CASE REPORT:

UROGENITAL TUBERCULOSIS PRESENTING AS IgA NEPHROPATHY AND RECURRENT CULTURE-NEGATIVE URINARY TRACT INFECTIONS

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Abstract. Tuberculosis is a public health problem that can cause extrapulmonary infections, including urogenital infections. We report here the case of a 29-year-old female with a 2-year history of dysuria and hematuria treated with multiple courses of antibiotics with urine cultures all negative. She was then diagnosed with IgA nephropathy based on a renal biopsy showing focal segmental glomerulosclerosis and mesangial IgA deposits without granulomata. A polymerase chain reaction (PCR) for urinary tuberculosis was positive for *Mycobacterium tuberculosis* complex. A chest radiograph was normal. The patient was treated with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and rifampicin for an additional 4 months. The patient responded well to treatment and her symptoms resolved completely. Urogenital tuberculosis should be considered in the patient who presents with dysuria and hematuria whose symptoms fail to improve with routine antimicrobials and who has a routine a urine cultures failing to show infection.

Keywords: IgA nephropathy, *Mycobacterium tuberculosis*, tuberculosis, urogenital

INTRODUCTION

Urogenital tuberculosis accounts for nearly 30% of non-pulmonary tuberculosis cases in developed nations (Daher *et al*, 2013). The most common route of infection in urogenital tuberculosis is blood-borne dissemination of the causative agent from a tuberculous lesion in the lung (Eastwood *et al*, 2001). In most urogenital tuberculosis cases, there is no evidence of active pulmonary disease at presentation (Yuan, 2015). In renal tuberculosis, finding epitheloid granulomata (with or without caseation) on a histology specimen suggests the diagnosis (Eastwood *et al*, 2001). IgA nephropathy is characterized by IgA immune complex deposits in glomerular

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mesangial areas or capillary loops, rather than by the presence of granulomata (Wang and Tao, 2018). Although IgA nephropathy is the most common form of primary glomerulonephritis, no infectious agent has been consistently associated with this disease and tuberculosis is a rare cause (Donadio and Grande, 2002; Wang and Tao, 2018). When there are no signs or symptoms of pulmonary tuberculosis and the histological findings suggesting renal tuberculosis are absent, diagnosing urogenital tuberculosis can be challenging. We present here a case of urogenital tuberculosis without pulmonary findings or histological findings consistent with tuberculosis, making diagnosis challenging.

CASE REPORT

A 29-year-old female presented to UKM Medical Centre with a 2-year history of dysuria, urinary frequency and hematuria. She had received multiple courses of antibiotics, including ciprofloxacin, ceftriaxone and amoxicillin-clavulanic acid, without resolution of symptoms. A previous renal ultrasound and urine culture were both normal. A gynecological evaluation was also normal. Three months ago, the patient had been previously diagnosed with having IgA nephropathy on renal biopsy showing focal segmental glomerulosclerosis and 3+ mesangial IgA deposits without granulomata (Fig 1). She gave no previous history of pulmonary tuberculosis, HIV infection or diabetes mellitus. She was also not on steroids or any other immunosuppressive therapy. The patient was a university student and did not smoke, consumed alcohol or use recreational drugs.

On presentation, her blood pressure was 122/76 mmHg, her pulse rate was 90 beats/minute, and her temperature was 37.5°C. Her body mass index was 18 (slightly underweight). On examination, the patient was alert, conscious and not in distress. She was neither pale, jaundiced nor cachexic. Examination of the cardiovascular and respiratory systems were unremarkable–S1 and S2 heart sounds were heard, there were no audible cardiac murmurs, costovertebral angle tenderness was absent, the air entry was good

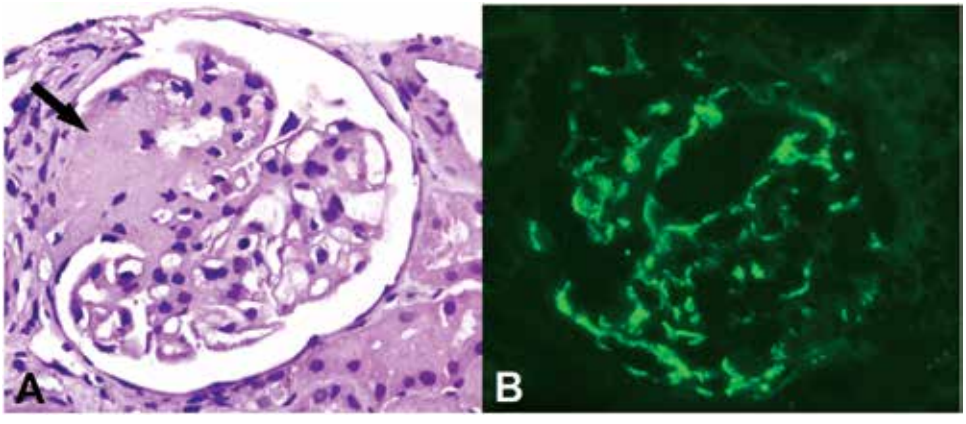

Fig 1-Renal biopsy findings (600x magnification). A: hematoxylin and eosin stain of the glomerulus (black arrow) with segmental sclerosis. B: immunofluorescent stain of the glomerulus showing 3+ granular mesangial IgA deposits.

and equal bilaterally, and no adventitious breath sounds such as rhonchi or crepitations were heard. On examination of the abdomen, it was soft and non-tender. No abdominal masses were felt–her liver and spleen were not palpable, and her kidneys were not ballotable.

The patient's blood test results are shown in Table 1. A significantly abnormal blood test result was an elevated erythrocyte sedimentation rate (32 mm/hr). A urine culture grown on cysteine-lactose-electrolyte-deficient (CLED) agar was negative. A urine specimen for real-time qualitative polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* (LyteStar™ TB/NTM PCR Kit 3.0, ADT Biotech, Malaysia) was positive initially and 3 weeks later (Table 2). A urine culture for mycobacteria on Lowenstein-Jensen (LJ) agar was negative. A chest radiograph was normal.

The patient was treated with ethambutol 1,100 mg, isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 1,600 mg and pyridoxine 10 mg daily for 2 months, followed by isoniazid 300 mg, rifampicin 600 mg and pyridoxine 10 mg daily for 4 months. The patient recovered completely without residual disease.

DISCUSSION

Urogenital tuberculosis is usually diagnosed by isolating *M. tuberculosis* on specific growth media, such as LJ agar (Yuan, 2015), but the process takes weeks. *M. tuberculosis* is usually not isolated on

Table 1
Selected laboratory results of study subject.

Test	Result	Reference range
Blood		
Total white blood cell count	11.3 x 10^9/l	(4.1 - 11.4) x 10^9/l
Neutrophil count	7.9 x 10^9/l	(3.9 - 7.1) x 10^9/l
Lymphocyte count	2.6 x 10^9/l	(1.8 - 4.8) x 10^9/l
Hemoglobin	13.7 g/dl	(11.6 - 15.1) g/dl
Hematocrit	42.4 %	(35.1 - 44.9) %
Platelet count	356 x 10^9/l	(171 - 399) x 10^9/l
C-reactive protein	0.09 mg/dl	<0.5 mg/dl
Erythrocyte sedimentation rate	32 mm/hr[a]	(1 - 20) mm/hr
Urine		
pH	6.0	5 - 8
Glucose	Normal	N/A
Bilirubin	Negative	N/A
Ketones	Negative	N/A
Nitrite	Negative	N/A
Leukocytes	100/μl[a]	N/A
Protein	1.5 g/l[a]	N/A
Blood	10 ml[a]	N/A
Protein:creatinine index	0.11 g/mmol creatinine[a]	<0.02 g/mmol creatinine

[a]Abnormal result.

Table 2
Real-time qualitative PCR results for *M. tuberculosis* complex.

	Specimen 1	Specimen 2
Cycle threshold value	28.6 cycles	35.7 cycles
Cycle threshold upper limit	<40 cycles	<40 cycles
Interpretation	*M. tuberculosis* complex DNA detected	*M. tuberculosis* complex DNA detected

PCR, polymerase chain reaction; DNA, deoxyribonucleic acid.

routine urine cultures due to low sensitivity and short incubation periods (Yuan, 2015). Thus, the clinician needs to have a high index of suspicion for mycobacterial infections when the patient presents with chronic urinary tract symptoms and sterile pyuria not responding to treatment (Daher *et al*, 2013). Patients with chronic symptoms should be considered for evaluation using LJ agar culture and molecular detection of mycobacterial DNA. Although urine mycobacterial culture has a poor sensitivity, a positive test is useful, especially in regions with high multi-drug resistant *M. tuberculosis* rates (Yuan, 2015).

Besides glomerulonephritis, urinary tract mycobacterial infection complications include interstitial nephritis and amyloidosis (Daher *et al*, 2013). Tuberculosis can cause IgA glomerulonephritis, crescentic glomerulonephritis, membranous glomerulonephritis and mesangioproliferative glomerulonephritis (Solak *et al*, 2013). The exact mechanism of how tuberculosis induces IgA nephropathy is unclear but has traditionally been thought to be cell-mediated (Wang and Tao, 2018). There is an increase in specific IgA antibodies against the mycobacterial antigen A-60 in the serum of affected patients (Alifano *et al*, 1996). The deposition of IgA mycobacterial antigen-antibody complexes in the kidney may activate alternative and lectin complement pathways, resulting in renal damage (Wang and Tao, 2018).

The usual treatment of urogenital tuberculosis consists of rifampicin, isoniazid, ethambutol, pyrazinamide and pyridoxine for 2 months, followed by rifampicin, isoniazid, and pyridoxine for 4 months (Eastwood *et al*, 2001; Daher *et al*, 2013). The duration of treatment is extended to at least 9 months in the case of *M. bovis*, due to its resistance to pyrazinamide (Lan *et al*, 2016). Many hospital laboratories are unable to speciate *M. tuberculosis* complex (even when using a molecular-based detection kit) but urogenital infections due to *M. bovis* are uncommon (Eastwood *et al*, 2001; Lara-Oya *et al*, 2016). There is no consensus on the use of glucocorticoids or other immunosuppressive therapy for patients with tuberculosis-associated IgA nephropathy. There is the concern that administering glucocorticoids may result in further spread of tuberculosis (Wang and Tao, 2018).

In conclusion, urogenital tuberculosis should be included in the differential diagnosis of patients with chronic urinary tract infection symptoms with normal routine culture results who fail to respond to appropriate treatment. However, tuberculosis cultures of the urine have a low sensitivity and testing for mycobacterial DNA should be considered in these cases.

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