

THE USE OF CYCLOSPORINE MODIFIES THE CLINICAL AND HISTOPATHOLOGICAL PRESENTATION OF TUBERCULOSIS AFTER RENAL TRANSPLANTATION

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SUMMARY

Tuberculosis is one of the most frequent opportunistic infections after renal transplantation and occurred in 30 of 1264 patients transplanted between 1976 and 1996 at Hospital São Paulo – UNIFESP and Hospital Dom Silvério, Brazil. The incidence of 2.4% is five times higher than the Brazilian general population. The disease occurred between 50 days to 18 years after the transplant, and had an earlier and worse development in patients receiving azathioprine, prednisone and cyclosporine, with 35% presenting as a disseminated disease, while all patients receiving azathioprine and prednisone had exclusively pulmonary disease. Ninety percent of those patients had fever as the major initial clinical manifestation. Diagnosis was made by biopsy of the lesion (50%), positivity to *M. tuberculosis* in the sputum (30%) and spinal cerebral fluid analysis (7%). Duration of treatment ranged from 6 to 13 months and hepatotoxicity occurred in 3 patients. The patients who died had a significant greater number of rejection episodes and received higher doses of corticosteroid. In conclusion, the administration of cyclosporine changed the clinical and histopathological pattern of tuberculosis occurring after renal transplantation.

KEYWORDS: Tuberculosis; Renal transplantation; Cyclosporine; Steroids.

INTRODUCTION

Infection is a frequent complication and one of the main causes of death in patients submitted to renal transplantation, even when considering the greater availability of diagnostic techniques and the increased efficacy of antimicrobial agents²⁹. This high frequency of infection is associated with the immunosuppressive therapy used in patients who are previously immunocompromised^{28,36}. In this situation, the incidence of tuberculosis (TB) is 0.5 to 1% in the United States and 1 to 4% in Europe, and can reach about 10% in underdeveloped/developing countries such as India^{32,33}.

Atypical clinical manifestations of TB are more often found in these groups of patients^{6,8,9,23,38,40} and the results are conflicting regarding the diagnostic value of the cutaneous test (PPD)³⁹. The use of chemotherapy immediately after transplantation is questioned and the impact of TB and of antituberculosis drugs on the patient and graft survival has not been established¹. Therefore, we studied the incidence of TB in 1264 renal transplant recipients and analyzed the clinical manifestations and the diagnostic methods used.

MATERIAL AND METHODS

A retrospective analysis of 1264 renal transplants was carried out at the Renal Transplant Unit of Hospital São Paulo, UNIFESP, and of

Hospital Dom Silvério Gomes Pimenta, São Paulo, during the period from June 1976 to March 1996. There were no exclusion criteria and all renal transplants performed during this period were considered eligible for the study. Tuberculosis was diagnosed in 30 of the 1264 transplant patients, with 22 receiving a graft from a living related and 8 from cadaveric donors. Seventeen patients received the renal graft from living haploidentical donors, 4 patients from an HLA identical donor and one from an HLA-distinct donor. The patients who received the transplant from cadaver donors were selected according to blood ABO compatibility, negative cross-match against HLA antigens and order of enrollment in the renal transplant program. The living donors were selected among family members based on ABO compatibility, HLA compatibility and negative cross-match against HLA antigens.

The diagnosis of TB was based on the following criteria: demonstration of alcohol acid-resistant bacilli (AARB) by bacterioscopy or microbial growth in culture, demonstration of caseous granuloma upon histopathological examination indicated by the presence of AARB, adenosine deaminase levels in the cerebrospinal fluid higher than 40 U/L or in the pleural effusion determined by the calorimetric method of Giusti³⁸.

Tuberculosis was classified, according to the site of isolation of *Mycobacterium tuberculosis*, into pulmonary TB when the bacterium was isolated from sputum and bronchial lavage, and extrapulmonary, when the bacterium was isolated from other tissues.

Immunosuppression consisted of a double therapy (azathioprine and prednisone) for patients transplanted up to 1986. From then on, cyclosporine was introduced and a triple therapy (azathioprine, prednisone and cyclosporine) was established. The initial dose of prednisone was 1.5 to 2 mg/kg/day and was then progressively reduced to 0.2 mg/kg/day on the 6th month. Azathioprine was administered at a dose of 1 to 2 mg/kg/day, being adjusted according to total leukocyte count. The initial cyclosporine A dose was 6 to 8 mg/kg/day, starting on the first post-transplant day, and adjusted to maintain its trough blood level between 100 and 250 ng/dL.

All patients with TB were initially treated using a combination of isoniazid (10 mg/kg), rifampicin (10 mg/kg) and pirazinamide (30 mg/kg), and subsequent combination with other drugs, when necessary. Pirazinamide was used only for the first 2 months of treatment while isoniazid and rifampicin were administered for 6 to 13 months. Hepatic function was monitored in all patients and hepatotoxicity was diagnosed when the alanine aminotransferase level increased four times, compared to the upper normal limit. Two patients had previously received isoniazid chemoprophylaxis.

The Student t-test was used for comparing continuous variables and $p < 0.05$ was set as the level of significance.

RESULTS

Tuberculosis was diagnosed in 30 patients (2.4%). Table 1 shows the demographic and clinical characteristics of the patients. Mean age was 33 years, ranging from 16 to 60 years. Twenty-one patients were males, 22 were white and 8 black. Mean weight was 52.7 kg and mean height 162 cm. The most frequent etiology of chronic renal insufficiency was chronic glomerulonephritis (70%). Mean time of dialysis was 32.2 months, ranging from 9 to 79 months. Twenty-six patients (86.7%) were on hemodialysis, 3 (10%) received continuous ambulatory peritoneal dialysis and one patient was on conservative treatment. Fifteen patients (50%) belonged to blood group type A, seven (23.3%) to group O, six (20%) to group B and two (6.7%) to group AB. Only one patient had received a second renal transplant.

The initial signs and symptoms of the disease are summarized in Table 2. Fever was the most frequently observed sign (90%), being generally intermittent and of low degree. Other common symptoms were weight loss (70%), cough (66.6%), profuse sweating (26.6%) and anorexia (20%). The lung was involved in 18 patients (60%). In 17 cases (57%) there was isolated lung involvement, in another case pleuropulmonary involvement was observed. Isolated pleural involvement occurred in 2 patients (7%), and in 4 cases other isolated sites were found to be affected (10%). Disseminated TB was observed in 6 cases (20%). Radiological chest findings are shown in Table 3.

No extrapulmonary TB was observed in patients receiving the double immunosuppression scheme, whereas the disseminated form was observed in 6/17 (35%) patients whose drug regimen included cyclosporine A (Table 4).

TB was diagnosed between 50 days and 18 years after transplantation, with four patients (13.3%) being diagnosed during the first 6 months after transplant, four (13.3%) during the following 6 months, five (16.6%)

Table 1

Demographic, clinical and laboratory characteristics of the 30 patients with TB

Number of patients	30
Mean age (years)	33 (16 - 60)
Gender, N (%)	
Male	21 (70)
Female	09 (30)
Race, N (%)	
White	22 (73.3)
Black	08 (26.7)
Weight (kg)	52.7 (\pm 11.2)
Height (cm)	162 (\pm 0.04)
Cause of renal failure, N (%)	
Chronic glomerulonephritis	21 (70.0)
Systemic arterial hypertension	02 (6.6)
Not determined	02 (6.6)
Diabetes	01 (3.3)
Other	04 (13.3)
Mean time on dialysis (months)	32.2 (9 - 79)
Mean follow-up time (months)	48.3 (50 days – 103 months)
First transplant, N (%)	29 (96.6)
Serum creatinine, mg/dl	2.43 (\pm 1.61)
Serum albumin, g/dl	3.65 (\pm 0.04)

Table 2

Signs and symptoms at the time when presenting with TB

	N	%
Fever	27	90.0
Weight loss	21	70.0
Cough	20	66.6
Sudoresis	8	26.6
Anorexia	6	20.0
Acute respiratory insufficiency	4	13.3
Lumbar pain	4	13.3
Chest pain	2	6.6
Cervical mass	2	6.6
Headache	2	6.6
Hoarseness	1	3.3
Ascites	1	3.3

Table 3

Radiologic findings of the chest in 26 patients with pleuropulmonary or disseminated TB

Chest X-ray pattern	N	%
Pulmonary infiltration	12	46.1
Pulmonary cavitation	06	23.0
Pulmonary condensation	04	15.3
Pleural hemorrhage	02	7.7
Pulmonary infiltration and pleural hemorrhage	01	3.8
Increased mediastinum	01	3.8

during the second year, and the remaining 17 cases after this period.

In patients receiving prednisone and azathioprine the manifestations of TB occurred at a later time. Of the 13 patients receiving the double scheme, the disease manifested in 11 after the first 3 transplant years (84.6%). In contrast, among the 17 patients using the triple immunosuppression scheme, TB occurred in 14 (82.3%) during the first 3 years of transplantation, with the disease being observed in 7 (41.1%) during the first year.

Primary extrapulmonary involvement occurred in one case before the end of the first year, and in 9 after the first transplant year. Three cases of disseminated TB were observed during the first transplant year.

In nine patients (30%) the diagnosis was established by direct staining of the bacillus in the sputum, and in two by microscopic examination of cerebrospinal fluid (CSF) smears. Nineteen patients were diagnosed by biopsy of the affected organs, with 10 cases being diagnosed by transbronchial biopsy, one of them together with cervical ganglion biopsy, three by pleural biopsy, one by biopsy of the pericardium and another

by biopsy of the cervical ganglion. In four patients TB was diagnosed at autopsy (Table 5).

The 19 biopsy cases were classified into three histological forms (Table 6): (a) “exudative” (four cases) characterized by a polymorphonuclear neutrophilic exudate, rupture of the basic tissue pattern with necrosis and a high amount of AARB; (b) “granulomatous” (three cases) characterized by the presence of typical tuberculous granulomas of the epithelioid form with occasional necrosis, giant cells and AARB, and (c) “mixed” (two cases) characterized by the presence of a neutrophilic exudate similar to that observed with the exudative form, and initial formation of epithelioid granulomas containing AARB. The exudative and mixed forms were associated with a poor clinical picture and were only observed when TB occurred during the first post-transplant year. The granulomatous form was mainly observed after the first post-transplant year. Of the 7 patients who died, four presented the granulomatous form, two the exudative form and two the mixed form.

Specific TB therapy consisted of different combinations of drugs, with isoniazid and rifampicin being used initially in all patients. The other drugs

Table 4

Tissues affected by TB in the total group of patients and in the groups receiving the double (azathioprine and prednisone) or triple (azathioprine, prednisone and cyclosporine) immunosuppression scheme

Localization	Double scheme N (%)	Triple scheme N (%)	Total N (%)
Lung	10 (77)	07 (41)	17 (57)
Pleura	02 (15)	01 (06)	03 (10)
Extrapulmonary	01 (08)	03 (18)	04 (13)
Disseminated	—	06 (35)	06 (20)
TOTAL	13	17	30

Table 5

Method of TB diagnosis in the 30 cases studied

MICROSCOPIC:	
AARB in sputum	09
Cerebrospinal fluid analysis	02
HISTOLOGIC:	
Tracheobronchial biopsy	10
Pleural biopsy	03
Tracheobronchial + ganglion biopsy	01
Pericardium biopsy	01
Autopsy	04

Table 6

Post-transplant year of TB diagnosis, immunosuppression scheme and histological presentation of 19 patients submitted to biopsy

TIME AFTER TRANSPLANT	IMMUNOSUPPRESSION SCHEME			
	AZA+PRED		AZA+PRED+CYA	
	N(%)	HISTOLOGY	N(%)	HISTOLOGY
1st year	1 (3)	1 exudative	7 (23) 3 exudative 2 mixed	1 granulomatous
2nd year	2 (6)		4 (13)	3 granulomatous
3rd year	3 (10)	1 granulomatous	3 (10)	1 granulomatous
4th year	0		1 (3)	
5th year	1 (3)	1 granulomatous	0	
6th year	2 (6)	1 granulomatous	1 (3)	1 granulomatous
7th year	0		0	
8th year	1 (3)	1 granulomatous	0	
9th year	1 (3)	1 granulomatous	1 (3)	1 granulomatous
10th year	3 (10)	1 granulomatous	0	

Abbreviations: AZA=azathioprine; PRED=prednisone; CYA=cyclosporine.

used were pirazinamide, ethambutol, streptomycin, ofloxacin, ciprofloxacin and azithromycin. Five patients showed an acute rejection episode after the beginning of therapy, three of whom did not recover renal function and returned to the dialysis program. Four of these patients used cyclosporine and three presented serum levels below 100 ng/dL, with a mean value of 91.75 ± 69.24 ng/dL, which was significantly lower ($p < 0.05$) than that observed for patients who were cured of TB and who maintained adequate renal function (162.16 ± 139.70 ng/dL). Two other patients received three different drug combinations due to hepatotoxicity and/or drug intolerance. The side effects observed were hepatotoxicity (2 cases), peripheral neuropathy (2 cases), hepatitis and neuropathy (1 case), gastritis, retrobulbar neuritis and labyrinthitis (1 case), and gout (1 case).

Of the 26 patients treated, 22 (84%) were cured, with treatment duration ranging from 6 to 13 months. Three patients died during treatment and one patient stopped treatment. No recurrence of the disease was observed in any case (Table 7).

Although the doses of azathioprine and cyclosporine were higher in the group of patients who died, they were not significantly different from those for the group of cured patients. However, the mean prednisone dose and the number of acute rejection episodes were significantly higher in the group of patients who died (Table 8).

DISCUSSION

The incidence of TB in patients with chronic renal insufficiency who receive renal transplant is higher than that observed for the general population, ranging from 0.5 to 1% in the United States, from 1 to 4% in Europe, being 3.5% in Saudi Arabia and ranging from 5.7 to 11.8% in India^{2,11}. This difference between continents reflects the variation in the incidence of TB in the respective general populations. We observed TB

in 2.4% of transplanted patients, a rate 5 times higher than the prevalence in the general Brazilian population which is estimated to be 0.5%^{25,30}.

Immunosuppression is the main factor predisposing to infection in transplant patients, however, it has not yet been established which drugs result in a higher risk²⁷. SAHN & LAKSHMINARAYAN reported reactivation of the disease in patients receiving high steroid doses^{17,31}, and MILLAR & HORNE observed more severe forms of TB in patients receiving more than 10mg/day of prednisone²¹. It was also shown that azathioprine causes dissemination of TB in experimental animals²⁴. Two studies^{13,26} did not report any relation between the incidence of mycobacterial infection and the use of cyclosporine as adjuvant in immunosuppression.

Among the studied patients diagnosed with TB, the oral prednisone dose and the number of treated rejection episodes were higher in those who died than in those who were cured. These results support the idea that the corticosteroid dose is related to the reactivation and severity of TB after renal transplantation³¹. TB was diagnosed in most of our patients (63.3%) during the first three years after the transplant, with 42% being diagnosed during the first year, a period during which the steroid dose was higher. The cases that occurred earlier tended to be more severe and had a higher mortality, which is in agreement with data reported previously by other authors^{1,22}. It is tempting to propose that, during this period, the immunosuppressive effect of previous uremia is still present, increasing the predisposition to infections^{3,4,12,15,24}. Of the five patients showing acute rejection during TB treatment, 4 presented blood cyclosporine levels lower than 100 ng/dL, corresponding to 50% of the level observed in patients without any alteration of graft function. This observation may explain the difficulties in finding the ideal dose for immunosuppression in order to prevent rejection and to minimize predisposition to opportunistic infections.

The histological pattern of the exudative form was observed during the first months after transplantation and was found to be associated with a poor prognosis. The granulomatous form showed a clinical picture similar to that found in non-immunosuppressed patients and occurred mainly after the first year of transplantation. One may speculate that high doses of corticosteroids play an important role in the presentation of the exudative form, preventing the organization of granulomas^{18,37}.

Fever was a predominant symptom and TB should be suspected in all transplant patients who present fever of not readily definable etiology, especially when the lung is affected. The AARB test employed in the affected system led to the diagnosis of 9 of the 30 patients. Bronchoscopy, a more aggressive approach, enabled the diagnosis of 11 patients.

Table 7

Evolution of the 30 patients with TB diagnosis after renal transplantation

Evolution	N	%
Cured after treatment – continue with functional graft	17	56.7
Cured after treatment – acute rejection and return to chronic dialysis	03	10.0
Cured after treatment - acute rejection controlled	02	6.6
Died during treatment	03	10.0
Died without treatment - diagnosis at autopsy	04	13.3
Left medical follow-up	01	3.3

Table 8

Dose of immunosuppressive drugs and number of acute rejection episodes in patients with a diagnosis of TB who died compared to those who were cured

	Azathioprine (mg/kg/day)	Prednisone (mg/kg/day)	Cyclosporine (mg/kg/day)	Number of acute rejection episodes
TB – cured (N=22)	1.63	0.41	5.19	1.60
TB – died (N=7)	1.84	0.65*	6.17	2.33**

* $p < 0.05$ and ** $p < 0.001$ compared to the cured group.

Pulmonary TB was the most common form of the disease and was diagnosed in 46% of our patients. QUINIBI *et al.*²⁷, in a review of 77 cases, found pulmonary lesion in 40% of patients and the disseminated form of TB in 33%. In a series from Southern India, pulmonary lesion occurred in 48%, while 26% presented disseminated infection^{19,34}. In the present study, simple radiologic examination of the thorax was abnormal in 86% of the patients with pleuropulmonary disease, with 46% presenting a miliary pattern. Mortality was lower when the disease was limited to the lung, and of the 7 patients who died, 5 had disseminated TB. Similar results have been reported in other studies^{35,37}.

The initially employed therapeutic regimen for TB did not differ from that used for the general population, but great caution is recommended for the combined use of antituberculosis and immunosuppressive drugs due to the high possibility of hepatotoxicity^{7,10,16,20}. The side effects of hepatotoxicity, gastric intolerance and peripheral neuritis led to discontinuation of treatment or to a change in the therapeutic scheme in 7 of 26 patients treated. Some authors avoid the use of rifampicin, even when serum cyclosporine levels are monitored¹.

Only 2 of the 30 patients were submitted to chemoprophylaxis after transplantation. Chemoprophylaxis with isoniazid (300 mg/day) for 12 months is indicated in the following situations^{5,14}: patients living in an endemic area of TB and with a positive family history, patients with a previous history of inadequate treatment, patients presenting a PPD test of more than 10 mm in diameter and patients with pulmonary calcification, pleural thickening and hilar prominence upon chest X-ray.

The cases presented here illustrate the importance of the diagnosis of TB in post-transplant patients and its therapeutic difficulties. Fever was the most common initial symptom, with an earlier and predominantly extrapulmonary incidence being more common in patients receiving cyclosporine in combination with azathioprine and prednisone, compared to those who received the double immunosuppression regimen only. The histological granulomatous form predominated in the diagnosed cases after the first year of transplantation, while the exudative and mixed forms were mainly observed during the first year.

RESUMO

O uso de ciclosporina modifica a apresentação clínica e histopatológica da tuberculose depois de transplante renal

A tuberculose é uma das mais frequentes infecções oportunistas encontradas após o transplante renal. A tuberculose foi diagnosticada em 30 de 1.264 pacientes que foram transplantados entre 1976 e 1996 na unidade de Transplante Renal do Hospital São Paulo – UNIFESP e no Hospital Dom Silvério Gomes Pimenta em São Paulo. A incidência de 2,4%, é cinco vezes superior à estimada para população geral brasileira. O diagnóstico foi realizado entre 50 dias a 18 anos após o transplante. Nos pacientes com esquema duplo de imunossupressão (prednisona e azatioprina), a manifestação inicial foi mais tardia, sendo que em 11 dos 13 pacientes ocorreu após os primeiros 3 anos de transplante. Enquanto com esquema tríplex (prednisona, azatioprina e ciclosporina), em 14 de 17 pacientes a doença ocorreu dentro dos primeiros 3 anos. Com esquema duplo de imunossupressão não houve manifestação de doença extra-

torácica, em contrapartida com esquema tríplex de imunossupressão a forma de apresentação disseminada ocorreu em 35% dos casos, sendo mais precoce e mais grave. A febre foi o sintoma clínico principal em 90% dos casos. O diagnóstico foi confirmado, em 50% (n=15) através da biópsia dos órgãos envolvidos, em 30% (n=9) através da pesquisa de bacilos álcool ácido resistentes (BAAR) no escarro, em 7% (n=2) no líquido céfalo-raquidiano e em 13% (n=4) através de necrópsia. O tempo de tratamento da tuberculose variou de 6 a 13 meses. A hepatotoxicidade relacionada ao tratamento, ocorreu em três casos. O número de tratamentos prévios de episódios de rejeição e a dose administrada de corticóides foram maiores nos pacientes que morreram com este diagnóstico, quando comparados ao grupo que respondeu ao tratamento. Em conclusão a forma clínica e histopatológica de apresentação da tuberculose é diferente após o transplante em pacientes utilizando ciclosporina, sendo a resposta ao tratamento influenciada pela dose prévia de corticóide.

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