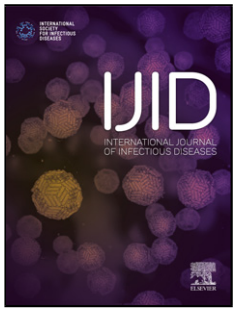

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Severe post-kala-azar dermal leishmaniasis successfully treated with miltefosine in an Ethiopian HIV patient

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Highlights

- Successful treatment of severe post-kala-azar dermal leishmaniasis with miltefosine
- Miltefosine was efficacious, safe and well tolerated in an Ethiopian patient

- Miltefosine can play a key role in post-kala-azar dermal leishmaniasis treatment
- Second East-African report on miltefosine and post-kala-azar dermal leishmaniasis
- Research on miltefosine combination therapy for post-kala-azar dermal leishmaniasis

Abstract

Post-kala-azar dermal leishmaniasis (PKDL) is a neglected tropical disease characterized by a dermatosis which often appears after successful treatment of visceral leishmaniasis caused by *Leishmania donovani*. PKDL treatment options are few and have severe limitations. In East-Africa, the standard treatment of PKDL is with daily painful potentially toxic sodium stibogluconate injections, administered for a prolonged duration of 30-60 days. In the Indian subcontinent, PKDL is mainly treated with miltefosine, a safer orally administered drug. However, in East-Africa, there is very limited experience in the use of miltefosine for treatment of severe PKDL, with only one published case report. Here we report a severe PKDL case in an Ethiopian HIV patient successfully treated with oral miltefosine (100 milligrams/day for 28 days). Miltefosine was efficacious, safe and well tolerated, suggesting that it can play an important role in the treatment of severe PKDL also in East-African patients. Further research is warranted.

Keywords. Post-kala-azar dermal leishmaniasis; miltefosine; treatment; HIV; Ethiopia; East-Africa.

Introduction

Post-kala-azar dermal leishmaniasis (PKDL) is a dermatosis which often appears after successful treatment of visceral leishmaniasis (VL) caused by *Leishmania donovani* (Zijlstra et al. 2003). Because of its *Leishmania donovani* association, PKDL is prevalent in East-Africa and the Indian subcontinent (Zijlstra et al. 2003).

PKDL skin rash may be macular, papular, nodular or mixed and usually starts around the mouth and may spread to the face, trunk, arms, and the rest of the body (Zijlstra et al. 2003). PKDL lesions are usually symmetrical, non-itchy, with intact sensation, which helps to differentiate it from other skin conditions such as leprosy (Zijlstra et al. 2003).

HIV infection is a major probable risk factor for developing PKDL. Others are malnutrition, young age, some drugs used for VL treatment, inadequate dosage of VL treatment regimens, *Leishmania donovani* and genetics (Zijlstra et al. 2003; Zijlstra 2016). PKDL diagnosis is usually made clinically, by a history of previous VL, the temporal association with VL, the distribution and appearance of the lesions, by ruling out other disorders, and by the response to treatment. When in doubt, parasitological confirmation may be done (Zijlstra et al. 2003).

There are *Leishmania* parasites in PKDL lesions and evidence that the sandfly vector may become infected from these lesions while taking a blood meal. Therefore, PKDL patients may play an important role in the anthroponotic transmission of VL, a deadly disease (Zijlstra et al. 2003; Mondal et al. 2018). Although PKDL is non-fatal, mucosal lesions in the mouth may cause difficulty in feeding, especially in children. Furthermore, disfiguring nodules may cause stigma and isolation, which can be a barrier for marriage, especially in girls (Zijlstra et al. 2003; World Health Organization 2010).

PKDL treatment options are few and have severe limitations. As most East-African PKDL patients (85%) heal spontaneously within one year, treatment is restricted to severe or complicated lesions (Zijlstra et al. 2003). In East-Africa, the standard treatment is daily

painful potentially toxic sodium stibogluconate (SSG) injections, for a prolonged duration of 30-60 days as inpatient (Zijlstra et al. 2003). The alternative treatment is liposomal amphotericin B which is safe and effective but its prolonged treatment course (20 days) makes it prohibitively expensive (World Health Organization 2010; Zijlstra 2016).

In the Indian subcontinent, PKDL is mainly treated with miltefosine, which is safer than SSG (Zijlstra 2016). However, in East-Africa, there is limited experience in the use of miltefosine for treatment of severe PKDL, with only one published case report (Belay et al. 2006). In this report we document a case of severe PKDL in an Ethiopian HIV patient treated with miltefosine.

Presentation of case

History

In October 2014, a 28 years old male Ethiopian presented at Abdurafi health center, a Médecins Sans Frontières supported health facility located in Abdurafi, north-west Ethiopia. The patient's main complaints were a non-itchy skin rash that started from around the mouth and spread to the rest of the face, upper chest and back during the previous one month. Between 2005 and 2006, he had been treated thrice for VL. In November 2013 and January 2014, he had been treated twice for severe PKDL, with daily SSG injections for one month. On each occasion the patient was cured. However, after cure, in both PKDL episodes, the lesions relapsed. In May 2014, he was diagnosed HIV positive and started on antiretroviral therapy (ART).

Examination

On general examination, he was in good general condition, fully conscious, afebrile, no pallor, no jaundice, no peripheral edema and well nourished. On dermatological examination, he had a dense nodular rash covering the whole face, spreading to the upper chest and back, and sensation was intact. There were few pustules on the facial lesions (Figure 1A−1E).

Investigations

White blood cells (5.60 x 10^3 cells/μL) and lymphocyte cells (1.51 x 10^3 cells/μL) were normal, suggesting a high CD4 cell count (World Health Organization 2004).

Diagnosis

Clinical diagnosis of severe PKDL grade 2 (Zijlstra et al. 2003). Parasitological confirmation was not done.

Treatment

Oral miltefosine (Impavido, Paladin Labs, Montreal, Canada) for 28 days (100 milligrams/day).

Follow-up

On the sixth treatment day, the patient reported gastrointestinal disturbances during the previous four days, with passage of mucoid stools (3–4 times/day). Stool examination results were normal and the symptoms subsided without treatment.

On the ninth treatment day, he complained of increasing itching over the lesions on the face. It was observed that the lesions with supra bacterial infection (pustules) were increasing. Therefore, we prescribed twice daily dressing of the infected lesions and amoxicillin/clavulanic acid 1 gram orally twice a day for 10 days. This resulted in cure of the supra bacterial infection and regression of the itching.

Outcome

At the end of treatment, there was flattening of the PKDL lesions and healing of the supra bacterial infection (Figure 1F – 1J). Subsequently, he was declared cured and discharged (World Health Organization 2010).

Discussion

SSG gives rise to potentially dose-dependent serious toxicity (cardiotoxicity, nephrotoxicity, pancreatitis) and may be fatal (Alvar et al. 1997). SSG-induced toxicity may be lowered with SSG and paromomycin combination therapy, as the paromomycin in the regimen significantly reduces the number of SSG doses required (Abongomera et al. 2016). Furthermore, SSG has been shown to result in high mortality when used for treatment of VL in HIV patients (Alvar et al. 1997).

Here, we document a case of severe PKDL in an Ethiopian HIV patient successfully treated with miltefosine. The treatment duration of 28 days was shorter than that of up to 90 days reported in India (Ramesh et al. 2015). As miltefosine may be teratogenic, it is contraindicated during pregnancy, and women of reproductive age must use effective contraception during and for three months after treatment (Dorlo et al. 2012). Furthermore, miltefosine may cause gastrointestinal symptoms (nausea and vomiting) (Dorlo et al. 2012). In this patient, there were mild gastrointestinal symptoms not warranting treatment interruption, and treatment was completed. Good tolerance to miltefosine has also been reported in VL treatment studies (Abongomera et al. 2018).

Reports from the Indian subcontinent show declining efficacy of miltefosine monotherapy and increasing treatment failure (Rijal et al. 2013; Ramesh et al. 2015). Therefore, research is needed on miltefosine in combination therapy (either with Liposomal amphotericin B or

paromomycin), in order to reduce treatment duration, increase efficacy, and reduce the risk for the development of resistance (Drugs for Neglected Diseases Initiative 2018).

A major study limitation is the lack of long term follow-up results. This is because the patient could not be traced. The population within this region is highly mobile. Studies show high risk of VL relapse in HIV patients, and the main predictors are not receiving secondary prophylaxis and ART (Cota et al. 2011; Abongomera et al. 2017). During this study, secondary prophylaxis was not routine clinical practice, however, the patient received ART. In the previous case report, both PKDL cases did not relapse after six months follow-up (Belay et al. 2006).

In this report, miltefosine was efficacious, safe and well tolerated, suggesting that it can play an important role in the treatment of severe PKDL also in East-African patients. This is the second case report from East-Africa documenting successful treatment of severe PKDL with miltefosine. More research is needed on miltefosine in combination therapy for severe PKDL.

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Ethical approval

The patient voluntarily gave a written informed consent for use of the images and case history for this report.

Conflict of interest

None

Author contributions

All authors have contributed to the study design, data collection, data analysis and writing.

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Figure legend

Figure 1. Severe post-kala-azar dermal leishmaniasis in an Ethiopian HIV Patient

(A) Frontal facial view before the start of treatment. (B) Left lateral facial view before the start of treatment. (C) Right lateral facial view before the start of treatment. (D) Upper part of the chest before the start of treatment. (E) Upper part of the back before the start of treatment. (F) Frontal facial view at the end of treatment. (G) Left lateral facial view at the end of treatment. (H) Right lateral facial view at the end of treatment. (I) Upper part of the chest at the end of treatment. (J) Upper part of the back at the end of treatment