Tuberculosis after renal transplantation: experience of one Turkish centre

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Abstract

Background. In this study, renal transplant recipients with tuberculosis of different organs, were retrospectively analysed with respect to prevalence, outcome and drug toxicity.

Patients and methods. In 520 patients, 22 (4.2%) tuberculosis of various organs was diagnosed. The time interval between transplantation and diagnosis of tuberculosis was 44.4±33.5 (range 3–111) months. In 18 (82%) of the patients, tuberculosis was detected after the first year of transplantation. The most common form was pleuro/pulmonary tuberculosis (54%), and other localizations included jejunum, liver, bone, and urogenital tract.

Results. Sixteen of the 22 patients responded favourably to the treatment and maintain excellent allograft function, whereas six patients (27.2%) died. Toxic hepatitis was seen in four (18%) patients, and one case was complicated with acute hepatocellular failure due to isoniazide (INH). However, of the 23 patients at risk of tuberculosis who had had INH prophylaxis for 1 year, neither tuberculosis, nor hepatotoxicity was observed.

Conclusion. Tuberculosis is a common infection of renal transplant recipients in developing countries. The peak incidence is after the first year of transplantation and mortality is considerable. Hepatotoxicity is a considerable risk of treatment, possibly as a result of additive toxic effects of immunosuppressive drugs.

Key words: tuberculosis; renal transplantation; chemotherapy

Introduction

Tuberculosis is frequent in developing countries. Because of drug-induced immunosuppression, renal transplant recipients are more prone to develop this infection, the risk being nearly 50 times higher than in the normal population [1]. Diagnosis and treatment of tuberculosis are more complicated in transplanted patients. The reasons include atypical presentation and interactions between antituberculous and immunosuppressive drugs. Since little information on large series is available, we analysed our single centre’s experience concerning prevalence, outcome and drug toxicity.

Patients and methods

Patients

Between 1983 and 1996, 520 renal allograft recipients (403 male, 117 female; 209 cadaveric, 213 living-related donor, 98 living-unrelated donor origin) were followed in our transplantation out-patient clinic. In 22 patients tuberculosis was diagnosed. They are the subjects of this retrospective analysis. Information on demographic characteristics, diagnostic methods, immunosuppressive and antituberculous therapy protocols, response to and complications of the therapies, and the outcomes of patients and allografts was obtained by reviewing patients’ charts.

Immunosuppressive protocol

All patients who were transplanted before 1988 had been taking azathioprine (AZA) 1 mg/kg/day, plus prednisolone (PRD) 7.5–10 mg/day as immunosuppressive therapy; after this date, triple therapy with cyclosporine (CycA) AZA and PRD or other double therapy protocols (CycA+PRD, CycA+AZA, or AZA+PRD) were used. In patients taking CycA, the dose was adjusted aiming at trough serum concentration of 100–300 ng/ml, according to time after transplantation. Blood CycA concentrations were monitored twice weekly within the first month of antituberculous therapy and once monthly thereafter, using a fluorescence polarization immunoassay (Tdx).

III Diagnosis of tuberculosis

Tuberculosis was diagnosed by:

(i) Demonstration of acid-fast bacilli in urine and sputum (n: 4) and/or growth in different culture specimens (n: 5).
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(ii) Histopathological examination of tissue specimens, \( n: 8 \).
(iii) Favourable response to antituberculous therapy in patients with:
(a) Chest X-ray changes indicating tuberculosis, \( n: 8 \),
(b) Fever of unknown origin when extensive investigation yielded no clue \( n: 1 \).

**Protocol of antituberculous therapy**

All of the patients had been treated with both INH and rifampicin, along with pyrazinamide and/or ethambutol for the first 2 months. Therapy was continued at least for 12 months. Liver function tests were monitored weekly in first month. Increased serum transaminase (>4-fold over the baseline) was taken as evidence of toxic hepatitis, INH was withheld until serum transaminase had returned to normal.

**Protocol of antituberculosis chemoprophylaxis**

Antituberculous prophylaxis was applied to patients who had a past history of tuberculosis, and/or tuberculosis sequelae on chest X-ray. INH was given at a dose of 300 mg/day for 1 year.

**Results**

**Demography**

Tuberculosis was diagnosed in 22 of 520 renal transplant recipients (prevalence: 4.2%). Nineteen patients were male and three female, all of whom were Caucasian. The mean age was 34.6 ± 6.4 (range 24–44) years. Patients received either triple (11 patients) or one of the double (CycA + PRD; eight patients), (AZA + PRD; three patients) therapy protocols. The time interval between transplantation and diagnosis of tuberculosis was 44.4 ± 33.5 months (range 3–111). In 18 (82%) of the patients, tuberculosis was detected after the first year of transplantation. Mean serum creatinine was 2.0 ± 1.6 mg/dl (range 0.9 and 8.0) and only in three patients’ serum creatinine was > 2 mg/dl, at the time of diagnosis. Four patients had a history of acute rejection and had taken high dose of steroids to reverse rejection.

**Localization of tuberculosis**

The most common site was lungs (eight patients; 36%), or pleura (four patients; 18%); i.e. pleuropulmonary involvement accounted for more than half of the cases. Isolated extrapulmonary tuberculosis was diagnosed in seven (31%) of the patients: granulomatous hepatitis with caseous necrosis in two patients (11%), and in one patient each: intestinal tuberculosis (see Figure 1), tuberculosis osteomyelitis, urogenital, pericardial and meningeal tuberculosis. Disseminated tuberculosis was seen in three patients, two of whom had miliary shadows on chest X-ray.

One of the patients with cavitary pulmonary tuberculosis developed meningeal tuberculosis 3 months after starting antituberculous therapy. Laryngeal tuberculosis appeared in another patient, with cavitary pulmonary tuberculosis 1 year after stopping antituberculous drugs.

**Clinical presentation**

Six of the patients presented with fever of unknown origin and were found to have miliary [1], isolated liver [1] or pulmonary [3] tuberculosis. Despite extensive investigations, the aetiology of the fever remained obscure in one patient. Because he responded favourably to antituberculous therapy, the diagnosis of tuberculosis was accepted. One patient with jejunal involvement was admitted with intestinal perforation. Other patients presented with low grade fever, constitutional symptoms and symptoms related to organ involvement.

**Results of diagnostic interventions**

Fifteen patients had pathological findings on chest X-ray (soft opacities/infiltration in six, pleural effusion in four, cavities in three, miliary shadows in two). Mycobacterium tuberculosis was isolated in four patients; from sputum [3] and urine specimens [1]. Caseating granuloma was detected in liver biopsies of...
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2 patients. All of the patients with pleural effusion, pericarditis and meningitis had exudative fluid with lymphocytic pleocytosis. In eight of the patients with tuberculosis, the diagnosis was confirmed by histopathological examination (pleura: four, jejunum: one, liver: two and bone: one). The Mantoux skin test was found negative in all nine patients in whom it was performed.

Results of the treatment and the outcome

Sixteen (72%) of the 22 patients responded favourably to the treatment and improved with excellent allograft function, whereas six (27%) deceased. Four of the patients died as a result of disseminated tuberculosis, despite cessation of immunosuppressive therapy. One patient died due to liver failure, which was probably the result of INH-mediated chronic active hepatitis, and another patient died because of jejunal perforation and sepsis.

Kaposi’s sarcoma developed in two patients with miliary tuberculosis 2 and 23 months after diagnosis of tuberculosis. Regarding allograft function, two of the patients had returned to haemodialysis within the following 6 months of therapy, both of whom had serum creatinine >2 mg/dl at the time of diagnosis of tuberculosis.

Side-effects of treatment

Toxic hepatitis was seen in four (18%) patients. After withdrawal of INH, serum transaminase levels rapidly returned to normal in the first week and excluding the above mentioned patient who progressed to chronic active hepatitis and liver failure, INH was readministered in all cases. Following reinstitution, no abnormality in serum transaminase was observed. Because of drug interaction between rifampicin and CycA, the dose of the latter was increased up to 4-fold in 10 of the patients in order to achieve target serum concentrations. In one of the patients, 2 weeks after start of antituberculous therapy, acute adrenal insufficiency developed, and symptoms improved when the daily steroid dose was increased.

Results of chemoprophylaxis

Twenty-three patients were at risk of tuberculosis (see above) and received prophylaxis with 300 mg INH/day for 12 months. Tuberculosis and toxic hepatitis developed in none of the patients. One patient with a history of tuberculous osteomyelitis had received a living non-related donor allograft in India; he did not receive INH prophylaxis and tuberculous osteomyelitis recurred in the same site 16 months after renal transplantation.

Discussion

In developed Western countries, the prevalence of tuberculosis in renal transplant recipients ranges from 1 to 4% [1,2]; whereas higher figures up to 11.5% have been reported from developing countries [3]. Our figure (4.2%) is moderately high, probably because of the relatively high frequency of tuberculosis in Turkey. The most common presentation is pulmonary/pleural involvement often followed by dissemination. In the literature, these two forms of involvement account for more than 3/4 of the patients [1,3,4]. Rubin [5] emphasized that the frequency of extrapulmonary tuberculosis is higher in organ transplant recipients as compared to patients who are not taking immunosuppressive drugs. Indeed, many cases of bone, soft tissue (skin or muscular involvement), small intestine, vulva, and larynx tuberculosis have been reported [3,6–9]. The proportion of isolated extrapulmonary tuberculosis was 7/22 patients (31%) in our series in agreement with the previous reports [1,3,4,10]. Because of the atypical clinical and laboratory findings, diagnosis of tuberculosis is more complicated in immunosuppressed patients. This may cause a delay in diagnosis and treatment. In our series, six of the patients (30%) presented with fever of unknown origin. In developing countries, tuberculosis is apparently a common cause of fever of unknown origin, especially after the first year of transplantation. Another major problem in these patients is the hepatotoxicity of antituberculous drugs, especially of INH. It seems to be safe to use of INH alone. Among 1033 patients who were on INH prophylaxis, it was reported that only three patients developed toxic hepatitis attributed to INH [11]. Recently, Antony et al. [12] reported that none of the 83 patients who had received INH prophylaxis had toxic hepatitis or required discontinuation of the drug. They proposed that the risk of INH hepatotoxicity is low and not different from normal individuals. It has been reported that administration of rifampicin together with INH increases the risk of hepatotoxicity up to 8% in nontransplanted patients. A fatal course was reported in 4.6% of the patients with toxic hepatitis [13]. Although this possibility has not been definitely proven, hepatotoxicity of AZA and CycA may contribute to this complication. In our series, we noted a >4-fold increase of serum transaminase levels in four patients (18%), i.e. more frequently than in nontransplanted patients [13], in agreement with the findings of Sakhija et al. [10].

By increasing hepatic microsomal cytochrome P-450 enzyme activity, rifampicine decreases CycA levels [14]. In our series, the dose had to be increased by 50–400% to achieve pretreatment serum concentrations. By close readjustment of the dosage and close monitoring, these levels had reached a steady state nearly 4 weeks after starting of rifampicine. Rifampicin may also increase the clearance of prednisolone and by decreasing net immunosuppressive state, may result in an increased risk of acute allograft rejection. We did not see any rejection episode during antituberculous therapy, but acute adrenal insufficiency was noted in one patient. After this experience, it became our routine practice to increase daily prednisolone dose by 50% just after starting rifampicin.
It is concluded that tuberculosis is a common infection of 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.

Acknowledgements. The authors gratefully thank Dr E. Ritz for his valuable comments on the manuscript.

References

Received for publication: 13.11.97
Accepted in revised form: 28.1.98