

Tuberculosis in renal transplant patients: The experience of a single center in Medellín-Colombia, 2005-2013

Tuberculose em pacientes transplantados renais: experiência de um único centro em Medellín-Colômbia, 2005-2013

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ABSTRACT

Introduction: Tuberculosis is a common opportunistic infection in renal transplant patients. **Objective:** To obtain a clinical and laboratory description of transplant patients diagnosed with tuberculosis and their response to treatment during a period ranging from 2005 to 2013 at the Pablo Tobón Uribe Hospital. **Methods:** Retrospective and descriptive study. **Results:** In 641 renal transplants, tuberculosis was confirmed in 12 cases. Of these, 25% had a history of acute rejection, and 50% had creatinine levels greater than 1.5 mg/dl prior to infection. The disease typically presented as pulmonary (50%) and disseminated (33.3%). The first phase of treatment consisted of 3 months of HZRE (isoniazid, pyrazinamide, rifampicin and ethambutol) in 75% of the cases and HZME (isoniazid, pyrazinamide, moxifloxacin and ethambutol) in 25% of the cases. During the second phase of the treatment, 75% of the cases received isoniazid and rifampicin, and 25% of the cases received isoniazid and ethambutol. The length of treatment varied between 6 and 18 months. In 41.7% of patients, hepatotoxicity was associated with the beginning of anti-tuberculosis therapy. During a year-long follow-up, renal function remained stable, and the mortality rate was 16.7%. **Conclusion:** Tuberculosis in the renal transplant population studied caused diverse nonspecific symptoms. Pulmonary and disseminated tuberculosis were the most frequent forms and required prolonged treatment. Anti-tuberculosis medications had a high toxicity and mortality. This infection must be considered when patients present with a febrile syndrome of unknown origin, especially during the first year after renal transplant.

Keywords: graft rejection; kidney transplantation; *Mycobacterium tuberculosis*.

RESUMO

Introdução: A tuberculose é uma infecção oportunista comum em pacientes transplantados renais. **Objetivo:** Oferecer uma descrição clínica e laboratorial de pacientes transplantados com diagnóstico de tuberculose e sua resposta ao tratamento durante o período entre 2005 e 2013 no Hospital Pablo Tobón Uribe. **Métodos:** Estudo retrospectivo descritivo. **Resultados:** Em 641 transplantes renais, a tuberculose foi confirmada em 12 pacientes. Destes, 25% tinham histórico de rejeição aguda e 50% apresentaram níveis de creatinina superiores a 1,5 mg/dl antes da infecção. A patologia geralmente se apresentava como pulmonar (50%) e disseminada (33,3%). A primeira fase do tratamento consistiu de três meses de HZRE (isoniazida, pirazinamida, rifampicina e etambutol) em 75% dos casos e HZME (isoniazida, pirazinamida, moxifloxacina e etambutol) em 25% dos pacientes. Durante a segunda fase do tratamento, 75% dos pacientes receberam isoniazida e rifampicina e 25% isoniazida e etambutol. A duração do tratamento variou entre seis e 18 meses. Em 41,7% dos pacientes, hepatotoxicidade foi associada ao início do tratamento da tuberculose. Durante o seguimento de um ano a função renal manteve-se estável e a taxa de mortalidade foi de 16,7%. **Conclusão:** A tuberculose foi responsável por diversos sintomas inespecíficos na população de transplantados renais estudada. Tuberculose pulmonar e disseminada foram as formas mais frequentes de acometimento e necessitaram de tratamento prolongado. Medicamentos contra a tuberculose apresentaram alta toxicidade e mortalidade. Esta infecção deve ser considerada quando o paciente apresenta síndrome febril de origem desconhecida, especialmente durante o primeiro ano após o transplante renal.

Palavras-chave: *Mycobacterium tuberculosis*; rejeição de enxerto; transplante de rim.

INTRODUCTION

Tuberculosis is an infectious disease caused by the microorganism *Mycobacterium tuberculosis*. This bacterium usually affects the lungs but can involve any organ. Tuberculosis is a frequent infection in the general population, with an overall prevalence of 169 per 100,000.¹ In transplant patients, tuberculosis becomes a serious opportunistic infection. Tuberculosis occurs on average 14 times more frequently in transplant patients than in the general population² and 50 to 100 times more frequently in endemic areas.^{3,4} The prevalence of tuberculosis in renal transplant patients varies widely in different parts of the world. The prevalence is less than 1% in Western countries, approximately 3 to 4% in South America and Southeast Asia, 4 to 6% in the Mediterranean and China, and nearly 15% in India and Pakistan.⁵⁻¹⁰ The route of transmission in the transplant population is typically from the reactivation of a latent focus of infection. However, tuberculosis can also be acquired by contact with infected people and, more rarely, transmitted by the donor.¹¹⁻¹⁴

The high prevalence of tuberculosis in transplant patients is explained by the use of immunosuppressive therapies.¹⁵ These drugs lead to changes in cellular immunity and block key defense mechanisms against mycobacterial infections.^{12,15,16} The diagnosis of tuberculosis in renal transplant patients is difficult,¹⁷ and treatment leads to a high risk of drug interactions and toxicity,^{5,11,12,15,18-21} which increases the risk of dysfunction and graft loss.²² This objective of this study was to obtain a clinical and laboratory description of transplant patients diagnosed with tuberculosis and their response to treatment during a period ranging from 2005 to 2013 at the Pablo Tobón Uribe Hospital in Medellín-Colombia, which is an endemic area for tuberculosis.

METHOD

This work is a retrospective study conducted at the Pablo Tobón Uribe Hospital in Medellín-Colombia, a tertiary referral center serving a population of 4 million inhabitants. Patients who underwent a renal transplant during the period of 2005 to 2013 and were diagnosed with tuberculosis were included in this study. Tuberculosis infection was confirmed by histology, molecular testing, or positive culture for

the *mycobacterium*. All data were obtained from medical records and recorded in a database in Excel. Demographic data such as age, sex, and the etiology of renal disease were recorded. Risk factors associated with tuberculosis, such as a history of previous rejection diagnosed by renal biopsy, induction therapy used at the time of transplantation, and immunosuppressive medication, were documented. The pharmacological treatment, associated complications, and treatment time for tuberculosis were recorded. Several outcomes were also evaluated, including mortality and graft survival.

SPSS software (version 18) was used for statistical analysis. A descriptive analysis of the data was performed by calculating frequencies and percentages of qualitative variables. Quantitative variables were described as means or medians with their respective standard deviation or quartiles according to the distribution of the data identified by the Shapiro Wills test.

The Ethics Committee of the Pablo Tobón Uribe Hospital approved this study. Furthermore, the ethical standards for human research stipulated in resolution 008430 of 1993 of the Department of Social Protection of the Republic of Colombia were followed. Researchers pledged to respect the confidentiality and privacy of the information recorded in clinical records. This work did not involve interventions on the population studied, such as direct physical examination, laboratory tests, or treatment application, and therefore posed no risk to the participants.

RESULTS

Between 2005 and 2013, 641 renal transplants were performed; a PPD was done on 570 patients (88.9%), for whom 163 had a positive result (≥ 5 mm). 234 patients received Isoniazid (the 163 patients with a positive PPD plus 71 patients for whom the test was not performed). During the study period 12 cases of tuberculosis were diagnosed. The baseline characteristics of these patients are presented in Table 1. All patients received a renal transplant from a deceased donor; 7 patients were men, and 5 were women. Ten patients (83.3%) received alemtuzumab (30 mg) followed by three intravenous methylprednisolone boluses (500 mg on day 1, 250 mg on day 2, and 125 mg on day 3). The other two patients received thymoglobulin and daclizumab

as induction therapy during the transplant. Three patients (25%) had at least one episode of acute rejection prior to infection. These patients were treated with methylprednisolone (500 mg intravenously daily for 3 days). The immunosuppressive medication was adjusted in two patients, and plasmapheresis was performed on the third patient. Six patients (50%) had graft dysfunction before the diagnosis of tuberculosis and creatinine levels greater than 1.5 mg/dl.

The age at the time of tuberculosis infection ranged from 17 to 73 years old with a median of 52.5 years old (p25-75 = 35-66.8). The average time between transplantation and diagnosis varied from 2 to 69 months (median of 9 months, p25-75 = 2.3-32.8). The time between the onset of symptoms and diagnosis was between 10 and 102 days (median of 25 days, p25-75 = 17.3-30). Eight patients developed tuberculosis in the first year after transplantation.

Pulmonary and disseminated tuberculosis were the most common clinical manifestations of the disease (Table 2). The organs and systems affected in the patients included the following: lung, 75% (9); lymph nodes, 16.6% (2); meninges, 16.6% (2); and bone 8.3% (1). The findings from imaging analysis are reported in Table 3. The most common symptoms manifested in these patients were cough (83.3%), prolonged fever (75%), headache (33.3%), lymphadenopathy (16.6%), diarrhea (8.3%), and pleural pain (8.3%). Ten patients required hospitalization for a period ranging between 14 and 72 days.

The first phase of the treatment consisted of three months of HZRE for 75% of the cases or HZME for 25% of the cases. Ten patients received between 9 and 10 months of treatment, one patient received 6 months of treatment, and another patient received 18 months of treatment (median of 10 months p25-75 = 9-10). The second phase of the treatment was conducted in 75% of cases with isoniazid and rifampicin and in 25% of cases with isoniazid and ethambutol. Five patients (41.7%) experienced hepatotoxicity associated with the use of isoniazid and rifampicin.

Coinfections with systemic cytomegalovirus infection, syphilis, candidiasis, and invasive *E. coli* infections were observed. Two patients died; the first patient died as a result of sepsis after 7 days of treatment, and the second patient died as a result of a severe bronchopleural fistula 6 months after starting the Anti-tuberculosis medications.

Renal function remained stable during follow-up. Creatinine levels had a median value of 1.4 mg/dl (p25-p75 = 1.03-1.87) before diagnosis, 1.25 mg/dl (p25-p75 = 0.9-1.57) after 6 months and 1.35 mg/dl (p25-p75 = 0.96-1.7) after one year of follow-up (Table 4). During the year of follow-up, mortality was 16.7%; of the surviving patients, one exhibited acute rejection with graft loss and resumed renal replacement therapy. Ten patients (83.3%) successfully completed the tuberculosis treatment and remain without relapses at the time of publication.

TABLE 1 GENERAL CHARACTERISTICS

	Sex	PPD*	Age	CRF etiology	Type of induction**	Maintenance therapy	Time between transplant and TB (months)
1	Male	0	17	Malformations	Alemtuzumab	Aza-Tac-Pred	11
2	Female	1	34	Glomerulopathy	Alemtuzumab	CyA-Pred	12
3	Female	13	38	Malformations	Thymoglobulin	MMF-CyA-Pred	3
4	Male	0	33	Glomerulopathy	Alemtuzumab	Aza-CyA-Pred	2
5	Male	0	73	Unknown	Alemtuzumab	Aza-CyA-Pred	5
6	Female	0	68	Glomerulopathy	Alemtuzumab	Aza-CyA-Pred	59
7	Female	4	57	Renal cysts	Alemtuzumab	Syr-Pred	69
8	Male	6	38	Diabetes	Alemtuzumab	MMF-Syr-Pred	38
9	Male	3	48	Glomerulopathy	Alemtuzumab	Aza-Tac-Pred	7
10	Male	7	63	Renal cysts	Alemtuzumab	CyA-Pred	2
11	Female	No data	58	Glomerulopathy	Daclizumab	MMF-CyA-Pred	17
12	Male	5	73	Glomerulopathy	Alemtuzumab	Tac-Pred	2

* All patients received methylprednisolone boluses during induction. ** PPD: Tuberculin test performed before renal transplant. CRF: Chronic renal failure; Aza: Azathioprine; Tac: Tacrolimus; Pred: Prednisolone; CyA: Cyclosporine; Syr: Sirolimus. Type of induction: Induction therapy performed during renal transplant. Maintenance therapy: Immunosuppressive medication used after renal transplantation.

TABLE 2 CHARACTERISTICS OF THE PATIENTS WITH TUBERCULOSIS

ID	Type of tuberculosis	Diagnostic methodology	Sensibility to HZRE	Phase 1 treatment	Phase 2 treatment
1	Pulmonary	BAL	All	HZRE	HR
2	Disseminated	BAL	All	HZEM	HE
3	Pulmonary	BAL	All	HZRE	HR
4	Lymph node	Lymph node Bx	All	HZEM	HE
5	Central nervous system	CSF	All	HZRE	HR
6	Pulmonary	Pleural Bx	All	HZEM	HR
7	Pulmonary	BAL	All	HZRE	HR
8	Disseminated	Joint Bx	All	HZRE	HR
9	Disseminated	CSF	All	HZRE	HR
10	Pulmonary	BAL	All	HZRE	HR
11	Pulmonary	BAL	No data	HZRE	HR
12	Disseminated	BAL	No data	HZRE	Death

BAL: Bronchoalveolar lavage; CSF: Cerebrospinal fluid culture; Bx: Biopsy; HZRE: Isoniazid, pyrazinamide, rifampicin and ethambutol; HZEM: Isoniazid, pyrazinamide, ethambutol and moxifloxacin; HR: Isoniazid, rifampicin; HE: Isoniazid, ethambutol.

TABLE 3 RADIOLOGICAL FINDINGS

1	Chest radiography: small left lobulated perihilar radiopaque image. HRCT: image of a lymphadenopathy mass in the left perihilar region compressing the main left bronchus. Increased density of the lung parenchyma in the lingula without bronchogram. Adjacent ground-glass opacity and small nodule with small satellite nodule.
2	Chest radiography: radiopaque image of the apical segment of the lower right lobe. Simple chest CT: soft tissue area located in the right lower lobe, measuring approximately 58 x 42 mm, with small satellite atelectasis, ground-glass opacity, and peripheral septal thickening. Right hilar prominence likely caused by lymphadenopathy.
3	Chest radiography: triangular opacity projecting over the heart secondary to a segmental atelectasis of the middle lobe. HRCT: compatible image with mass <i>versus</i> lymph node cluster in the right perihilar region and paratracheal and pericardial regions. Atelectasis of the middle lobe. Calcified perihilar left ganglion.
4	Chest radiography: normal.
5	Chest radiography: normal.
6	HRCT: consolidated image of the upper right lobe with air bronchogram and small cavitation <i>versus</i> bronchiectasis. Additionally, multiple small subcentimeter nodules can be observed next to the opacity.
7	Chest CT: mixed ground-glass infiltrates in both lungs with bilateral nodular images.
8	HRCT: consolidated image of the two lung apices with presence of calcified nodules. Bronchiectasis in the right upper lobe.
9	HRCT: 1.6-cm nodule image in the superior segment of the right lower lobe with pleural contact (granuloma). Right perihilar lymphadenopathy and presence of right mediastinal mass.
10	Chest radiography: perihilar and pericardial reticulonodular micronodular interstitial infiltrates more prominent on the left side.
11	Chest radiography: left perihilar image suggesting consolidation with an atelectasis component.
12	Chest radiograph: bilateral alveolar opacities suggesting cardiac decompensating. Contrast CT: ground-glass area with central acinar nodules and a budding tree pattern.

HRCT: High-resolution chest tomography.

DISCUSSION

The prevalence of tuberculosis in a group of renal transplant patients from a single center was 1.87%. This level is lower than those reported in other South

American studies by Marquez (2.8%), Biz (2.4%) and Matuck (4.5%).^{9,21} This low prevalence of tuberculosis might be due to the integration of the tuberculin test as part of our pre-transplant protocol and the fact that patients with tuberculin values greater or equal

TABLE 4 EVOLUTION OF THE PATIENTS AFTER SIX MONTHS AND ONE YEAR OF TREATMENT

Patient	Creatinine level at the time of diagnosis (mg/dl)	Creatinine level after six months (mg/dl)	Creatinine level after one year (mg/dl)	Need for renal replacement therapy after one year
1	0.9	0.9	0.8	No
2	1.28	1.57	1.48	No
3	1.89	1.25	1.73	No
4	2.09	1.9	1.91	No
5	1.17	0.94	1.06	No
6	0.99	0.68	1	No
7	0.9	1.01	0.96	No
8	1.8	4.4	10	Yes
9	1.5	1.44	1.65	No
10	1.31	0.9	1.35	No
11	1.9	1.56	NA	Death
12	1.76	NA	NA	Death

NA: Not applicable.

to 5 mm receive isoniazid prophylaxis. Furthermore, patients for whom we could not perform a PPD due to lack of availability are given prophylaxis as well due to the high prevalence of tuberculosis in our country. This protocol has been proven to be successful in other studies to decrease the incidence of tuberculosis after renal transplant.¹⁰ For example, a meta-analysis revealed that isoniazid prophylaxis in patients with latent tuberculosis, diagnosed either by tuberculin or interferon gamma testing, significantly improves the prevention of tuberculosis in renal transplant patients.²² Currently, the British Thoracic Society suggests that all patients on the transplant waiting list should be screened for latent tuberculosis. If these patients are found positive, they are treated with 300 mg isoniazid for prophylaxis for 6 months.¹⁹ Alemtuzumab, used as induction therapy in 83.3% of the patients, could also have accounted for the low incidence of tuberculosis in the population studied. Alemtuzumab is a humanized monoclonal antibody that leads to a rapid and sustained depletion of T lymphocytes.⁶ Previous studies have demonstrated a low incidence of mycobacterial infection in patients induced with alemtuzumab.⁶

In the group of patients studied here, tuberculosis occurred mainly during the first year after transplantation (66.6%), which could be explained by a possible reactivation of undetected latent tuberculosis; the median time to the emergence of symptoms was 9 months, similar to the data reported in other studies by Marques *et al.*⁹ (median of 6.53

months), Lattes *et al.*²³ (13 months), and Lopez de Castilla *et al.*⁷ (11.2 months). For this reason, tuberculosis should be considered as part of the differential diagnosis performed in patients with fever of unknown origin, especially during the first year after renal transplant.

In this study, the time between onset of symptoms and diagnosis had a median of 25 days, which is similar to results reported by Marques *et al.*⁹ and to those found in the general population.²⁴ This late diagnosis is due to the differences observed in the clinical manifestations of tuberculosis between renal transplant patients and the general population. Tuberculosis in renal transplant patients is characterized by nonspecific symptoms, frequent extrapulmonary manifestations³ and symptoms indistinguishable from other infections.²⁰ In our study, the most frequent form of manifestation was pulmonary tuberculosis (50%), followed by disseminated tuberculosis (33.3%) and extrapulmonary tuberculosis (16.6%). In our study, chest radiographs or HRCT suggested the presence of opportunistic infections such as tuberculosis in all patients with respiratory complications. This indicates that these two diagnostic methodologies are complementary rather than exclusive.

Four drugs were included in the three months of the first phase of the anti-tuberculosis medications (HZRE in most patients). Two drugs were used in the second phase, which lasted 6 to 9 months. This treatment is recommended by clinical practice guidelines and has been documented in other studies.^{3,9} Furthermore,

an anti-tuberculosis medication of renal transplant patients for less than nine months is associated with an increase in mortality.⁹ One of the major findings of this study is that hepatotoxicity associated with the use of isoniazid and rifampin was observed in a higher percentage of patients than in other studies.^{3,9,16} Therefore, the use of fluoroquinolones may be a treatment option in these patients.

It is also important to consider that the interactions between the anti-tuberculosis medications and immunosuppressive drugs, such as rifampicin, can lower serum levels of calcineurin inhibitors^{6,22} and increase the risk of a renal graft rejection. For this reason, it is important to monitor the serum levels of these drugs and make appropriate adjustments. In this study, renal function remained stable in most patients, and only one patient suffered acute rejection and therefore lost the organ (8.3%). This incidence was lower than the results reported in other studies by Marquez *et al.*⁹ (44%) and Chen *et al.*³ (19%).

In this study, patient mortality associated with tuberculosis was 16.7% and was higher than mortalities reported by Marquez *et al.*⁹ (12%), Lattes *et al.*²³ (9.1%) and Chen *et al.*³ (12.9%).

In conclusion, we found that tuberculosis in renal transplant patients manifested with varied and nonspecific symptoms. Pulmonary and disseminated tuberculosis were the most common subtypes and required longer anti-tuberculosis medications. These treatments had a very high toxicity, high mortality, and important rates of rejection and graft loss. This infection should be considered when the patient manifests febrile syndrome of unknown origin, especially during the first year after renal transplantation, and its treatment should be rigorous and strictly monitored.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is not conflict of interest in this study. The results of this study have not been published previously.

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