Cutaneous leishmaniasis due to *Leishmania aethiopica*: A therapeutic challenge

Laura Mengeot, MD,[a] Jean-Cyr Yombi, MD,[b] and Marie Baeck, MD, PhD[a]
Brussels, Belgium

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INTRODUCTION

Cutaneous leishmaniasis (CL) is a chronic infectious skin disease caused by a group of protozoan parasites of the *Leishmania* genus. Parasites are transmitted to humans via the bite of sandflies. *Leishmania aethiopica*, one of the most neglected species, is the main causative agent of CL in Ethiopia, with infection characterized by reduced sensitivity to conventional drugs. Although the incidence of imported cases of CL is increasing in nonendemic areas, *L aethiopica* is rarely reported in travelers. We report a case of localized CL due to *L aethiopica* in a Belgian traveler.

Abbreviations used:

CL: cutaneous leishmaniasis
PDT: photodynamic therapy

CASE REPORT

A 64-year-old white man presented to our outpatient dermatology department with a 3-month history of a growing plaque of the left cheek. He was otherwise healthy with no relevant medical history. He gave written informed consent for the publication of his photographs and case details. Six months prior to the onset of the lesion, he had traveled for 2 weeks to Ethiopia, where he visited the Amhara region in the north-western Ethiopian Highlands.

The lesion initially appeared as a painless, slowly growing erythematous papule (15 mm) with progressive extension and evolution into a purple-red indurated plaque with a diameter of 24 mm (Fig 1, *A*).

Histopathologic analysis of skin biopsy samples showed a chronic histiocytic granulomatous infiltrate with presence of macrophages containing numerous cytoplasmic endoparasites (2-3 μm in diameter). The diagnosis of CL was proposed. *L aethiopica* was identified on another skin sample by polymerase chain reaction targeting the "Hsp70" gene.

The patient was first treated with a 5-day course of intravenous amphotericin B liposomal in accordance with the World Health Organization guidelines (5 mg/kg/day),[1] which was followed by clinical improvement. However, the patient experienced complete relapse 3 weeks later. A second course of amphotericin B liposomal was initiated but had to be stopped after 4 days due to severe nephrotoxicity (urea, 80 mg/dL [normal range, 15-50 mg/dL]; creatinine, 2.15 mg/dL [normal range 0.60-1.30 mg/dL]; estimated glomerular filtration rate, 31 mL/min/1.73 m^3 [normal value $\geq$ 60 mL/min/1.73 m^3]). The patient received a cumulative dose of 2,400 mg of liposomal amphotericin B.

Combined treatment with oral posaconazole (400 mg per day) and sensitized photodynamic therapy (PDT) once a week was then started. Unfortunately, posaconazole was discontinued after 7 days due to hepatoxicity. However, the PDT sessions were well tolerated for 16 weeks, and the patient was irradiated with red light for 15 minutes from an Aktilite CL 128 lamp (Galderma Nordic AB, Uppsala, Sweden) at a light dose of 75 J/cm^2 per treatment session, after an application time of methyl aminolevulinate of 3 hours. After the first sessions the lesion reduced in size, but no further clinical

From the Department of Dermatology[a] and Department of Internal Medicine and Infectious Diseases[b], Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels.
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Correspondence to: Marie Baeck, MD, PhD, Department of Dermatology, Cliniques Universitaires Saint-Luc (UCL), Avenue Hippocrate 10, B-1200 Brussels, Belgium. E-mail: marie.baeck@uclouvain.be.

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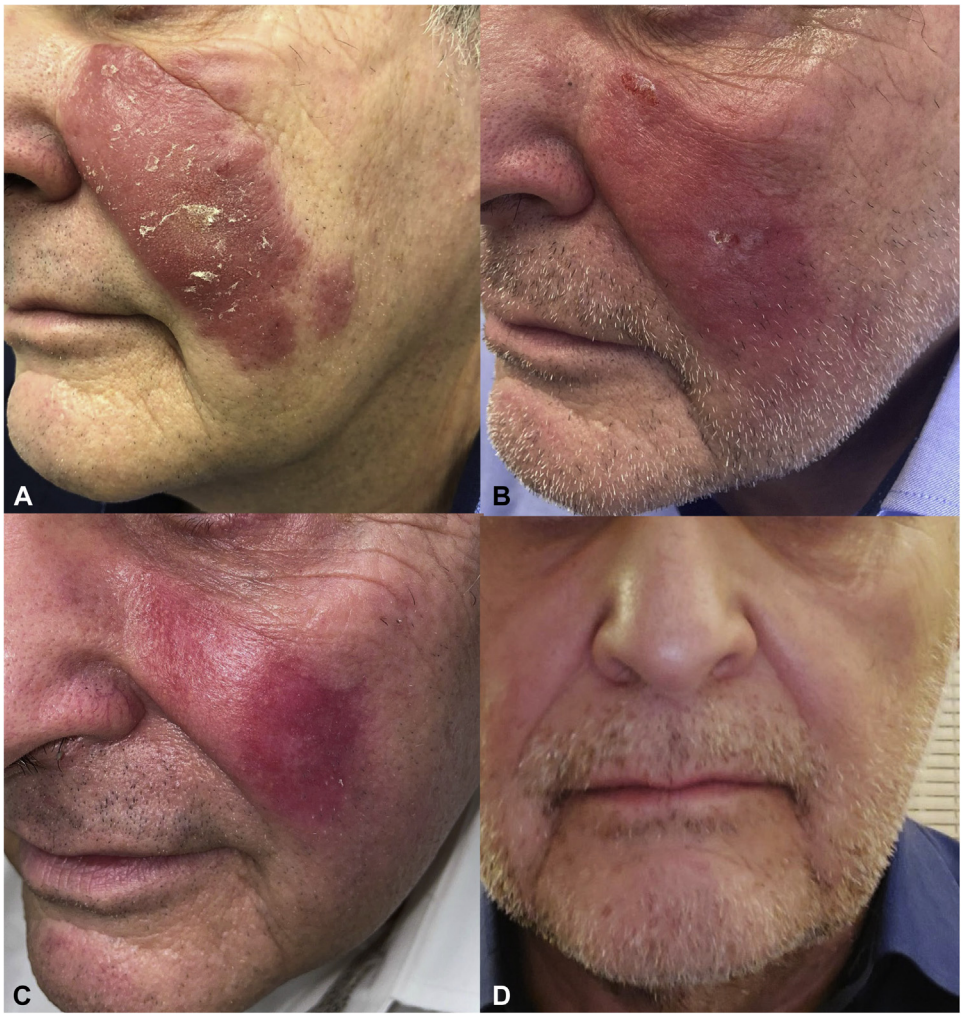

Fig 1. **A**, Clinical aspect at the time of the first consultation with a purple-red indurated plaque with a diameter of 24 mm on the left cheek. **B**, Clinical development with significant improvement after 10 sessions of sensitized photodynamic therapy (PDT). **C**, Clinical aspect after 45 days of treatment with meglumine antimoniate, with post-inflammatory erythema. **D**, Six-month follow-up after the end of treatment with meglumine antimoniate, with no sign of relapse.

response was observed after session number 10 (Fig 1, *B*).

Given the loss of efficacy of the last PDT sessions, a polymerase chain reaction analysis of an additional skin biopsy was performed and revealed persistent *Leishmania* activity. This led to the initiation of a treatment with pentavalent antimonials. The patient received a daily 1.5 g/5-mL intramuscular injection of meglumine antimoniate for 45 days resulting in the complete resolution of the lesions (Fig 1, *C*) and no sign of relapse 6 months later (Fig 1, *D*).

DISCUSSION

CL affects around 20,000 to 50,000 people annually in Ethiopia, with *L aethiopica* as the main pathogen involved.[2] It is considered to be a zoonotic disease, with hyraxes serving as animal reservoirs, and is traditionally reported to occur in the areas along the mountain ridges, in the high-plateau regions.[3]

The most frequent presentation of infection due to *L aethiopica* is localized CL affecting the face, as was the case in this patient.

CL treatment remains a challenge whichever the *Leishmania* species. For several decades, first-line treatment was based on pentavalent antimonials. However, with the increasing concern about the development of resistance against this treatment, the World Health Organization now recommends liposomal amphotericin B as first-line treatment in Asia, Europe, and Africa. Alternative treatment regimens include other systemic therapies, such as pentamidine, miltefosine, antifungal agents (azoles), as well

as local therapies like thermotherapy, cryotherapy, carbon dioxide laser, or PDT.[4] Miltefosine is an oral agent, initially developed for cancer treatment, which appears to be effective against CL, although its mechanism of action remains unknown.[5] Despite its growing use as a first-line CL treatment in some countries, we did not consider miltefosine due to safety concerns, inaccessibility in Belgium, and the unsatisfactory results of a recent pilot study using this molecule for the treatment of CL in Ethiopia.[6] Therefore, amphotericin B liposomal was used as first-line therapy.

Posaconazole is an antifungal agent—a first-generation triazole—and part of the ergosterol biosynthesis inhibitors group. Ergosterol biosynthesis being an essential requirement for trypanosomatid parasites, such as *Leishmania*,[7] several clinical trials have recently showed the potent effect of posaconazole against *Leishmania*; however, these have been mainly conducted on CL caused by *Leishmania amazonensis*.[8] Our literature search revealed no other reports of the use of posaconazole for the treatment of *L aethiopica*. Unfortunately, as the treatment was interrupted after 1 week in our patient because of liver toxicity, we cannot conclude on the effectiveness of this medication for treating *L aethiopica* CL.

The use of PDT as an alternative therapeutic approach was justified by several reports that demonstrated some success in treating superficial CL.[9-11] In the present case, after initial failure of first-line liposomal amphotericin B therapy, sensitized PDT alone did not cure the condition. However, the first sessions of PDT resulted in significant reduction in size of the lesion, possibly due to the 7-day association with posaconazole. Combined therapy may, therefore, have proven to be beneficial, if it had not been interrupted.

Cryotherapy was not chosen as a treatment option due to the high risk of pain given the size and location of the lesion.

Similarly, intralesional injection of antimonials was considered; however, given the risk of scarring and the proximity of the ocular region, systemic treatment was preferred. Systemic pentavalent antimonials are the most commonly used drugs against *Leishmania* infections in Ethiopia.[4] Despite the lack of robust clinical trials, including high-level randomized clinical trials, multiple case reports and retrospective data have demonstrated their efficacy.[12]

CONCLUSION

CL caused by *L aethiopica* is scarcely encountered in travelers, and we have here reported a rare case diagnosed and treated in Belgium. *L aethiopica* species is still poorly known, and therapeutic guidelines are based on limited evidence. We consecutively used amphotericin B liposomal, posaconazole, PDT, and systemic pentavalent antimonials. This case demonstrates the therapeutic resistance of CL caused by *L aethiopica* and the possible value of combining therapies. Glucantime antimonate led to complete healing of the infection. However, the potentiating effect of the previously received treatments should be considered, in particular the association with PDT.

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Conflicts of interest

None disclosed.

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