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Short Communication

Multiple relapses of visceral leishmaniasis in a patient with HIV in India: a treatment challenge

Shalom Patole [a,*], Sakib Burza [b], George M. Varghese [a]

[a] Department of Medicine and Infectious Diseases, Christian Medical College, Vellore, Tamil Nadu, India
[b] Médecins Sans Frontières, New Delhi, India

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SUMMARY

Visceral leishmaniasis (VL) is an opportunistic infection of HIV-infected people in several endemic countries, and the management of this co-infection poses numerous challenges. We describe a patient with HIV infection and visceral leishmaniasis who failed to respond to miltefosine monotherapy and subsequently relapsed following two further different regimens of liposomal amphotericin B. He was then successfully treated with a combination of 30 mg/kg liposomal amphotericin B and 14 days of 100 mg/day oral miltefosine.

1. Introduction

Leishmaniasis and HIV co-infection has gained clinical importance in several countries where both infections are endemic. The host defense against leishmaniasis in general, and *Leishmania donovani* in particular, is T-cell-dependent. Accordingly, patients with HIV infection are not only more susceptible to leishmaniasis, but also pose significant diagnostic as well as therapeutic challenges. The clinical presentation in this group of patients may not be specific, whilst therapeutic failure and relapse are more common in co-infection. Thus there are serious implications with respect to visceral leishmaniasis (VL) elimination strategies in areas where the disease burden of HIV and VL overlap.

Single-dose 10 mg/kg liposomal amphotericin B is currently the World Health Organization (WHO) recommended first-line treatment for VL in the Indian sub-continent.[1] However, its efficacy in HIV co-infected patients has not been documented and there are neither established guidelines nor randomized controlled trials to guide decision-making in such patients. Furthermore, high relapse rates and difficulty in eradication of Leishmania amongst HIV-infected patients are well described, with limited evidence available regarding the best treatment strategies.[2] In this case report we describe the failure of three monotherapies in such a patient, with subsequent successful treatment using high-dose combination therapy.

2. Case report

A 43-year-old male from Jharkhand (a state in eastern India endemic for VL) presented to a local hospital with a 6-month history of low-grade fever and malaise associated with anorexia and weight loss. He was diagnosed with both HIV-1 infection based on serial serology testing and visceral leishmaniasis based on rK-39 serology, and was commenced on a 28-day course of oral miltefosine 100 mg/day in two divided doses, as per the Indian national guidelines for the treatment of VL. He was not started on antiretroviral therapy (ART) at that stage.

Within 3 months of completing the treatment he presented to the Christian Medical College in Vellore with recurrence of fever, fatigue, and weight loss. Physical examination demonstrated pallor and an enlarged liver and spleen, 5 cm and 8 cm below the costal margin, respectively. Laboratory evaluation revealed hemoglobin (Hb) of 8.2 g/dl, total white blood cell count of 8.2×10^9/l, platelets of 86×10^9/l, and a CD4 count of 127 cells/μl. Bone marrow aspiration confirmed *L. donovani*. The patient was treated for VL

* Corresponding author. Tel.: +91 9626947604.
E-mail address: shalom_patole@yahoo.co.uk (S. Patole).

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using a single dose of 10 mg/kg intravenous liposomal amphotericin B (AmBisome, Gilead, USA). This regimen was lower than the total dose of 40 mg/kg recommended in 2010 by the WHO for HIV–VL co-infection, which is based primarily on experience of *Leishmania infantum* and HIV co-infection in Europe. The 10 mg/kg single-dose regimen has been shown to be highly effective in the Indian context, albeit in immunocompetent patients.[3] The patient was commenced on tenofovir, emtricitabine, and efavirenz for HIV, with co-trimoxazole prophylaxis. He responded well and was discharged as initial cure following the treatment.

At the 3-month follow-up, although afebrile, he was found to have increased splenomegaly despite reporting full compliance with ART. A repeat bone marrow examination again demonstrated *L. donovani* bodies, and the CD4 count was found to be 121 cells/μl. He was therefore treated with a generic lipid formulation of amphotericin B (Fungisome; Lifecare Innovations, India) at a dosage of 2 mg/kg for 2 weeks, receiving a cumulative dose of 28 mg/kg, to which he again appeared to respond well and was discharged again as an initial cure. This regimen was chosen as an alternative to AmBisome due to the financial constraints of the patient, and took into account the lack of published safety data and non-inferiority studies for higher doses of this particular preparation of amphotericin B for the treatment of VL compared to AmBisome.[3]

He presented again after 6 months with a 4-week history of malaise and fatigue despite continued adherence to ART. On examination he demonstrated splenomegaly 6 cm below the costal margin, Hb of 9.9 g/dl, and a CD4 count of 77 cells/μl, with a plasma HIV viral load of 63 copies/ml. A repeat bone marrow aspirate revealed a high density of *L. donovani* bodies.

Considering the history of multiple relapses to amphotericin B preparations and the initial treatment failure with miltefosine, the patient was admitted and treated with a combination regimen of concurrent liposomal amphotericin B (AmBisome) in six doses of 5 mg/kg spread over 14 days (total dose 30 mg/kg) and oral miltefosine 50 mg twice daily for 14 days. The treatment was well tolerated with no adverse events or deterioration in biochemical markers, and the patient was discharged with an initial cure. The patient's condition improved over the 12 months following the final treatment, which was reflected in a sustained improvement in CD4 counts of 316 cells/μl, 421 cells/μl, and 451 cells/μl at 3, 6, and 12 months of follow-up, respectively. At 18 months, the patient continued to be symptom-free with weight gain, improved Hb, and complete regression of hepatosplenomegaly.

3. Discussion

This case demonstrates the challenges in treating HIV and Leishmania co-infection for two reasons: first the higher rate of relapses and second the inefficiency of a single drug regimen. Both HIV and VL affect T-cell-mediated immunity and thus tend to act synergistically in reducing the effectiveness of the patient's immune responses. Co-infections with Leishmania and HIV have thus been associated with higher relapse rates of VL, a delayed response to ART, and higher HIV viral loads. These patients may have atypical clinical presentations of leishmaniasis and are more likely to have false-negative results when tested for VL with current standard rapid diagnostic kits.[4]

In 2010 the WHO expert committee recommended a single dose of 10 mg/kg liposomal amphotericin B as first-line treatment for VL in the Indian subcontinent.[1] However, its efficacy in HIV co-infection remains untested, and indeed highlights the absence of evidence for this particular clinical scenario. Liposomal amphotericin B monotherapy, 20 mg/kg, has been used relatively successfully in the Indian setting, however far higher relapse and early mortality rates were still seen when compared to patients not known to be infected with HIV receiving the same regimen.[2,5] In the Ethiopian setting, high-dose monotherapy with liposomal amphotericin B was associated with a 32% parasitological failure rate in HIV–VL co-infected patients.[2] In such cases, repeated treatment with monotherapies may potentially lead to increased resistance and treatment failures, which has already been described with oral miltefosine in the Indian subcontinent. Meanwhile, resistance mechanisms to amphotericin B deoxycholate have already been described in clinical isolates of *L. donovani*.

Based on the synergistic properties of liposomal amphotericin B and miltefosine, the compassionate use of this combination has been suggested for multiple relapses of VL in HIV–VL co-infection.[4] Considering the treatment history, this patient was admitted and treated with a concurrent combination of liposomal amphotericin B (AmBisome) in six doses of 5 mg/kg spread over 14 days (total dose 30 mg/kg) and oral miltefosine 50 mg twice daily for 14 days. Lower doses of this combination have already been shown to be safe and effective in immunocompetent patients in the Indian context,[3] and this regimen allowed the entire treatment to be administered under close inpatient supervision without an extended patient stay, which may have major economic consequences for typical VL patients in the Indian subcontinent.

The CD4 count remained persistently low in this patient despite rigid adherence to ART over a 9-month period, during which he relapsed and was treated twice for VL. At the initiation of the final treatment round with combination therapy, his CD4 count was the lowest it had been since ART was initiated at 77 cells/μl, with a very low viral load. Following treatment with this combination regimen, the patient remained relapse-free at 18 months and sustained a CD4 count >350 cells/μl. This suggests that the recovery of immune function that allowed final cure of the VL was not solely attributable to the control of HIV, but rather was in part due to the effective treatment of VL with this combination. This in turn may have broken the vicious cycle of synergy that HIV and VL co-infection has on the immune and hematopoietic systems.

The importance of recognizing the special needs of co-infected patients should not be underestimated, and region-specific guidelines need to be developed by the appropriate national programs to recognize the problem and assist physicians in managing this otherwise very challenging scenario. Indeed, all HIV patients with a history of spending significant periods in VL endemic areas should be screened for VL, whilst all patients diagnosed with VL should conversely be screened for HIV. Additionally, the use of monotherapy in those patients at high risk of relapse should be reconsidered.

In conclusion, this instructive case suggests that monotherapies with low-dose liposomal amphotericin B, lipid complex amphotericin B, and 28 days of miltefosine may result in treatment failure in HIV–VL co-infected patients, especially in those with low CD4 counts. Combination therapy with liposomal amphotericin B (30 mg/kg) and miltefosine (100 mg per day for 14 days) may result in a successful outcome. In the longer term, the appropriate management of HIV–VL co-infected patients may have an important role in reducing the reservoir of the parasite thus working towards the ultimate aim of disease elimination.

Conflict of interest: The authors declare no conflicts of interest.

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