ELSEVIER

A Case of Multidrug-Resistant Monoarticular Joint Tuberculosis in a Renal Transplant Recipient

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ABSTRACT

Tuberculosis (TB) is a common opportunistic infection after renal transplantation. The risk of TB in renal transplant recipients is reported to be 20 to 74 times higher than in the general population. Although extrapulmonary TB occurs frequently, isolated ankle joint TB is a rare form of extrapulmonary TB infection. It is often difficult to diagnose because of its atypical presentation; management is complex, especially with multidrug-resistant TB, the need for a prolonged course of therapy, and the risks of drug interactions and drug toxicity. We report herein a case of a 60-year-old female renal allograft recipient who developed multidrug-resistant ankle joint TB 11 months after her deceased donor renal transplantation. She presented to the emergency department with escalating pain and swelling of the left ankle, difficulty in ambulation, and a low-grade fever. An x-ray of the ankle revealed an effusion and soft tissue swelling. A synovial fluid culture was performed which tested positive for acid fast bacilli which grew a multidrug-resistant form of *Mycobacterium tuberculosis*. She was initially treated with isoniazid, rifampin, ethambutol, and pyrazinamide; then therapy was tailored secondary to the resistant nature of the organism. She received a combination of extensive debridement of the joint and institution of second-line anti-TB therapy with pyrazinamide, ethambutol, moxifloxacin, and ethionamide. To our knowledge, no other cases of multidrug-resistant TB have been reported in the literature after renal transplantation. This case shows both an atypical presentation of TB and the difficulties in managing a transplant patient with this disease.

TUBERCULOSIS (TB) is a commonly observed opportunistic infection in solid organ transplant recipients, and is found more frequently among patients who have undergone renal transplantation [1–4]. The incidence of TB in renal transplant recipients has been reported to be between 0.35% and 1.2% in the United States [3]; this incidence is 20- to 74-fold higher than in the general population [2,3]. When accompanied by diagnostic difficulties, a delay in initiating treatment and associated drug toxicity, TB significantly increases morbidity and mortality in renal transplant recipients [3].

Pulmonary TB is the most common mycobacterium disease reported among renal transplant recipients [1–5]. Extrapulmonary TB also occurs frequently and is reported to be between 16% and 30 % [1,3,5]; however, the diagnosis of the disease is difficult and often delayed due to its atypical presentation. Furthermore, management of TB is challenging because of the side effects of anti-TB agents and their potential interactions with immunosuppressive therapies resulting in inadequate immunosuppressive levels that may lead to graft rejection [2,3]. The following is a case report of a renal transplant recipient who had an atypical presentation of *Myobacterium tuberculosis* and the difficulties encountered with the management of her disease.

CASE REPORT

A 60-year-old female recipient of a deceased donor renal allograft presented to the emergency department (ED) 11 months after her renal transplantation with escalating pain and swelling of the left ankle of 4 days duration. The patient's medical history included end-stage renal disease secondary to adult polycystic kidney disease

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and hypertension. The patient is a native of the Philippines and had no history of exposure to TB or travel to endemic areas in the 8 years before or after transplantation. She was vaccinated with bacillus Calmette-Guérín before transplantation. The pretransplantation tuberculin test was negative and chest x-ray showed no evidence of active, reactivated, or latent TB.

At the time of transplantation, she received 5 doses of thymoglobulin at 1.5 mg/kg and 4 doses of methylprednisolone (cumulative dose of 2.5 g) for induction. She was also started on tacrolimus and mycophenolic acid (MPA) for maintenance immunosuppression with a prednisone taper after therapy for induction. She was tapered off prednisone within a month of transplantation. In addition, the patient and the donor were both seropositive for cytomegalovirus (CMV) and Epstein-Barr virus. She was administered trimethoprim/sulfamethoxazole for 6 months for urinary tract infection prophylaxis and pneumocystis jiroveci pneumonia prophylaxis, valgancyclovir for 100 days for CMV prophylaxis, and nystatin for 3 months for fungal prophylaxis. Five months after transplantation, the patient developed acute cellular rejection, BANFF type IIA, and was consequently treated with 7 doses of thymoglobulin (1.5 mg/kg) and 3 doses of methylprednisolone (500 mg each). Moreover, 5 mg of prednisone daily was added to her maintenance immunosuppressive medications.

Three months before her presentation to the ED, she had reported pain and swelling of her left ankle at a post-transplantation examination. An x-ray of her ankle showed an effusion and she was referred to a rheumatology clinic where she underwent arthrocentesis. The results showed 1200/mm^3 total nucleated cells with 7% lymphocytes, 91% monocytes, 2% eosinophils, and no neutrophils. Moreover, gram stain and culture were negative and no crystals were observed by polarized microscopy. The patient's available medical records did not document whether synovial fluid had been sent for acid fast bacilli (AFB) stain or culture. Her rheumatologic investigation including rheumatoid factor, antinuclear antibody, anti-Ds DNA and complement levels were all normal. The patient was treated with an intra-articular corticosteroid injection for a presumed diagnosis of inflammatory arthropathy. Three weeks before the patient's presentation to the ED, she returned to the rheumatology clinic for recurring symptoms and received a second dose of intra-articular corticosteroid.

On presentation to the ED, the patient reported pain and swelling in her left ankle with difficulty in ambulating. She also reported a low-grade temperature of 100.2 °F. Additional review of symptoms was unremarkable. On physical examination, vital signs were unremarkable; the patient's left ankle was swollen, tender to palpation, and warm to touch without any erythema. She was able to flex and extend her ankle joint but active and passive range of motion induced pain. The remainder of the physical examination was unremarkable. Laboratory studies showed a white blood cell (WBC) count of 6.6 $\times$ 10 E^3, hemoglobin 10.3 g/dL, hematocrit 32%, platelets 229 $\times$ 10 E^3, erythrocyte sedimentation rate 84, C-reactive protein 12.2, sodium 138 mEq/L, potassium 4.2 mEq/L, blood urea nitrogen 23 mg/dL, serum creatinine 1.5 mg/dL, glucose 129 mg/dL, albumin 3.3 mg/dL, aspartate transaminase (AST) 18 unit/L, and alanine transaminase (ALT) 25 unit/L. X-ray of the left ankle revealed an effusion and soft tissue swelling without underlying periosteal reaction, fracture, or dislocation of the left ankle. Joint aspiration of the left ankle showed 2400/mm^3 total nucleated cells with 96% neutrophils. No crystals were observed under polarized microscopy. Magnetic resonance imaging of the left ankle showed moderately extensive edema within the talus, tibiotalar synovitis, and a small joint effusion. The patient's culture from the synovial fluid was AFB positive and thus she underwent extensive evaluation for pulmonary TB. Chest x-ray and computerized tomographic scan of the chest did not reveal any cavitary lesions and her sputum culture for AFB was negative. Her tuberculin skin test was negative as well. The patient underwent arthroscopic debridement and irrigation twice and her synovial fluid was sent again for culture and found to be positive for AFB.

She was empirically started on clarithromycin, ethambutol, and rifabutin. After the identification of the M. *tuberculosis*, she was placed on a regimen of four drugs which included isoniazid (INH), rifampicin, ethambutol, and pyrazinamide. This regimen was modified based on the final culture and sensitivity report which revealed a multidrug-resistant form of TB. The organism was resistant to isoniazid and rifampin, and sensitive to pyrazinamide and ethambutol. The patient was then placed on the pyrazinamide, ethambutol, moxifloxacin, and ethionamide based on the recommendations of the infectious disease specialists. During her hospital stay, her tacrolimus level was monitored daily as anti-TB medications decrease the concentration of calcineurin inhibitors. Dosage of the patient's tacrolimus was challenging because it needed to be adjusted as needed to maintain therapeutic levels. MPA was discontinued secondary to the patients' risk of not responding to treatment in the setting of being immunosuppressed with a multidrug-resistant organism. Thus, she was continued on tacrolimus and prednisone as maintenance immunosuppression. She tolerated the treatment and remained in the hospital for 4 weeks. On discharge, her renal function was stable with a serum creatinine level of 1.6 mg/dL (her baseline), WBC of 4.2 $\times$ 10 E^3, AST of 10 unit/L, ALT of 12 unit/L and normal bilirubin levels. She was scheduled for follow-up examination in the infectious disease clinic for further management of the TB.

DISCUSSION

TB is an opportunistic infection common in renal transplant recipients. The prevalence of TB varies from 0.4% to 15% depending on the endemic areas [6]. In the United States, it is reported as 0.5% to 1.7% [7] in renal transplant recipients. Although its occurrence is less frequent in the United States, it occurs at a rate that is 35 times higher in the renal transplant population compared to the general population [7]. Morbidity and mortality from TB is high in renal transplant recipients compared to recipients without TB [7]. Mortality within 1 year, after diagnosis in renal transplant recipients, varies from 23% to 32% [7,8].

Although TB in transplant recipients can occur as a primary infection acquired by the donor graft or secondary to exposure after transplantation, it commonly occurs from reactivation of a latent infection in the recipient [3,6]. Although it most commonly manifests as pulmonary TB [3,4], extrapulmonary (16%–30%) and disseminated (10%–33%) disease can also occur [1,3,5,9].

Extrapulmonary sites include the gastrointestinal tract, lymph nodes, skin and soft tissues, central nervous system, urinary tract, pericardium, and the musculoskeletal system. TB in the bones and joints is rarely reported. Ascher et al reported three cases of TB involving monoarticular joints among 845 renal allograft recipients [10]. Elsewhere in the literature, TB has been reported as 1% in the musculoskeletal system, with joint TB occurring rarely [3,8].