Tuberculosis in Iranian Kidney Transplant Recipients: A Single-Center Experience

A. Ghafari, K. Makhdoomi, P. Ahmadpoor, A.T. Afshari, M.M. Fallah, and K. Rezaee

ABSTRACT

Introduction. Renal transplantation recipients are at a high risk of developing tuberculosis (TB) following transplantation, especially in developing countries, with high incidences of morbidity and mortality. In this report, we examined the risk factors and impact of TB on the outcome of kidney transplantation.

Patients and methods. Among 1350 living donor Iranian kidney transplantations, 52 (3.9%) had TB diagnosed in various organs. Of these, 7 (13.5%) had TB pretransplantation and 40 (76.9%) were men. The overall mean age was 32.6 ± 10.5 years.

Results. The interval between transplantation and diagnosis was 54.6 ± 48.23 (range 4 to 140) months. In 34 (65.6%) patients TB was diagnosed after the first year posttransplantation. Pleuro/pulmonary TB was the most common form (68%). All posttransplant TB patients received a quadriple antituberculosis therapy; pyrazinamide, rifampicin, ethambutol, and isoniazide). Hepatotoxicity was seen in 16 (30%) patients, including 12 mild cases with normalization after temporary withdrawal of isoniazide and rifampicin, and four were severe, but mortality was not attributable to hepatocellular failure. Twelve patients (23%) died. Chronic allograft dysfunction occurred in 34 (65%) patients, 19 (37%) with graft loss. Pre-TB patients showed comparable posttransplant courses.

Conclusion. TB is a common infection among renal transplant recipients in developing countries. The peak incidence is after the first year of transplantation and mortality is considerable. Hepatoxicity is a considerable risk of treatment, possibly as a result of additive toxic effects of immunosuppressive drugs. Chronic allograft nephropathy is a serious complication that has a negative impact on the graft survival.

TUBERCULOSIS (TB) IS FREQUENT in developing countries. Because of drug-induced immunosuppression, renal transplant recipients are 50-fold more prone to develop this infection than the normal population.[1,9] Diagnosis and treatment of TB are more complicated in transplant patients. The reasons include atypical presentation and interactions between antituberculous and immunosuppressive drugs. The objective of this study was to report our experience with TB among Iranian living donor kidney transplant recipients.

PATIENTS AND METHODS

Between 1989 and 2005, 1350 living donor renal transplantations were performed: 763 males and 587 females from 52 living related and 1298 living unrelated donors. We reviewed hospital patient records and outpatient follow-up charts. TB was documented in the 52 renal transplant recipients, who are the subject of this retrospective analysis. We obtained information on demographic characteristics, diagnostic methods, immunosuppressive and antituberculous therapy, response to and complications of the treatment and patient and allograft outcomes.

Immunosuppressive Protocol

The immunosuppressant regimens varied in our kidney transplant recipients with TB according to the time of transplantation. All transplant patients pre-2000 received cyclosporine (CsA; 10 mg/kg/d),

From the Department of Internal Medicine, Division of Nephrology (A.G., K.M., P.A.), Department of Urology, Division of Renal Transplantation, (A.T.A., M.M.F.), and Department of Internal Medicine, Division of Pulmonary Diseases, (K.R.) Urmia University of Medical Sciences, Urmia Iran.

Address reprint requests to Ali Ghafari, Department of Internal Medicine, Division of Nephrology, Urmia University of Medical Sciences, Urmia, Iran. E-mail: ghaf_ali@yahoo.com

0041-1345/07/$–see front matter
doi:10.1016/j.transproceed.2007.03.013

azathioprine (AZA; 2 to 3 mg/kg/d) in addition to steroids. A bolus of methylprednisolone (500 mg) was given from days 0 to 2, then prednisolone at a dose of 1 mg/kg/d for 1 week, with a subsequent tapering to 0.15 mg/kg/d after 3 months. The CsA dose was adjusted to maintain the CsA blood trough level between 150 and 300 ng/mL in the first 6 months and between 125 and 175 ng/mL thereafter. After 2000, other protocols evolved, mycophenolate mofetil (MMF) was used instead of AZA. One hundred forty five (11%) patients received antithymocyte globulin (ATG) either as an induction protocol or as treatment of steroid-resistant acute rejection. Acute rejection episodes were treated with methylprednisolone pulses (500 mg/d for 3 days).

Diagnosis of Tuberculosis

Patients with clinical manifestations suggesting TB were thoroughly investigated. TB was diagnosed by one or more of the following methods: (1) demonstration of acid-fast bacilli in sputum and urine and/or growth in various culture media; (2) demonstration of mycobacterial tuberculosis antigens in blood, sputum, or urine using polymerase chain reaction; (3) demonstration of caseating granuloma by histopathological examination of tissue specimens; (4) favorable response to antituberculosis therapy in patients with: (1) chest x-ray changes indicating tuberculosis or (2) fever of unknown origin when extensive investigation yielded no clue.

Protocol of Antituberculosis Therapy

For the first 2 months all posttransplant TB patients received a quadriple antituberculosis therapy: pyrazinamide, rifampicin, ethambutol, and isoniazide. Therapy continued with rifampicin and INH at least for 9 months. Liver function tests were monitored weekly in first month. Increased serum transaminases (more than threefold over the baseline) was considered to be evidence of toxic hepatitis; INH was withheld until serum transaminases returned to normal.

Protocol of Antituberculosis Chemoprophylaxis

Antituberculosis prophylaxis was applied to patients who had a past history of TB, tuberculosis squeal on chest x-ray, or positive Mantoux test (induration $>$ 15 mm). INH was given at a dose of 300 mg day for 6 months.

Statistical Analysis

Statistical analysis was performed using SPSS. Group mean values were compared by Student *t* test, while chi-square tests were used for comparison of proportions. Kaplan-Meier curves were constructed for graft survivals in the two groups of transplant recipients. A P value $<$ .05 was considered significant.

RESULTS

Demographic Features

TB was diagnosed in 52 (3.9%) of 1350 renal transplant recipients (Table 1). Of these, seven had TB pretransplantation and 40 (76.9%) patients were males. The overall mean age was 32.6 ± 10.5 years (range 26 to 55). Patients received either AZA (18 patients) or MMF (34 patients) plus CsA and prednisone as therapy protocols. The time interval between transplantation and diagnosis of TB was 54.6 ± 48.23 months (range 4 to 140). In 34 patients (65.6%), TB was diagnosed after the first year posttransplantation. Mean serum creatinine was 1.8 ± 1.4 mg dL (range 0.7 and 6.0), in 17 patients the serum creatinine was $>$2 mg dL, at the time of diagnosis. Twenty patients (38.2%) had a history of acute rejection episodes treated with high-dose prednisolone and/or ATG before TB diagnosis.

Table 1. Comparison Between TB and non-TB Patients

	TB (n = 52)	Non-TB (n = 1298)	P
Age (y)	32.6 ± 10.5	30.21 ± 12.6	.07
Sex (M/F)	40/12	784/514	.001
Primary immunosuppression			
CsA, AZA, Pred	31	766	
CsA, MMF, Pred	21	530	.2
ALG	5	140	.5
Chronic rejection	25	188	.005
Post transplant hepatic dysfunction	16	83	.005
Causes of death			
Cardiovascular	4	64	
Respiratory	2	38	
Gastrointestinal	1	10	
Hepatic	0	7	
Cerebral	1	28	
Infection	4	51	
Malignancy		19	

TB, tuberculosis; CsA, cyclosporine; AZA, aziothioprine; Pred, prednisone; ALG, antithymocyte giobulin.

Localization of TB

The most common site was lungs (20 patients; 38%) or pleura (16 patients; 30.5%). Isolated extrapulmonary tuberculosis was diagnosed in 10 (19%) patients. Urinary TB was diagnosed in three patients (5.7%). Disseminated TB was seen in three patients, two of whom had miliary shadows on chest x-ray.

Clinical Presentation

Twenty-six (50%) patients who presented with fever of unknown origin were found to have miliary (six patients) or pulmonary (15 patients) TB. Despite extensive investigations, the etiology of the fever remained obscure in five patients. Because they responded favorably to antituberculous therapy, a diagnosis of TB was accepted. Other patients presented with low-grade fever, constitutional symptoms, or symptoms related to organ involvement.

Results of Diagnostic Interventions

Thirty-two (61.5%) patients had pathological findings on chest x-ray: infiltration in 12, pleural effusion in 10, miliary shadows in seven, or cavities in three. *Mycobacterium tuberculosis* was isolated from sputum in 22 patients. Caseating granuloma to were detected in the lymph node biopsies of seven patients. All patients with pleural effusion showed an exudative fluid with lymphocytic pleocytosis. In

Table 2. Outcome Among Patients Who Develop Posttransplant TB and non-TB Kidney Transplant Patients

	TB (n = 52)	Non-TB (n = 1298)
Living with functioning graft	29 (55.8%)	921 (71%)
Living on dialysis	11 (21.2%)	160 (12.3%)
Died with functioning grafts	4 (7.6%)	137 (10.5%)
Died on dialysis	8 (15.4%)	80 (6.2%)

11 patients with TB, the diagnosis was confirmed by histopathological examination. The Mantoux skin test was negative in all 21 patients in whom it was performed.

Results of the Treatment and the Outcome

Forty (78.8%) of the 52 patients responded favorably to the treatment by improvement, whereas 12 (22%) were deceased (Table 2). Four patients died as a result of disseminated TB, despite cessation of immunosuppressive therapy. Four patients died due to cardiovascular events. Two patients died due to respiratory failure, one due to gastrointestinal bleeding and another, cerebral hemorrhage. Chronic allograft nephropathy occurred in 34 (65%) patients. Nineteen (36.5%) patients returned to hemodialysis within the following 1 year of therapy.

Side Effects of Treatment

Toxic hepatitis was seen in 16 (30%) of the patients. After withdrawal of INH, serum transaminases levels returned to normal. Following reinstitution, no abnormality was observed in serum transaminases.

Results of Chemoprophylaxis

One hundred twenty patients were at risk of TB and received prophylaxis with 300 mg INH per day for 6 months. TB developed in 10 (8.2%) of the patients.

DISCUSSION

In developed Western countries, the prevalence of TB in renal transplant recipients ranges from 1% to 4%,[1,2,11] whereas higher prevalences up to 11.5% have been reported from developing countries.[3] In our series of 1350 living donor renal allograft recipients, 52 patients developed posttransplant TB, an incidence of 3.9%, which is moderately high probably due to the relatively high frequency of TB in Iran. The most common presentation is pleuropulmonary involvement.[11] In the literature, these two forms of involvement account for more than 75% of patients.[1,3,4] Rubin emphasized that the frequency of extrapulmonary TB is higher among organ transplant recipients compared with patients who are not taking immunosuppressive drugs.[5] The proportion of isolated extrapulmonary tuberculosis was 17/52 (32%) patients in our series, which agrees with previous reports.[1,3,4]

Immunosuppressive drugs are by far the main predisposing factor to infection in kidney transplant recipients.[9] MMF and ATG are known to impair host defense mechanisms; however, we observed no significant difference between the administration of MMF and ATG in TB versus non-TB recipients. Because of the atypical clinical and laboratory findings. The diagnosis of TB is more complicated in immunosuppressed patients. This may cause a delay in diagnosis and treatment. In our series, 26 (50%) patients presented with fever of unknown origin. In developing countries, TB is apparently a common cause of fever of unknown origin, especially after the first year of transplantation. The time to onset of TB symptoms posttransplantation varies. Some investigators observed a bimodal distribution: the majority of cases appeared early during the first 12 months posttransplantation.[1,8] In our group, 34 patients (65.6%) developed TB after 1 year posttransplantation.

Standard therapeutic TB regimens vary widely,[10] depending on renal function and on the presence of hepatic damage. There is no agreement on how many and which drugs should be used or on the optimal duration of treatment regimens. However, most reports suggest that three drugs should be used and that treatment should last at least 1 year. Some authors have advocated longer treatment regimens.[3] However, shorter 6- to 9-month courses have been equally effective for renal transplant TB patients especially in nonendemic areas.[14] We used a protocol of quadruple antituberculosis therapy: (pyrazinamide and ethambutol for 2 months; rifampicin and isoniazide for 9 month). In our series, 40 (78.8%) of 52 patients responded favorably to the treatment, whereas 12 (22%) were deceased.

Hepatotoxicity is a considerable risk, possibly as a result of additive toxic effects of immunosuppressive drugs.[6,7] In our series, we noted a more than three fold increase of serum transaminases levels in 16 patients (30%), which was severe enough to require cessation of rifampicin and/or INH in six patients. Mortality due to hepatic cell failure was not encountered in any of our tuberculous patients.

Chronic allograft dysfunction remained a major problem to overcome in our tuberculous kidney transplant recipients. Chronic allograft dysfunction occurred in 65% of the patients with 37% of them losing their grafts. Other authors have reported similar findings.[10,12,13]

We concluded that TB is a common infection among renal transplant recipients in developing countries. The peak incidence is after the first year of transplantation. Mortality is considerable. The risk of hepatotoxicity of antituberculous treatment is considerable, possibly as a result of the additive toxic effects of immunosuppressive drugs. Chronic allograft nephropathy is a serious complication that had a negative impact on the graft survival.[6,7,9,11–13]

REFERENCES

1. Qunibi WY, al-Sibai MB, Taher S, et al: Mycobacterial infection after renal transplantation report of 14 cases and review of the literature. Q J Med 77:1039, 1990

2. Higgins RM, Cahn AP, Porter D, et al: Mycobacterial infections after renal transplantation. Q J Med 78:145, 1991

3. Sakhuja V, Varma PP, Kathuria P, et al: Bone tuberculosis: an unusual case of mycobacterial infection in a renal allograft recipient. Nephrol Diat Transplant 8:868, 1993

4. Malhotra KK, Dash SC, Dhawan IK: Tuberculosis and renal transplantation observations from an endemic area of tuberculosis. Postgrad Med J 62:359, 1986

5. Rubin RH: Infectious disease complications of renal transplantation. Kidney Int 44:221, 1994

6. Thompson JE: How safe is isoniazid? Med J Aust 3:165, 1978

7. Antony SJ, Ynares C, Dummer JS: Isoniazid hepatotoxicity in renal transplant recipients. Clin Transplant 1:34, 1997

8. Aguado JM, Herrero JA, Gavalda J, et al:

9. De Paula FJ, Azevedo LS, Saldaniia LB, et al: Tuberculosis in renal transplant patients. Rev Inst Med Trop Sao Paulo 29:268, 1987

10. Vachharajani T, Abreo K, Phadke A, et al: Diagnosis and treatment of tuberculosis in hemodialysis and renal transplant patients. Am J Nephrol 20:273, 2000

11. Klote MM, Agodoa LY, Abbott K: Mycobacterium tuberculosis infection incidence in hospitalized renal transplant patients in the United States, 1998-2000. Am J Transplant 5:1163, 2005

12. Peschke B, Ernst W, Gossmann J, et al: Antituberculous drugs in kidney transplant recipient's treatment with cyclosporine. Transplantation 56:236, 1993

13. Chan GL, Sinnott JT, Emmanuel PJ, et al: Drug interactions with cyclosporine: focus on antimicrobial agents. Clin Transplant 6:141, 1992

14. Riska H, Gronhagen-Riska C, Ahonen J: Tuberculosis in renal allograft transplantation. Transplant Proc 19:4096, 1987