TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Visceral leishmaniasis in hematopoietic stem cell transplantation

doi:10.1111/j.1432-2277.2012.01487.x

Dear Sir,

Visceral leishmaniasis (VL) is a parasitic disease caused by the *Leishmania donovani* complex. The most important endemic areas are Southern Asia, the Middle East, the Mediterranean, and Brazil [1]. Immunocompromised patients have a higher incidence and severity of VL than immunocompetent patients, and a marked tendency to suffer relapses [1]. During the last two decades, cases of VL in transplanted patients have been increasingly reported, most of them being observed in the Mediterranean basin [2]. So far, there have been 77 reported cases of VL in solid organ transplant recipients (57 kidney, 11 liver, 4 heart, 2 lung, 2 kidney plus pancreas, and pancreas 1) [2–5]. Fever is the most common symptom of VL in organ transplanted patients (94% of the cases). However, splenomegaly is reported less frequently than in immunocompetent patients [6].

A 60-year-old man with acute lymphoblastic leukemia refractory to chemotherapy underwent cord blood transplantation (CBT). It was supported by the co-infusion of a low number of T-cell-depleted, mobilized hematopoietic stem cells from a third party donor (''dual'' CBT). Patient pretransplant and third party donor CMV serology were positive. Blood CMV pp65 antigenemia and DNA determination by polymerase chain reaction (PCR) were performed weekly during the first 6 months. The patients had been living in an endemic region, namely the central Iberian Peninsula.

On day +110 the patient presented positive serum CMV DNA that was treated with ganciclovir for 3 weeks. On day +151 the patient reported fever, profuse sweating, rhinorrhea, odynophagia, and liquid diarrhea, without blood or pus, during the preceding 7 days. At that time he was receiving prophylactic treatment with fluconazole 100 mg qd, acyclovir 400 mg tid and sulfadoxine/pyrimethamine 500/25 mg qd. The spleen was palpated 5 cm below left costal margin. A chest X-ray was normal. Laboratory tests showed 6300 leukocytes/μl and 3270 neutrophils/μl, 14.5 g/dl of hemoglobin and 34 000 platelets/mm^3 (the previous count was 146 000 platelets/mm^3) Blood cultures were negative. Stool cultures revealed normal bowel flora. Leishmania serology was positive with a titer of 1:320 (IgG indirect immunofluorescence test, anti-rk39). The diagnosis of VL was confirmed by positive bone marrow culture (Novy-Nicolle-McNeal medium) and by the identification of numerous Leishmania amastigotes in the bone marrow aspirate (hematoxylin–eosin stain). Leishmania PCR in bone marrow was negative. Interestingly, parasites were also observed in granulocytes in peripheral blood (hematoxylin–eosin stain, Fig. 1). Liposomal amphotericin B (3 mg/kg IV qd) was administered for 2 weeks. The fever disappeared after 4 days and the platelet count slowly returned to normal. Consequently, liposomal amphotericin B was administered weekly for 5 weeks, and then monthly for the following 3 years. No relapses have occurred during 6 years' follow-up.

Three cases of LV in HSCT patients have been previously reported [7–9]. Two patients received allogenic, and one patient autologous, HSCT. In one case CMV disease had been detected during the previous 3 months. The mechanism of infection was presumed to be reactivation in two patients and primary infection in one patient. The time of presentation after HSCT was 1, 3, and 23 months, respectively. The clinical presentation consisted of fever in one patient and pancytopenia in the other two (50%). In two patients, amastigotes of Leishmania were seen in peripheral blood smears. All patients were treated with

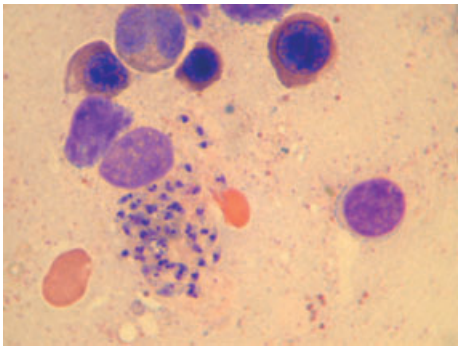

Figure 1 Granulocyte in peripheral blood with intracellular leishmania amastigotes.

liposomal amphotericin B. All patients recovered, however, one suffered three relapses.

The incidence of VL at our hospital is very low (0.2%). Moreover, the number of cases of VL in endemic regions is significantly lower in HSCT recipients than in other immunocompromised patients, such as kidney transplant recipients [10]. The low rate of VL (and other infections, such as tuberculosis) in HSCT suggests that some unknown factor, other than the degree of cell-mediated immunosuppression, may have a role in the pathogeny of opportunistic infections in transplant patients [7–9].

Two of four patients presented CMV disease during the 3 months prior to VL. An immunomodulatory effect of CMV replication in promoting Leishmania reactivation cannot be ruled out [11].

Unlike that observed in solid organ transplantation recipients, most cases were detected during the first year after transplantation [10]. This fact may justify the inclusion of VL in the differential diagnosis of fever during the first months in those HSCT patients who have lived in or traveled to an endemic area.

Leishmania serology was positive in three patients (75%). This is consistent with that observed in SOT but is in sharp contrast with findings in patients with HIV-associated VL [1]. Bone marrow aspiration and direct microscopic examination constitute the most frequently used diagnostic procedures for VL confirmation. Amastigotes appear as round or oval bodies in monocytes and macrophages [12]. It should be noted that in three cases (75%), granulocyte intracellular Leishmania amastigotes were seen in peripheral blood smears. This fact, which has previously been observed in other immunocompromised individuals, such as those infected by HIV, constitutes a very useful diagnostic tool [7,8]. The sensitivity of Lesihmania PCR in bone marrow ranges between 70% and 90% which could explain the negative result in our patient [6,13,14].

Despite the small number of HSCT patients with VL, it must be emphasized that none died because of this infection. The cure rate of VL in HSCT was similar to that observed in SOT recipients (84%) but definitely superior to that observed among HIV -positive disease patients (range 55–66%) [2]. This favorable result may be influenced by the possible low clinical severity in patients who were diagnosed when they presented with pancytopenia alone. Another factor may be that all patients were treated with liposomal amphotericin B [15]. Despite the absence of controlled clinical studies, liposomal amphotericin B seems more advisable than pentavalent antimonials because of its efficacy, lower toxicity, and ease of administration [2].

One of the four cases suffered several relapses before secondary prophylaxis with liposomal amphotericin B was prescribed. The information obtained during the present study does not allow us to make definitive recommendations about the indication of secondary prophylaxis. In any case, the tendency of VL relapse in immunocompromised patient infections may support the recommendation of secondary prophylaxis [7].

Guiomar Bautista,[1] Antonio Ramos[2] and Santiago Gil[1]
1 Department of Hematology, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain
2 Department of Internal Medicine (Infectious Disease Unit), Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain
e-mail: aramos220@gmail.com

Conflicts of interest

The authors declare no conflict of interest.

Funding

No funding.

Acknowledgements

The authors wish to thank Martin Hadley-Adams for assisting with the English language and preparation of the manuscript.

References

1. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodefi ciency virus (HIV)-infected and non-HIV-infected patients. *Medicine* 2001; **80**: 54.
2. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. *Lancet Infect Dis* 2008; **8**: 191.
3. Postorino MC, Bellantoni M, Catalano C, *et al.* Visceral leishmaniasis reactivation in transplant patients: a minireview with report of a new case. *J Nephro* 2011; **24**: 530.
4. Simon I, Wissing KM, Del Marmol V, *et al.* Recurrent leishmaniasis in kidney transplant recipients: report of 2 cases and systematic review of the literature. *Transpl Infect Dis* 2011; **13**: 397.
5. Clemente WT, Faria LC, Romanelli RM, *et al.* Visceral leishmaniasis in liver transplant recipients from an endemic area. *Transplantation* 2011; **91**: 806.
6. Gatti S, Gramegna M, Klersy C, *et al.* Diagnosis of visceral leishmaniasis: the sensitivities and specifi cities of traditional methods and a nested PCR assay. *Ann Trop Med Parasitol* 2004; **7**: 667.
7. Rodríguez-Wilhelmi P, Panizo C, Ruza E, Rocha E. Tratamiento con anfotericina B liposomal en tres pacientes

inmunodeprimidos con leishmaniasis visceral. *Med Clin (Barc)* 2001; **116**: 37.
8. Sirvent-von Bueltzingsloewen A, Marty P, Rosenthal E, *et al.* Visceral leishmaniasis: ew opportunistic infection in hematopoietic stem-cell-transplanted patients. *Bone Marrow Transplant* 2004; **33**: 667.
9. Agteresch HJ, van't Veer MB, Cornelissen JJ, Sluiters JF. Visceral leishmaniasis after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2007; **40**: 391.
10. Fisher RA. Cytomegalovirus infection and disease in the new era of immunosuppression following solid organ transplantation. *Transpl Infect Dis* 2009; **11**: 195.
11. Hernández-Pérez J, Yebra-Bango M, Jiménez-Martínez E, *et al.* Visceral leishmaniasis (kala-azar) in solid organ transplantation: report of five cases and review. *Clin Infect Dis* 1999; **29**: 918.
12. Pavli A, Maltezou HC. Leishmaniasis, an emerging infection in travelers. *Int J Infect Dis* 2010; **14**: e1032.
13. Fraga TL, Brustoloni YM, Lima RB, *et al.* Polymerase chain reaction of peripheral blood as a tool for the diagnosis of visceral leishmaniasis in children. *PCR Mem Inst Oswaldo Cruz* 2010; **105**: 31.
14. Pandey K, Pandey BD, Mallik AK, *et al.* Diagnosis of visceral leishmaniasis by polymerase chain reaction of DNA extracted from Giemsa's solution-stained slides. *Parasitol Res* 2010; **107**: 727.
15. Bern C, Adler-Moore J, Berenguer J, *et al.* Liposomal amphotericin B for the treatment of visceral leishmaniasis. *Clin Infect Dis* 2006; **43**: 917.