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Complicated Cutaneous Leishmaniasis in a Patient under Combined Immunosuppression

Leishmaniose Cutânea Complicada num Doente sob Imunossupressão Combinada

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ABSTRACT

Species associated with visceral leishmaniasis, such as *L. infantum*, may be responsible for cutaneous leishmaniasis (CL), particularly in the Mediterranean region. In immunosuppressed hosts, classification as complicated CL is essential, as the risk of mucosal leishmaniasis warrants systemic therapy. We report the case of a 47-year-old male living in Portugal, with Fabry disease and receiving immunosuppressive treatment with adalimumab and methotrexate for Crohn's disease. There was no travel history outside of Europe. He presented a two-year-old, 5.5 cm plaque with a well-defined hyperkeratotic elevated border and central, painless ulceration on his back. The biopsy revealed parasites inside macrophages suggestive of *Leishmania*, and PCR identified the species as *L. infantum*. A biopsy via nasal endoscopy excluded mucosal involvement. Classification as complicated CL dictated treatment with liposomal amphotericin B and subsequent topical paramomycin. The rarity of CL in Portugal may delay its diagnosis, especially in autochthonous infections. Treatment choice is complicated by the heterogeneity of drugs available worldwide. As the global prevalence of CL increases, it is important to be aware of this diagnosis.
Keywords: Immunosuppression Therapy; Leishmaniasis, Cutaneous; Neglected Diseases

RESUMO

Espécies associadas à leishmaniose visceral, como *L. infantum*, podem ser responsáveis por leishmaniose cutânea (LC), particularmente no Mediterrâneo. Nos doentes imunodeprimidos, a classificação como LC complicada é essencial, pois o risco de leishmaniose mucosa obriga ao tratamento sistémico. Homem de 47 anos, residente em Portugal, com doença de Fabry e imunodeprimido com adalimumab e metotrexato por doença de Crohn. Sem viagens fora da Europa. Apresentava placa de 5,5 cm de bordos bem definidos, elevados, hiperqueratóticos, com ulceração central indolor há dois anos na região dorsal. A biópsia revelou parasitas em macrófagos sugestivos de *Leishmania*. *L. infantum* foi identificada por PCR. A endoscopia nasal com biópsia excluiu atingimento da mucosa. A classificação como LC complicada ditou tratamento com anfotericina B lipossómica e subsequente paramomicina tópica. A raridade da LC em Portugal pode atrasar o diagnóstico, especialmente em infeções autóctones. A escolha terapêutica é complicada pela heterogeneidade mundial nos fármacos disponíveis. Com o aumento na prevalência global da LC, é imperativo estar sensibilizado para este diagnóstico.
Palavras-chave: Doenças Negligenciadas; Leishmaniose Cutânea; Terapia de Imunossupressão

INTRODUCTION

Cutaneous leishmaniasis (CL) is caused by a protozoa of the *Leishmania* genus transmitted by the sandfly.[1] In the Old World, it is generally caused by *Leishmania major*, *Leishmania tropica,* or *Leishmania aethiopica*, but species associated with visceral leishmaniasis may also be responsible, such as *L. infantum*, which is particularly important in the Mediterranean region.[2,3]

The global prevalence of CL is increasing due to many factors, including the rising number of immunosuppressed hosts.[2,4] Control of *Leishmania* requires a Th1-dependent cell-mediated immune response, including cytokines like TNF-α, meaning patients with immunosuppressive conditions are at increased risk of both primary and reactivation CL, often with atypical and more severe presentations.[4,5] CL in immunosuppressed hosts is classified as complicated due to the risk of mucosal leishmaniasis (ML), which can occur concurrently or following untreated CL, and is characterized by mucosal destruction and hence disfigurement.[1,5,6] ML is typically associated with New World infection by the *Viannia* subgenus, but it has also been described as to Old World species, particularly among immunocompromised hosts, including *Leishmania infantum*.[1,2] In immunosuppressed hosts, this classification as complicated CL is essential, as systemic therapy is warranted to reduce the associated risk of ML and increase the chances of a definite cure.[1,7]

CASE REPORT

We present the case of a 47-year-old male living in Vila Real, Portugal, with Fabry disease and receiving immunosuppressive treatment with adalimumab (40 mg every two weeks) and methotrexate (10 mg per week) for Crohn's disease. He reported no travel history outside Europe, other than past visits to Italy and Hungary. The patient was referred due to a two-year-old painless enlarging lesion on his back (Fig. 1). During the physical examination we observed a 5.5 cm plaque with a well-defined hyperkeratotic elevated border and fleshy surface, with central painless ulceration,

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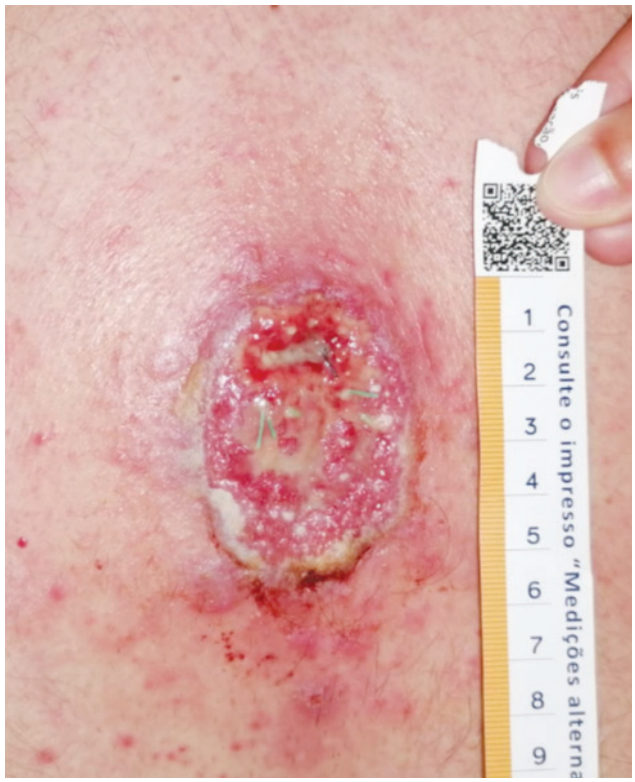

Figure 1 – Main lesion at the initial evaluation, a 5.5 cm plaque with a well-defined hyperkeratotic elevated border and fleshy surface, with central painless ulceration

accompanied by a second smaller ulcerated nodule and various inflammatory satellite papules.

A biopsy was performed at the border of the main ulcerative lesion. The histopathological examination revealed parasites in the amastigote form inside macrophages in the upper dermis suggestive of *Leishmania* (Fig. 2). For definite diagnosis we opted for molecular detection of parasite DNA through polymerase chain reaction (PCR), which further identified the species as *L. infantum*. Parasite isolation by *in vitro* culture is not available in our region. Due to symptoms of nasal congestion and increased secretions which could be suggestive of mucosal involvement, a nasal endoscopic examination was performed with blind biopsies that excluded ML. Peripheral blood and bone marrow PCR studies were also both negative.

This case was classified as a complicated localized CL, not only because the main lesion was greater than 5 cm in diameter, but mainly due to the host's immunosuppression. We opted for hospitalization for liposomal amphotericin B administration, 3 mg/kg for seven consecutive days (Fig. 3), followed by a weekly administration for five weeks. Adalimumab was suspended during treatment.

There was significant healing following systemic therapy, but we opted for further management of the residual lesions with local treatment with topical paromomycin (Fig. 4). Follow-up at 10 months revealed a flattening skin lesion with decreased size, improving inflammatory signs and

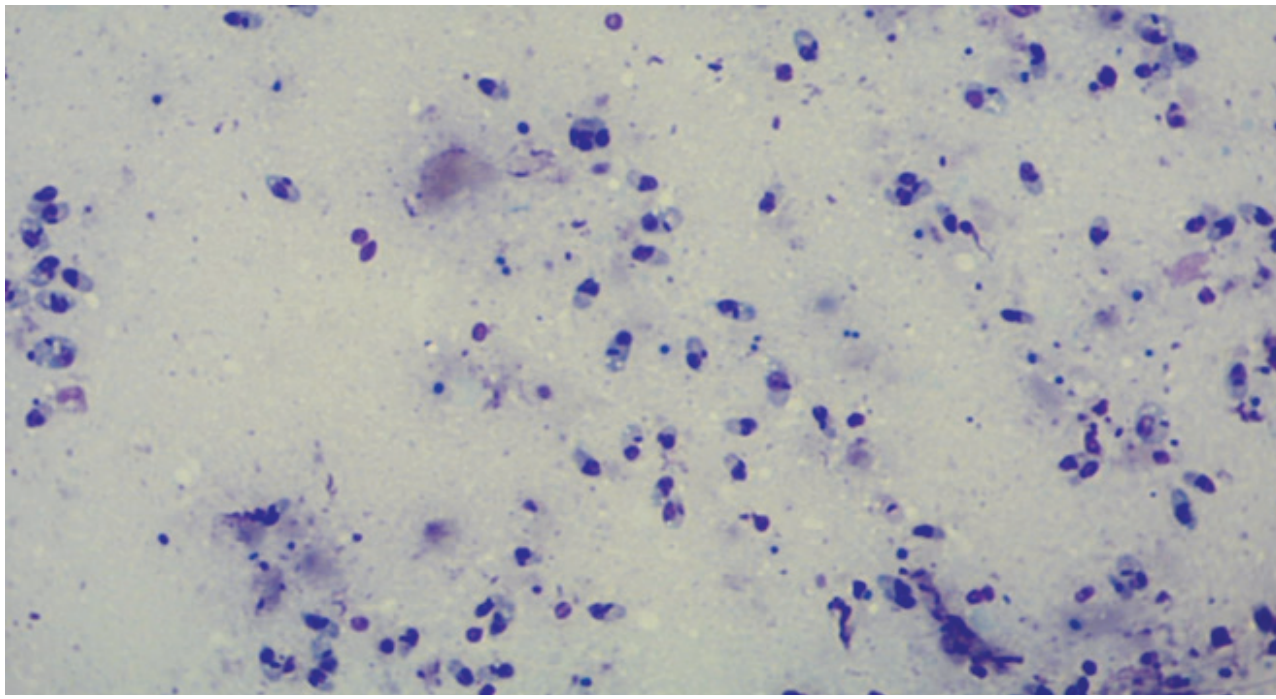

Figure 2 – Histopathology of the main lesion revealed parasites in the amastigote form inside macrophages in the upper dermis suggestive of *Leishmania*

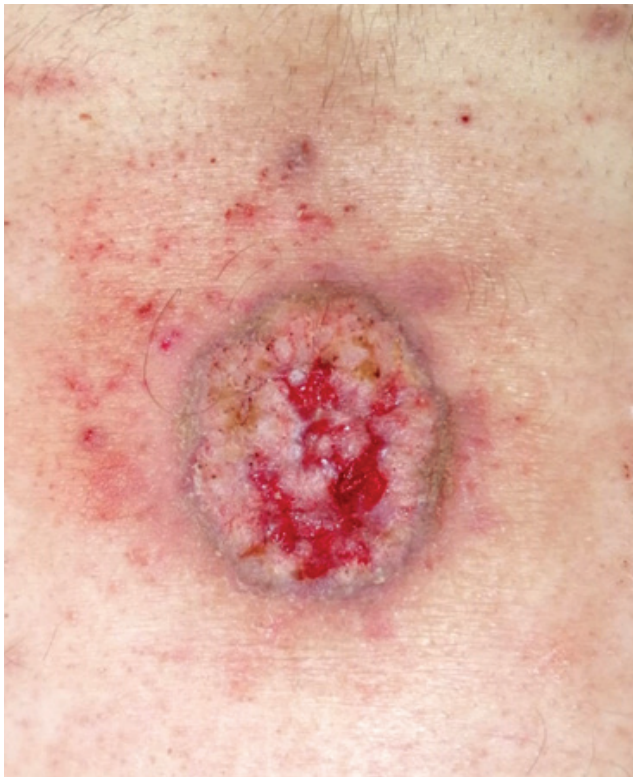

Figure 3 – Main lesion after liposomal amphotericin B administration for seven consecutive days

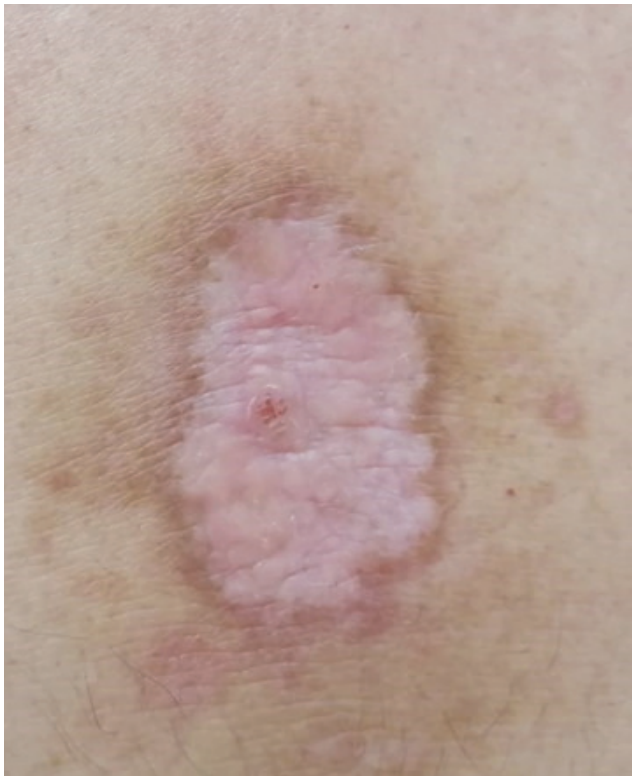

Figure 4 – Main lesion at three months follow-up, with significant healing

reepithelization of the ulcers (Fig. 5).

DISCUSSION

Leishmaniasis is endemic in Portugal since the 1940s.[3] Similarly to other countries in southwestern Europe, *L. infantum* has been the only agent identified in autochthonous cases of CL.[3] However, in contrast to neighboring countries, CL is very rare in Portugal, which highlights the relevance of this case.[3]

Treatment choices are complicated by the paucity of trials, but also by the heterogeneity of drugs available worldwide.[8] The benefits of treatment are not limited to the reduction in the associated risk of ML but also include acceleration of skin lesion healing with decreased scarring, and reduced likelihood of recurrence, which is especially important among those immunocompromised due to the possibility of persistence of the parasite.[6,7,9]

Although amphotericin B deoxycholate has great efficacy against CL, its use is limited by toxicity, and liposomal amphotericin B circumvents some of these adverse effects.[6] Its efficacy appears to be greatest in patients with *L. infantum*.[10] Further studies are needed to fully evaluate its appropriate dose and duration of treatment.[6] Other parenteral systemic therapy options with activity demonstrated against both Old and New World infection, but unavailable in our region, include the pentavalent antimony agents[6]; and pentamidine, with clinical response demonstrated in infections due to *L. infantum*, but generally used as second-line therapy due to its adverse effects.[6,11] Oral systemic therapy options include miltefosine, but it is not readily available in our region and has limited data regarding its efficacy for Old World CL use, even though a study has shown parasite load decline for *L. infantum*.[6,12] Since the azoles present limited efficacy and treatment failure is common, they are usually reserved for non-ML associated infection in which the cutaneous involvement is not amenable to local therapy.[6] In addition, the azoles should be tailored to the specific species, with a case report demonstrating the success of posaconazole in the treatment of *L. infantum*.[6,13]

Local therapy is usually considered in uncomplicated CL initially managed with clinical observation that does not heal spontaneously after six weeks.[1] However, it can also be used for follow-up management of complicated CL not fully healed after systemic treatment. For this, we chose topical paromomycin, which has shown therapeutic activity against both Old and New World CL ulcerative lesions, although there is no specific evidence regarding its efficacy with *L. infantum*.[6,14] Cryotherapy and thermotherapy are reserved for

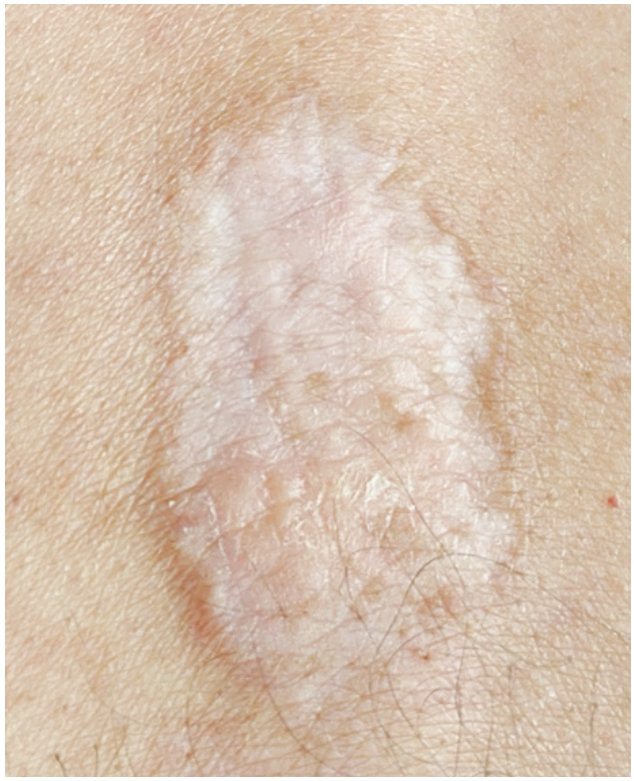

Figure 5 – Main lesion at ten months follow-up, a flattening skin lesion with decreased size, improving inflammatory signs and reepithelization of the ulcer

small, nonulcerated lesions of recent onset.[6] Intralesional therapy with pentamidine or amphotericin is another option that has been used successfully for the treatment of both Old and New World CL, in contrast to the more commonly used pentavalent antimonial drugs.[15]

This patient represented a challenge in many ways. First, the rarity of CL in Portugal delays its diagnosis, especially in autochthonous infections which is the most likely scenario in this case. Second, management of an immunosuppressed host has particularities, since systemic therapy is warranted. Third, the limited repertoire of drugs available in Portugal makes treatment choices even harder. As the global prevalence of CL increases, doctors worldwide should be alert to its diagnosis and subsequent classification and treatment.

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PREVIOUS AWARDS AND PRESENTATIONS

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AUTHOR CONTRIBUTIONS

AC, ASS: Writing and critical review of the manuscript.
JR, MAA, ALV: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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