Risk factors, clinical features and outcomes of visceral leishmaniasis in solid-organ transplant recipients: a retrospective multicenter case–control study

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Abstract

Visceral leishmaniasis (VL) is a rare disease in solid-organ transplant (SOT) recipients. Therefore, little is known about the risk factors and disease behavior in the transplant setting. This multicenter, matched case–control study (1:2 ratio) was designed to determine the risk factors, clinical features and outcomes of VL among this population. Control and case subjects were matched by center, transplant type and timing. Thirty-six VL cases were identified among 25 139 SOT recipients (0.1%). VL occurred 5.7-fold more frequently in Brazil than in Spain, presenting a median time of 11 months after transplantation. High-dose prednisone in the preceding 6 months was associated with VL. Patients were diagnosed over 1 month after symptom onset in 25% of cases. Thirty-one patients (86%) were febrile upon diagnosis, 81% exhibited visceromegaly and 47% showed pancytopenia. Concomitant infection was common. Parasites were identified in 89% of patients; the remaining patients were diagnosed by serology. The majority of the patients received amphotericin B. Relapses occurred in 25.7% of cases, and the crude mortality rate was 2.8%. VL after SOT is related to the VL prevalence in the general population. Delayed diagnosis frequently occurs. Liposomal amphotericin is the most commonly used therapy; mortality is low, although relapses are common.

Keywords: Parasitic infection, posttransplant infection, solid-organ transplant, tropical diseases, visceral leishmaniasis
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Introduction

Visceral leishmaniasis (VL) is an uncommon disease even in endemic zones. Solid-organ transplant (SOT) recipients have an increased risk of VL, but the effect of higher incidence rates on the frequency of VL in SOT is unknown. VL can occur after

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primary infection through a sandfly bite, via transplanted organs, blood products or reactivation of latent infections. Although more than 100 VL case reports have been described and reviewed in the literature [1–5], there is a lack of information regarding risk factors, the role of immunosuppression and disease outcome across different types of transplantation. The recognition and management of VL remains challenging even in transplant recipients from endemic regions [6–11].

The present study was designed to determine the frequency, risk factors, clinical characteristics and prognosis of VL in SOT in two countries, Spain and Brazil, in which leishmaniasis is endemic, although with different incidences in the general population.

Materials and methods

Setting and study population

This retrospective study was conducted at ten Spanish hospitals (included in the Spanish Network for Research in Infectious Diseases [REIPI]) and two centers in Brazil. All patients diagnosed with VL from January 1995 to June 2012 and January 1995 to December 2011 at the participating transplant centers in Spain and Brazil, respectively, were included. The patients were identified using transplantation program databases. The initial identification was followed by a detailed medical records review. The study was approved by the institutional review board of the IMIBIC (Instituto Maiomônides de Investigación Biomédica de Córdoba)-Hospital Universitario Reina Sofia.

For risk factor analysis, a matched case–control study (1:2 ratio) was performed. The control subjects were matched by three factors: institution, type of transplantation and time of follow-up after transplantation. Recipients who underwent transplantation immediately before and after the index case patient and who survived at least as long as that patient's elapsed time to the diagnosis of VL were eligible to be control subjects.

Definitions

A VL diagnosis was established on the basis of clinical manifestations combined with the demonstration of parasites using one of the following methods: microscopy, culture, polymerase chain reaction (PCR) and positive serology (indirect immunofluorescence $\geq$1/80 or direct agglutination test [DAT rK39] or enzyme immunoassay). The time of event was defined as the time of VL diagnosis after transplant. Pancytopenia was defined as haemoglobin <12 g/dL, leukocytes <4000/mm^3 and platelets <150 000/mm^3, and severe pancytopenia was established as haemoglobin <10 g/dL, leukocytes <1000/mm^3 and platelets <100 000/mm^3.

VL was considered cured if a patient remained asymptomatic for 1 month after the end of treatment. For patients who survived longer than 1 month, recurrence or relapse was diagnosed when symptoms, signs or laboratory abnormalities reappeared at least one month after the end of treatment. Mortality was considered related to VL when the infection had not been cured by the time of death.

The following variables were analysed as potential risk factors: sex, age, diabetes mellitus within the preceding 6 months, human immunodeficiency virus (HIV) serology, previous VL, prophylaxis with intravenous amphotericin B and cytomegalovirus disease or replication within the preceding 6 months. An immunosuppressive status at the time of the event was defined as follows: an elevated mean calcineurin inhibitor level within the preceding 30 days (>15 μg/mL for tacrolimus and >300 ng/mL for cyclosporin), prior use of everolimus and sirolimus, history of high-dose prednisone therapy within the preceding 6 months ($\geq$20 mg of prednisone for >1 month or >2 pulses of 1 g of intravenous methylprednisolone), lymphocyte-depleting antibody treatment within the preceding 12 months and allograft rejection within the preceding 6 months.

Microbiologic studies

Leishmania serology, antigen detection, PCR and culture were performed at each center using routine tests, according to the manufacturers' instructions.

Statistical analysis

To detect differences between groups, the χ^2 test (or Fisher's exact test, when indicated) was used with continuity correction for categorical variables, and the Student's *t* test was used for continuous variables. The VL-free survival time was calculated by Kaplan-Meier curves and compared by the log-rank test. Univariate and multivariate analyses (binary logistic regression) were performed to identify potential risk factors. All reported p values are two-tailed.

Results

Epidemiology

The frequency of VL by country and transplanted organ is shown in Table 1. Thirty-six VL cases were identified among 25 139 SOT recipients at 12 participating hospitals, representing 0.1% of all transplant recipients. VL cases appeared in 25 (0.2%) of 12 895 kidney recipients, four (0.05%) of 8681 liver recipients, six (0.2%) of 2669 heart recipients and one (0.2%) of 894 lung recipients. The frequency of VL was 5.7-fold higher in Brazil (0.5%) than in Spain (0.1%).

