Mycobacterial infection in a series of 1261 renal transplant recipients

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Objective To describe the incidence and clinical characteristics of mycobacterial infection in renal transplant recipients.

Methods We retrospectively analyzed the cases of mycobacterial infection in a series of 1261 renal transplants carried out in our Unit of Renal Transplantation from 1980 to 2000. Demographic parameters and clinical antecedents such as age, cause of end-stage renal disease, time of follow-up of the graft, previous renal function and type of immunosuppression were considered. Moreover, the clinical onset, diagnostic tools, treatment policy and evolution were studied. The pathogenesis of the different types of mycobacteria isolated was also analyzed. Diagnosis was made with the Ziehl–Neelsen staining method. Culture was performed by the conventional Löwenstein–Jensen method and the Bactec-460 radiometric method.

Results We found mycobacterial infection in 27 patients (2.1%), due to *Mycobacterium tuberculosis* in 20 cases, *M. kansasii* in five patients, and *M. fortuitum* in two patients. The mean elapsed time from the renal transplant was 20.5 months; the infection appeared in 18 patients during the first eight months after transplantation. The clinical onset was pulmonary infection in 17 cases (12 *M. tuberculosis* and five *M. kansasii*); five had urinary symptoms (three *M. tuberculosis* and two *M. fortuitum*); three cases of *M. tuberculosis* infection had abdominal symptoms; another one began with a perineal tuberculous abscess; the rest of the patients were asymptomatic. The types of specimen on which microbiological identification was carried out were, in decreasing order: sputum and/or bronchial washing/pleural aspiration, urine, feces, gastric and peritoneal fluids, bone marrow and blood. The first-line drug isoniazid had the highest resistance index in the susceptibility test. Clinical dissemination was observed in eight patients, four of whom died. Another three patients had a significant impairment in renal function, and in one of these patients an allograft nephrectomy was necessary due to a severe septic syndrome.

Conclusions Mycobacterial infection, mainly by *M. tuberculosis*, has an important impact on kidney transplant recipients, particularly during the first year after surgery. Diagnosis often presents some difficulties, and a delay in treatment represents a determinant factor for the evolution, with a risk of death or permanent damage in renal function. Therefore, early diagnosis is mandatory. When the Mantoux reaction is positive, antituberculous prophylaxis seems advisable.

Keywords Mycobacteria, renal transplant, infection

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OBJECTIVE

Infection by mycobacteria in kidney transplant recipients is not rare, *Mycobacterium tuberculosis* being the most frequently isolated pathogen in our geographic area. The other mycobacteria (non-tuberculous mycobacteria) that cause infection, *M. kansasii*, *M. chelonae*, *M. fortuitum*, *M.*

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marinum and the *M. avium* complex, have a lower incidence. Kidney transplant recipients have a higher incidence of mycobacterial infection than the general population, due to cellular immunosuppression. In our environment, with a high prevalence of tuberculosis, it is very important to address this problem.

We retrospectively analyzed the impact of mycobacterial infection both on the renal graft and on the patient in a series of 1261 kidney transplants carried out in our unit over the last 20 years.

METHODS

This was a retrospective study analyzing those cases of infection caused by mycobacteria in our Unit of Renal Transplantation from 1980 to 2000. The study included 1261 renal grafts. The etiology of the end-stage renal disease (ESRD) in this group of kidney transplant recipients was mainly glomerulonephritis (13 cases), followed by interstitial pathology (11 cases), and polycystic renal disease (three cases). The mean time spent in the hemodialysis program was 35.9 months (25–60 months). The source of the graft, in the vast majority of cases (98.8%), comprised brain-dead heart-beating cadavers. In the rest of the cases, the graft came from living related donors.

The immunosuppressive drugs used were prednisone, cyclosporin A, azathioprine, mycophenolate mofetil, and tacrolimus. The immunosuppressive regimen combined two or three drugs, and was modified according to the graft evolution and appearance of toxicity (renal function impairment). Initially, the prednisone dose was 30 mg/day; this was reduced fortnightly, to reach a maintenance dose of 10 mg/day in the sixth month. The dose of cyclosporin A was 7 mg/kg per day, with variations according to blood levels (between 100 and 150 ng/mL). The dose of azathioprine was 1.5 mg/day, with a gradual reduction such that the treatment could be stopped in the third month. In the final two years, cyclosporin A was replaced by tacrolimus (0.1 mg/kg/day), and azathioprine by mycophenolate mofetil (1.5–2 g/day). During post-transplant follow-up, periodic surveillance cultures for mycobacteria were done at three, six and 12 months, and yearly thereafter.

The time between the kidney transplant and infection was analyzed, and so were the different clinical manifestations related to the affected organ and the presence of dissemination of infection.

Diagnosis was made with the Ziehl–Neelsen stain method. Culture was performed with the conventional Löwenstein–Jensen method and the Bactec-460 radiometric method (Johnson Laboratorie Towson, Baltimore, MO, USA; Becton-Dickinson, Madrid, Spain).

Microbiological identification was carried out by conventional methods (time of growth, morphology and stain pattern of the colony (pigmentation of the colony), niacin production, nitrate reduction, detection of catalase, etc). Sensitivities to the traditional antituberculous drugs were tested (isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide), and, with the help of the multiple ratio method, the sensitivities of second-line antituberculous drugs were also studied (para-aminosalicylate, kanamycin, capreomycin, cycloserine, and ethionamide). In some cases, the microbiological diagnosis was complemented with the pathoanatomic study of biopsy samples, where specific tuberculous granulomata were identified.

The treatment, its effectiveness, its side-effects and its pharmacologic interactions were also recorded. Finally, the evolution of the infectious process, and its effects on the graft and on the patient generally, and the patient's survival rate concluded the study.

RESULTS

Infection by mycobacteria developed in 27 (2.3%) of the 1261 renal transplant recipients. Twenty patients (74%) were infected with *M. tuberculosis*, five (19%) with *M. kansasii*, and two (7%) with *M. fortuitum*. The mean age of this group of patients was 43.9 years (range 21–62), and men predominated (17/27 cases). The main characteristics of the patients are described in Tables 1 and 2.

The mean duration of previous hemodialysis was 35.9 months (range 25–60). The causes of ESRD were glomerulonephritis in 13 (48%) cases, interstitial nephropathy in 11 (41%) cases, and polycystic renal disease in three (11%) cases.

Twenty patients (74%) showed good graft function (creatinine (Cr) <2 mg/dL, and urea <100 mg/dL). The other seven patients (26%) developed moderate renal failure (Cr levels between 2 and 5 mg/dL, and urea levels between 100 and 200 mg/dL).

Table 1 Main characteristics of patients infected by *M. tuberculosis*

Patient no.	Sex	Age (years)	Time after transplant (months)	Tuberculin test	Previous tuberculosis	Radiologic alteration	Type of disease	Specimen on which identification was carried out	Outcome
1	Male	48	7	Positive	No	No	Pulmonary	Sputum	Cured
2	Female	49	9	Negative	No	No	Pulmonary	Sputum	Cured
3	Male	45	4	Positive	Yes	Yes	Pulmonary	Bronchial washing, pleural effusion	Disseminated. Died
4	Male	36	114	Negative	No	No	Urinary	Urine	Cured
5	Female	32	2	Positive	Yes	Yes	Pulmonary	Bronchial washing	Disseminated. Cured
6	Female	37	56	Negative	No	No	Asymptomatic	Urine	Cured
7	Male	21	10	Positive	No	No	Intestinal	Feces, gastric aspirate	Disseminated. Cured
8	Female	46	15	Negative	No	No	Pulmonary	Bronchial washing	Cured
9	Male	33	5	Positive	No	No	Pulmonary	Sputum, bronchial washing	Disseminated. Cured
10	Male	38	39	Negative	No	No	Urinary	Urine	Cured
11	Male	55	7	Positive	No	No	Pulmonary	Sputum	Cured
12	Male	43	6	Positive	Yes	Yes	Intestinal	Blood, gastric aspirate, feces, BMA, PA	Disseminated. Died
13	Female	34	71	Negative	No	No	Skin abscess	Abscess aspirate	Cured
14	Female	36	40	Negative	No	No	Pulmonary	Bronchial washing	Cured
15	Male	32	8	Negative	No	No	Urinary	Urine	Cured
16	Female	38	12	Negative	No	No	Pulmonary	Bronchial washing	Cured
17	Male	39	35	Positive	No	No	Intestinal	Gastric aspirate, feces	Disseminated. Died
18	Male	45	6	Negative	No	No	Pulmonary	Bronchial washing	Cured
19	Female	34	44	Positive	No	No	Pulmonary	Sputum, feces	Disseminated. Cured
20	Male	50	28	Negative	No	No	Pulmonary	Sputum	Cured

PA, peritoneal aspirate; BMA, bone marrow aspirate.

Table 2 Main characteristics of patients infected by *M. kansaii* and *M. fortuitum*

Patient no.	Sex	Age (years)	Time after transplant	Mycobacterial species	Type of disease	Place of identification	Outcome
21	Male	62	7	*M. kansasii*	Pulmonary	Sputum, bronchial washing	Cured
22	Female	47	6	*M. kansasii*	Pulmonary	Sputum	Cured
23	Male	31	6	*M. kansasii*	Pulmonary	Bronchial washing, pleural effusion	Disseminated. Died
24	Male	51	7	*M. kansasii*	Pulmonary	Sputum	Cured
25	Female	58	2	*M. kansasii*	Pulmonary	Bronchial washing	Cured
26	Male	50	2	*M. fortuitum*	Urinary	Urine	Cured
27	Male	55	6	*M. fortuitum*	Urinary	Urine	Cured

The mean elapsed time from the renal graft to the infectious process was 20.5 months (range: 2–114). However, infections appeared in 18 (67%) cases during the first eight post-transplantation months. The most frequent initial clinical manifestations were: pleuropulmonary in 17 cases (63%), urinary in five cases (19%), intestinal in three cases (11%), and a perineal tuberculous abscess in one case (4%); the remaining case was asymptomatic (4%).

M. tuberculosis was isolated in 12 cases with pleuropulmonary manifestations, and *M. kansasii* in five patients. Intestinal manifestations were due to *M. tuberculosis* in all cases. Urinary infection was caused by *M. tuberculosis* in three cases and by *M. fortuitum* in two cases. Therefore, *M. kansasii* always produced respiratory infection, whereas *M. fortuitum* was always responsible for urinary infection.

Eight patients (30%) underwent clinically evident dissemination; seven cases involved *M. tuberculosis*, and one case *M. kansasii*.

Infection with *Mycobacterium tuberculosis*

In total, 12 men and eight women had *M. tuberculosis* infections (1.6%). The mean ages were 40.4 and 38.3 years, respectively (range: 21–55). The mean time of immunosuppression was 25.9 months, but 11 of the 20 cases appeared during the first year after the graft. The renal function previous to the infectious process was normal in 16 of 20 (80%) patients.

Pulmonary manifestations

Twelve of 20 cases (60%) showed respiratory problems, the main symptoms being fever, cough, expectoration, pleuritic pain, and non-specific symptoms (weight loss or night sweats). The chest radiograph showed non-segmental consolidation in all cases, with a miliary pattern in four and pleural effusion in three. Dissemination of infection occurred in four of the 12 cases; one of them required allograft nephrectomy (since the graft was established as the septic focus), another died, and, in a third, renal function was permanently impaired.

Intestinal manifestations

Three (15%) patients presented with abdominal pain, fever and constitutional symptoms: there was dissemination of infection in all three. One of them had an intestinal perforation that required urgent surgical treatment (intestinal resection). The other two died, one of them after a severe intestinal hemorrhage secondary to a tuberculous duodenal ulcer, and the other as a direct consequence of a septic syndrome complicated by multiple antimicrobial resistance.

Other clinical manifestations

Three (15%) patients had irritative urinary symptoms and fever; another one developed a perineal tuberculous abscess, and his condition improved after surgical drainage; the remainder of the patients with infection were completely asymptomatic.

Infection with *Mycobacterium kansasii*

In total, three men and two women had *M. kansasii* infections (18.5%). The mean age was 49.8 years (range: 31–62). The time of immunosuppression was 5.6 months (range: 2–7). All patients had pulmonary manifestations with fever and foci of pneumonic consolidation; one patient died of acute respiratory failure due to massive dissemination.

Infection with *Mycobacterium fortuitum*

The two cases were men (50 and 55 years old), and the infection appeared after two and six months of immunosuppression, respectively. The clinical onset comprised micturitional symptoms and fever, and the urinalysis showed the presence of sterile pyuria. The evolution after treatment was, in both patients, excellent.

Elapsed time from graft transplantantion to clinical onset was different depending on the microorganism involved (Table 2).

Microbiological parameters

The specimen for the microbiological identification depended on the organs involved and the presence or absence of dissemination. In those patients with pleuropulmonary manifestations, the bacillus was identified from sputum and bronchial washings or from the pleural fluid. In patients with urinary symptoms, the microorganism was isolated from urine. When an infectious disseminated process was suspected, samples were collected from multiple locations; consequently, in the three cases of intestinal tuberculosis, the mycobacterium was present in pleuropulmonary secretions, urine, and feces. Furthermore, in pathoanatomic studies, granulomata were identified in biopsy samples of lung, peritoneum, ileal wall, and laryngeal mucus.

In 18 patients, the pattern of resistance to antituberculous drugs was analyzed, always including isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide, among others. One isolate of *M. tuberculosis* was resistant to isoniazid, rifampicin and streptomycin, and the patient was treated with ethambutol, pyrazinamide, and the second-line drug para-aminosalicylic acid. On the other hand, *M. kansasii* was often resistant to isoniazid (four of five cases), and *M. fortuitum* was resistant to the four drugs (Table 3).

Treatment

The first-line antituberculous drugs were isoniazid, rifampicin, and ethambutol. Streptomycin and pyrazinamide were used as a fourth drug or as a substitute for ethambutol. Doses were those recommended: isoniazid 300 mg/day, rifampicin 600 mg/day, and ethambutol depending on the renal function. Changes in immunosuppressive drugs were made according to levels and variations of antituberculous drugs (according to the levels of immunosuppressive and antituberculous drugs used). As secondary effects attributed to these drugs, we must emphasize effects on the liver, marked by mild and temporary elevations in the levels of transaminases in three cases. In one case, ethambutol caused skin desquamation associated with urticaria and deterioration of renal function. Rifampicin and cyclosporin A are metabolized by the same cytochrome (P-450), so it was necessary to increase the cyclosporin A dose or, in some other cases, to replace the rifampicin with pyrazinamide. In four cases, it was necessary to increase the doses of cyclosporin, and in three cases, to substitute rifampicin for pyrazinamide.

The duration of treatment was at least 9 months, but among the cases of miliary tuberculosis or disseminated infection, a longer duration and the use of a fourth drug was necessary in eight cases. When the infection was due to atypical mycobacteria, our choice of treatment was strictly based on the antibiogram in order to avoid the foreseeable high index of antimicrobial resistance. Therefore, for *M. kansasii*, isoniazid was replaced by ciprofloxacin, and for *M. fortuitum*, treatment was with aminoglycosides, amoxicillin–clavulanic acid, and cephalosporins.

Evolution

There was significant impairment of renal function in three patients (11%). Allograft nephrectomy was needed in one of these cases (due to

Table 3 Antimicrobial sensitivity (available in only 18 cases)

	Number susceptible to			
	Isoniazid	**Rifampicin**	**Ethambutol**	**Streptomycin**
Mt (11)	10	10	11	10
Mk (5)	0	5	5	5
Mf (2)	0	0	0	0

Mt, *M. tuberculosis*; Mk, *M. kansasii*; Mf, *M. fortuitum*.

infectious dissemination by *M. tuberculosis* with graft infection). In the rest of the cases, there was a mild deterioration of renal function but later recovery.

The mean follow-up was 54.4 months (range: 7–122). In one patient, a clinical recurrence after three months of treatment was detected, requiring a change of the antituberculous drugs and the use of a fourth drug.

DISCUSSION

The pathogenic nature of the mycobacteria, apart from *M. tuberculosis*, is not well known. Infection by mycobacteria usually appears in immunocompromised subjects and with a typical onset of pulmonary manifestations. However, mycobacteria sometimes cause lymphadenitis, cutaneous and osteoarticular infections, and, less frequently, infection of the genitourinary tract and of the central nervous system (meningitis). Dissemination is not a frequent event. Diagnosis is often difficult, because the patients are immunocompromised, and consequently they show atypical manifestations [1].

In our series, *M. tuberculosis* presented with serious intestinal manifestations in three cases, and with a subcutaneous abscess in another case. *M. kansasii* showed pulmonary manifestations similar to tuberculosis. Dissemination appeared in only one case, but with lethal consequences. *M. fortuitum* was responsible for two urinary infections of less importance.

Mycobacterium tuberculosis

The incidence of tuberculosis in kidney transplant recipients varies according to the prevalence in the general population, and is higher in areas such as India or South Africa, where this disease is endemic. In several series, prevalences of 0.35–1.2% in the USA, 0.7–5% in Europe and 5–15% in South Africa and India have been described; these prevalences are up to 100 times higher than those in the general populations of these countries [2–8]. In our series, the incidence was 1.6%, which is slightly higher than previously reported in Spain by Aguado et al. [9]. Prophylaxis with isoniazid (300 mg/day) and pyridoxine (25 mg/day) is not routinely carried out, since these drugs are toxic and the resistance levels to isoniazid are increasing. In our unit, prophylaxis with isoniazid (for 9 months) is carried out in patients with radiologic features compatible with old pulmonary infection or a positive Mantoux reaction (a purified protein derivative (PPD) skin test was performed as soon as the patient was included in the waiting list for a cadaveric transplant), as long as active tuberculosis is ruled out (by means of a sputum study with Ziehl–Neelsen stain and Lowenstein culture), and provided that there are no contraindications to isoniazid administration (previous hepatitis due to isoniazid and acute hepatic disease). Follow-up includes mycobacterial cultures. According to Singh and Paterson [6] and Qunibi et al. [7], the indications for prophylaxis with isoniazid for a year are: tuberculin test >5–10 mm before the transplant without previous treatment; evidence of an old tuberculous untreated lesion on chest X-ray; a history of inappropriate tuberculosis treatment; contact with patients with active disease; and an incorrectly treated donor with a medical history of tuberculosis or a positive tuberculin test without adequate prophylaxis. In the series of Higgins et al. [4] (11 cases of mycobacterial infection out of 633 renal transplants), there were no cases of tuberculous infection among the patients who received prophylaxis. However, among those patients without prophylaxis (in spite of a higher risk as a result of being in an endemic area), a tuberculous infection developed in 22% (six of 27 patients). Riska et al. [8] stated that prophylaxis with isoniazid was not indicated for those patients whose tuberculosis had been properly treated. Clinical experience shows that isoniazid alone is effective as prophylaxis but is not completely protective.

The number of patients reported in the majority of published series is less than 10, and so our series is one of the largest reported. The clinical onset in other series usually occurred before the end of the first year after transplantation [7], and patients with a positive tuberculin test developed tuberculosis earlier [6]. In our series, the average time of presentation was 25.9 months, but infection appeared in 11 patients during the first 12 months after transplantation. The mean age of our patients was 39.6 years, which is very close to that reported by Qunibi et al. [7], where 71% of patients were under 40 years old.

Activation of latent tuberculosis in a context of immunodeficiency is more likely to disseminate, becoming worse if the patient also presents other immunodeficiency factors, such as uremia [7].

Infection from contaminated donors is also possible [10,11]. On the other hand, contamination from bronchoscopes or endotracheal intubation has also been reported [12].

Fever is the most common symptom, together with anorexia and night sweats. Specific clinical manifestations vary depending on the affected organ. In pulmonary infection, expectoration and pleuritic pain are very common; the most frequent radiologic patterns are focal infiltration and a miliary pattern. In our series, fever was recurrent, and miliary dissemination was found in four cases. In one such case, an allograft nephrectomy was required, owing to septic problems associated with severe renal failure.

Intestinal infection is the most frequent extrapulmonary manifestation. Abdominal pain and intestinal bleeding are the most common clinical features [6]. In our series, dissemination occurred in three cases, with subsequent massive hemorrhage and intestinal perforation in two of them. The third patient died because of dissemination and resistance to the first-line antituberculous drugs.

Urinary tuberculosis is relatively uncommon, with an incidence of 7.1–11% in the most important series [6,7]. In our study, it accounted for 15% of cases. Other areas less often affected are skin, muscle, and the osteoarticular system. Tuberculous meningitis and brain abscess appear in the context of dissemination. In our series, a patient presented with a perineal abscess; tuberculous granulomas were identified in another patient through a larynx biopsy, and a third case presented with a tuberculous subcutaneous abscess.

Tuberculous dissemination occurs in 40–64% of cases [6,7] versus 0.6–1.4% in the general population [13]. In our series, dissemination occurred in 35% of cases. The most frequent clinical features are fever, cough, abdominal pain, dyspnea, and fatigability, and the mortality rate is about 37%. The type of immunosuppression seems to play an important role, since several authors report a higher dissemination risk if OKT3 anti-cell (anti-CD3 monoclonal antibody) is used [6,14]. John et al. [15] did not find differences in the incidence of dissemination between patients treated with cyclosporin and those treated with conventional immunosuppression.

In the general population, the most common antituberculous therapy has comprised isoniazid and rifampicin for at least six to nine months, with a third drug during the first two months. Riska et al. [8] advised a similar treatment for renal transplant patients for nine months, although longer treatments have also been recommended [2,7,16]. When pyrazinamide is substituted by other drugs, the treatment should be extended (12–18 months) [6]. The most serious drawback associated with antituberculous treatment is the severe rejection due to interaction between rifampicin and cyclosporin. In such cases, an immunosuppressive dose adjustment or rifampicin substitution is required [17].

Isoniazid-related hepatotoxicity appears in 9% of patients between the first and the sixth week of treatment [6,18].

There is a direct relationship between renal function impairment and mortality. In our series, three (15%) patients died and another two had serious renal function impairment. In another patient, allograft nephrectomy was required.

The most important risk factors are the type of clinical onset and the presence of dissemination. Graft rejection and OKT3 or anti-T-cell antibodies are also important. Age, time from the graft and hepatotoxicity are not described as predictors of a poor prognosis [6].

Non-tuberculous mycobacteria (*Mycobacterium kansasii* and *Mycobacterium fortuitum*)

The transmission of these opportunists is usually aerial, but direct inoculation in soft tissues due to surgery is also possible [1]. Up to 43% of infections by mycobacteria in renal transplant recipients are due to atypical mycobacteria, the most usual microorganism (75% of cases) being *M. kansasii* [7].

In a worldwide review by Patel et al. [19], the most frequent clinical manifestations were skin abscess, lesions in the osteoarticular system and pulmonary symptoms. There are ten described cases caused by *M. fortuitum* whose main clinical manifestation was granulomatosis that required surgical debridement. These lesions were located in the arms and lower limbs.

In our series, a patient with massive dissemination of *M. kansasii* from a pulmonary focus died. The two cases of infection by *M. fortuitum* could have been caused by urologic manipulation. Infections by atypical mycobacteria appeared in all our cases during the first year after transplantation (with mean times of four months for *M. fortuitum* and 5.6 months for *M. kansasii*).

Dissemination is not a frequent event [19], but if present, has lethal consequences unless it is treated early [20]. The atypical mycobacteria except *M. kansasii* and *M. marinum* are often resistant to antituberculous drugs [21]. This should be taken into account before the start of treatment, and a previous antibiogram is advisable. Infection by *M. fortuitum* requires different drugs, the most usual being amikacin, cephalosporins, doxycycline, erythromycin, and quinolones [20].

CONCLUSIONS

There is a high incidence of infection by mycobacteria in renal transplant recipients, especially during the first year after transplantation, *M. tuberculosis* being the most frequent microorganism involved in our geographic area. Non-tuberculous mycobacteria have a much smaller impact on such patients. An early diagnosis is still crucial, because any delay in treatment is a determining factor for the evolution of the renal graft and represents an increased mortality risk. Taking into account the high levels of antimicrobial resistance, an antibiogram is a sensible guide to treatment. Finally, in areas of high prevalence of tuberculosis, chemoprophylaxis is recommended in patients with positive Mantoux tests.

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