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Review: Renal Tuberculosis in the Modern Era

Elizabeth De Francesco Daher,* Geraldo Bezerra da Silva Junior, and Elvino José Guardão Barros

Department of Internal Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil; School of Medicine, Health Sciences Center, University of Fortaleza, Fortaleza, Ceará, Brazil; Department of Internal Medicine, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

Abstract. Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*. The disease remains as an important public health problem in developing countries. Extrapulmonary TB became more common with the advent of infection with human immunodeficiency virus and by the increase in the number of organ transplantation, which also leads to immunosuppression of thousand of persons. Urogenital TB represents 27% of extrapulmonary cases. Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease. Renal involvement by TB infection is underdiagnosed in most health care centers. Most patients with renal TB have sterile pyuria, which can be accompanied by microscopic hematuria. The diagnosis of urinary tract TB is based on the finding of pyuria in the absence of common bacterial infection. The first choice drugs include isoniazide, rifampicin, pirazinamide, ethambutol, and streptomycin. Awareness of renal TB is urgently needed by physicians for suspecting this disease in patients with unexplained urinary tract abnormalities, mainly in those with any immunosuppression and those coming from TB-endemic areas.

INTRODUCTION

Tuberculosis (TB) is a disease that in most cases is caused by *Mycobacterium tuberculosis*; however, some cases can be caused by other *Mycobacterium* species in the *M. tuberculosis* complex.[1] The disease became a serious public health problem in Europe during the industrial revolution, when the increases in population and population agglomeration in large cities were common; at that time, TB was responsible for more than 30% of all deaths.[1]

The incidence of TB is increasing, mainly in the developing world. According to the World Health Organization, approximately nine million new cases occur each year worldwide.[2] Most cases are in Asia (55%) and Africa (31%), followed by the eastern Mediterranean region (6%), Europe (5%), and the Americas (3%).[2] Brazil is one of the 20 countries with the higher number of cases, and had 72,194 new cases in 2007, which corresponds to an incidence rate of 38 cases/100,000 persons.[2]

Extrapulmonary TB became more common with the advent of infection with human immunodeficiency virus (HIV) and the increase in organ transplantation, which results in in immunosuppression of organ recipients.[3] Urogenital TB represents 27% of extrapulmonary TB cases, according to data from the United States, Canada, and England. It is the third most frequent form of extrapulmonary TB after pleural TB and lymphatic TB[4] and occurs by hematologic dissemination of pulmonary TB in almost all cases.

IMMUNOSUPPRESSION AND TUBERCULOSIS

Development of immunosuppressive therapies is also responsible for the increase in the number of extrapulmonary TB cases. Patients who have undergone kidney transplantation, especially those who have used potent immunosuppressive drugs, are more susceptible to *M. tuberculosis* infection by reactivation of latent infections and primary infections.[5] Matuck and others [6] showed that 4.5% (44 of 982) of renal transplant patients contracted TB. However, renal disease caused by *Mycobacterium* species is rare in immunocompetent persons.[6] *Mycobacterium* spp. can be found in urine, water, and the environment but are not pathogenic. Treatment of patients with bladder cancer with Calmette-Guérin bacillus (BCG) has also been reported as a cause of urogenital TB.[7]

TUBERCULOSIS AND HIV

Persons infected with HIV have a 20–37 times greater risk of TB than those who are not infected with HIV. In 2010, there were 8.8 million new cases of TB, of which 1.1 million were in patients infected with HIV.[8] Tuberculosis is the most frequent opportunistic infection in patients infected with HIV and is also associated with significant mortality in this population.[9] It is estimated that 10% of TB patients in the United States are infected with HIV.[10] In a study with 532 HIV patients admitted to a tertiary hospital in our region, TB was present in 13% of patients, and severe forms of renal impairment were associated with increased mortality.[11] Among the challenges of genitourinary TB are increasing drug resistance and co-infection with HIV.[12]

Infection with HIV increases the susceptibility for TB infection and disease progression. Tuberculosis can occur in any phase of HIV infection, ranging from asymptomatic to established acquired immunodeficiency syndrome.[13] Infection with HIV is associated with a higher risk for extrapulmonary TB.[10] In a recent study in Brazil with 66 patients with HIV and TB, extrapulmonary TB was observed in 31.8% of cases, of which 54% were ganglionar TB.[13] Nourse and others[14] in a study with 12 children with HIV and TB found a mean CD4 cell count of 508 cells/μL; four patients had nephrotic range proteinuria and hypoalbuminemia. Three of these patients had renal impairment. Renal biopsy specimens showed a severe interstitial inflammatory infiltrate and mild-to-moderate mesangial proliferation. An interstitial granuloma was seen in one patient. After treatment for TB, the proteinuria resolved and renal function improved. The authors concluded that TB contributes to proteinuric renal disease in HIV-infected children and that the renal disease improves after treatment for TB.[14]

*Address correspondence to Elizabeth De Francesco Daher, Rua Vicente Linhares 1198, CEP 60135-270, Fortaleza, Ceará, Brazil. E-mail: ef.daher@uol.com.br

TUBERCULOSIS-ASSOCIATED OBSTRUCTIVE KIDNEY INJURY

Conte and others[15] reported a woman who sought medical care because of dyspepsia. She had diabetes mellitus type 1 and retinopathy. She had a serum creatinine level of 1.2 mg/dL, a glomerular filtration rate (GFR) of 69 mL/minute, proteinuria < 1 g/day, hematuria, and leukocyturia. There was a progressive increase in creatinine (2 mg/dL) and a decrease in the GFR (28 mL/minute). The urinary volume was 900 mL/day and blood pressure was 130/80 mm Hg. Urinalysis showed 10 erythrocytes/high-power field, a pH 6.0, and a specific gravity 1,015. Pre-renal and renal causes of renal insufficiency were excluded. Investigation of post-renal kidney injury was conducted with ultrasound, pyelogram, and tomography. An increase in the size of the right kidney was found, with a reduction in renal parenchyma and moderate dilation of collecting system in the left kidney. After contrast infusion, it was not possible to see the right kidney. There were no calcifications. The right kidney was removed and histopathologic examination showed findings compatible with TB nephropathy. Treatment with isoniazid (300 mg/day), rifampicin (600 mg/day), and ethambutol (400 mg/day) was started, and a progressive reduction in the levels of creatinine (0.7 mg/dL) was observed, as well as improvement of urine sediment (5 erythrocyte/high-power field and 5 leukocytes/high power-field).

This case suggests the possibility of TB as a cause of obstructive kidney injury, which is reversible after specific treatment and surgery. Unilateral ureteral constriction, probably secondary to tuberculous nodules in renal mucosa at the level of the ureteropelvic junction, along with renal dysfunction in the contralateral kidney, leads to development of acute kidney injury. The clinical manifestations of renal TB are commonly unilateral and involve approximately 3% of all patients with TB, and bilateral kidney involvement is uncommon and can lead to chronic kidney disease.[16]

PATHOPHYSIOLOGY OF KIDNEY INJURY IN TUBERCULOSIS

Renal involvement in TB can be part of a disseminated infection or a localized genitourinary disease.[17,18] Pulmonary infection is the primary focus in most cases. After exposition, the bacilli remain stored in macrophages, where they slowly multiply. In most cases, the primary infection is self-limited. The kidneys are commonly affected in milliary TB, where milliary lesions can be found in renal tissue as a result of hematogenic dissemination, particularly in the cortical region.[18] In some patients with pulmonary or disseminated TB, there is evidence of renal failure without evidence of typical localized lesions in the renal parenchyma. In these patients, interstitial nephritis (Figure 1) is commonly found, and in some patients, acid-fast bacilli can be found by Ziehl-Neelsen staining (Figure 2).

The hematogenic dissemination occurs after a vessel erosion, generally a vein in the lung, with emboli containing microorganisms, which falls into systemic circulation. *Mycobacterium tuberculosis* needs determinate environmental conditions to proliferate, which causes its predilection to some organs, including the kidney, epididymis, terine tube, bone marrow, and encephalus.[17,18]

In the kidneys, the preferred place for colonization by *M. tuberculosis* is the medullary region, where granulomatous lesions can occur, with caseous necrosis, leading to local tissue destruction. The renal lesion begins at the cortex, which tends to heal when the person is resistant to this organism. Subsequently, the bacilli migrate to the cortico-medullary junction and builds cortical granulomas. These granulomas remain stable during many years, and during reactivation the organisms

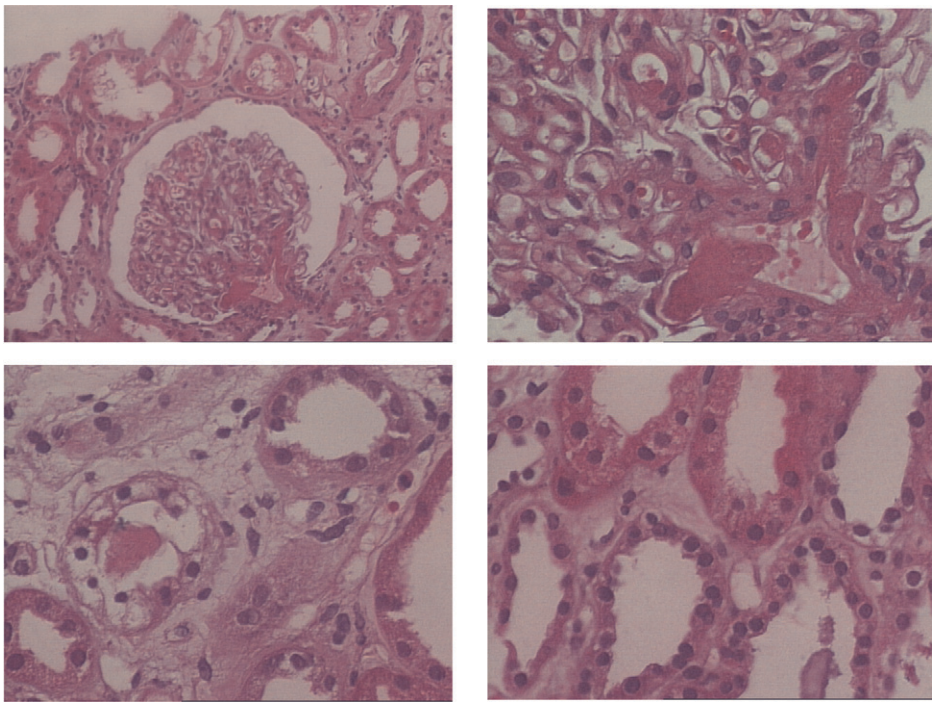

FIGURE 1. Renal biopsy specimen of a patient with renal tuberculosis showing interstitial nephritis. H&E, 200×.

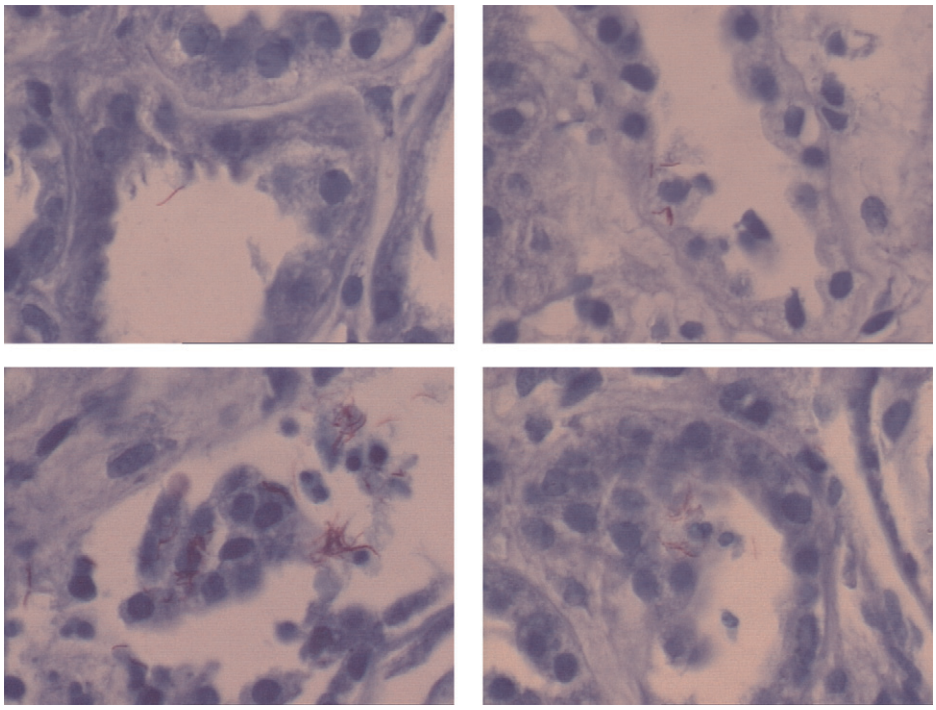

FIGURE 2. Renal biopsy specimen of a patient with renal tuberculosis showing acid-fast bacilli (Ziehl-Neelsen staining). H&E, 400×.

invades the renal medulla and causes papillitis. With disease progression, extensive areas of papillary necrosis can cause formation of cavities that destroy the renal parenchyma and can migrate into the collecting system. The infection can cause vascular insufficiency in renal papillae, leading to papillary necrosis. The dissemination of infection to renal pelvis can cause a tuberculous pyelonephritis, which can evolve to pyonephrosis. The infection generally disseminates from the ureter to the bladder, causing granulomatous lesions associated with fibrosis. These processes occur slowly over several years. In the ureter, the lesions cause a series of dilations intercalated with strictures, which constitutes one of the most important TB signs that can be seen in the pyelopgram. When the obstruction is total and more distal, a megaureter can occur[19] (Figure 3).

The renal lesions can disseminate beyond the renal capsule and lead to development of mass lesions, simulating a neoplastic lesion. The ureteral involvement can cause segmentar stenosis and dilations, leading to urinary obstruction and urine reflux.[18] Advanced disease can cause infundibular and pelvic stenosis. The involvement of renal calices can be unique or multiple in one or both kidneys. The end results are organ destruction, renal function loss, and diffuse calcifications.[17] The pathophysiology of renal TB is shown in Figure 4.

The pathogenesis of renal TB can be divided into two forms: renal involvement during disseminated infection and localized genitourinary disease. In both cases, the lesions depend fundamentally on the immunologic status of the person, pathogen virulence, and the site of infection.

In milliary TB (disseminated form), most tubercles are located in the renal cortex, and can be as large as 3 mm in diameter.[18] Histologically, milliary TB is characterized by epithelioid granuloma, frequently with giant cells. In patients with this form, renal function is abnormal. Uremia is more related to interstitial nephritis.[18] In immunocompromised patients, granulomas are poor structured, with less caseous necrosis.

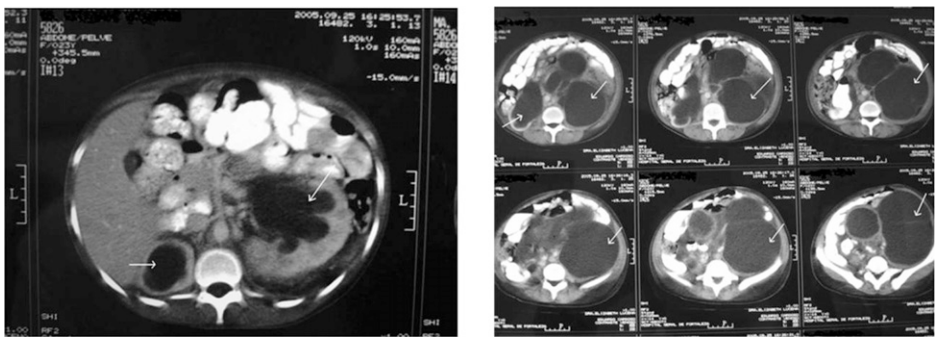

FIGURE 3. Computed tomographic image of a patient with renal tuberculosis showing enlargement of both kidneys, cortical thinning with low density, markedly dilated calyces, and severe dilation of ureter (megaureter). Adapted with permission from Daher et al.[24]

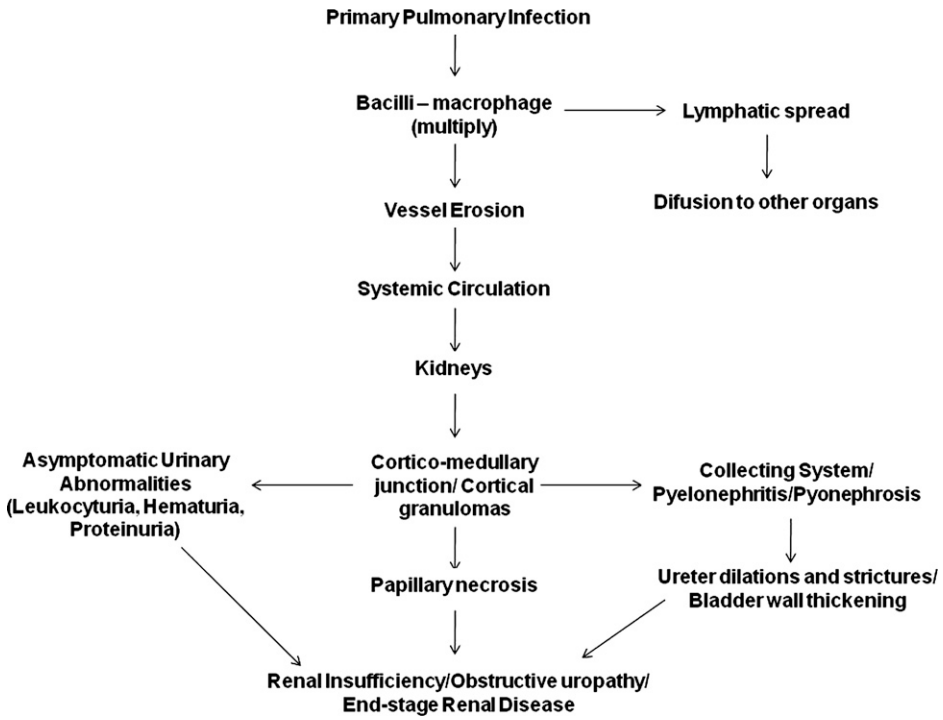

FIGURE 4. Pathophysiology of renal tuberculosis.

In more severe cases, the most common pattern is histiocytes containing multiple bacilli intracytoplasmatic.[18] When renal TB occurs, it is important to suspect immunologic aggression, and corticosteroids should be included in the treatment.[18]

In localized renal disease, origin of the bacilli is pulmonary. During diagnosis of renal TB, lung disease is rarely found, although clinical and radiologic traces of TB might be observed. Localized renal disease seems to be a consequence of a previous pulmonary primary infection.[18,19] In approximately 25% of elderly patients, there is genitourinary involvement during TB reactivation.[16]

CLINICAL MANIFESTATIONS

The most common infection caused by the *M. tuberculosis* is pulmonary infection. The high prevalence of pulmonary TB in Brazil enables its prompt recognition and treatment, but the extrapulmonary forms seem to be rarely diagnosed and can be considered a neglected disease. It is important that all physicians know the clinical and laboratory features of extrapulmonary TB to identify this disease and provide correct specific treatment.

The most prevalent clinical presentation is pulmonary cavitations, usually accompanied by productive cough, fever, night sweating, and wasting. However, after a primary respiratory inoculation, widespread seeding of bacilli may occur and typical lesions may develop in other locations, such as the pleural cavity, lymph nodes, and eventually the urogenital tract.[20]

Urogenital TB is a frequent extrapulmonary location for *M. tuberculosis* lesions.[20] Typically, lesions (tuberculous granulomata) initiate in the kidneys, and spread distally to the ureters, bladder, and testicles. A lengthy period occasionally separates the primary infection and an established diagnosis of urogenital tuberculosis. Early granulomatous kidney disease may present as proteinuria, pyuria, and loss of kidney function. Isolated hematuria is another possible manifestation of renal TB. Lower urinary symptoms occur whenever the disease spreads down to the ureters and bladder. Urinary symptoms suggestive of urinary tract infection, accompanied by pyuria and hematuria with no bacterial growth, suggest urogenital TB. Advanced disease may cause obstructive uropathy, bladder defects, and loss of kidney function.[21] Ultrasonography, computerized tomography, and magnetic nuclear resonance will demonstrate grossly distorted ureters, with alternating stenotic and dilated areas, reduced bladder volume, hydronephrosis, and reduced kidneys in advanced disease.[21,22] Intravenous urography may show chalice distortion or cavities suggestive of pelvic lesions of TB and loss of right kidney function.[21,23]

CUTANEOUS AND RENAL TUBERCULOSIS

There is association between renal and cutaneous TB. We treated a 40-year-old woman ale who was given an established diagnosis of cutaneous TB (erythema induratum of Bazin).[24] She had nodular erythematous-violaceous lesions that were painful and showed some ulcerations (Figure 5). Some months later, the patient had urinary symptoms, including dysuria and polaciuria. A urine examination showed an acidic urine (pH 5.0), hematuria, and pyuria, with urine culture positive for *M. tuberculosis*. Specific treatment was instituted (rifampicin, isoniazid, and pyrazinamide), and resulted in complete regression of cutaneous and renal symptoms.[24]

TUBERCULOSIS AND INTERSTITIAL NEPHRITIS

The association between the infection by *M. tuberculosis* and interstitial nephritis illustrates the chronic pattern the disease can present. Mallinson and others[25] reported three patients

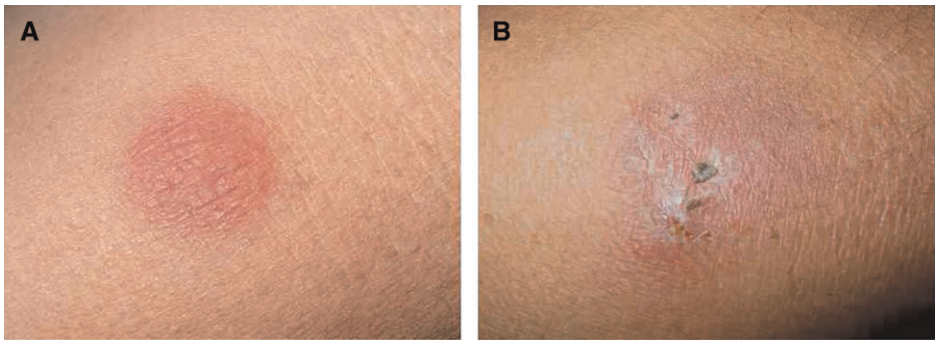

FIGURE 5. Erythema induratum of Bazin (nodular vasculitis) in a patient with renal tuberculosis. Erythematous nodules on posterior aspect of the lower legs and some of them ulcerated. **A**, non-ulcerated. **B**, ulcerated and crusted. Adapted with permission from Daher and others.[24]

with advanced renal disease, all with chronic tubulointerstitial nephritis with granulomas and caseous necrosis. Results for acid-fast bacilli were positive in two of these patients. One patient has also had tuberculous peritonitis, and there was evidence of TB in the thoracic radiography in two of these patients.[25]

A 44-year-old man who was admitted to a hospital in southern Brazil had a history of malaise and weight loss (20 kg), with progressive worsening for two months before admission. He sought medical care and had daily fever, dizziness, and vomiting. He had a recent diagnosis of HIV infection (one month earlier). He denied using intravenous drugs or any previous diseases. At a physical examination, he was ill, sleepy, and had no neurologic deficits. He had a blood pressure of 80/50 mm Hg, a heart rate of 110 bpm, normal cardiopulmonary auscultation, and a painful abdomen without any masses or organomegaly. Laboratory tests showed a hemoglobin level of 9.8 mg/dL, a hematocrit of 29.3%, a platelet count of 255,000/mm^3, a creatinine level of 1.5 mg/dL, a potassium level of 4.9 mEq/L, and a bicarbonate level of 19 mEq/L. Computed tomography showed cervical, axillary and mediastinal lymphadenomegalies, pericardial effusion, and mesenteric lymphadenomegaly.

He was initially treated for septic shock and received cefepime for 7 days. He showed progressive worsening of kidney function (maximum creatinine level = 4.8 mg/dL, urea level = 228 mg/dL) and a decrease in platelet count (minimum = 85,000/mm^3). A renal biopsy was then performed and showed 20 glomeruli, 3 with sclerosis and 3 with intracapillary fibrin thrombi, interstitial fibrosis, and tubular atrophy in 15–20% of renal parenchyma, with focal inflammatory infiltrate, mild intimal proliferation in arteries, and fibrinous necrosis in arterioles (Figure 1). Ziehl-Neelsen staining was positive for acid-fast bacilli (Figure 2). The diagnosis was thrombotic microangiopathy, interstitial nephritis, and renal TB (Barros EJG and others, unpublished data).

TUBERCULOSIS AND GLOMERULOPATHY

Chronic TB can complicate with amyloidosis and is an important cause of chronic kidney disease in India,[26] and probable underdiagnosis in many countries. There are several cases of TB associated with different forms of glomerulonephritis, but there is no proven relationship with TB as the primary cause. We recently treated a patient who had a diagnosis of lupus nephritis who was then found to have renal tuberculosis. A urine culture was positive for acid-fast bacilli, and a renal biopsy showed proliferative glomerulonephritis (De Francesco Daher E and others, unpublished data) (Figure 6). Shribman and others[27] reported one case of milliary TB complicated by focal proliferative glomerulonephritis, with immunedeposits in glomerular region, but with no granulomas.

TUBERCULOSIS AND CHRONIC KIDNEY DISEASE

Despite prevention and relative widespread availability of specific treatment, the underdiagnosis of TB remains a reality in many parts of the world, and this increases the chance of progression of kidney disease to end stage renal disease (ESRD). Although the prevalence of TB is higher in developing

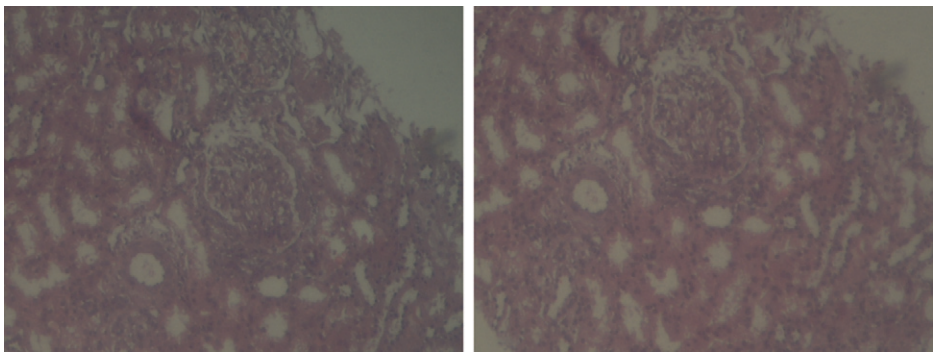

FIGURE 6. Renal biopsy specimen of a patient with renal tuberculosis and systemic lupus erythematosum showing a focal proliferative glomerulonephritis. H&E, 200×.

countries, most cases of ESRD are seen in developed countries, which is a result of underdiagnosis in the developing world.[18] This fact limits the knowledge about the real effect that TB has on kidney disease and its progression.

The European Renal Association and European Dialysis and Transplant Association reported that 0.65% (n = 195) of patients admitted for dialysis had TB as the primary cause.[28] This incidence was similar to that found over the past few years. Greece has the highest incidence of TB (4.5% of new cases). We have seen a recent apparent increase in the cases admitted to the emergency department with uremia caused by renal TB,[21,23,29] and this can be attributed to an increase in the incidence of renal TB or an increase in the medical suspicion of this infection, which leads to correct diagnosis of ESRD etiology.

TUBERCULOSIS AND DIALYSIS

Tuberculosis, mainly pulmonary TB, has been observed among patients undergoing hemodialysis and peritoneal dialysis.[30–32] Usual clinical manifestations are fever, anorexia, weight loss, and a history of TB, associated with a social group at risk for TB.[18] Woeltje and others[33] showed that 48 of 307 patients undergoing dialysis had a positive tuberculin-purified protein derivative (PPD) skin test result, but no evidence of radiographic abnormalities.

Data regarding prevalence of TB among dialysis patients are scarce, mainly in the developing countries, where the disease in endemic. Tuberculosis seems to be more common today than in the past among patients receiving peritoneal dialysis, who have a high incidence of peritoneal TB.[30,34–37]

Tuberculosis among hemodialysis patients can also occur because of infection with *Mycobacterium* and is observed mainly as the pulmonary form (disseminated or cutaneous).[18] Contamination of dialysis equipment is an important risk factor for disease transmission.[18]

TUBERCULOSIS AND TRANSPLANTATION

Tuberculosis is also an important complication among patients who had undergone kidney transplantation (incidence = 0.35–35%).[35,38] Risk factors for TB after kidney transplantation include a positive PPD skin test result and previously healed TB lesions visible by pre-transplantation chest radiography.[39] The frequency of TB among patients receiving a kidney transplant is higher than that in the general population because of immunosuppression. Its prevalence is 1% in North America and 1–4% in Europe, but is more common in the developing world. In India, it was estimated to be 11%.[40]

In most instances, post-transplantation TB manifests as pulmonary infection, but in one-third of these cases the disease is disseminated. Dridi and others[41] reported five cases of TB among 368 (1.3%) kidney transplant receptors over 22 years. Three patients had pulmonary lesions, one with lymphadenopathy. Five patients had disseminated disease, which manifested as pulmonary and genitourinary TB. The main findings were fever, anorexia, weight loss, and palpable lymphadenopathy.[41]

Basiri and others[42] conducted a retrospective study comparing 120 patients who had TB after renal transplantation (study group) with 440 patients without TB (control group). Both groups underwent transplantation during 1984–2003 in Iran. The main clinical findings were cough (49.2% in the study group versus 0.2% in the controls; $P = 0.001$), productive cough (45.8% versus 0.2%; $P = 0.01$), fever (78.2% versus 0.5%; $P = 0.01$), nocturnal sudoresis (33.3% versus 0.2%; $P = 0.01$), weight loss (33.3% versus 0%; $P = 0.01$), and hemoptysis (10.8% versus 0%; $P = 0.01$). Both groups received prednisolone in similar doses (1.5 and 1.9 mg/kg; $P = 0.5$); 23 patients in the study group (19.2%) and 73 controls (16.6%) received mycophenolate mofetil in similar doses (19.5 mg/kg and 19.25 mg/kg, respectively; $P = 0.5$). Cyclosporine was administered to 113 patients (94.2%) and 412 controls (93.6%) ($P = 0.5$) in identical doses (3.8 mg/kg). No patient was infected with HIV; 77 study patients (64.2%), and 1 control (0.2%) had radiologic evidence of TB post-transplantation ($P = 0.01$). The main radiologic abnormalities found in both groups were apical infiltration and cavities (57.2% versus 0.2%), pleural effusion (22% versus 0%), and a milliary pattern (11.7% versus 0%).[42]

Patients with a history of TB during dialysis have a higher risk for developing post-transplantation TB. It is important to consider that because of immunosuppression, a delay in diagnosis can occur because of false-negative PPD skin tests results; 29% of transplantation patients have Tb caused by environmental *Mycobacterium* spp.[43] Mortality rates are approximately 30%, which might be caused by delayed diagnosis.[18]

Several renal transplant centers perform prophylaxis with isoniazide for a one-year period in patients at high risk for developing TB. In most centers in Brazil, a country to which TB is endemic, the consensus is to give prophylaxis with isoniazide to every patient with a positive PPD skin test result (> 10 mm), but a recommendation to initiate prophylaxis in patients with a PPD skin test result > 5 mm is being considered. In a series of 633 patients who underwent renal transplantation and who had prophylaxis, no case of TB was seen.[43] Among 27 patients considered to be at high risk for developing TB and who had not underwent prophylaxis, 6 (22%) had TB. Eastwood and others[18] recommended prophylaxis for one year in patients at high risk for TB. The duration of immunosuppression is dependent on the efficacy of the prophylaxis. In patients in whom immunosuppression is decreased early, treatment with isoniazide can last less than one year.

Disseminated TB in the absence of renal insufficiency or renal disease is frequently associated with hypercalcemia. In these cases, levels of calcitriol (1,25-dihydroxi-D_3) are increased, presumably as a result of an increase in the synthesis of active vitamin D because of activation of macrophages present in the granuloma.[44] There are some reports of patients receiving hemodialysis who show an association between disseminated TB, urogenital TB, and hypercalcemia.[45]

DIFFERENTIAL DIAGNOSIS

Renal TB is underdiagnosed in most health care centers. Most patients have urinary tract infection (acute cystitis) and only after a therapeutic failure directed against the usual bacterial urinary infections, with persistent pyuria associated with a negative urine culture, a diagnosis of renal TB is suspected. Some patients have lumbar or suprapubic pain, hematuria, polacyuria, and nocturia, which initially suggests acute bacterial cystitis.[18] More than 90% of assymptomatic patients have sterile pyuria, which can be accompanied by microscopic hematuria.[46] Less than 10% of patients with renal TB have symptoms of renal colic. The classical symptoms of TB (vespertine fever,

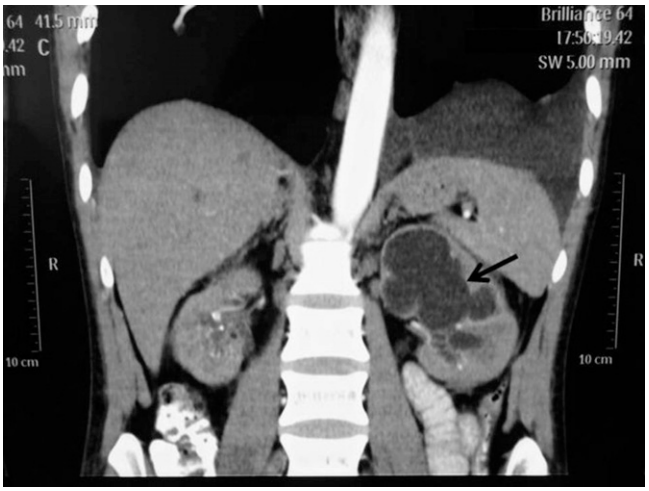

FIGURE 7. Contrasted tomographic image of a patient with renal tuberculosis and end-stage renal disease showing enlargement of the pyelocalycial system of the left kidney and right kidney exclusion. Adapted with permission from Lima and others.[29]

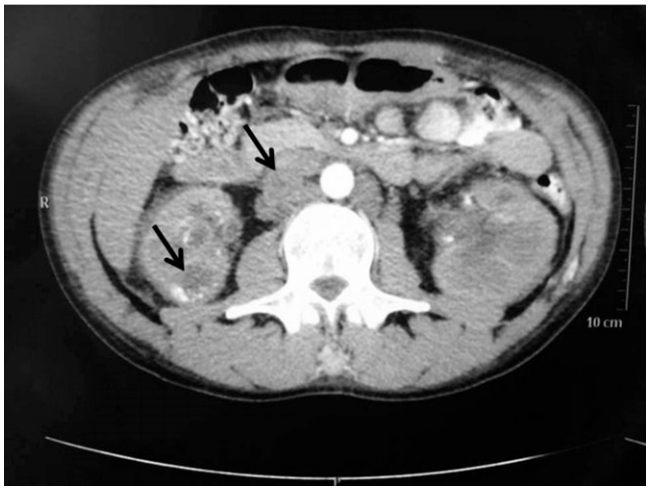

FIGURE 9. Contrasted tomographic image of a patient with renal tuberculosis and end-stage renal disease showing a complex cyst (Bosniak IIF) in the right kidney and retroperitoneal lymphadenomegaly. Adapted with permission from Lima and others.[29]

nocturnal sudoresis, and weight loss) are not common in patients with renal TB.[18] Only one-third of patients have radiologic abnormalities.[18]

Renal TB should be investigated in men with diagnosis of genital TB because of their frequent association. Patients with a scrotal mass should have surgery, and when genital TB is diagnosed, renal TB should be suspected and investigated.[46]

The diagnosis of urinary tract TB is based on pyuria in the absence of common bacterial infection. In the initial phases, it is possible to detect abnormalities in pyelogram, including a unique renal calice with parenchymal necrosis, associated with calcification. Other findings, such as caliceal distortion, ureter stenosis, and bladder fibrosis are suggestive of advanced disease. Ultrasound can detect caliceal dilation and ureteral obstruction. In patients with bilateral ureteral distortion, the disease progression leads to a significant decrease in the GFR and might evolve to ESRD.[19,29] Contrasted tomography can detect renal exclusion in the setting of TB progression to ESRD (Figures 7 and 8) and lymphadenomegaly (Figure 9).[23,29] Patients suspected of having renal TB should also be screened for asymptomatic pulmonary lesions, such as cavitations or nodules (Figure 10).[23] Nuclear magnetic resonance can also detect pyelocaliceal system and ureter dilation (Figure 11).[23]

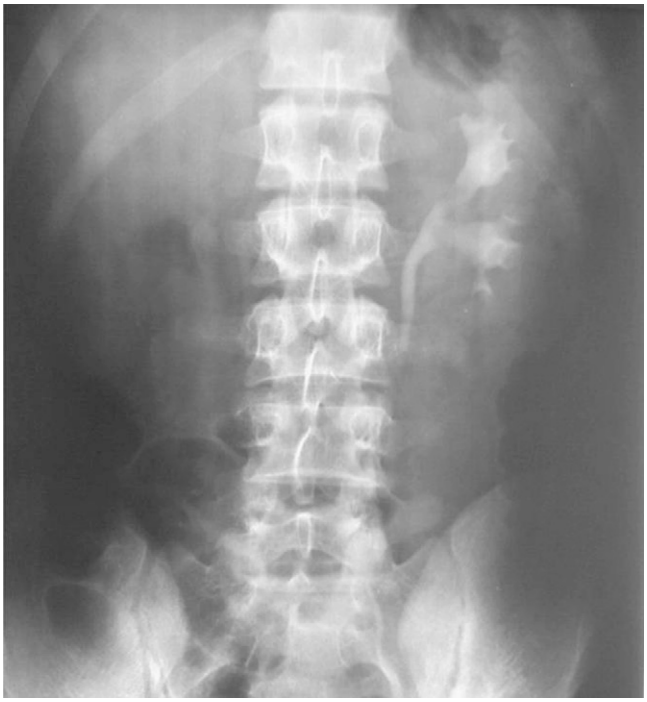

FIGURE 8. Pyelogram of a patient with renal TB and chronic kidney disease showing right kidney silence. Adapted with permission from Oliveira and others.[23]

EVALUATION OF LABORATORY DIAGNOSIS

A diagnosis of TB is usually made by isolation of the pathogen in urine samples or by tissue biopsy. Acid-fast bacilli can

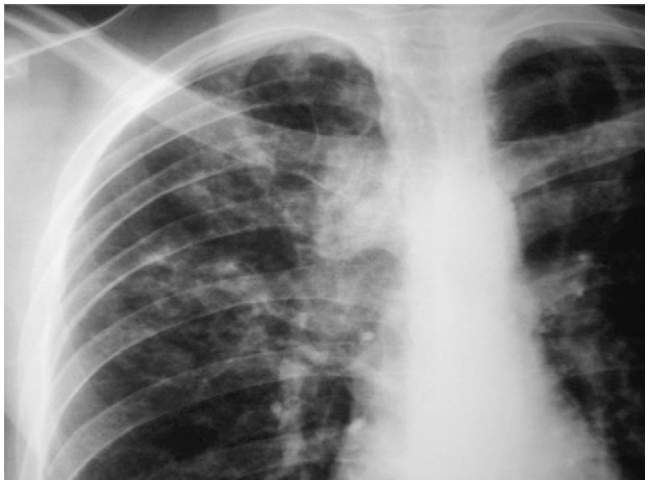

FIGURE 10. Chest radiograph showing small nodules scattered in the right lung in a patient with renal tuberculosis and chronic kidney disease. Adapted with permission from Oliveira and others.[23]

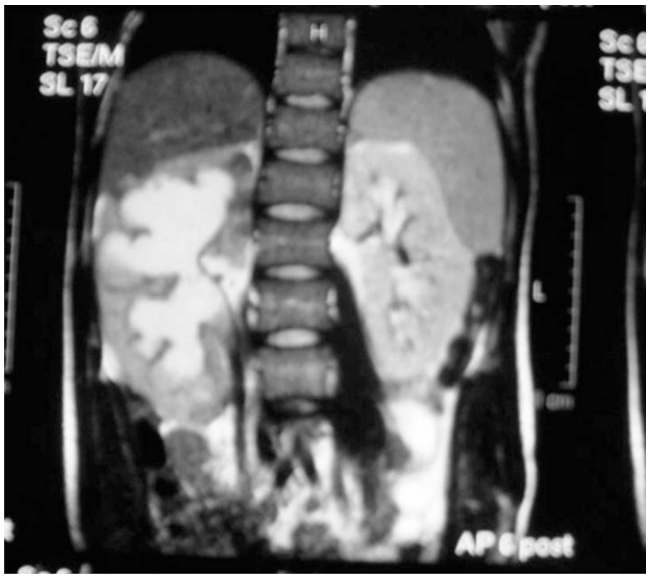

FIGURE 11. Nuclear magnetic resonance imaging showing severe dilation of right pyelocaliceal system and proximal ureter. Adapted with permission from Oliveira and others.[23]

be seen in centrifuged urine by Ziehl-Neelsen staining. One should pay attention when only few bacilli are seen because it can be the result of urine contamination by environmental non-pathogenic *Mycobacterium* spp., which can lead to false-positive results.[18]

Urinalysis may vary from mild changes, such as proteinuria and leukocyturia, to extreme pyuria, sometimes accompanied by hematuria. Urine cultures are regularly negative, unless there is severe bladder dysfunction. However, urine cultures for detecting mycobacteria by using Lowenstein-Jensen solid culture medium, may be useful. Multiple samplings should be obtained to increase test sensitivity. *Mycobacterium* spp. culture and identification results provide a specific diagnosis, but might not be available for 2–3 weeks or longer.[19] Polymerase chain reaction (PCR) techniques, such as the direct Gen-Probe MAD test, has been recently used. It is a reliable and rapid diagnostic test. Cystoscopy and a biopsy is particularly recommended because it enables visualizing and sampling bladder lesions and might be the most reliable test to use.[19]

Acid-fast bacilli culture. Microscopic testing for acid-fast bacilli has low sensitivity. Conversely, culturing the pathogens has high sensitivity, but it takes 6–8 weeks to obtain a result. These characteristics limit diagnosis and treatment. In investigations of renal TB, a search for acid-fast bacilli in urine and urine culture should be conducted with at least three different samples. There are some characteristics in a urine examination that suggest a diagnosis of renal TB, such as acid pH, leukocyturia and/or hematuria, associated with negative urine culture for the usual bacteria that causes urinary tract infection.

Molecular biology for diagnosis of TB. More recently, molecular biology techniques have been used to obtain results faster and with greater sensitivity for detecting *M. tuberculosis* and other *Mycobacterium* spp. These techniques can also establish the pattern of sensitivity to antimicrobial drugs in cases of suspected drug resistance, which can be a problem in TB-endemic areas. These techniques are based on PCR for different regions of the bacterial genome, such as insertion sequence *6110*,16S ribosomal DNA, and the gene coding heat-shock protein 65. There are several commercially available methods for detecting the *M. tuberculosis* complex in biological material. These methods include the PCR-based Amplicor (Roche, Basel, Switzerland), the ligase chain reaction (Abbott Systems, Abbott Park, IL), transcription-mediated transcription (Gen-Probe, San Diego, CA) and RAPID-BAP-MTB assay (AsiaGen, Tainan, Taiwan).[45] However, these methods do not differentiate *M. tuberculosis* from other *M. tuberculosis* complex species, and this differentiation is useful in guiding therapy and clarifying epidemiologic issues. The methods based on PCR followed by digestion with restriction enzymes (PCR-restriction fragment length polymorphism) have the advantage of differentiating *Mycobacterium* species.[47–50] Some studies suggest that although urine contains inhibitory substances, the PCR is sensitive and specific in detecting pathogens.[51] Polymerase chain reaction in detecting *M. tuberculosis* in urine have a sensitivity that varies from 25% to 93% and a high specificity (95–100%).[52–55]

TREATMENT

All patients with active or latent TB needs specific treatment. The first-choice drugs include isoniazide, rifampicin, pirazinamide, ethambutol, and streptomycin. After diagnosis, chemotherapy with three or four drugs should be immediately initiated and last for at least six months.[56,57] Two regimens can be used. The first-line regimen, which is used for six months, is rifampicin, isoniazide, and ethambutol or pirazinamide daily for two or three 3 months; and isoniazide and rifampicin twice a week for three of four months.[57] The second-line regimen, which is used for nine months, is isoniazide, rifampicin, ethambutol, or pirazinamide daily for two or three months, followed by isoniazide and rifampicin, twice a week, for six to seven months.[58] Rifambutin can substituted for rifampicin to decrease drug interactions with drugs used in the treatment of HIV infection (protease inhibitors and transcriptase reverse non-nucleoside inhibitors).[58]

According to the new guidelines by the Brazilian Ministry of Health, it is recommended that all TB patients be treated with four drugs: rifampicin, isoniazide, pirazinamide and ethambutol for six months[59] (Table 1). The second-line regimen is less effective than the first-line regimen cited above and is suggested for patients who cannot tolerate the first-line regimen. Second-line anti-TB drugs include capreomycin, ciprofloxacin, clofazimine, cycloserine, ethionamide, kanamycin, levofloxacin, ofloxacin, and aminosalicylic acid.[57]

There was an increase in the resistance to tuberculostatic drugs in HIV patients. Isolated resistance to isoniazide should be treated with rifampicin, pirazinamide, and ethambutol for six months. If rifampicin resistance is suspected, treatment with isoniazide and ethambutol for 18 months or isoniazide, pirazinamide, and streptomycin for 9 months should be used.[58]

Patients with loss of renal function should receive the usual doses of rifampicin, isoniazide, pirazinamide, and ethionamide because these drugs have billiary excretion properties and are metabolized into compounds that are not excreted by the kidneys.[18] However, caution should be used when administering streptomycin, other aminoglycosides, and ethambutol

TABLE 1
Treatment for adults and adolescents with tuberculosis, 2010*

Drugs, body weight (kg)	Units/dose	Duration of treatment, months
Rifampicin (150 mg), isoniazide (75 mg), pirazinamide (400 mg), ethambutol (275 mg)†		2
20–35	2 pills	
36–50	3 pills	
> 50	4 pills	
Rifampicin/isoniazide 300 mg/200 mg or 150 mg/100 mg		4
20–35	1 pill (300/200 mg)	
36–50	1 pill (300/200 mg plus 150/100 mg)	
> 50	2 pills (300/200 mg)	

*Adapted from the guidelines of the Ministry of Health, Brazil, 2010.
†A pill is available that contains all four amounts of these drugs.

because these drugs have renal excretion properties.[18] Ethambutol can cause optic neuritis, which is reversible, if the dose is reduced according to the GFR: 25 mg, three times a week, if the GFR is 50–100 mL/minute and twice a week if the GFR is 30–50 mL/minute. Streptomycin and other aminoglycosides can cause ototoxicity and nephrotoxicity and should not be used in patients with decreased renal function.[18]

Encephalopathy is an uncommon complication of treatment with isoniazide and is usually prevented by treatment with piridoxine (25–50 mg/day). Some patients who undergo hemodialysis have encephalopathy induced by isoniazide that does not respond to piridoxine, but reversion occurs when the drug is withdrawn.[18] Because rifampicin affects the metabolism of drugs commonly used as immunosuppressors (e.g., corticosteroids, cyclosporine), the serum concentration of this drug should be monitored.[18]

Fibrotic alterations can be decreased by use of corticosteroids in association with anti-TB drugs. Despite these alterations, patients with advanced disease or those with a delayed diagnosis might require surgery.[57] Treatment of disease caused by environmental *Mycobacterium* spp. should be conducted according to results of an *in vitro* sensitivity test for anti-TB drugs.[18]

INVASIVE PROCEDURES

Invasive procedures or surgery are indicated in certain situations: hydronephrosis drainage (ureter dilation or percutaneous nephrostomy), abscesses and collection drainage, definitive treatment of renal TB (partial nephrectomy), superior urinary tract reconstruction, bladder dilation, ureter reconstruction, and genital TB.[58,60] A pyelogram or ultrasound is indicated every six months in the first two years of treatment in cases of ureteral stenosis to detect obstructive uropathy and treat this condition.[19] In a study in Russia conducted during 1960–1996, surgical treatment was necessary in 55% of 2,364 patients with urogenital TB.[61] In 37.4% of cases, surgical removal of an organ was performed, and conservative surgery was performed in 22.4% of cases.[61] The reconstruction procedures, such as pyelo-ureteral anastomosis, uretero-caliceal anastomosis, caliceal reconstruction, uretero-ureteral anastomosis, and ureter substitution by ileus represented 40.1% of surgical modalities performed.[61]

FINAL CONSIDERATIONS

Tuberculosis has a high incidence in developing countries. There is a worrisome underdiagnosis of renal TB, which leads to development of renal insufficiency, chronic kidney disease, and ESRD, all preventable situations with correct and early specific therapy. New research is needed to trace the main forms of clinical presentations of renal TB, as well as to develop new more efficacious diagnostic methods and less toxic anti-TB drugs. Because of changes in HIV/acquired immunodeficiency syndrome and increases in iatrogenic immunosuppression associated with new medical advances, physicians must be aware of suspected renal TB in patients with unexplained urinary sediments. Any immunosuppressive patients and patients from TB-endemic areas should raise the threshold of suspicion for this subtle yet highly morbid disease.

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Authors' addresses: Elizabeth De Francesco Daher, Department of Internal Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil, E-mail: ef.daher@uol.com.br. Geraldo Bezerra da Silva Junior, Department of Internal Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil, and School of Medicine, Health Sciences Center, University of Fortaleza, Fortaleza, Ceará, Brazil, E-mail: geraldobezerrajr@yahoo.com.br. Elvino José Guardão Barros, Department of Internal Medicine, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil, E-mail: elvino.barros@gmail.com.

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