Case Report: Successful Treatment of Cutaneous Leishmaniasis Caused by *Leishmania aethiopica* with Liposomal Amphotericin B in an Immunocompromised Traveler Returning from Eritrea

Philipp Zanger,* Ina Kötter, Armin Raible, Tesfaye Gelanew, Gabriele Schöniar, and Peter G. Kremsner

Institut für Tropenmedizin, Medizinische Klinik, Onkologie, Hämatologie, Klinische Immunologie, Rheumatologie und Pulmonologie, und Medizinische Klinik, Gastroenterologie, Hepatologie, Infektionskrankheiten Eberhard Karls Universität, Tübingen, Germany; Institut für Mikrobiologie und Hygiene, Charité, Universitätsmedizin Berlin, Berlin, Germany; Faculty of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

Abstract. Cutaneous leishmaniasis caused by *Leishmania aethiopica* is rarely encountered outside disease-endemic areas and there have been no clinical trials evaluating its pharmacotherapy. We describe the treatment of cutaneous leishmaniasis caused by *L. aethiopica* using liposomal amphotericin B in an immunocompromised traveler returning from Eritrea.

Cutaneous leishmaniasis (CL) caused by *Leishmania aethiopica* is rarely encountered outside disease-endemic areas and there have been no clinical trials evaluating its pharmacotherapy. Under resource limited conditions, antiparasitic treatment of *L. aethiopica* infection relies largely on pentavalent antimonials. However, treatment failure is frequent and systemic application of these drugs is potentially harmful.^{1–4} Evidence for the efficacy of less adverse chemotherapeutics is needed. We report treatment of CL caused by *L. aethiopica* using liposomal amphotericin B (LAmB) outside a disease-endemic region.

A 38-year-old man from Eritrea and a permanent resident in Germany over the past 22 years had a 6 × 5 cm skin lesion over his left zygomatic bone. Eleven months earlier, he had returned from a one-year stay in Eritrea where he had visited the coastal area of Asmara and the highlands of the Debub Region. Without an obvious reason, he had stopped taking methotrexate and leflunomid for treatment of rheumatoid arthritis during his stay abroad. Because of increasing inflammation of his left ankle and wrist after returning to Germany, the patient had been treated with infliximab, methotrexate, and prednisolone over the past six months. Two weeks after initiation of this regimen, he recognized a small papule on his left cheek that had gradually progressed to a large lesion seen at the time of hospitalization (Figure 1A).

Skin biopsy specimens for histologic analysis and culture were obtained. Microscopically, a chronic lympho-plasmacellular infiltration with increased content of eosinophilic granulocytes was dominant. Amastigote *Leishmania* or granulomata were not present. Specific staining results for fungi and mycobacteria were negative, and cultures did not demonstrate *Leishmania*.

However, sequences specific for Old World species could be detected in extracted DNA.⁵ For species differentiation, we amplified and sequenced the ribosomal internal transcribed spacer region 1 separating the 18S and 5.8S ribosomal RNA genes, which showed infection with *L. aethiopica* (GenBank accession no. FN252411).^{6,7} IgG against recombinant rK39 antigen (immunochromatographic test) and a low positive IgG titer of 1:80 against *L. donovani* promastigote antigens

(indirect immunofluorescence test, cutoff value = 1:40) were detected. An abdominal ultrasound scan, a full blood count, and a polymerase chain reaction for *Leishmania* spp. from the buffy coat did not suggest visceral disease.

We stopped treatment with infliximab and administered 4.4 g LAmB (60 mg/kg body weight) in doses of 200 mg/day for 22 days through a peripheral venous line. Other than mild and transient renal impairment, this therapy was well tolerated. The lesion started to resolve during the third week of LAmB therapy. At discharge, treatment with hydroxychloroquine and sulfasalazine was initiated. However, one month later, this regimen was changed to etanercept, prednisolone, and methotrexate because of increasing rheumatic disease activity. Despite restarting therapy with tumor necrosis factor- α (TNF- α) antagonists, the facial lesion showed further improvement without signs of recurrent leishmaniasis on a follow-up visit 12 months after completion of LAmB therapy (Figure 1C).

Leishmania aethiopica is known to cause CL in Ethiopia and Kenya, where its distribution is closely related to the habitat of rock hyraxes, the specific hosts, and restricted to the highlands. Cutaneous leishmaniasis is frequently observed in Tigray alongside the border of Ethiopia and Eritrea.¹ However, *L. aethiopica* has not been reported in Eritrea in publications indexed in PubMed. Moreover, current maps depicting the distribution of *L. aethiopica* do not indicate its endemicity in Eritrea because they are based on classic field research from the late 1960s that did not encompass areas north of Lake Tana.^{8–10} However, our results and the medical history of our patient strongly suggest the presence of *L. aethiopica* in the highlands of Eritrea.

The clinical spectrum of leishmaniasis is to a large extent a function of the immune response of the host. Immunodeficiency, in particular disturbances of the type 1 helper T cell-mediated immunity can impair containment of intracellularly viable parasites and promote manifestation and progression of disease. Tumor necrosis factor- α is a key cytokine in granuloma formation, and its antagonization is known to be associated with an increased risk for granulomatous infections.¹¹ Histologic findings in our patient, characterized by a lack of granulomata and the predominance of a lympho-plasmacellular infiltrate, indicate a Th2-driven immune response and are consistent with an effect of the TNF- α antagonist infliximab on the pathogenesis of CL in our patient.

The patient has most likely newly acquired infection with *L. aethiopica* during his visit in Eritrea because he had received

*Address correspondence to Philipp Zanger, Institut für Tropenmedizin, Wilhelmstraße 27, 72074 Tübingen, Germany. E-mail: philipp.zanger@med.uni-tuebingen.de

FIGURE 1. Aspect of cutaneous leishmaniasis caused by *Leishmania aethiopica* before (A), 3 weeks (B), and 12 months (C) after completion of treatment with liposomal amphotericin B and 11 months after restarting treatment with a tumor necrosis factor- α antagonist drug (C).

immunosuppressive therapy years before traveling there without any signs of reactivation of latent infection. Nevertheless, we can not rule out that his infection was acquired before he migrated to Germany. This alternative explanation in turn would imply that the use of TNF- α antagonists when compared with traditional immunosuppressive regimens is associated with an increased risk of reactivation of latent leishmaniasis, a hypothesis that is supported by one study, which found a significantly shorter time to onset of opportunistic leishmaniasis in patients who had received anti-TNF- α therapy.¹² However, the question of whether our patient had newly acquired this infection or not does not invalidate the conclusion of probable presence of *L. aethiopica* in Eritrea because he had never visited any of the currently recognized regions in which this organism is endemic.

Various findings suggest that CL caused by *L. aethiopica* is different from other Old World forms of CL with respect to its potential to cause non-localized manifestations. For instance, after an outbreak of *L. aethiopica*, mucocutaneous leishmaniasis (MCL) developed in 19% of patients,¹³ and in a cross sectional survey from northern Ethiopia, 17% of patients with Old World CL were reported to have had mucocutaneous disease.¹ In addition, diffuse CL, a particularly disfiguring and difficult to treat manifestation of leishmaniasis, has been originally described in patients from Ethiopia.¹⁴ Although also sporadically observed in infections with other species, diffuse CL of the Old World appears to be particularly associated with *L. aethiopica* infection.^{14,15}

Treatment of CL in travelers should ideally incorporate results from clinical trials and *in vitro* susceptibility testing together with knowledge of the risk for MCL into a species-specific therapeutic approach. For many cases of Old World CL, topical therapy is regarded as treatment of first choice whereas systemic chemotherapy is only advocated for large lesions, facial location, or signs of lymphatic spread.¹⁶ In contrast, for most species causing New World CL, systemic antiparasitic therapy is considered mandatory for preventing MCL.^{16,17} If one considers the high proportion of associated MCL recently reported, it might be prudent to choose an approach similar to that recommended for the treatment of most patients with New World CL and to advocate systemic therapy for localized Old World CL caused by *L. aethiopica*.¹³ Systematic investigations on the risk of MCL in *L. aethiopica* infection are needed to clarify this area of uncertainty.

In our patient, the location and large size of the lesion, its ill-defined characteristics (Figure 1A), and the concomitant immunodeficiency with a potential of mucosal spread prompted our decision to initiate systemic treatment. We chose LAmB on the basis of its excellent *in vitro* activity against *L. aethiopica*.¹⁸ Analogous with the recommended dosage for treatment of MCL, we administered a total of 4.4 g LAmB (60 mg/kg body weight) over 22 days.^{16,17} This treatment was well tolerated and led to rapid clinical improvement. We can only speculate to what extent modification of the antirheumatic treatment regimen contributed to the long-term outcome of our patient. However, on the basis of the long half-life of infliximab, we argue that the rapid clinical response supports efficacy of the treatment with LAmB rather than sole improvement caused by reconstitution of the immune system after discontinuing anti-TNF- α therapy. Moreover, immunosuppressive therapy with an alternative TNF- α antagonist was recommenced at a stage where the lesion was still present, which suggested that its reactivation was prevented by prior inactivation of most amastigotes by LAmB treatment.

We report treatment of CL caused by *L. aethiopica* with LAmB. If one considers the burden of disease reported from Ethiopia^{1,13} and the reportedly poor response to pentavalent antimonials,¹⁻⁴ clinical trials evaluating the pharmacotherapy of complicated CL caused by *L. aethiopica* are urgently needed.

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Authors' addresses: Philipp Zanger and Peter G. Kremsner, Institut für Tropenmedizin, Wilhelmstraße 27, 72074 Tübingen, Germany, E-mails: philipp.zanger@med.uni-tuebingen.de and peter.kremsner@uni-tuebingen.de. Ina Kötter, Medizinische Klinik, Onkologie, Hämatologie, Klinische Immunologie, Rheumatologie und Pulmonologie, Otfried-Müller Straße 10, 72076 Tübingen, Germany, E-mail: ina.koetter@med.uni-tuebingen.de. Armin Raible, Medizinische Klinik, Gastroenterologie, Hepatologie, Infektionskrankheiten, Otfried-Müller Straße 10, 72076 Tübingen, Germany, E-mail: armin.raible@med.uni-tuebingen.de. Tesfaye Gelanew, Institut für Mikrobiologie und Hygiene, Campus Charité Mitte, Dorotheenstraße 96, 10117 Berlin, Germany and Faculty of Medicine, Addis Ababa University, PO Box 9086, Addis Ababa, Ethiopia, E-mail: tesfayegela2002@yahoo.com, Gabriele Schönan, Institut für Mikrobiologie und Hygiene, Campus Charité Mitte, Dorotheenstraße 96, 10117 Berlin, Germany, E-mail: gabriele.schoenian@charite.de.

Reprint requests: Philipp Zanger, Institut für Tropenmedizin, Wilhelmstraße 27, 72074 Tübingen, Germany, E-mail: philipp.zanger@med.uni-tuebingen.de.

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