MYCOBACTERIAL INFECTIONS IN RECIPIENTS OF KIDNEY ALLOGRAFTS. A SEVENTEEN-YEAR EXPERIENCE

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SUMMARY

During a 17-year period (1966-1983), 519 patients received renal allografts at the Johannesburg Hospital. Ten patients developed mycobacterial infections (MBI) in their post-transplant period — a prevalence of 1,7%. Eight were due to Mycobacterium tuberculosis (M. tuberculosis); of the remaining two, one was due to Mycobacterium kansasii and one to Mycobacterium forthuitum. Two patients died as a direct result of MBI.

The lung was the commonest site of infection — 7 cases — with M. tuberculosis as the infecting organism. Extrapulmonary primary sites of infection were seen in 3 cases, and they included brain and meninges, skin, subcutaneous tissue and adjacent joints.

Risk factors for developing MBI were analyzed with the aid of a control group of transplant recipients and showed that socioeconomic factors, payed a significant role in predisposing to MBI.

Immunosuppresive treatment and the degree of kidnet allograft function did not appear to favor the occurrence of MBI. Twenty patients known to have had pre-transplant pulmonary tuberculosis and given isoniazid (INH) prophylactic treatment post-transplantation have to date not shown any signs of tuberculosis reactivation. These facts may suggest that systematic INH prophylaxis may have a role in preventing MBI among patients undergoing renal transplantation in areas of high prevalence of tuberculosis as is the case of Third-World population groups.

RESUMO

Infecções por micobactérias em receptores de transplantes renais. Uma experiência de 17 anos.

Na unidade de transplantação do hospital de Johannesburgo, ao longo de um período de 17 anos (1966--1983), 10 indivíduos, de um total de 519 receptores de transplante renal, foram alvo de infecção por Micobactérias (IMB) — prevalência de 1.7%; oito por Micobacterium tuberculosis, um por Micobacterium Kansasii e um por Micobacterium fortuitum. Dois doentes faleceram como consequência destas IMB.

O pulmão foi o local de infecção mais frequente — 7 casos de M. tuberculosis. O cérebro e meninges, pele, tecido celular subcutâneo e articulações adjacentes foram os outros locais extrapulmonares de infecção.

Com a ajuda de um grupo de doentes transplantados de control, foi possível identificar factores sócio--económicos como predisponentes de IMB; por outro lado o regime terapêutico de imunosupressão e o grau de disfunção do enxerto renal transplantado, não pareceram estar associados a ocorrência de tais infecções.

A administração de isoniazida pós-transplante, a 20 doentes com um passado de tuberculose pulmonar, revelou-se eficaz na prevenção destas infecções, pois nenhum destes doentes apresentou até à data, quaisquer sinais de reactivação tuberculosa. Este facto poderá servir de justificação para a recomendação do uso sistemático de isoniazida como agente profilático da reactivação de IMB, em doentes receptores de transplante renal, oriundos de áreas com grande incidência de tuberculose, tal como é característico em indivíduos de grupos populacionais do Terceiro-Mundo.

INTRODUCTION

Mycobacterial infections in recipients of renal transplants, though uncommon, are associated with significant morbidity and mortality. A few reports have stressed the significantly high proportion of atypical, non-tuberculous mycobacteriae found in this group of chronically immunosuppressed patients [1-4].

In South Africa tuberculosis presents a major health problem and accounts for 83 percent of all notified infectious diseases. The risk of infection varies among the different population groups, being 2,2 percent in Blacks, 0,6 percent in those of mixed race, 0,4 percent in Asians, 0,1 percent in Whites [5]. In the present report we analyze retrospectively the experience of Johannesburg Hospital's Transplant Unit with mycobacterial infections occurring in recipients of renal transplants. The diagnosis, clinical features and treatment are described. Predisposing factors are examined, and suggestions for prophylaxis against mycobacterial infections in renal transplant recipients are discussed.

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PATIENTS AND METHODS

Five-hundred-and-nineteen patients receiving 589 kidney grafts over a 17-year period (from 1966 to December 1983) were studied. One-hundred-and-four received grafts from related living donors (RLD), in addition to which there were four pairs of identical-twin recipients. There were 429 white, 43 indian, 17 mixed-race and 20 black recipients. The immunosuppressive regimen used in these patients has been previously reported[6]; in brief, it can be divided into three main time periods: (1) 1968-71: high doses of prednisolone coupled with azathioprine and ALG; (2) 1972-78: high doses of prednisolone coupled with azathioprine; and (3) 1979-84: a lower dose prednisolone regimen coupled with azathioprine. During the latter half of 1983 some of these patients had been treated with cyclosporine and low-dose steroids (personal communication, 1984); nevertheless they have been included in this analysis as the latter drug combination has not influenced the pattern of mortality and morbidity in our patients as a whole.

Treatment of rejection episodes consisted of methylprednisolone (250-1000 mg) as a daily intravenous injection for 3 to 5 days. Pre-transplant chest radiography was obtained and was normal in all subjects. Tuberculin tests were not done preoperatively and none of the patients had been immunized with BCG.

To evaluate the influence of corticosteroid therapy on renal function following transplantation upon the development of mycobacterial infection (MBI), cumulative and steroid dosage at time of infection, as well as serum creatinine levels (used to assess renal function) were analyzed, both in the infected and control groups. Control subjects were obtained by selecting the three recipients of a cadaver (CD) graft transplanted consecutively after each individual MBI patient who had a functioning graft for at least one year, and had not had any evidence of MBI during the post-transplant period, nor had at any time received isoniazid (INH) treatment. In patients known to have pulmonary tuberculosis (PTB) prior to transplantation, INH was routinely used for prophylaxis against tuberculosis reactivation for a minimum period of 18 months.

Twenty patients (14 black, 3 Indian and 3 mixed-race) out of a cohort of 519 patients were known to have had PTB prior to transplantation. They were given prophylactic INH treatment following their kidney transplant. To date, none has developed any signs or symptoms of mycobacterium tuberculosis reactivation. Treatment of active post-transplantation MBI consisted of triple antimycobacterial drug combination, planned to be administered for at least 8 months, followed by INH maintenance therapy for at least a further 10 months (Table 1). Statistical methods included Chi square and t-test for comparative analysis of patient group data. Results, where indicated, are reported as mean ± 1 SD.

TABLE 1 **Treatment regimen for mycobacterial infections**

DRUG	DOSAGE*
RIFAMPICIN	Body weight < 50 kg - 450 mg
RIFAMPICIN	Body weight > 50 kg - 600 mg
ETHAMBUTOL	25 mg/kg/body weight
ISONIAZID**	300 mg if normal renal function
ISONIAZID	200 mg if impaired renal function
PYRAZINAMIDE***	1,5 gr

* Daily dosage for 8 months
** Used as maintenance therapy for a further 10 months
*** Used as fourth drug when failure of triple drug regimen

RESULTS

Ten cases proven MBI were diagnosed, giving a prevalence of 1,7%; 8 were due to Mycobacterium tuberculosis (M. tuberculosis), 1 to Mycobacterium kansasii (M.kansasii) and 1 to Mycobacterium forthuitum (M. forthuitum) (Tables 2 and 3). The median time of diagnosis was 10,9 months post-transplantation (3-33 months) with 9 patients presenting within the first year. Of the affected individuals, 9 were male and 1 female, with ages ranging from 27 to 45 years (mean 36,8 years). Seven patients were white and 3 were black, representing 1,6% and 15% respectively of the total white and black patients who received transplants in our unit. Two patients died as a direct result of their original MBI (cases 9 and 10). None of the patients were given prophylactic antituberculosis INH treatment prior to or after transplantation.

The pertinent features of the various case presentations of patients who developed MBI are summarized in the following sections. Methods of selection of controls provided us with 30 subjects for comparison.

Cases 1 to 7 (Table 2)

Pulmonary tuberculosis (PTB) occurred in 7 patients, all of whom were male; 4 were white and 3 black, in whom a history of contact with cases of active tuberculosis was obtained. The mean age was 31,2 years with a range of 27-45 years. In all these patients infection occurred during the first year post-transplantation (3-12 months). Two were RLD graft recipients. In 6 of the 7 patients the clinical presentaion was dominated by the presence of systemic symptoms which included fever, weight loss, malaise, night sweats and dry cough. The remaining patient (case No. 4) presented with shortness of breath and a pleural effusion without previous systemic manifestations. Diagnosis was verified bacteriologically in all patients; in 3 by sputum smear and cultures (cases 1, 2, 3), and in the remaining 4 by bronchoscopy or pleural biopsy. Chest X-ray revealed pleural effusion in 2 cases (Nos. 4, 6), and lung infiltrates — either diffuse or affecting predominantly the right upper lobe — in the other 5. Urine and bone-marrow cultures were negative in all cases. At the time of diagnosis the mean serum creatinine for this group was 172 μ mol/l with a range of 80-210μmol/l. None of the patients was diabetic or had acquired steroid-induced carbohydrate intolerance. The mean daily dosage of prednisolone at time of diagnosis was 16,0 ± 4,5 mg vs 15,4 ± 5,5 mg for the control group (p = NS). Five patients had been treated for rejection episodes. All were treated with triple drug combinations planned to be given for at least 18 months following the regimen shown in Table 1. Although serum drug concentrations were not measured, no toxic effects from anti-tuberculosis therapy were seen in any of the patients. All affected subjects were successfully treated; pulmonary infiltrates regressed in all, and positive sputum cultures reverted to negative. Two patients (Nos. 2, 7) developed chronic graft rejection, reaching endstage allograft failure 18 months post-transplantation, and requiring transfer back to dialysis. All the other PTB treated patients maintained adequate renal function.

Case No. 8 (Table 3)

A 36-year old male with chronic renal failure secondary to membranoproliferative glomerulonephritis (GN) Type II

received a RLD kidney graft. Prior to transplantation he had a nephrotic syndrome and a positive C, nephritic factor. This glomerular lesion recurred 26 months after transplant (biopsy-proven) and was again associated with a severe nephrotic syndrome (24-hour protein excretion 6 gr; serum albumin 28 gr/*l*). Thirty-three months after receiving his kidney graft he presented with erythema nodosum of the legs and two weeks later an erythematous indurated lesion on his right elbow associated with effusion and inflammation of the joint. No systemic symptoms were present. At the time of infection he was mildly hypertensive and his serum creatinine was 170 μmol/*l*. Immunosuppressive therapy at the time consisted of azathioprine 100 mg and prednisolone 12,5 mg daily. He had been treated for graft rejection once previously in the first month post-transplantation. Diagnosis was made by skin biopsy of the involved area, culture of which showed a M kansasii infection. Concomitantly, analysis of the joint effusion revealed a high white cell count with predominance of polymorphonuclear leucocytes. Roentgenographic study of the elbow joint showed only some surrounding soft-tissue swelling. Chest X-ray at the time of diagnosis was normal, sputum and urine smears were negative. Full blood count and blood glucose were within normal limits. This patient was treated with INH, ethambutol and rifampicin. Six months after initiation of therapy the skin lesion had entirely healed and there was complete resolution of the arthritis of the right elbow. The patient, however, developed chronic allograft rejection and returned to hemodialysis 4,5 years after his kidney transplant. No recurrence of MBI has been noted to date.

TABLE 2 **Clinical data of patients with pulmonary mycobacterial infections**

Case No.	Age Sex Race	Underlying Renal Disease	Kidney Source	Primary Site of Infection	Myco-bacterial species	Onset Post Transplant (Months)	Presen-tation	Diag-nosis	CXR	Renal Function	Rx	Outcome
1	38 M/W	Focal segmental Hyalinosis	RLD	Lung	M. tuberc	3	Systemic symptoms*	Sputum, Bronch-oscopy	RUL Infiltrate	Creat 140 Urea 9,6	INH Eth Rif	Alive Well
2	45 M/W	Chronic GN	CD	Lung	M. tuberc	12	Systemic symptoms	Sputum	Bilateral lung infiltrate	Creat 150 Urea 9,6	INH Eth Strep	Alive (Hemodyal)
3	32 M/W	Chronic GN	CD	Lung	M.tuberc	3	Systemic symptoms	Sputum	RUL Infiltrate	Creat 145 Urea 10,1	INH Eth Rif	Alive Well
4	39 M/W	Obstructive uropathy	CD	Lung	M. tuberc	12	Pleural effusion, Dyspnea	Pleural biopsy	Pleural effusion Fibrosis	Creat 180 Urea 7,2	INH Eth Rif	Alive Well

TABLE 2 (CTD) **Clinical data of patients with pulmonary mycobacterial infections**

Case No.	Age Sex Race	Underlying Renal Disease	Kidney Source	Primary Site of Infection	Myco-bacterial species	Onset Post Transplant (Months)	Presen-tation	Diag-nosis	CXR	Renal Function	Rx	Outcome
5	27 M/B	Chronic GN	RLD	Lung	M. tuberc	12	Systemic symptoms	Bronch-oscopy	RUL infiltrate	Creat 80 Urea 5,1	INH Eth Rif	Alive Well
6	37 M/B	Malignant hypertension	CD	Lung	M. tuberc	6	Systemic symptoms	Bronch-oscopy	Loculated effusion Pleural reaction	Creat 160 Urea 9,6	INH PZA Rif	Alive Mild renal impairment
7	39 M/B	Chronic GN	CD	Lung	M. tuberc	4	Systemic symptoms	Pleural biopsy	Bilateral upper lobe infiltrate	Creat 210 Urea 11,2	INH Eth Rif	Alive (Hemodyal)

* Systemic symptoms (fever, malaise, weight loss, night sweats). For abbreviations see under Table 3

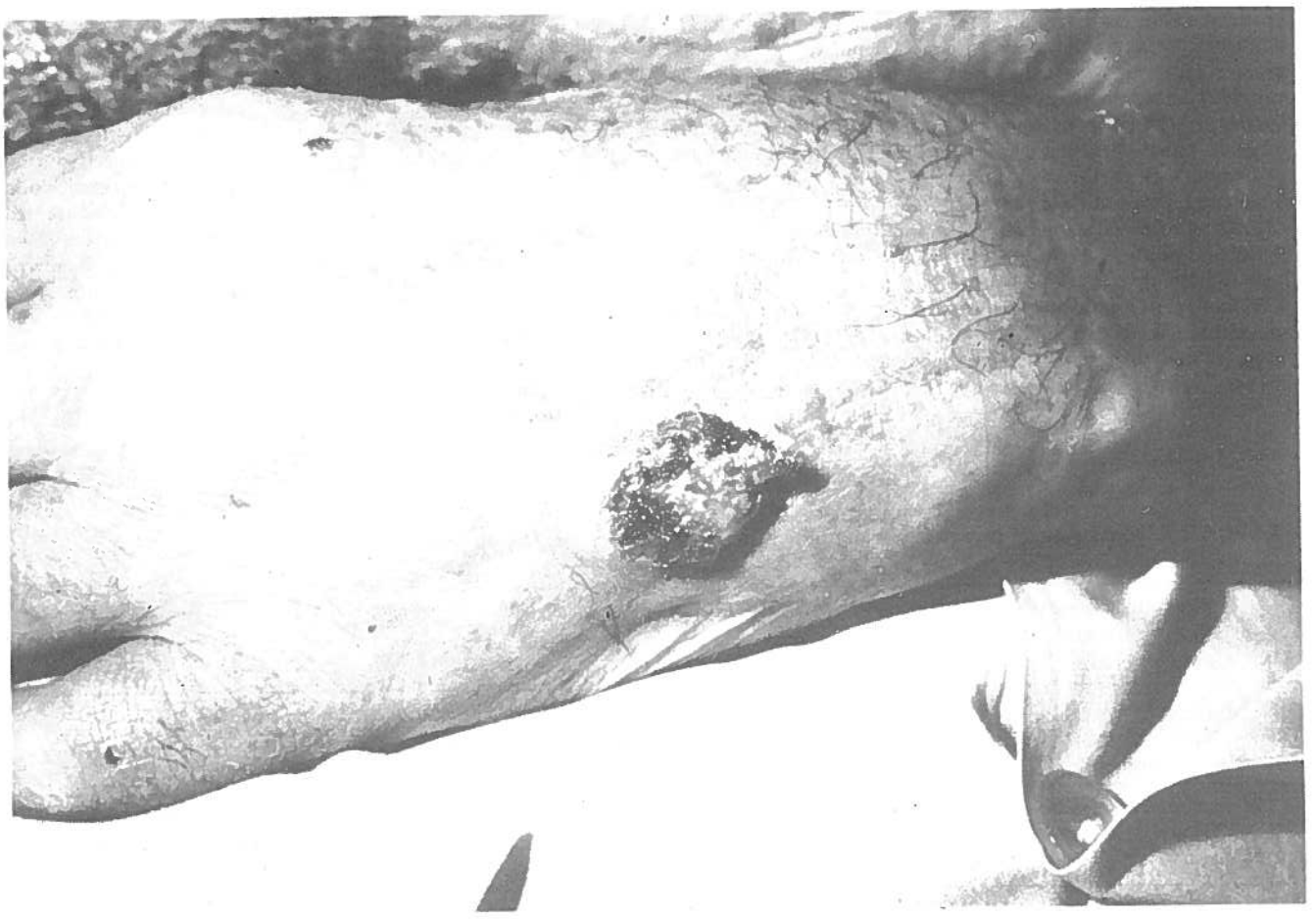

Figure 1 Skin ulcer of the left hand found to be due to M. forthuitum infection.

TABLE 3 **Clinical data of patients with extrapulmonary mycobacterial infections**

Case No.	Age Sex Race	Underlying Renal Disease	Kidney Source	Primary Site of Infection	Myco-bacterial species	Onset Post Transplant (Months)	Presen-tation	Diag-nosis	CXR	Renal Function	Rx	Outcome
8	36 M/W	Membrane-proliferative GN type II	RLD	Skin, sub-cutaneous tissue, elbow joint	M. kansasii	33	Erythema nodosum, fever, skin lesion, arthritis elbow	Skin biopsy	Normal	Creat 170 Urea 9,7	INH Eth Rif PZA	Alive Normal
9	42 M/W	Scleroderma	CD	Skin, sub-cutaneous tissue, wrist joint	M. forthui-tum	12	Hand abscess, wrist arthritis	Skin biopsy	Normal	Creat 150 Urea 8,3	INH Eth Rif CTX	Died*
10	33 F/W	Chronic GN	CD	Brain abscess**	M. tuberc.	12	Focal signs, mental confu-sion, pyrexia	Excision, pus culture	Normal	Creat 155 Urea 8,3	INH Eth Rif	Died*

* Died 10 months after presentation with dissemination of infection to other skin sites and lung
** Developed TB meningitis after M. tuberculosis brain abscess, and died

Abbreviations: INH = isoniazid; Eth = ethambutol; Rif = rifampicin; PZA = pyrazonamide; CTX = co-trimoxazole; GN = glomerulonephritis; Creat = creatinine; RLD = related living donors; CD = cadaver (grafts)

Case No. 9 (Table 3)

A 42-year old male with renal failure secondary to scleroderma received a CD kidney graft. One year post-transplantation he presented with an ulcer of the left hand and a swollen, painful left wrist joint (Fig. 1). He lacked any constitutional symptoms and enjoyed normal renal function. His therapy consisted of azathioprine 75 mg and prednisolone 15 mg daily. He had been treated for graft rejection twice in the first month post-transplantation. No history of tuberculosis (TB) or diabetes was obtained. A skin biopsy of the affected area was performed, and smears revealed abundant acid-fast bacilli. A M. forthuitum bacillus was grown from the tissue culture. Analysis of synovial fluid from the left wrist joint showed a high white cell count, predominantly polymorphonuclear leucocytes. Chest X-ray, full blood count, blood glucose, urine and sputum smears and cultures were all normal or negative. The patient was treated with INH, ethambutol and rifampicin, to which co-trimxazole was added, but despite this therapy he died 10 months later of progression of the disease with dissemination to the skin over the left tigh, scrofuloderma and diffuse lung involvement.

Case No. 10 (Table 3)

A 33-year old female with chronic renal failure secondary to chronic GN received a CD kidney allograft. Renal function was satisfactory (serum creatinine 155 μmol/*l*). One year post-transplantation she presented again, confused, pyrexial and with neurologic localizing signs. Prodromal constitutional symptoms were absent. A brain CAT scan showed an abscess in the left parietotemporal region which was surgically excised. Pus from the abcess revealed abundant M. tuberculosis bacilli. Chest X-ray on admission was normal, urine and blood cultures were negative. At the time of diagnosis she was taking azathioprine 25 mg and prednisolone 15 mg daily. There was no history of diabetes, tuberculosis or TB contacts. She was treated with INH, ethambutol and rifampicin for 8 months, and thereafter with INH alone. She improved rapidly and remained well clinically for 32 months, with normal chest X-rays and negative bacteriology for acid-fast bacilli. At the end of this time, however, she was readmited, pyrexial and semi-comatose, dying in cardiorespiratory arrest 3 hours after admission. Post-mortem examination revealed TB meningitis with all leptomeninges thickened and purulent.

Potential risk factors in MBI patients vs controls are detailed in Table 4. There were no statistically significant differences in the mean daily steroid dosage (at time of infection) or of cumulative steroid dosage between infected and control subjects. In the infected group the number of rejection episodes/patient/year was 1,8 ± 0,4 vs 1,6 ± 0,6 in the control group, which again was not statistically significant. The serum creatinine was similar in the two groups and revealed good graft function. Mycobacterial infection occurred in 15% of all the black patients transplanted vs 1,6% of all whites transplanted: this is highly significant statistically ($p < 0,0001$). It is important to note that the 3 affected black patients were subjected to greater physical stress, and lived in areas of poor housing and overcrowding (Table 4). They also admitted to possible TB contacts with close relatives prior to transplantation.

DISCUSSION

Despite the well recognized susceptibility of renal transplant recipients to infection, particularly of the lungs[6], only relatively few cases of MBI have been previously reported [1-4, 8-11]. The prevalence of MBI found in this series (1,7%) is in accordance with the published data [1, 8-10]. Atypical MBI was present in 20% of our patients, which also concurs with some reports where the proportion of non-tuberculous mycobacteria was 24,1% [2-4]. However, others reported atypical MBI in 42,8% of cases [1]. The lung was the commonest primary site of infection (70%). On one occasion the lung was secondarily infected as a result of dissemination of M. forthuitum infection from skin.

TABLE 4 **Potential Risk Factors for Mycobacterial Infections**

	Infected Group* (n = 10)	Non-infected Group (n = 30)	P value
Mean age at transplant	36,8 (27-45 yrs)	37,2 (29-47 yrs)	NS
Mean steroid dosage at time of infection (mg/day)	15,5 ± 3,9	15,4 ± 5,5	NS
Cumulative steroid dosage (mg/day)	62,2 ± 16,3	58,2 ± 17,1	NS
No. of rejections (patients/year)	1,8 ± 0,4	1,6 ± 0,6	NS
Mean serum creatinine (μmol/l)	154 ± 33	152 ± 26	NS
Sex Ratio (M:F)	9:1	5:1	NS
Poor socioeconomic background **	3 (Blacks)	—	—

* Seven Whites and 3 Blacks, representing 1,6% of all Whites and 15% of all Blacks transplanted ($p < 0,001$).
** Defined as malnutrition, physical stress and residence in areas of poor housing and overcrowding.

Extrapulmonary primary sites of infection were seen in 3 cases (30%); in 1 patient brain and meninges were infected with M. tuberculosis; in the other 2 patients skin, subcutaneous tissue and adjacent joints were infected with atypical non-tuberculous agents.

Most patients with PTB presented with systemic symptoms — fever, weight loss, malaise and night sweats — in contrast to patients with non-tuberculous mycobacterial skin infections in whom constitutional symptoms were absent. No patient had any history of pre-transplant PTB, although, as already pointed out, in 3 black patients, possible TB contacts with close relatives, prior to transplantation, were admitted; none had miliary disease.

The occurrence of PTB in our group of patients probably represents the recrudescence of healed (dormant) or latent disease. This assumption is supported by: (1) the occurrence of TB within a year of renal transplantation; (2) a renal transplant population coming from an area where TB is highly prevalent[5], and (3) absence of a miliary pattern of presentation. This high incidence of PTB found in our black patients (15% vs 1,4% in whites) is in accordance with figures reported from South Africa where the distribution of PTB is 82% in blacks and 1% in whites. Unfavorable socioeconomic conditions, poor housing, overcrowding and malnutrition have been postulated as significant contribution factors favoring the development and spread of tuberculosis among the black population.

In this group of patients, pre-transplant screening of latent or dormant mycobacterial infection by tuberculin-skin testing is difficult to interpret, and thus valueless, because of a high incidence of cutaneous anergy seen in these subjects with impaired cell-mediated immunity secondary to chronic renal failure.

It is important to note that bronchoscopy and lung or pleural biopsies were the means of diagnosis in 4 of the 7 PTB patients; repeated sputum smears and cultures had failed to reveal the infecting organism.

A short comment is appropriate concerning the 2 cases of non-tuberculous mycobacterial skin infections (cases 8, 9), in both of which diagnosis was made by skin biopsy. Roentgenographic studies of the affected joints were negative, which is in accordance with the known low incidence of bone involvement[12]. X-ray evidence of bone destruction is present, usually only with advanced disease[12]. Synovial fluid and smears were rich in polymorphonuclear leucocytes, and the high white cell count suggested the possibility of acute pyogenic bacterial infection rather than tuberculosis.

Analysis of risk factors for MBI in our patients revealed the mean cumulative and mean steroid dosages at time of diagnosis, as well as the number of rejection episodes/patient/year, to be not statistically different from the control group used for comparison, as was the mean serum creatinine at the time of the infective episode (Table 4). However, in case No. 8, a severe nephrotic syndrome could well be a significant factor contributing to the development of MBI.

However, in contradiction to the cumulative dose of immunosuppression or renal function, socioeconomic conditions and nutritional status were more important risk factors.

Treatment of MBI in recipients of transplanted kidneys is still not well defined, and there are several reasons for this. First-line anti-tuberculous drugs are not free of toxic effects, particularly in the presence of renal allograft dysfunction; drugs excreted by the kidney include INH, streptomycin and ethambutol. In addition, rifampicin, being an hepatic enzyme inducer, may interfere with immunosuppressive therapeutic agents which have to be given at a higher dosage. The length of treatment is also debatable, although there is some evidence that a long course of treatment is most effective. This appears to be a major importance in cases of meningeal or brain tuberculosis, where, and as illustrated by our case no. 10, the short course, (18 months), of triple drug therapy adopted, is likely to be the main if not the sole reason for the latter development of fatal TB meningitis. Our therapeutic regimen (Table 1) was generally successful and free of toxic effects, suggesting that treatment for MBI in renal transplant recipients is not different from that recommended for the ordinary patient, but potential drug toxicity should always be considered.

In countries where there is a relatively high incidence and an increased risk of reactivation of PTB among the black and coloured population groups undergoing transplantation the policy of long-term post-transplantation INH prophylaxis in those with a history of tuberculosis or highly suspected TB contact has been adopted. Of the 20 patients in our transplant unit known to have had previous PTB, and who received INH prophylaxis, none has to date had signs of M. tuberculosis reactivation.

Further studies are necessary to define strategies for the prevention and adequate treatment of MBI among kidney transplant recipients. The use of new immunosuppressive regimens, a high degree of clinical suspicion and aggressive diagnostic intervention, whenever indicated, may have an important role to play when renal transplantation is undertaken, especially among Third-World population groups.

ABBREVIATIONS

CAT	**Computerized arterial tomography**
CD	**Cadaver Grafts**
GN	**Glomerulonephritis**
INH	**Isoniazid**
MBI	**Mycobacterial infections**
M. forthuitum	**Mycobacterium forthuitum**
M. kansasii	**Mycobacterium kansasii**
M. tuberculosis	**Mycobacterium tuberculosis**
PTB	**Pulmonary tuberculosis**
RLD	**Related living donors**
TB	**Tuberculosis**

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