

Case Report

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Membranous nephropathy associated with tuberculosis—a case report

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ABSTRACT

Rationale: Genitourinary tuberculosis can develop during the disease course of disseminated disease and the distinctive histological finding is epithelioid granuloma with or without caseation and accompanied Langhans-type giant cells. Barely, the lesion is only restricted to kidney involving both glomerular and extraglomerular compartment. Association with immune complex-mediated glomerulonephritis has been sparsely reported in the literature.

Patient concern: A 42-year-old non-diabetic, non-hypertensive male presented with generalized body swelling and frothing of urine for 3 months.

Diagnosis: Membranous nephropathy with tuberculous interstitial nephritis.

Intervention: Anti-tuberculous therapy for extrapulmonary tuberculosis was administered along with low dose corticosteroid.

Outcomes: Reduction of proteinuria was achieved at one month follow-up visit.

Lessons: Tuberculosis should be considered as a potentially treatable cause of secondary membranous nephropathy as pharmacotherapy greatly helps improve the outcome.

KEYWORDS: Tuberculosis; Membranous nephropathy; Renal biopsy

1. Introduction

Genitourinary tuberculosis is the second most common form of extra pulmonary tuberculosis, which may be sequelae of systemic disseminated infection or as a localized disease[1]. The morphological spectrum varies from interstitial nephritis to advanced cavitating lesions depending on virulence of organism and patient's immune status. Secondary amyloidosis is also reported. Barely, the infection is restricted to only kidney involving both glomerular and extraglomerular compartment.

Association with immune complex mediated glomerulonephritis was sparsely reported in literatures and IgA nephropathy was the dominant one. Immune complex mediated crescentic

glomerulonephritis (GN), collapsing GN and membranoproliferative GN are other rarely reported entities[2].

Here, we present a case of tubercular interstitial nephritis and membranous nephropathy with demonstration of acid-fast bacilli in renal biopsy. Informed consent was taken from the patient before presenting the case report.

2. Case report

A 42-year-old non-diabetic, non-hypertensive Indian male presented with generalized body swelling and frothing of urine for 3 months. The patient had no history of cough, shortness of breath, chest pain, fever, rash, mucosal ulcer, arthralgia, headache, visual disturbances, psychosis or seizures. General physical examination showed pallor with appreciable oedema, pulse rate of 92 beats per minute, blood pressure of 120/80 mmHg and respiratory rate of 20 breaths per minute. Systemic examination was unremarkable. Laboratory workup revealed normal renal function with baseline creatinine of 0.8 mg/dL and serum blood urea nitrogen was 45 mg/dL. Urine examination revealed 3+ albumin and 10-12 red blood cells/high power field, however, no dysmorphic red blood cells were identified. Bence Jones protein was absent. The 24-hour urine proteins were 7.6 g/total volume (2 600 mL) (normal range: < 150 mg per day). His serum albumin was 1.6 g/dL (normal range: 3.4-5.4 g/dL), haemoglobin 9.2 g/dL (normal range: 13.2-16.6 g/dL), total leukocyte count $6 \times 10^9/L$ with a normal differential

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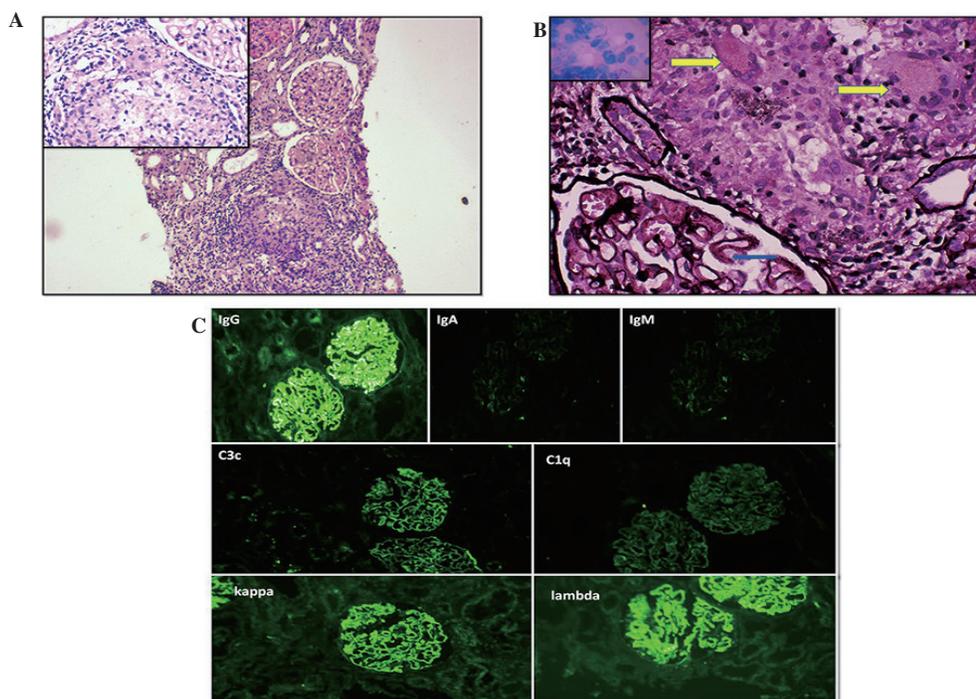


Figure 1. Histopathology of the kidney biopsy and the immunofluorescent image of a 42-year-old non-diabetic, non-hypertensive male presented with generalized body swelling and frothing of urine for 3 months. A: Light microscopy (H&E stain, 100 \times) shows three enlarged glomeruli showing uniform diffuse and global glomerular basement membrane thickening. Adjacent tubulointerstitial compartment reveals moderate interstitial fibrosis and tubular atrophy with presence of epithelioid granuloma surrounded by lymphoplasmacytic cells. Inset shows high power view (Periodic acid Schiff stain, 200 \times). B: Light microscopy (JMS stain, 200 \times) shows portion of a glomerulus with uniform diffuse and global glomerular basement membrane thickening with appreciable spikes (blue arrow). Adjacent tubulointerstitial compartment reveals presence of epithelioid granuloma with Langhans' giant cells (yellow arrows). Inset reveals presence of acid fast bacilli (ZN stain, 1000 \times). C: Fluorescein isothiocyanate labelled immunoglobulin G, A and M, complement component 3 and 1q, kappa and lambda; 200 \times) using frozen specimen-fine granular positivity along GBM in IgG (4+), C3c (1+), C1q (trace), kappa (2+) and lambda (3+).

count and platelets of $1.51 \times 10^9/L$. Fasting and post-prandial blood sugar and liver function tests were within normal limits. Coagulation workup revealed a prothrombin index of 100%. Lipid profile showed that serum total cholesterol was 388 mg/dL. Serum complement levels were normal. His antinuclear antibody, myeloperoxidase antineutrophil cytoplasmic antibodies and proteinase-3 antineutrophil cytoplasmic antibodies were negative. Serum protein electrophoresis did not show "M-band". Human immunodeficiency virus, hepatitis B surface antigen and anti-hepatitis C virus antibodies were negative. Ultrasound examination revealed enlarged kidneys (right kidney 12.5 cm and left kidney 11.5 cm) with mildly raised cortical echogenicity and blurred cortico-medullary differentiation.

A renal biopsy was performed under ultrasound guidance. Two cores received were processed and examined. Total 22 glomeruli were identified among which one was globally and two glomeruli were segmentally sclerosed with adhesions. Rest and the non-sclerosed tufts showed mild mesangial matrix expansion and focal hypercellularity. Periodic acid Schiff stained section showed uniform diffuse and global thickening of glomerular basement membrane. Silver methenamine stained section revealed appreciable subepithelial spikes. There was no evidence of any endocapillary or

extracapillary proliferation. Bowman's capsule collagenisation was noted in one glomerulus. The tubules showed moderate atrophy with colloid cast. Granular casts and inspissated hyaline casts were also appreciated at places. The interstitium showed moderate fibrosis with epithelioid granuloma surrounded by lymphoplasmacytic infiltrate along with foci of necrosis (Figure 1A). Arteriosclerosis was identified at places. Interstitial fibrosis with tubular atrophy was moderate (30%). Ziehl-Neelson stained section showed presence of acid-fast bacilli (Figure 1B). Immunofluorescence findings of glomerular compartment were conducted for all immunoglobulin heavy chains (immunoglobulin G, A and M); complements (complement component 3 and 1q) and immunoglobulin light chains (kappa and lambda). Fine granular glomerular basement membrane positivity was observed in IgG (4+), C3c (2+), C1q (1+), kappa (3+) and lambda (3+) (Figure 1C). Overall features were suggestive of membranous nephropathy with tuberculous interstitial nephritis in view of presence of granuloma with caseous necrosis and acid fast bacilli. No other organ involvement was noted on a repeat and detailed clinical and radiological examination.

Standard anti tubercular therapy regimen comprising of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed

by 4 months of isoniazid and rifampicin was initiated. Low dose corticosteroid was also added. Reduction of proteinuria was achieved at one month follow-up visit.

3. Discussion

Genitourinary system is involved in 4%-5% cases of extrapulmonary tuberculosis[1]. Renal involvement in tuberculosis was divided into four categories depending on the proportion of tissue damage ranging from non-destructive lesion to widespread destructive form. Histological hallmark is epithelioid granuloma with or without caseation and accompanied Langhans-type giant cells[3].

Various pathogens like bacteria, fungus, virus and parasites are associated with glomerulonephritis but tuberculous bacilli were rarely reported. The criteria during establishing the association between the infection and immune complex mediated glomerulonephritis are (1) documented proof of infection before development of the glomerulonephritis; (2) morphological features corroborative with post infectious glomerulonephritis; (3) the lack of other systemic aetiological factors responsible for the glomerular changes; and (4) positive response to anti-infection drug therapy. Streptococcal infections, human immunodeficiency virus, hepatitis C virus, or hepatitis B virus infections are responsible for a range of immune complex mediated glomerulonephritis. Glomerulonephritis as a sequela of tuberculous infection were barely reported[4].

The histological forms of GN that have been reported with tuberculosis were IgA nephropathy, membranoproliferative GN and crescentic GN[2,5,6]. Evidence of tuberculosis causing membranous glomerulonephritis are sparse[7]. Two cases of membranous nephropathy with granulomatous interstitial nephritis were reported from India, where in one case acid-fast bacilli could be identified on renal biopsy[8] and in the other, acid-fast bacilli was not found but showed an ulcerated tuberculin test with improvement to anti-tubercular treatment[9].

The postulated hypothesis for development of membranous pattern of injury associated with infection depending on the size of infective particles is either subepithelial latent deposition of circulating immune complex or genesis of in situ immune complex mediated by auto-antigen formation[4]. *Mycobacterium tuberculosis* can activate both cell mediated and humoral immunity and type 4 hypersensitivity reaction that is responsible for development of glomerulonephritis in disseminated disease[5,9]. Complex interaction between T cells and B cells are also a contributing factor[10]. But, our case presented with membranous nephropathy and interstitial nephritis in absence of any other organ involvement. The identification of the acid-fast bacilli in the renal biopsy helped in confirming tubercular aetiology in membranous nephropathy which is further strengthened by the improvement of the symptoms with anti-tubercular treatment.

Thus, tuberculosis should be considered as a potentially treatable cause of secondary membranous nephropathy as the institution

of pharmacotherapy greatly helped in improving the outcome in our case. Nevertheless, it is challenging to identify and demands an awareness regarding the association to reduce the number misdiagnosis and missed diagnosis.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

SM and BK developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both SM and PM contributed to the final version of the manuscript. RA supervised the project.

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