

Double - Trouble- Relapsing Leishmaniasis in a Virologically Suppressed HIV Positive Patient

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Abstract

We present a case of a middle aged male, with long standing retroviral disease on second line ART (Anti-Retroviral Therapy) with three episodes of visceral leishmaniasis diagnosed on bone marrow examination treated with a combination of liposomal amphotericin B and miltefosine.

Introduction

Visceral leishmaniasis (VL) is endemic in some states of India. It is a known opportunistic infection in HIV positive individuals with high mortality if untreated and increased frequency of relapses. As per literature, relapses of VL have been observed in cases of ART (Anti-Retroviral Therapy) failure. Our patient was virologically well suppressed on second line ART but he still developed two relapses which as per our knowledge has not been reported from India. This case also highlights the importance of effective dosage of amphotericin and bone marrow examination post therapy to document cure.

Case

A 35 year old male, farmer from Bihar, known case of retroviral disease on ART (anti-retroviral therapy) since eight years, visited our outpatient department in March 2014 with a history of low grade fever, easy fatigability and dull aching left hypochondriac pain since six months. At other hospital, he was initially

started on d4T+3TC+NVP (Stavudine + Lamivudine + Nevirapine) regimen in 2005 which was changed three years later in 2008 to d4T+3TC+LPV/r (Stavudine + Lamivudine + Boosted Lopinavir) regimen. His previous investigations were not available. He was diagnosed with visceral leishmaniasis (VL) in 2010 and treated with liposomal AMB (Amphotericin B) 15 mg/kg in 3 divided doses daily for 28 days. ART regimen was changed to AZT+3TC+LPV/r. Since d4T was phased out, it was replaced by Zidovudine (AZT). Patient improved clinically. Eight months later, patient had a relapse which was retreated with liposomal AMB 5mg/kg for 6 doses with Miltefosine 50 mg twice a day for 28 days after which he symptomatically improved. During this 4 years period, patient had effective HIV viral RNA suppression.

On examination, he was pale and had massive splenomegaly - 10 cm below left costal margin. His hemogram revealed pancytopenia. His CD4 count was low - 64 but HIV viral load was 72 copies/ml. Bone marrow aspirate showed macrophages studded with LD (Leishmania Donovani) bodies (Figure 1).

In march 2014, we treated his second relapse with liposomal AMB 4mg/kg/day from day1-day5, then at day 10,17,24,31,38 with Miltefosine 50mg twice a day for 28 days. Hemogram, creatinine and electrolytes were monitored regularly. ART regimen consisting of AZT+3TC+LPV/r was continued. At the end of treatment, his

splenomegaly regressed, cytopenias improved and bone marrow was normal. At 1 year follow-up, he was stable without any signs of relapse.

Discussion

Leishmaniasis is an important opportunistic infection in HIV patients, especially in severe immunodeficient patients. India, Nepal, Bangladesh, Sudan and Brazil account for 90% of world's VL burden, with India being the worst affected. Almost all cases of VL/HIV co-infection have been found to have fewer than 200 CD4+ cells/ml blood, and about 50% meet the AIDS-defining criteria during their first episode of VL. Its incubation period is between 2 – 6 months¹ transmitted through bites of phlebotomine sandflies.²

VL is an AIDS defining condition and is an indication for starting ART irrespective of patient's CD4 count.² The clinical manifestations of VL in HIV-infected individuals may be similar to those seen in HIV-negative cases; fever, pancytopenia and hepatosplenomegaly, are found in 75% of all the HIV-positive cases. Following dissemination of the parasites, however, they may develop unusual, multi-organ pathology.¹ The clinical case definition of Primary VL is fever for more than 2 weeks with malaria excluded or treated in the presence of splenomegaly or lymphadenopathy and wasting.² Unusual manifestations like gastro-intestinal involvement, respiratory involvement, reactivation of arthritis, cutaneous involvement can be seen in such patients.^[1] Demonstration of amastigotes in smears of tissue aspirates is the gold standard for diagnosis. The sensitivity of splenic smears is >95% whereas smears of bone marrow (60 - 85%) and lymph node aspirates (50%) are less sensitive. Serological tests are commonly negative

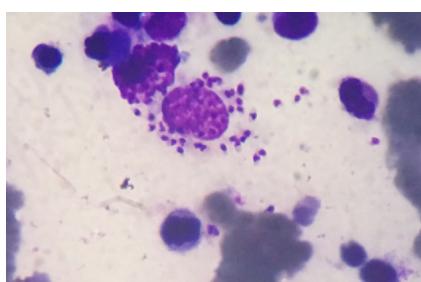


Fig. 1: Bone marrow aspirate (100x) showing a macrophage studded with LD (Leishmania Donovani) bodies

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in immunocompromised patients.³ Although rK39 ELISA is sensitive and important in epidemiological studies, it may remain positive upto 24 months after treatment.⁴ Hence, it was not done in our patient.

Treatment of VL-HIV co-infection is difficult as both HIV and Leishmania attack the immune system, they respond less effectively to ART and anti-leishmanial treatment like Sodium stibogluconate have unacceptable high mortality (16.33 %) during treatment.² Liposomal AMB is the drug of choice for VL-HIV coinfection – both for primary treatment and for treatment of relapses. A total dose of 40mg/kg administered as 4mg/kg on days-1-5,10,17,24,31,38 is considered and approved by FDA.³ Almost all the cases of co-infection are very prone to VL relapses, even after carefully managed antileishmanial treatment.¹ Most patients relapse within 1 year.³ These new episodes are usually recrudescences reflecting an inability of host's immune system to control leishmanial infection. The characterization of leishmania isolates from same patients during different episodes of VL indicate that very few relapses are the result of post treatment infection.⁵ HIV patients who have demonstrable parasites will relapse much sooner than those who have achieved parasitological cure. In coinfected patients in East Africa, MSF recently demonstrated that high dose Liposomal AMB in Ethiopian HIV-Primary VL co-infected patients led to an initial cure in only 74% cases which was further reduced to 38% in relapsed patients. Combination of Liposomal

AMB with Miltefosine in HIV positive VL patients enhances its effectiveness and lowers treatment failure rates as compared to monotherapy.² Dose of Miltefosine - for children aged 2-11 years is 2.5mg/kg/day, for more than 12 years and < 25kg – 50 mg/day, 25-50 kg – 100 mg/day, >50 kg – 150 mg/day orally for 28 days.⁶ Initiation of effective HAART regimen is mainstay in HIV-VL co-infection and most relapses are due to ineffective HAART and high HIV viral replication.⁵ Our patient was treated with FDA recommended dose of liposomal AMB for 10 days along with oral miltefosine for 28 days. Our patient is unique as he developed two relapses while being virologically suppressed on second line ART. Our patient did not have documented evidence of parasitological cure after treatment in first two episodes. Only evidence of clinical cure was present with resolution of splenomegaly and clinical symptoms. Thus, it is strongly recommended to document "parasitological cure" after completion of regimen² in form of bone marrow or splenic aspiration for absence of LD bodies, especially in HIV positive patients.

Secondary prophylaxis with Liposomal AMB has been shown to delay relapses but no regimen has been established as optimal.³ In a retrospective study of Pintado et al, it was shown that patients treated with monthly pentavalent antimonial or liposomal amphotericin were significantly less likely to relapse. In the only open, prospective and randomized clinical study till date

where patients treated with ABLC (Amphotericin B lipid complex) (3 mg/kg every 21 days) were compared to those not receiving prophylaxis, after 1 year follow up, 50 % patients treated with ABLC relapsed compared to 78% in nontreated patients.⁵

Conclusion

VL is an AIDS defining illness and HAART should be initiated irrespective of CD4 count. Relapse is reported in HIV positive individuals with high HIV viral load and ineffective HAART. Our case signifies that relapse may occur even on effective HAART regimen but large case studies are needed to establish this. Documentation of cure post treatment is strongly recommended to prevent relapse. Liposomal AMB with Miltefosine combination regimen has been shown to prevent relapse.

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