Tuberculosis and renal transplantation – observations from an endemic area of tuberculosis

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Summary: Ninety-five renal transplant recipients from an endemic area of tuberculosis were investigated to find out the prevalence and course of tuberculosis in pre- and post-transplant periods. Eleven patients had tuberculosis in the pre-transplant period – pulmonary (2), pleural (2), miliary (1), abdominal (2), lymph node (5) and pericardial (1). They were transplanted after antituberculous therapy of 3 to 6 months with satisfactory results. The anti-tuberculous treatment was usually continued for 2 years. Only one of the above 11 patients had evidence of tuberculosis in the post-transplant period. Nine patients developed tuberculosis for the first time in the post-transplant period – pulmonary (4), pleural (1), miliary (1), lymph node (4) and pericardial (1). There was no mortality due to tuberculosis. Thorough search for tuberculosis is mandatory both during pre-transplant assessment and post-transplant follow-up in areas of endemic tuberculosis.

Introduction

Tuberculosis is still endemic in many parts of the world. Its incidence in the general population of India has been estimated at between 1 and 1.3% (National Tuberculosis Institute, 1974; Goyal *et al.*, 1978). The frequency of tuberculosis in patients on maintenance haemodialysis has been found to vary between 6–16 times as high as in the general population (Papadimitriou *et al.*, 1979; Lundin *et al.*, 1979; Sasaki *et al.*, 1979; Malhotra *et al.*, 1981). Tuberculosis therefore, poses an important problem in renal transplant recipients especially in areas of endemic tuberculosis. This paper reports our experience.

Materials and methods

Ninety-five renal transplant recipients seen at the Renal and Transplant Unit of the All India Institute of Medical Sciences, New Delhi, formed the subjects of this study. Special screening was done for possible tuberculosis during the maintenance haemodialysis and post-transplant periods. Specific investigations included tuberculin skin test, radiological studies, cultures of sputum, urine, pleural fluid, ascitic fluid and cerebrospinal fluid for acid fast bacteria (AFB);

biopsy of lymph node, pleura, liver and bone. Whenever the clinical picture was very suggestive of tuberculosis and a definitive diagnosis could not be substantiated by the above mentioned investigations, a therapeutic trial with anti-tuberculous drugs was given. The patients showing good therapeutic response were labelled as probable cases of tuberculosis.

In patients where tuberculosis was detected during the period of maintenance haemodialysis in the pre-transplant period, the dose regime was isoniazid (INH) 200 mg/day, ethambutol 7.5 mg/kg/day, rifampicin 450–600 mg/day. Pyridoxine was given (10 mg/day) in patients receiving INH during pre-transplant chemotherapy.

The treatment protocol in post-transplant tuberculosis was as follows: patients were given a combination of INH 300 mg/day, rifampicin 450–600 mg/day and ethambutol 15 mg/kg/day for an initial period of 3 months. They were treated for the subsequent 15 months with a combination of INH and ethambutol only.

Observations

Pre-transplant period

Eleven out of 95 renal transplant patients had tuberculosis in the pre-transplant period (Table I). There

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Table I Tuberculosis (TB) in renal transplant recipients in pre-transplant period

No.	Age & sex	MHD period before detection of TB (months)	Diagnosis of TB				Therapeutic trial	Follow-up period and progress after transplantation
			Clinical	Radiology	Culture	Histology		
1	30M	5½	fever, cough	Apical coin lesion lung	Sputum neg	nd	+	6 years 9 months, died fungal infection
2	21M	0	glands	negative	nd	gland		4 days, died due to surgical complications
3	22M	1	fever, glands	negative	nd	gland		One week, died AR
4	23F	9	fever, pleural effusion, ascites, liver +	pleural effusion	pleural & ascitic fluid-negative	mesentery liver & spleen		6 months, died CR
5	27M	1	fever, ascites, negative liver +	negative	Ascitic fluid-negative	negative	+	6½ years, well
6	40F	½	fever, glands	negative	nd	gland		6 years, CR now
7	42M	1	fever, glands	negative	nd	gland		5 years, well
8	23M	3	fever, glands	negative	nd	gland		3½ years, well
9	22M	7	pericarditis	pericardial effusion, apical lesion lung	effusion negative	nd	+	3½ years, well
10	40M	4	fever, pleural effusion, bone pain	pleural effusion, lumbar disc lesion	effusion negative	nd	+	2 years, well
11	28M	4	fever, abdominal pain	negative	nd	mesentery		1½ years, well

MHD = maintenance haemodialysis; nd = not done; AR = acute rejection; CR = chronic rejection; + = positive.

were five cases of lymphadenopathy, the cervical group being involved in 4 cases and external iliac in the other. The diagnosis of tuberculosis was documented by lymph node biopsy in all these cases. There were 2 cases (nos. 4 & 11) in which tubercles were seen on the peritoneum when pre-transplant appendicectomy was done; tubercles were also seen in the liver and spleen in one of these patients. In two cases there was suggestive clinical and radiological evidence of pulmonary tuberculosis with a positive therapeutic response to anti-tuberculous treatment (nos. 1 & 9). One patient had a unilateral pleural effusion along with tuberculosis of the lumbar spine (no. 10). One patient had exudative ascites and hepatomegaly (no. 5); this patient became afebrile after 2 weeks of anti-tuberculous treatment and his ascites disappeared completely in 6 weeks. All these patients were treated with anti-tuberculous drugs for a period of 3 to 6 months before they were transplanted. The anti-tuberculous drugs were given for a minimum period of 18 months. Out of these 11 patients, only one patient (no. 1) had evidence of tuberculosis in the post-transplant period.

This was seen at autopsy in the form of hilar lymphadenopathy.

Post-transplant period

Nine patients who had no tuberculosis in the pre-transplant period showed evidence of tuberculosis in the post-transplant period (Table II). In two patients (nos. 12 & 13) tuberculosis was not manifest clinically or on laboratory investigations in life but was found only at autopsy. The life of the transplant was 5 months and 2 months in these cases and they died due to causes other than tuberculosis. In the remaining 7 patients there was clinical, radiological and laboratory evidence of tuberculosis. The major form of tuberculous involvement was pulmonary which was observed in 5 cases. Lymphadenopathy was found in 3 cases. One case had pericardial effusion and another had pleural effusion, the aspirate was exudate in both these cases and they showed positive therapeutic response to anti-tuberculous therapy. The time interval between the occurrence of tuberculosis after

Table II Occurrence of tuberculosis (TB) in recipients in the post-renal transplant period

No.	Age & sex	Time of detection of tuberculosis after transplant	Diagnosis of TB				Therapeutic trial	Follow-up period and progress after transplantation
			Clinical	Radiology	Culture	Histology		
12	13M	5 months	asymptomatic	negative	nd	Lung & hilar glands at autopsy		Died, gastrointestinal bleed
13	20M	2 months	asymptomatic	negative	nd	hilar glands at autopsy		Died, AR
14	30M	2 y 8 months	gland fever	negative	nd	gland		4 years, well
15	26M	11 months	pericarditis	pericardial effusion	negative	nd	+	1½ years, died CR
16	24M	2 y, 1 month	fever, cough	apical lesion lung	sputum negative	nd	+	1 year, died CR
17	36M	1 y 5 months	fever	apical lesion lung	gastric lavage	nd		3 years, well
18	29M	1 y	Fever	Apical pneumonia	Sputum	nd		3 years, well
19	42M	6 months	fever weight loss	miliary mottling lung	negative	nd	+	1½ years, well
20	38M	1 y 1 month	fever pleural effusion	pleural effusion	effusion negative	nd	+	1 year, well

+ = positive; nd = not done; AR = acute rejection; CR = chronic rejection.

transplantation varied from 6 months to 32 months in these 7 patients. All of them were treated with anti-tuberculous drugs for a minimum period of 18 months and some of them are still continuing treatment. Five of these patients are doing very well and two patients have died due to chronic rejection.

Discussion

Tuberculosis poses a very important problem in renal transplantation programmes in areas of endemic tuberculosis (Malhotra *et al.*, 1981). A considerable number of patients for renal transplant in India have an antecedent tuberculous infection, the incidence being 11.5% in this study; such a high incidence of tuberculosis in the pre-transplant period has, however, not received much comment previously (Coutts *et al.*, 1979; Ascher *et al.*, 1978; Riska & Kuhlback, 1979; Walker *et al.*, 1981). There is difficulty in the diagnosis of tuberculosis in patients with advanced chronic renal failure because the normal clinical manifestations of infection may be absent or may be atypical (Boulton-Jones *et al.*, 1979; Nakhla & Goggin, 1973). Attention has been drawn to the cryptic form of miliary tuberculosis in the adults (Proudfoot *et al.*, 1969). This type of tuberculosis does not present the usual clinical and radiological features of miliary tuberculosis and is frequently missed in life. This is more likely to happen in patients on mainten-

ance haemodialysis. Pleuro-pulmonary involvement and lymphadenopathy were the major forms of tuberculous disease in our patients during the pre-transplant period. Difficulty was experienced in documenting a definite diagnosis of tuberculosis in 4 cases. Though the clinical, radiological and other investigations were highly suggestive, we had to depend upon a positive therapeutic response to make the diagnosis.

The incidence of tuberculosis in the post-transplant period was 9.5% in this study. These observations are in contrast to a very low incidence of tuberculosis reported in the post-transplant period in several series (Ascher *et al.*, 1978; Coutts *et al.*, 1979; Riska *et al.*, 1979; Walker *et al.*, 1981). The high incidence in our study can be explained by the fact that our patients lived in an area of endemic tuberculosis.

The clinical manifestations of tuberculosis in transplanted patients who are on immunosuppression are likely to be obscured and it may be difficult to detect them early. In two of our patients there was no suspicion of tuberculosis during life and the diagnosis could be made only at autopsy. Pulmonary involvement is the most frequent form of presentation of tuberculosis in the post-transplant period (Riska *et al.*, 1979; Ascher *et al.*, 1978; Coutts *et al.*, 1979). This is consistent with our experience. Ascher *et al.* (1978) however, found joint tuberculosis as the initial presentation in all three cases seen by them, though miliary involvement was observed in two cases later on. The earliest clinical manifestation of tuberculosis in the

post-transplant period was seen at 6 months in this study. The chances of occurrence of tuberculosis are higher during the earlier months of transplantation when immunosuppression is heavy.

There was no mortality due to tuberculosis in any of our cases. The experience of other workers has been similar (Ascher *et al.*, 1978; Walker *et al.*, 1981; Coutts *et al.*, 1979). Riska & Kuhlback (1979) observed that 4 out of their 10 transplant cases having tuberculosis died; however, autopsy did not reveal active tuberculosis in any of the treated patients. It appears that with effective anti-tuberculous treatment, the outcome of renal transplantation is not adversely affected.

A combination of rifampicin, INH and ethambutol has been usually employed for treatment, with satisfactory results. The correct duration of anti-tuberculous treatment has not been established. In most studies, treatment was continued for one and a half to two years. The side effects of antituberculous drugs in our experience were infrequent. We encountered INH

hepatitis in one patient and had to abandon the drug. There were cutaneous side effects with rifampicin in two patients, which settled down with reduction of the dose. Ethambutol did not cause significant adverse effects in any of our patients. Opinion regarding chemoprophylaxis in renal transplantation is highly controversial. One has to weigh benefit from long term anti-tuberculous drugs against their possible side effects.

None of the patients in this study had tuberculosis of the urinary tract. Tuberculosis as a cause of end stage renal disease is rare in our experience. In our 180 patients on maintenance haemodialysis over a period of 10 years, tuberculosis was found to be the cause of end stage renal disease in two cases only. These cases however, could not come on our transplant programme because of non-availability of suitable kidney donors. Therefore, we have no experience with the ileal conduit which is required in such cases.

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