normal. Otherwise, her medical, travel, and family histories were unremarkable.

The physical examination revealed a blood pressure of 104/60 mmHg, body temperature of 37.0°C and body mass index of 18.22 kg/m2. The patient presented moderate pallor and bilateral pitting pedal edema. No palpable lymphadenopathy or skin rash was noted. Laboratory analyses yielded the following values: hemoglobin, 8.0 g/L; white blood cell count, 5700/μL; platelet count, 202,000/μL; serum creatinine, 85 μmol/L; blood urea nitrogen, 3.5 mmol/L; serum uric acid, 389 μmol/L; serum total cholesterol, 4.68 mmol/L; and triglycerides, 2.89 mmol/L. She had low serum albumin levels (29.7 g/L) with normal liver function. Serum IgG, IgA, IgM, IgE, complement, free κ and λ light chains were all within normal range. Erythrocyte sedimentation rate was 125 mm/h. Cryoglobulins, hepatitis B virus or hepatitis C virus were all within normal range. Erythrocyte sedimentation rate was 2.38 g. The estimated glomerular filtration rate was 83 ml·min⁻¹·1.73 m⁻². Kidney ultrasonography revealed the normal diameters of the kidneys without good corticomedullary differentiation.

At day 2 of admission, renal biopsy was performed. By light microscopy, the kidney specimen contained 16 glomeruli with a cellular crescent in one of them [Figure 1c and 1d]. The mesangial areas were slightly enlarged by proliferated mesangial cells and increased matrix. Mild to moderate neutrophilic infiltration was noted in some glomeruli. Silver staining showed thickened glomerular basement membranes with small projections (spikes). Tubules showed patchy atrophy. There was no granuloma in the renal tissue sample. Arterioles were unremarkable. Immunofluorescence staining was positive for IgG and C3, both in the mesangium and along the glomerular capillary wall [Figure 1e and 1f]. Similar staining intensity of kappa and lambda light chains was also noted. The glomeruli were negative for IgA, IgM, and C1q, as well as IgG4 and PLA2R, indicating secondary rather than primary MN. In electron micrographs, electron-dense deposits were observed in the sub-epithelial regions as well as the mesangial area [Figure 1g and 1h]. Intriguingly, the discrete subepithelial deposits looked like humps. Some of them were up to 2 μm wide and 2 μm long. Congo red staining was negative. A pathological diagnosis of MN with crescent formation most likely secondary MN was made.

To explore the cause of MN, the girl underwent computed tomography of lung and abdomen. High-resolution computed tomography (HRCT) of the chest showed multiple consolidations with cavities disseminating throughout both lungs, especially the upper lobes, and the enlargement of mediastinal lymph nodes with calcification [Figure 1a and 1b], a tuberculosis-like pattern. Both tuberculin skin test and polymerase chain reaction (PCR)
Figure 1: (a and b) High-resolution computed tomography of the chest, showing multiple consolidations with cavities disseminated throughout both lungs, especially the upper lobes; (c and d) light micrographs showing thickened glomerular capillary loops with neutrophilic infiltration, mesangial cell proliferation and cellular crescent in Bowman’s space; (e and f) immunofluorescence images showing granular staining for IgG and C3 in the mesangium and along the glomerular capillary wall; (g and h) electron micrograph of a glomerulus, showing numerous electron-dense deposits both in the sub-epithelial and mesangial regions.

for *M. tuberculosis* in urine were overtly positive. Therefore, the diagnosis of tuberculosis was definite. We also carried out urine culture for *M. tuberculosis*, which takes 6–8 weeks.

The patient received a four-drug anti-tuberculosis regimen comprising isoniazid (300 mg/d), rifampin (450 mg/d), pyrazinamide (1500 mg/d) and ethambutol (1200 mg/d) for the first 2 months, followed by isoniazid and rifampicin for the next 4 months. After 1-month treatment, the patient’s 24-h urinary protein excretion decreased to 0.78 g without gross hematuria. Approximately, 8 weeks later, positive urine culture for *M. tuberculosis* was obtained. Four months after anti-tuberculosis medication, urinary findings were normal and lung imaging showed significant improvement. Serum albumin and hemoglobin levels returned to normal ranges. One year later, the girl was still in good health.

To our knowledge, the membranous pattern of glomerular lesions with crescent formation secondary to tuberculosis is unique and has fewly been reported in the literature so far. Although the present patient’s biopsy showed features of MN, immunofluorescence and electron microscopy data, and the presence of cellular crescent, proliferation of mesangial cells, and neutrophils infiltration (assessed by light microscopy) indicate an underlying disease process such as infection, lupus nephritis, or anti-neutrophilic cytoplasmic antibodies-associated GN.\(^3\) Based on clinical data, autoimmune diseases, neoplasia, drug use and hepatitis virus infection were all ruled out. Abnormal findings of HRCT offered a clue to suspect tuberculosis. A final diagnosis of MN with crescent formation secondary to tuberculosis was contemplated based on positive detection of *M. tuberculosis* in urine by PCR and culture. The patient’s favorable response to anti-tuberculosis therapy also demonstrated the cause-and-effect relationship between glomerular lesions and tuberculosis. Tuberculosis-associated with GN complicates the choice and sequence of therapeutic options of immunosuppressive agents and/or anti-tuberculosis drugs. Recent data have revealed that tuberculosis-associated with various forms of GN shows different responses to various treatment options.\(^4\) Anti-tuberculosis drugs, which decrease the mycobacterial load from circulation, may reduce antigen load and consequently immune complex formation.\(^5\) In our case, the concerned patient presented with nephritic proteinuria, normal serum urea, and creatinine values as well as active tuberculosis in urine; hence, immunosuppressive therapy was not initiated. Anti-tuberculosis therapy alone provided satisfactory results. On the other hand, these findings suggest an etiological relationship of MN with tuberculosis in the present case.

In summary, several points should be emphasized based on the present case. First, tuberculosis can affect the kidney more insidiously. It may be misdiagnosed as primary GN, because of nonspecific manifestations. Second, renal biopsy is important in securing an accurate diagnosis, prior to treatment commencement. Third, anti-tuberculosis therapy can effectively alleviate both tuberculosis and the associated GN.

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**Conflicts of interest**

There are no conflicts of interest.

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