

## RENAL ALLOGRAFT TUBERCULOSIS: A CASE REPORT

Hussam Alsoub, MD, CABM; Faraj S. Al Alousi, MD, CABM;  
Abdulrazzaq Haider, MD, FASCP

Renal transplant recipients are susceptible to a variety of infections with both common and opportunistic pathogens as a result of immunosuppressive therapy.<sup>1</sup> These infections cause significant morbidity and mortality.<sup>2</sup> In developing countries, poor socioeconomic conditions contribute to higher rates of infections in immunosuppressed patients.<sup>3</sup> Little attention has been given to mycobacterial infections compared to other opportunistic infections, such as *Pneumocystis carinii* and *Cytomegalovirus* in renal transplant recipients.<sup>4</sup> Earlier reports emphasized the rarity of tuberculosis (TB) in these patients,<sup>5,6</sup> however, more recent ones have documented high incidence of TB in renal transplant recipients.<sup>7,8</sup> Qunibi et al.<sup>8</sup> noted the presence of TB in 14 of 403 renal transplant recipients operated over a nine-year period, giving an incidence rate of 3.5%. On reviewing the literature, Singh et al.<sup>9</sup> found 437 cases of TB in renal transplant recipients. TB in these patients carries significant mortality and morbidity, and may jeopardize the function of renal allograft.<sup>10</sup> In this study, we report the involvement of a renal allograft by the infection in a patient with miliary TB, and review pertinent literature.

### Case Report

A 50-year-old man with chronic renal failure secondary to nephrolithiasis and recurrent urinary tract infection received a living-related renal transplant in February 1990. He had an uneventful postoperative course and was maintained on azathioprine, cyclosporin, prednisolone, prazosin, metoprolol, and nifedipine. Ten months after transplantation, he developed a sudden rise in his serum creatinine to 5 mg/dL. Investigations revealed normal ultrasound of the transplanted kidney with no evidence of obstruction. Renogram revealed normally perfused kidney. Renal biopsy revealed findings suggestive of cellular rejection. He was given methyl prednisolone and antilymphocyte globulin. His creatinine level dropped to 2.1 mg/L but never returned to normal. The patient developed progressive decline in renal function, ending in

end-stage renal failure. Table 1 shows serial measurements of renal functions, urinary protein excretions and blood pressure in the post-transplant period. The renal allograft was removed in January 1994. Histologic examination of the removed graft revealed evidence of chronic rejection. It also showed areas of interstitial granulomatous inflammation with caseation necrosis suggesting TB of the graft. The patient was not given anti-tuberculous treatment.

The patient was readmitted in March 1994, with complaints of fever, chills, cough, abdominal pain, and weight loss of one month's duration. His past history was unremarkable, and had no history of contact with a tuberculous patient. Details about the patients's tuberculin skin test (PPD) status prior to transplant and donor chest radiograph were not available. No chemoprophylaxis for TB was given to the patient in the post-transplant period. Physical examination revealed an ill-looking pale patient, with a temperature of 39°C, blood pressure of 140/90 mm Hg, pulse rate of 90/min., basal crepitations, hepato-splenomegaly, and tender right upper quadrant. Laboratory investigation revealed hemoglobin of 8.1 g/dL, WBC count of 4300/mm<sup>3</sup>, platelet of 73,000/mm<sup>3</sup>, normal liver transaminases, and alkaline phosphatase of 200 IU/L. HIV ELISA test, and PPD were negative. Chest radiograph revealed cardiomegaly, small bilateral pleural effusions, and interstitial infiltrate in both basal areas. Bone marrow examination revealed multiple granulomas with central necrosis. Ziehl-Neelsen stain for acid fast bacilli was positive, and culture of bone marrow aspirate later on grew *Mycobacterium tuberculosis* which was sensitive to isoniazid, rifampin, ethambutol, and streptomycin. Based on the result of bone marrow examination showing acid fast bacilli, a diagnosis of disseminated TB was made, and the patient was given isoniazid, rifampin, ethambutol, and ciprofloxacin. Steroids were not given. His hospital course was complicated by the development of hepatic encephalopathy and severe gastrointestinal bleeding, and he expired after 50 days of hospitalization.

### Discussion

Tuberculosis is a significant opportunistic infection in renal allograft recipients worldwide. Its incidence as reported in the literature varies according to ethnic and geographic factors from less than 1% in the West<sup>11</sup> to 15% in some developing countries.<sup>12</sup> The incidence of TB

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From the Departments of Internal Medicine, and Pathology and Laboratory Medicine, Hamad Medical Corporation, Doha, Qatar.

Address reprint requests and correspondence to Dr. Alsoub: Hamad Medical Corporation, PO Box 3050, Doha, Qatar.

Accepted for publication 5 July 2002. Received 30 September 2001.

TABLE 1. Serial measurements of serum creatinine, urinary protein excretion and blood pressure in the post transplant period.

Date	Serum creatinine (mg/dL)	Urine dipstick for protein	24-hour urinary protein excretion	Blood pressure (mm Hg)
17-12-1990	1	N		140/09
24-03-1990	1	N		110/70
12-05-1990	0.9	N		130/80
23-06-1990		N		150/80
04-12-1990	5			
23-02-1991	2.6	30 mg/dL		
18-05-1991	3.4	>300 mg/dL	3.4 gm	
03-08-1991	3.7	100 mg/dL		150/80
28-12-1991	4.3	100 mg/dL		

among transplant recipients is 37- to 50-fold higher than that among the general population.<sup>8,13,14</sup> This increased incidence is believed to be related to the effect of immunosuppressive drugs used in these patients, especially steroids, azathioprine, and antilymphocyte serum.<sup>15</sup> The dose of steroids may be critical. Doses of 10 mg or less of prednisolone are rarely associated with TB, however, higher doses, especially when used with azathioprine or chlorambucil are associated with increased risk of developing TB.<sup>16</sup> In addition, the presence of uremia before transplantation may contribute to this increased susceptibility by altering phagocytosis, serum bactericidal activity, and lymphocyte transformation.<sup>17</sup> TB in these patients is predominantly the result of reactivation of an old dormant tuberculous focus. Rarely, it is caused by nosocomial acquisition, or donor transmission.<sup>9</sup>

The clinical features of TB can be unusual, and may be masked because of the blunted response to infection.<sup>4,7,8</sup> In addition, extrapulmonary lesions are more frequent in patients following transplantation compared to patients without immunosuppression.<sup>8,9</sup> Disseminated TB is common in renal transplant patients, accounting for 40% of cases,<sup>9</sup> in marked contrast to the 0.6%-1.4% incidence in the general population.<sup>18</sup> Disseminated TB in these patients commonly presents as fever of unknown origin.

Pulmonary TB continues to be the most common form of TB in renal transplant recipients, occurring in 51% of cases.<sup>9</sup> Chest radiograph is abnormal in the majority of renal transplant patients with TB, showing focal infiltrate, nodules, miliary pattern, pleural effusion, and diffuse interstitial infiltrate.<sup>9</sup> Tuberculous infection of the kidney occurs in 11% of renal transplant recipients.<sup>9</sup> Renal allograft involvement by tuberculous infection, in all reported cases but one, was part of disseminated TB.<sup>9</sup> The overall mortality among renal allograft recipients with TB is 29%. Risk factors for mortality include disseminated disease, prior rejection, and receipt of OKT3 or anti-T cell antibodies.<sup>9</sup>

Treatment of TB in renal transplant patients is not different from that in the normal host, however, the use of rifampin must be undertaken with caution because of its frequent drug interaction, and blood levels of immunosuppressive drugs should be monitored.<sup>8,9</sup> The literature on the role of steroids in the treatment of patients with miliary tuberculosis suggests lack of effect. However,

steroids could have been beneficial in our patient because of the possibility of adrenal insufficiency secondary to suppression of the pituitary-adrenal axis from previous steroid therapy.<sup>19</sup> Although the issue of chemoprophylaxis against TB has remained controversial, isoniazid prophylaxis for high-risk patients is desirable.<sup>9,12,20</sup>

Our patient had progressive loss of graft function resulting in end-stage renal failure. The graft was removed, and the histology revealed evidence of both chronic rejection and tuberculous interstitial granulomatous nephritis. The cause of renal allograft failure is mostly due to chronic rejection, however, the superimposed tuberculous interstitial granulomatous nephritis contributed to this failure. Tuberculous interstitial granulomatous nephritis is a very rare condition in the course of kidney transplantation. Only seven cases have been described in the international literature.<sup>21,22</sup> Diagnosis is frequently delayed because it requires histopathologic examination of the graft. In the cases described, graft loss was a frequent outcome, as was the case in our patient. Our patient was unfortunate, in that the diagnosis of TB was not suspected as the cause of graft failure, and treatment was delayed for almost seven weeks, when he presented with miliary TB. This delay in treatment contributed to the poor outcome.

In conclusion, tuberculosis is a common and serious condition in renal transplant recipients. Because such infection carries a significant mortality and morbidity and may jeopardize the function of renal allograft, especially when there is delay in diagnosis and treatment, physicians who treat renal transplant recipients should be familiar with the manifestation of mycobacterial disease in this group of patients. A thorough search for TB is mandatory during pre- and post-transplant follow-up. Chemoprophylaxis against TB with isoniazid for high-risk patients seems advisable.

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