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Presentation, diagnosis, and treatment outcome of tuberculous-mediated tubulointerstitial nephritis

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Insidious *Mycobacterium tuberculosis* infection causing tubulointerstitial nephritis is a rare disorder. Here we report on a single-center case series of patients with tubulointerstitial nephritis due to tuberculosis, addressing clinicopathologic features and treatment outcome. Twenty-five adult patients with clinical evidence of tuberculosis and significant renal disease were assessed, 17 of whom had a kidney biopsy and were subsequently diagnosed with chronic granulomatous tubulointerstitial nephritis as the primary lesion. All patients were given standard antitubercular treatment, with some receiving corticosteroids, and showed a good response in clinical symptoms and inflammatory markers. Nine of the 25 patients, however, started renal replacement therapy within 6 months of presentation. Of the remaining 16, renal function improved for up to a year after presentation but subsequently declined through a median follow-up of 36 months. This case series supports that chronic tubulointerstitial nephritis is the most frequent kidney biopsy finding in patients with renal involvement from tuberculosis. Thus, a kidney biopsy should be considered in the clinical evaluation of kidney dysfunction with tuberculosis since tubulointerstitial nephritis presents late with advanced disease. A low threshold of suspicion in high-risk populations might lead to earlier diagnosis and treatment, preserving renal function and delaying initiation of renal replacement therapy.

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Tuberculosis (TB) of the genitourinary tract, like other forms of the disease, is caused by members of the *Mycobacterium tuberculosis* complex. Globally, it is estimated that 9.2 million new cases and 1.7 million deaths from TB occurred in 2006, of which 0.7 million cases and 0.2 million deaths were in human immunodeficiency virus (HIV)-positive people.[1] Most of the TB infections are in the lung, but extrapulmonary TB accounts for 20–25% of the total worldwide disease burden, and in 12% of cases there is both pulmonary and extrapulmonary TB.[2] The genitourinary system is the second most common site of extrapulmonary TB, affected in 15–20% of nonpulmonary infections, but isolated genitourinary TB is a feature in just 4% of patients.[2] The global incidence of TB per capita peaked around 2003 and appears to have stabilized or begun to decline by 2006,[1] but the incidence of TB in the United Kingdom and particularly in London continues to rise.[3] The incidence of this disease is much higher in ethnic minority populations in the United Kingdom, and has also been found to be higher in patients with chronic renal failure.[4–6] Although the epidemiology of *pulmonary* TB in England and Wales and identification of at-risk groups is well defined from previous National surveys,[7] the epidemiology of genitourinary TB is not well described.

TB can cause renal impairment in a variety of ways. TB of the kidneys leading to renal failure is an important, although rare, cause of renal failure as it is potentially treatable. Genitourinary TB has been well described in the form of a 'classical' presentation with sterile pyuria, pelvicalyceal deformities, and (usually) systemic symptoms.[8] However, tubulointerstitial nephritis (TIN) due to TB is a more insidious and less well-recognized form of renal involvement in TB, which has previously been described in a small case series from our center.[9] Subsequent case reports have been infrequent and with small patient numbers. There is evidence that subclinical TIN was present in $>25\%$ of patients with pulmonary TB in a small biopsy series.[10] However, this is likely to include patients with drug-induced interstitial nephritis, as most of the patients were on treatment with antitubercular agents at the time of biopsy. Tuberculous TIN has been found to be more common in patients from the Indian subcontinent,[9] and has been postulated to be because of a pauci-immune-complex-mediated inflammatory reaction.[11] A single-center series of 394 consecutive

patients undergoing diagnostic renal biopsy in west London has also shown an increased incidence of interstitial nephritis of unknown etiology in the subgroup of patients from the Indian subcontinent, with 15 out of the 19 patients with unexplained interstitial nephritis being of Indian origin.[12]

The mainstay of treatment in this disease is the standard recommended regimen of antitubercular therapy consisting of 6 months of isoniazid and rifampicin, supplemented in the first 2 months with pyrazinamide and ethambutol.[13] However, in view of the evidence for irreversible optic neuritis with ethambutol treatment in patients with significant renal impairment,[14] some renal units have a policy of withholding ethambutol treatment and initiating treatment with three agents followed by standard course of two agents. Our unit has a policy of individualized therapy under the supervision of a nephrologist and a chest physician specializing in TB in such patients. There are no data on steroid therapy in TB TIN and neither the British Thoracic Society/National Institute for Clinical Excellence in the United Kingdom nor the Centre for Disease Control/American Thoracic Society in the United States[15] specifically recommend steroid therapy in the treatment of TB TIN. However, this is with the caveat that the guidelines are focused on the treatment of classical deforming genitourinary TB rather than TB TIN. The evidence for steroid treatment in idiopathic TIN remains ill defined[16] in the absence of trial data, which is not surprising in view of the rarity of the condition. Our policy now is to initiate steroid treatment at the dose of 0.5 mg per kg body weight of prednisolone in patients with severe and progressive renal dysfunction and a diagnosis of TB TIN, with tapering of the steroid dose after 2 months of treatment.

There is a paucity of data on the impact of therapy on long-term outcome, the risk of drug toxicity, and progression of chronic kidney disease (CKD) in TB TIN. We present the largest single-center series of TIN due to TB treated with a combination of antitubercular treatment and corticosteroids.

RESULTS

Patients

In all, 25 adult patients were assessed by the renal unit between January 2001 and August 2008 with clinical evidence of TB and significant renal disease. In total, 17 patients (68%) underwent a renal biopsy. The cohort of 25 patients included 2 patients (8%) who had HIV co-infection, of whom one underwent a renal biopsy.

The median age at presentation was 40 years (range 20–75 years) with 11 male patients. Of the 25 patients, 19 were of Indo-Asian ethnic origin and 6 patients were of Black African origin (Table 1). Co-morbidity varied with the country of origin of the patient, with two out of six patients of Black African origin presenting with HIV co-infection and sputum-positive TB; the remaining patients did not have HIV co-infection and presented with more indolent symptoms. The total length of stay in the United Kingdom varied from 6 months to 30 years, with six patients having been here for >20 years; three were born in this country.

Table 1 | Demographics of patients with tubercular interstitial nephritis

Parameter	Value
Median age (range)	40 (20–75)
Male gender (%)	44
Race and country of birth	
Black/African	6
Somalia	3
Zambia	1
Uganda	1
Ethiopia	1
Indo-Asian	19
South Asian	13
Kenya	3
United Kingdom	3
Median follow-up (range)	36 months (6–72 months)

South Asian patients included patients born in India, Pakistan, and Bangladesh.

Of the eight non-biopsied patients, five had microbiological evidence of TB (Figure 1). Three had presented with *M. tuberculosis* culture-positive sputum, of whom one patient had HIV infection with miliary shadowing on chest X-ray, and an early-morning urine culture (EMU) positive for TB. One patient developed granulomatous uveitis with *M. tuberculosis* culture-positive tuberculous peritonitis after presenting with dialysis-requiring renal failure. One patient had axillary and cervical lymphadenopathy with histological and microbiological evidence of TB on lymph node biopsy.

The remaining three non-biopsied patients had pyrexia of unknown origin with systemic symptoms of disease, of whom one had three family members with active TB living in the same house, one had retroperitoneal and mediastinal lymphadenopathy, and one had chest X-ray evidence of old TB. All eight patients not biopsied had small (<8.5 cm) smooth kidneys on imaging by computerized tomography or ultrasound examination. The patient with HIV co-infection had normal-sized (11.5 cm, 12.0 cm bipolar length) kidneys on ultrasonography but was not biopsied as he was EMU positive.

Of the 17 patients who underwent a renal biopsy, all had chronic renal impairment, were treatment-naive for HIV and TB, and were diagnosed with TIN.

Of these 17 patients, 8 (47%) were asymptomatic and were biopsied on the basis of active urinary sediments with a rapidly progressive renal failure. Of these eight, five (62.5%) gave a history of systemic symptoms of unexplained weight loss and fever over the preceding 4 to 12 months. Additionally, three patients (37.5%) gave a history of urinary frequency and nocturia. Two patients were 31- and 42-year-old males without significant prostatomegaly or residual urine, whereas the third patient was a 35-year-old female with dysuria and urinary frequency. Two patients were asymptomatic at presentation.

Two out of the eight patients with no evidence of TB elsewhere were initially treated empirically with oral steroids