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CASE REPORT

Visceral leishmaniasis in heart transplant patients in the endemic state of Ceará, Brazil: a report of two cases

Leishmaniose visceral em pacientes submetidos a transplante cardíaco no estado do Ceará, área endêmica no Brasil: um relato de dois casos

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Abstract

Visceral leishmaniasis (VL) in transplant patients is a serious disease, with atypical and aggressive manifestations, compromising patient survival. During the period from 2008 to 2012, 126 heart transplants were performed in the state of Ceará, Brazil, of which, two patients developed VL. Fever, pancytopenia and hepatosplenomegaly were the common clinical signs. Both patients were diagnosed and properly treated, but the first one had a clinical relapse and died, five months after treatment. These findings emphasize the importance of investigating VL in heart-transplant patients in endemic areas and highlight the importance of early diagnosis and treatment for favorable clinical outcomes.

Keywords: Visceral leishmaniasis. Heart transplant. Immunosuppression. Parasitic infections. Transplant recipient

Resumo

Leishmaniose visceral em pacientes transplantados é uma doença séria com manifestações atípicas e agressivas, comprometendo a sobrevivência do paciente. Durante o período de 2008 a 2012, 126 transplantes cardíacos foram realizados no Estado do Ceará, Brasil, dos quais dois pacientes desenvolveram leishmaniose visceral. Febre, pancitopenia e hepatoesplenomegalia foram sinais clínicos comuns. Ambos os pacientes foram diagnosticados e apropriadamente tratados, mas o primeiro teve uma recidiva e morreu cinco meses após o término do tratamento. Esses achados enfatizam a importância de investigar a leishmaniose visceral em pacientes de transplante cardíaco de áreas endêmicas e enaltecem a importância do diagnóstico e tratamento precoces para um desfecho clínico favorável.

Palavras-chave: Leishmaniose visceral. Transplante cardíaco. Imunossupressão. Infecção parasitária. Receptor de transplante.

INTRODUCTION

From 2006 to 2010, 18,168 cases of visceral leishmaniasis (VL) were registered in Brazil, with the highest concentration of cases occurring in the Northeastern region[1]. The Northeastern state of Ceará is highly endemic and from 2001 to 2012, 6.016 cases of VL were confirmed[2].

VL, as a complication in immunosuppressed patients, has become increasingly frequent, particularly in HIV-infected and transplant patients. In these individuals, VL can occur after primary infection through a sandfly bite, via transplanted organs, blood products or reactivation of latent infections. VL is a rarely reported disease among transplant recipients, but, when established, it is a life-threatening disease, with atypical and aggressive manifestations[3,4]. Since the beginning of the 1990s, the number of published VL cases has quadrupled and it is most commonly associated with kidney, liver and bone marrow transplantation[4,5,6,7], while it is a very rare disease in heart transplant recipients, with few published reports. Hernandéz-Peréz et al., 1999[8], for example, reported a case of VL in a heart transplant recipient in Spain, which occurred one year after transplantation. The patient died, despite treatment with meglumine antimoniate. Frapier et al., 2001[9], reported a case of VL in a heart transplant recipient after 10 years of transplantation, in France. Despite the therapy with amphotericin B and pentavalent antimonial drugs, the patient had a fatal outcome, after 10 days of treatment. Finally, Larocca et al., 2007[10], described the first case of VL in a heart transplant patient, in Italy, after one year of transplantation. The patient was treated with liposomal amphotericin B and complete clinical remission was observed in four months.

Thus, the objective of this paper was to present the cases of VL in heart-transplant patients from an endemic area for leishmaniasis, discussing the clinical-epidemiological features of the disease.

METHODS

From 2008 to 2013, asystematic clinical follow-up of all heart-transplant patients assisted between 2008 and 2012

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was performed in order to identify cases of VL. The patients submitted to heart transplant and the organ donors were not screened for asymptomatic LV or previous contact with Leishmania spp. Additionally, the transplant patients did not receive prophylactic treatment with amphotericin B. All patients were monthly monitored in the first year post-transplant and quarterly thereafter. If the patient had at least one of the signs of the clinical triad of VL (fever, hepatosplenomegaly and pancytopenia)[1,7], the patient would be investigated for the disease, through myelogram, to search for Leishmania spp. amastigotes, indirect immunofluorescence (IFI - Leishmaniose Humana - Bio-Manguinhos, FioCruz) and immunoassay analysis of the K39 antigen (Kalazar DetectTM, InBios International).

Diagnosis of VL was established when clinical and laboratory features were present (positive parasitological examination or reactive immunofluorescence titer of 1:80, after excluding other differential diagnoses); or when clinical and epidemiological features were present (cases from endemic areas, with clinical suspicion without laboratory confirmation, with favorable response to therapy)[1,7].

RESULTS

During the period studied (2008-2012), 126 heart transplants were performed, of which two patients were diagnosed with VL. No specific tests to detect asymptomatic leishmaniasis or prior contact with Leishmania sp. were carried out in donor and in transplant recipients before and after transplant.

The first patient, a 21-year-old male, diagnosed with dilated cardiomyopathy of ischemic origin, was submitted to heart transplant at the Messejana Dr. Carlos Alberto Gomes Studart Hospital, Fortaleza, Ceará, Brazil, in November 2008. Immunosuppressive therapy was performed with mycophenolate mofetil (1g/day) and tacrolimus (6 mg/day). The patient was admitted in July 2009, 8 months after transplantation, for presenting daily fever. Physical examination revealed mucocutaneous pallor and hepatosplenomegaly. Laboratory tests showed pancytopenia (Hb 10.7 g/dL, leukocytes 1470/mm3, platelet count 92,200/mm3), negative blood and urine bacterial and fungal cultures and negative Vidal's reaction. Amastigotes of Leishmania sp. were not seen in the bone marrow aspirate, but indirect immunofluorescence was positive for VL (titer of 1/80). The patient received treatment with meglumine antimoniate (20 mg/kg/day, for 28 days), with clinical and hematological recovery and no adverse events were observed. No secondary prophylaxis was instituted. The patient had a clinical relapse, five months after treatment, and died. The patient presented no signs of concomitant infections with other pathogens, thus, VL was the most likely cause of death.

The second patient, a 51-year-old male with ischemic cardiomyopathy, was submitted to heart transplantation at the same hospital in April 2010. The patient was on immunosuppressive therapy with mycophenolate mofetil (1g/day) and tacrolimus (6 mg/day). In September 2013, pancytopenia was observed in routine blood tests, when the patient reported mild anorexia and sporadic low-grade fever. Physical examination revealed mild mucocutaneous pallor without hepatosplenomegaly. Laboratory data showed pancytopenia (Hb: 10.1g/dL, leukocytes 2,863/mm3, platelet count 88,000/mm3) and mild hypergammaglobulinemia (3.4 globulin). K39 antigen was negative, but the myelogram was positive for Leishmania sp. The patient was treated with liposomal amphotericin B (3 mg/kg/day, for seven days) with rapid clinical and hematological recovery, and was uninterruptedly maintained on secondary prophylaxis with amphotericin B deoxycholate (0.7 mg/kg/dose every 15 days). The patient has been followed without evidence of recurrence.

DISCUSSION

The clinical presentation of VL in transplant patients is similar to that observed in immunocompetent patients[4,11]. There is a clinical triad that is classical for VL, which includes fever, visceromegaly and pancytopenia. However, a recent review has shown that only 1/3 of the patients show these classical signs[12]. This is why, in this study, VL was considered a diagnostic hypothesis when transplant patients presented at least one sign of the classical clinical triad for this disease. The first patient described had fever as the main symptom, which is the most common reported alteration, present in 94%-100% of transplant patients with VL[4,6]. Regarding the presence of hepatosplenomegaly, it has been described that this clinical alteration is less common in immunosuppressed than in immunocompetent patients[4]. We believe that the absence of the main symptoms in the second patient is likely due to early diagnosis and fast start of appropriate therapy.

VL usually appears as a late complication after transplantation, with the clinical onset occurring around 18 months after the procedure[3,4]. In this study, the first patient had VL nine months after transplantation, possibly representing an activation of latent disease, while the second patient developed VL forty-three months after transplantation, possibly due to a new infection[13]. However, these hypotheses are difficult to prove because patients are not routinely screened for previous Leishmania infection and a history of symptomatic infection can be missing[14]. Despite the risk of reactivating a latent infection or transmitting the parasite to a healthy recipient, VL screening is not routinely performed because the diagnostic value of serologic and molecular screening of asymptomatic donors and recipients remains unclear[12].

Direct analysis of Leishmania amastigotes in bone marrow aspirate is the most used method for the diagnosis of VL[12]. The sensitivity of the method in transplant patients is high, ranging from 90 to 98%[4,15]. However, this method did not confirm diagnosis in the first patient, possibly because only one bone marrow sample was analyzed. In addition, serological tests for Leishmania have shown good results for diagnosis of VL in transplant patients[16]. However, in this study, the search for antibodies against the recombinant antigen K-39 in the second

patient was negative, contrasting the literature reports of high sensitivity (>95%) and specificity (98%) of this technique in solid organ transplant recipients[4]. Even though serology is minimally invasive and can be routinely used for VL diagnosis in solid organ transplant recipients, serological assays cannot distinguish between prior exposure and active infection [12].

Therefore, considering the advantages and disadvantages of each diagnostic technique, it is a consensus that the best approach for diagnosing VL is the combination of methods. It has been reported, for example, that microscopy combined with PCR and culture diagnosed VL in up to 89% of cases[12]. Hence, even though three diagnostic approaches (clinical signs, microscopy and serology) were included in this study, the number of VL cases among the assessed patients may have been underestimated and the use of a simple molecular technique, such as PCR, may increase the detection rate of Leishmania spp. from clinical specimens, improving diagnosis[12].

The best treatment for VL in solid organ transplant patients is yet to be determined. However, liposomal amphotericin B seems to be the best choice, especially in HIV-negative immunocompromised individuals, such as transplant patients, as it directly attacks the protozoan membrane, independently of the immune status of the patient. Antimonial drugs, on the other hand, require a preserved cellular immunity and are associated with 100% recurrence rates in immunocompromised individuals. Additionally, liposomal amphotericin B has lower toxicity, requires shorter treatment duration and is easy to administer[17]. In the first case reported in this study, meglumine antimoniate was used because liposomal amphotericin B was not available. Moreover, there is no consensus regarding the benefits of using secondary prophylaxis after treatment of VL[12], but in this study and in previous reports, this strategy reduced the number of clinical relapses[12].

These cases indicate that early diagnosis and treatment of VL are the key for therapeutic success. However, several issues still need to be addressed in heart-transplant patients, including the need of implementing pre-transplant screening tests for VL in doors and recipients, the determination of the best treatment protocol and the need of instituting a secondary prophylaxis.

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