



Case report

Cutaneous leishmaniasis in non-endemic countries: An emerging yet neglected problem



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ABSTRACT

Cutaneous leishmaniasis (CL) is the most common leishmaniasis syndrome, yet a neglected disease in industrialized non-endemic countries, where it has become an emergent problem. The lack of clinical experience, evidence-based literature and availability of some treatments complicates its management. We report a CL case in a 30 year-old man returned from Brazil, with a cutaneous ulcerated lesion, where it was possible to isolate *Leishmania braziliensis/guyanensis* complex (subgenus *Viannia*). An initial course of treatment with miltefosine was attempted, but considering the lack of response, liposomal amphotericin B was used, with very good results. Our report highlights the obstacles faced in the diagnosis and treatment of New World CL in non-endemic countries and the need for more funding and research.

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Introduction

Leishmaniasis is a vectorial parasitic disease, transmitted by female sandflies (*Phlebotomus*, *Lutzomia*) and caused by a protozoan of the genus *Leishmania* (at least 23 pathogenic species). It has a wide spectrum of clinical presentations (asymptomatic infections, ulcerated cutaneous or destructive mucosal lesions, fatal visceral involvement), producing 3 syndromes: cutaneous (CL), mucosal (ML) and visceral leishmaniasis (VL). Each of these syndromes have their own unique geographic distribution, reservoirs and vectors, differing in clinical manifestations and treatment. It is estimated that 350 million people are at risk of CL, the most reported syndrome. Despite being recognized in scattered foci in approximately 100 countries, with an overall prevalence of 12 million cases (2 million per year), >90% are reported by a limited number of countries (Afghanistan, Algeria, Brazil, Colombia, Costa Rica, Ethiopia, Islamic Republic of Iran, North Sudan, Peru and the Syrian Arab Republic) [1]. Even though it is a growing anthroponosis in these countries, it has been a long-forgotten problem to the industrialized and non-endemic world, considered by the World Health Organization a severely neglected and uncontrolled disease. Due to new international migratory flows, the number of reported cases in non-endemic countries has been growing in the last decades, being one of the 10 most common dermatologic disorders in the returning traveler [2] and a growing concern in conflict areas (military operations in

Afghanistan, Iraq or Syrian Arab Republic) [3,4]. Everyday, non-endemic countries welcome thousands of immigrants, returning travelers and soldiers at risk of CL and are mostly unprepared to diagnose or manage this disease.

In this study, we report a CL case in an immigrant recently returned from Brazil, emphasizing the obstacles faced in its approach, diagnosis and treatment.

Case

A 30 year-old Brazilian man presented with a 1.5-months history of an enlarging skin lesion on the dorsum of his right hand. There was no relevant medical past history. He had moved to Portugal in the previous week and had been travelling in Brazil for 4 months in the states of Acre and Rondonia. He went backpacking to forested regions, walking long distance trails and camping in the jungle without using mosquito nets, insecticide or repellent. He admitted to multiple insect bites. In one bite site, he reported the appearance of a small macule that evolved into a papulonodular lesion and slowly enlarged to a painless shallow circular ulcer, with well-defined and raised borders. Two weeks before this lesion appeared, he remembered feeling feverish and noted an enlarged ipsilateral axillary lymph node.

By the time the patient presented to us for care, the lesion measured 3.5 cm in diameter. He felt very anxious, since it was reaching his thumb, and he worked as a barber but denied any other symptoms. Physical examination was unremarkable besides this single skin lesion and an axillary lymphadenopathy measuring 1 cm. Initial laboratory testing was normal (complete blood count and differential, C reactive protein (CRP), erythrocyte sedimentation rate

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(ESR), renal and liver function tests and electrolytes). Fourth generation HIV-1/2 assay was negative. Considering the clinical and epidemiological picture, CL diagnosis was suspected and a biopsy sample from the ulcer margin was performed. Direct microscopy and histopathological exam were negative for *Leishmania spp*, but culture and PCR identification were positive. Molecular techniques identified *Leishmania braziliensis/guyanensis* complex (subgenus *Viannia*). Although asymptomatic, considering the risk of ML, the patient was submitted to an otorhinolaryngologic examination, which excluded mucosal involvement. Besides local wound care, a 28-day course of miltefosine (50 mg three times a day, *per os*) was initiated as soon as available. By the 2nd week of treatment, the lesion continued to grow, and there were signs of bacterial superinfection (pain and purulent exudate), which were successfully treated with a 1-week course of antibiotics (flucloxacillin and clindamycin).

By the 3rd week, the lesion reached 5 cm in diameter, and nodular lymphangitis was noted (Figs. 1, 2), affecting the whole limb. After discussing with the patient the available options, it was mutually agreed that he would be hospitalized to start liposomal amphotericin B. An initial 10-day course was given (2 mg/kg/d in the first 5 days, then 3 mg/kg/d), with significant improvement, followed by 3 other administrations on days 17, 24 and 31 (total dose 34 mg/kg). By the end of the treatment the lesion was almost completely re-epithelized, and 1 month after its completion there was only an atrophic and depigmented scar (Fig. 1).

Discussion

CL is the most common syndrome associated with *Leishmania*. Considering the geographic distribution of the infectious species, CL is divided into New World – Eastern Hemisphere (Latin America) and Old World – Western Hemisphere (Mediterranean basin, north and east Africa, Middle East, South Asia) disease. This classification has diagnostic and prognostic importance, because ML mainly occurs in the New World (associated with *Viannia* subgenus), with Brazil, Peru and Bolivia reporting 90% of cases [5]. Although rare, occurring in 2–5% of *L. (V.) braziliensis* infection (rarer with *L. (V.) panamensis* or *guyanensis*), ML may lead to mucosal destruction and disfigurement and requires systemic treatment. Mucous membrane involvement of the upper airways (nose, oral cavity, pharynx or larynx) usually starts months or years after the healing of the initial skin lesion, although they can be concurrent events [5]. This makes parasitological diagnosis with species identification crucial. However, direct parasite identification and culture have variable sensitivity (50–90%) [1,5,6], and PCR based molecular techniques (sensitivity 95%) are not always available. Clinical diagnosis in an endemic area has an elevated pretest positivity value, and cases from the “mucosal belt” (Peru, Bolivia, Brazil) should receive systemic treatment, considering the probable involvement of *Leishmania (Viannia)* and the risk of ML



Fig. 2. Nodular lymphangitis.



Fig. 1. Evolution of lesion since the beginning of treatment till 1 month after its conclusion.

[7]. Our patient had an infection with this subgenus, which is not surprising considering his origin (Brazil) and clinical presentation. Systemic symptoms sometimes precede the development of cutaneous infection in *L.(V.)braziliensis*, and nodular lymphangitis is well-described in *L.(V.)guyanensis* and *braziliensis* infection [5,6].

CL treatment is still an area of uncertainty. Local wound care and prompt recognition and treatment of bacterial superinfections are important. The use of anti-leishmania agents depends on empirical local experience gathered at endemic regions, lacking well-controlled comparative trials. The decision to treat is not straightforward: it depends on the severity of the initial presentation (number, size of lesions and its progression, mucosal involvement), patient background (e.g. immune status), species involved, available resources and impact on the patient [1,8]. Most CL cases are self-limited and the available therapeutic agents have important side effects, being local therapy a very reasonable choice for uncomplicated CL. Cryotherapy, thermotherapy, topical paromomycin and intralesional antimonials are some of the most used topical treatments [9]. In this case systemic treatment was required considering the complex clinical presentation (large lesion, ipsilateral lymphadenopathy, nodular lymphangitis) and the identification of *Viannia* subgenus (to prevent future ML) [10].

Pentavalent antimonials (SbV), liposomal amphotericin B and miltefosine are all options for anti-leishmanial treatment in a *Leishmania (Viannia)* infection.

There is a long history of experience with SbV, which have been the most commonly used treatment in endemic areas. A usual 20-day course of 20 mg/kg/d (IV/IM) produces an overall cure rate of 58–100% [5,7,8] but is associated with numerous side effects leading to its discontinuation in 25% of patients [8]. Serious side effects include potentially life threatening arrhythmias, renal and hepatic toxicity, pancreatitis and myelosuppression [6,7]. Furthermore in non-endemic areas it is not easily available nor frequently used, making its management difficult and a cause of anxiety.

Miltefosine is the only drug approved by the FDA (2014) for CL treatment, including *L.V. braziliensis*, *panamensis* and *guyanensis* [8]. It is usually well-tolerated, with self-limited headaches and gastrointestinal symptoms being the most common side effects. Clinical cure can be achieved in 50–90% according to some series [7,8]. However, its long half-life and prolonged oral treatment course (with multiple doses per day) should be remembered and might be associated with increased likelihood of resistance already reported in Asia with VL [11]. This was our patients' preferred regimen, given the oral administration.

Liposomal amphotericin B has been used for a long time in VL, but its use in CL has been limited by its cost and lack of a standardized regimen. Although rarely used in endemic countries because of its cost, it is a very appealing option for non-endemic ones, where it is easily available and familiar. Furthermore, amphotericin deoxycholate (more toxic than liposomal) is consistently used in endemic areas to treat CL when SbV fails, with good results [6]. Case series also suggest that it could be particularly useful in ML [12]. Suggested regimens are usually extrapolated from VL treatment, involving 2–3 mg/kg/d until a total cumulative dose of 18–21 mg/kg [7]. In endemic countries such as Brazil, higher doses of 20–40 mg/kg may be used [6]. After an initial miltefosine course, this was our chosen regimen, with very satisfactory results. Treatment response was evaluated by clinical cure criteria: size reduction of >50% 4–6 weeks after treatment and total re-epithelization after 3 months [6–8] – both criteria were met ahead of time. Parasitological cure was not pursued, since this seldom occurs. Persistence of parasites in the host can lead to later reactivation during periods of immunosuppression. This patient will be followed for a minimum period of 2 years, and suspicious symptoms of mucosal involvement will be actively pursued to exclude reactivation [6,7,13].

Conclusion

We report a New World cutaneous leishmaniasis case, diagnosed and treated in a non-endemic country, emphasizing the obstacles faced, especially due to paucity of clinical experience, evidence-based literature (to support our decisions) and the unavailability of some common treatments. This is an emergent disease that should prompt more funding and research – it has been neglected for too long.

Conflict of interests statement

The authors have no conflicts of interest to disclose.

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Consent section

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author statement

All authors have contributed to the manuscript.

- Joana Vasconcelos: conceptualization, methodology, writing – original draft, writing – review & editing.
- João Torres: conceptualization, methodology, writing – review & editing.
- Joana Granado: conceptualization, methodology, writing – review & editing.
- Teresa Baptista: conceptualization, methodology, writing – review & editing.
- Kamal Mansinho: conceptualization, methodology, writing – review & editing.

All authors read and approved the final version of the manuscript

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