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Abstract. We describe a case of post-kala-azar dermal leishmaniasis occurring after diagnosis of visceral leishmaniasis in an HIV-1–infected woman. The skin lesions did not recover after treatment with oral miltefosine at 100 mg/day for five cycles of 28 days but responded to treatment with liposomal amphotericin B.

INTRODUCTION

Post-kala-azar dermal leishmaniasis (PKDL) is a possible complication of visceral leishmaniasis (VL) characterized by a macular, maculo-papular, and nodular rash. It is mainly seen in Sudan and India, where *Leishmania donovani* is the classic agent, and it probably plays an important role in interepidemic periods of VL, acting as reservoir for parasites. PKDL has recently been described also in HIV-1–infected subjects after the start of antiretroviral (ARV) treatment, likely as expression of immune reconstitution disease. The standard treatment is still based on antimony-derived drugs and, in presence of antimony-resistance, amphotericin B has been suggested, as alternative treatment.

Miltefosine, an alkylphosphocholine analog, is the first oral drug effective against VL and cutaneous leishmaniasis (CL). Thus far, miltefosine has been registered for leishmaniasis treatment in several countries. Miltefosine has been also used as off-label drug for compassionate use in the treatment of HIV-Leishmania co-infection, both in VL and in severe disseminated CL, and it is of potential interest in PKDL, although few data concerning treatment of PKDL in humans are reported.

In this report, we describe the case of an HIV-1–infected woman with PKDL that did not respond to oral miltefosine but recovered after treatment with liposomal amphotericin B (L-AmB).

CASE REPORT

In September 2003, a 40-year-old woman, HIV-hepatitis B virus (HBV) co-infected since 1987, presented at the Clinic of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy, with non-itching, erythematous nodular lesions and plaques on the face and maculo-papular rash on the extensor surfaces of both forearms and thighs (Figure 1A).

Six months before reporting to us, the patient had developed fever, weakness, and hepatosplenomegaly. A highly antiretroviral treatment (HAART) was started because of immunodeficiency status (Figure 2). Previously, ARV protease-inhibitor sparing treatments had been discontinuously taken by the patient. Two weeks later, the patient was hospitalized because of the persistence of symptoms, and VL was diagnosed by demonstration of *Leishmania* amastigotes in a bone marrow aspirate and biopsy. Treatment with L-AmB was administered concomitantly to HAART with a favorable clinical outcome.

In July 2003, multiple maculo-papular, non-itching skin lesions appeared on the patient’s face and limbs, evolving into nodules and plaques on cheeks, nose, and peri-oral region. HAART was stopped by the patient’s decision and restarted with the same regimen in August 2003 because of the severe immunodeficiency status. In suspicion of PKDL, we performed a punch biopsy of the skin lesions at forearm. The diagnosis of PKDL was confirmed by standard histologic examination (hematoxylin–eosin and Giemsa stain), culture (NNN medium), and quantification of *Leishmania* spp. DNA by real-time polymerase chain reaction (PCR; Figure 2). Parasite DNA was undetectable in whole peripheral blood samples, whereas serology was positive (1:1,280 by the immunofluorescent test). Follow-up was performed by periodic clinical examination and Leishmania DNA quantification in punch biopsies.

The patient was treated with five cycles of oral miltefosine (100 mg/day for 28 days, repeated after a 15-day interruption) from October 2003 to May 2004, without side effects. HAART was interrupted to reduce the potential effects of immune reconstitution and to avoid possible drug–drug interactions from the second to the fourth cycle, when it was restarted because of worsening of immunodeficiency status (Figure 2). We observed a slow, progressive improvement of skin lesions on the face and forearms (Figure 1B), with disappearance of maculo-papular rash on the thighs until the fourth cycle. Concomitantly a reduction of the parasite load was detected in punch biopsy from the lesions at forearm; on course of the fifth cycle, a worsening of the clinical picture with appearance of new maculo-papular lesions at the limbs and a mild increase of the parasite load was observed (Figure 2). The titer of anti-Leishmania antibodies was unchanged. We discontinued miltefosine and switched to L-AmB treatment (3 mg/kg/day for 4 consecutive days, interrupted on the fifth day because of renal failure and repeated at Day 10, weekly for six times, and once every other week for four times). A fast, progressive, and sustained improvement of skin lesions was observed after six doses of L-AmB (Figure 1C). Only a mild erythema was still visible on the face at the end of treatment.

No relapse occurred during the subsequent follow-up. A complete recovery of the erythema was observed, together with a sustained immunologic and virological restoration (CD4+ cells count and HIV-1 RNA, respectively, of 584 cells/μL, and viral load of 2 copies/mL).
We described a case of an HIV-1–infected woman with a previous episode of VL who developed PKDL, likely in relation to HAART-induced immune reconstitution. PKDL failed to respond to oral miltefosine but was later treated successfully with liposomal amphotericin B.

Miltefosine was chosen because of patient’s refusal to receive long-term intravenously therapy and on the base of reports of efficacy in subjects with disseminated VL and CL.14,15

In our case, miltefosine showed a limited efficacy until the fourth cycle and a failure during the fifth cycle. Our report is discordant with regard to other PKDL cases treated with miltefosine, described in HIV-Leishmania co-infected subjects (miltefosine as maintenance treatment in two subjects and as single antiparasitic treatment in another two), and in an HIV-negative, antimony-unresponsive Indian case.3,9–11 There are several reasons that may explain the failure in our case.

First, there was the possible onset of drug resistance. The intermittent schedule of drug administration might have favored the selection of resistant strains. In fact, miltefosine has a long-term half-life (150–200 hours), and sub-therapeutic levels of the drug, potentially able to generate the emergence of resistance, may remain for some weeks after a standard course of treatment.14 It is likely that, in our case, viable parasites might have been exposed to sub-therapeutic drug levels in the interval free-drug, because no complete resolution of skin lesions was obtained after the first cycle. In addition, the use of miltefosine as a single drug and the dosage used might have further contributed to the selection of resistant strains. With regard to combination therapy, as reported in other infectious diseases (e.g., malaria, tuberculosis, HIV), the use of two drugs with different modes of action might reduce the chance of selection of resistant mutants, increase efficacy, and shorten the duration of treatment.14,15 With regard to the dosage, miltefosine at a daily dose of 100 mg was studied in Indian subjects weighing 40 kg, but this dose may be low for subjects with a higher weight such as our patient, who weighted 64 kg.4,15 Nevertheless, data referring both to the use of miltefosine at higher doses for a period > 28 days and to combination therapy were not available at that time in which we treated the subject.

Second, we can not rule out an impact on the evolution of the skin lesions by HAART discontinuation and resumption. HIV-1 infection and related immune mechanisms (cytokines, immune-reconstitution syndrome) are crucial in the evolution of Leishmania infection, including PKDL.1,2 The pathogenesis of PKDL seems largely immunologically mediated, and this interpretation is corroborated by the evidence that in HIV-infected subjects with VL, PKDL may develop after the start of HAART, likely as a manifestation of an immune reconstitution disease.7 In our case, the recovery of immune function induced by HAART might have been a key role in causing PKDL. Similarly, it is possible that resumption of HAART on the fourth cycle may have contributed to worsening of the skin lesions despite miltefosine administration. A limit of our observation is that a measurement of cytokines levels was not performed. We also hypothesized an interaction between antiretroviral drugs and miltefosine. However, because the latter is not metabolized by cytochrome P450 enzymes (CYP) in vitro, a metabolic competition with other drugs (e.g., antiretroviral drugs) metabolized by these CYP isozymes is unlikely.16

Finally, the sensitivity of Leishmania species to miltefosine is a relevant issue in the outcome of the treatment; in fact,
variations in sensitivity of Leishmania species to various drugs have been documented. A limit of our case is that we were not able to define Leishmania spp.

In summary, in our case, treatment with oral miltefosine was apparently less effective and slower-acting than L-AmB. A complete disappearance of the skin lesions together with a reconstitution of the immune system was observed after treatment with L-AmB and HAART. No relapse occurred during the 4-year follow-up.

Based on this report and additional data from the literature,6,14,15 both longer courses and higher doses of miltefosine, as well as combination therapies, may be worth investigating in HIV-infected subjects with PKDL.

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REFERENCES

11. Sundar S, Kumar K, Chakravarti J, Agrawal D, Agrawal S,


