ORIGINAL ARTICLE INFECTIOUS DISEASES

Clinical features and outcomes of tuberculosis in transplant recipients as compared with the general population: a retrospective matched cohort study

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Abstract

There are no previous studies comparing tuberculosis in transplant recipients (TRs) with other hosts. We compared the characteristics and outcomes of tuberculosis in TRs and patients from the general population. Twenty-two TRs who developed tuberculosis from 1996 through 2010 at a tertiary hospital were included. Each TR was matched by age, gender and year of diagnosis with four controls selected from among non-TR non-human immunodeficiency virus patients with tuberculosis. TRs (21 patients, 96%) had more factors predisposing to tuberculosis than non-TRs (33, 38%) (p <0.001). Pulmonary tuberculosis was more common in non-TRs (77 (88%) vs. 12 TRs (55%); p 0.001); disseminated tuberculosis was more frequent in TRs (five (23%) vs. four non-TRs (5%); p 0.005). Time from clinical suspicion of tuberculosis to definitive diagnosis was longer in TRs (median of 14 days) than in non-TRs (median of 0 days) (p <0.001), and invasive procedures were more often required (12 (55%) TRs and 15 (17%) non-TRs, respectively; p 0.001). Tuberculosis was diagnosed post-mortem in three TRs (14%) and in no non-TRs (p <0.001). Rates of toxicity associated with antituberculous therapy were 38% in TRs (six patients) and 10% (seven patients) in non-TRs (p 0.014). Tuberculosis-related mortality rates in TRs and non-TRs were 18% and 6%, respectively (p 0.057). The adjusted Cox regression analysis showed that the only predictor of tuberculosis-related mortality was a higher number of organs with tuberculosis involvement (adjusted hazard ratio 8.6; 95% CI 1.2–63). In conclusion, manifestations of tuberculosis in TRs differ from those in normal hosts. Post-transplant tuberculosis resists timely diagnosis, and is associated with a higher risk of death before a diagnosis can be made.

Keywords: Haematopoietic stem cell transplant recipients, *Mycobacterium tuberculosis* infection, solid organ transplant recipients, transplantation, tuberculosis
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Introduction

Transplant recipients (TRs) are at increased risk of active tuberculosis, mainly through reactivation of a latent infection

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[1–6]. The incidence of tuberculosis in a geographical area correlates with its incidence in the general population; in immigrant populations, it is more reflective of the countries of origin. Either way, the incidence of tuberculosis in TRs is higher than in the general population, with differences by type of transplant [3,5–8]. One Spanish study showed an annual tuberculosis incidence of 512 cases per 100 000 TRs (lung transplant recipients showed the highest incidence (2072/100 000 patients)), as compared with 19 cases/100 000 persons in the general population [6].

Tuberculosis remains one of the most serious post-transplant infections, with mortality rates of 10–40% [1,2,5,7–11]. Despite recently published guidelines for the management of post-transplant tuberculosis [12–15], the diagnosis and treatment of tuberculosis after transplantation remain challenging, because of the potential side effects of antituberculous agents and interactions with immunosuppressive drugs [2,3,16–21].

No previous studies have compared tuberculosis in TRs with tuberculosis in other immunocompromised or immunocompetent hosts. Although tuberculosis in TRs is considered to have a different presentation and a worse outcome than tuberculosis in the general population, possible differences are not well characterized.

The aim of this study was to compare the characteristics and outcomes of tuberculosis in TRs and in patients from the general population.

Materials and methods

Setting, study design, and patients

This study was conducted at the Hospital Clínic Universitari, a tertiary-care university hospital in Barcelona with active organ transplantation programmes, including kidney, kidney–pancreas, liver, heart and haematopoietic stem cell transplantation.

We used a retrospective matched cohort study to compare clinical features and outcomes of tuberculosis in patients who had received (transplant cohort) or had not received (control cohort) a solid organ or stem cell transplant. All patients had a definitive tuberculosis diagnosis established by isolation of *Mycobacterium tuberculosis* (from any clinical sample).

Patients were identified from clinical microbiology laboratory and transplantation programme databases. We included all TRs who were culture-positive for tuberculosis diagnosed from January 1996 through December 2010. Non-TRs were selected from a list of all patients with culture-positive diagnoses of tuberculosis in our centre during the same period. For each year of the study, the order of the list of culture-positive tuberculosis diagnoses was randomized. Every TR with tuberculosis on the list was paired with the next four tuberculosis patients (the non-TRs) who fulfilled the matching criteria, namely, human immunodeficiency virus (HIV)-negative patients who had not received a transplant, matched further according to gender, age (±2 years), and year of tuberculosis diagnosis. HIV patients were excluded because of the specific characteristics of tuberculosis in this patient group as compared with HIV-negative patients [22].

Throughout the study period, any hospitalized or ambulatory patient with suspicion of tuberculosis was tested at our centre; most patients diagnosed with tuberculosis in primary-care centres in the area were also referred to our hospital, where *M. tuberculosis* cultures were repeated. Any patient with active tuberculosis was treated and followed up by tuberculosis experts in the Infectious Diseases Service for at least the duration of tuberculosis treatment.

Clinical data and definitions

Data were obtained from the patient's medical records with a standard case report form. Variables collected for all patients included: demographic features; underlying conditions; Charlson comorbidity score [23]; date of onset of tuberculosis symptoms; clinical presentation and radiographic findings; tuberculin skin test (TST) results; procedures used to obtain a definitive tuberculosis diagnosis; time to diagnosis; number of sites with tuberculosis involvement; type and number of antituberculous drugs prescribed; antituberculous drug-related toxicity; length of follow-up following tuberculosis diagnosis; date of last follow-up and status of the patient at that time; and date and cause of death during follow-up, if appropriate. For TRs, the following information was recorded: type of transplant and date; pre-transplant TST tests; clinical and/or radiological evidence of pre-transplant tuberculosis; treatment of latent infection; and time to tuberculosis diagnosis after transplantation.

Information collected about the presence of other well-known factors predisposing to tuberculosis (excluding transplantation) included: diabetes mellitus, chronic renal failure/haemodialysis, silicosis, gastrectomy, jejunoileal bypass, haematological malignancies, carcinoma of the head or neck, alcohol consumption, and therapy with corticosteroids (prednisone or prednisone equivalent administered at >15 mg/day for $\geq$1 month) or other immunosuppressive agents [24–26].

TST results were interpreted according to American Thoracic Society and CDC recommendations [27]. Organ involvement by tuberculosis was considered to be definite if *M. tuberculosis* was isolated from the organ, and probable when patients with a confirmed tuberculosis diagnosis had acid-fast bacilli smear and/or histopathological findings consistent with tuberculosis, and/or signs/symptoms highly suggestive of tuberculosis involvement (with no alternative diagnosis) that

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