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Case Presentation

An atypical case of cutaneous leishmaniasis caused by Leishmania infantum in Portugal

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Abstract

Leishmaniasis is a parasitic disease caused by an intracellular protozoan that belongs to the genus *Leishmania* and is transmitted by a phlebotomine sandfly. In Southwest Europe, including Portugal, cutaneous leishmaniasis is considered a rare disease of unknown or underestimated prevalence. *Leishmania infantum* is the only species identified as responsible for the autochthonous cases.

We report the case of a 66-year-old man with an erythematous, painless plaque on the mid face region, accompanied by nasal obstruction with 9 months of evolution. The initial diagnoses were: lymphoma, subcutaneous mycosis, Wegener's granulomatosis, and lupus vulgaris. The diagnosis of leishmaniasis was based on histopathology findings and identification of L. *infantum* by DNA based methods. Blood cultures, abdominal ultrasound and myelogram ruled out systemic involvement. The patient was treated with intravenous meglumine antimoniate (20 mg per kg/day) for four weeks, without major side effects.

We emphasize the importance of this case because human cutaneous leishmaniasis has rarely been diagnosed in Portugal and some cases are atypical, such as the situation herein described.

Keywords: Atypical cutaneous leishmaniasis, Leishmania infantum, meglumine antimoniate

Introduction

Leishmaniasis is a parasitic disease caused by an intracellular protozoan that belongs to the genus *Leishmania* and is transmitted by phebotomine sandflies. More than twenty pathogenic species have been identified leading to a broad range of clinical manifestations, probably as the result of the distinctive host-parasite interaction.

Cutaneous leishmaniasis is the most common form of this disease. According to the Center for Disease Control, more than ninety countries are affected and the number of new cases range from approximately 0.7-1.2 million per year [1]. In North Africa and the Middle East, the majority of cases are caused by *Leishmania major* and *L. tropica*. However, in southwestern european countries, such as Portugal, Spain, Italy, France, and Malta, *L. infantum* is the only species that has been identified as a causative agent of autochthonous cutaneous leishmaniasis in humans [2].

In Portugal, cutaneous leishmaniasis was described for the first time in 1943 [3]. It is not considered an officially reported disease, so the true prevalence is unknown. We present a case of an atypical cutaneous leishmaniasis from a rural area of Southern Portugal, successfully treated with intravenous meglumine antimoniate.

Case Report

A 66-year-old man, residing in a rural area of Portalegre (South of Portugal) presented with an erythematous plaque on the mid face area that had appeared nine months earlier. He noted nasal obstruction, but denied fever, weight loss, or other systemic complaints. The lesion started as a small pustule in the right nasal vestibule, evolving to an erythematous plaque localized on the cutaneous upper lip. Within the next six months, it increased progressively in size, extending to both cheeks and bridge of the nose (6x5cm) (Figure 1a). He was evaluated by a general practitioner and was first medicated with topical corticosteroids, then successively with oral terbinafine, corticosteroids, and amoxicillin without improvement. There was no evidence of lymphadenopathy or hepatosplenomegaly. He never traveled abroad and his medical history was positive only for type 2 diabetes mellitus, controlled with 100mg of sitagliptin.

At admission, the peripheral blood counts, chemistry panel, viral serology including HIV1 and HIV2, VDRL, IGRA test, and auto-immunity studies were unremarkable or negative, except for: GGT-260 (<73 U/L), C-reactive protein-1.02 (<0,5 mg/dL), LDH- 427 (208-378 U/L), and ferritin-570.7 (22-322 ng/mL), which were higher than normal. The fungal and mycobacteria tests of skin samples were negative.

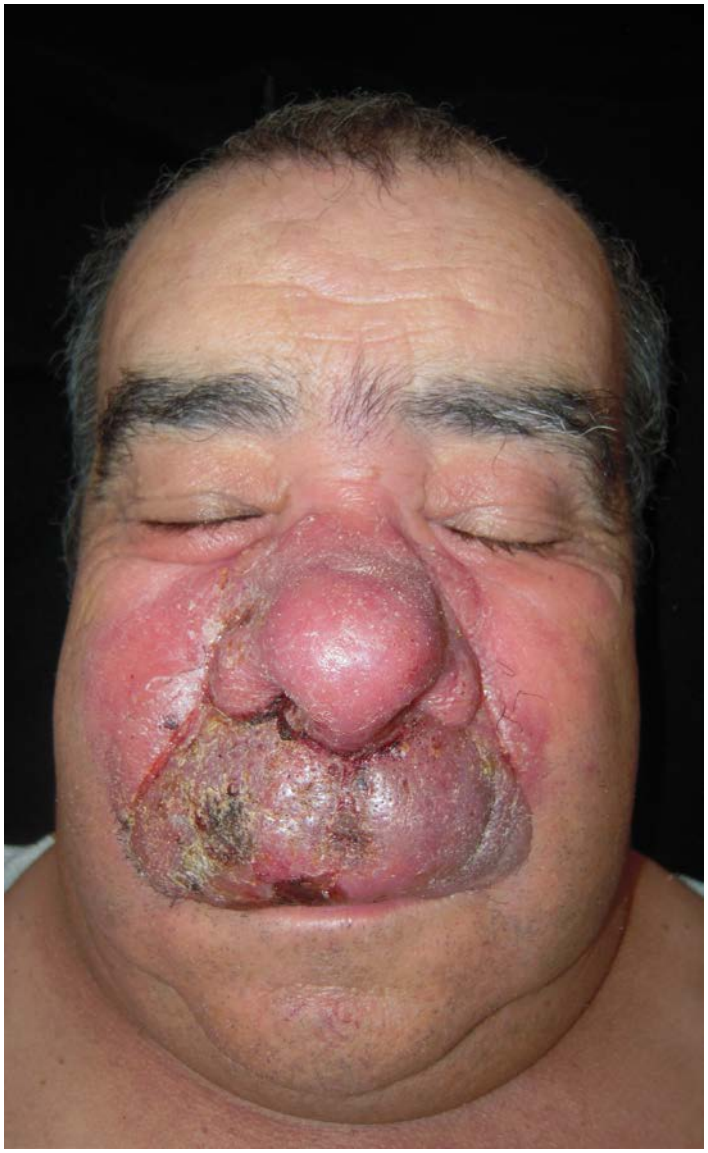

Figure 1a: Erythematous crusted plaque of the mid face

Facial magnetic resonance imaging revealed an exophytic lesion centered on the upper lip. The growth extended to the nose base, partially obstructing the right nasal vestibule and ending apparently on the posterior aspect of the nasopalatine canal, without extension to the hard palate (Figure 2).

Skin biopsy revealed a dermal diffuse inflammatory infiltrate composed by lymphocytes and histiocytes. *Leishmania* amastigotes were identified in the cytoplasm of dermal macrophages, in the sections stained with periodic acid-Schiff reagent (Figure 3). The serology for *Leishmania* and the blood culture in Nicolle-Novy-MacNeal medium were negative, but the skin biopsy culture was positive for *Leishmania spp. Leishmania infantum* genotype B, was identified by the nuclear ribosomal internal transcribed spacer 1- polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) analysis, and kinetoplastideal DNA-PCR–RFLP. Abdominal scan and microscopy of bone marrow aspirate excluded systemic involvement.

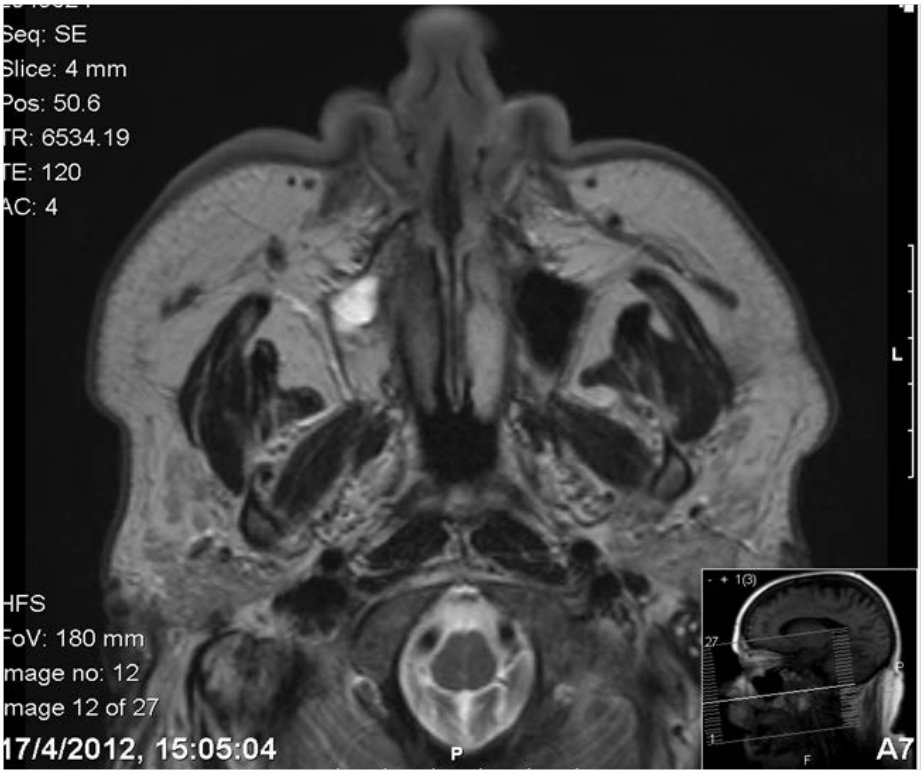

Figure 2: Partial obstruction of right nasal vestibule

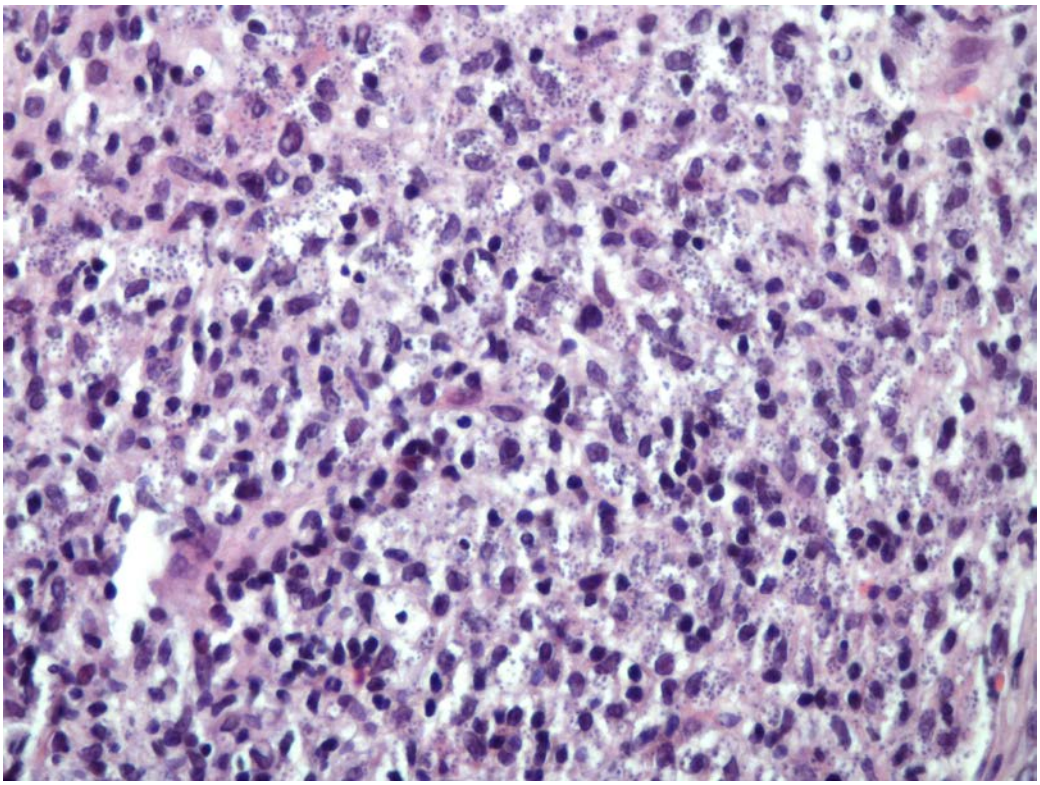

Figure 3: Amastigotes in cytoplasm of dermal macrophages

The patient was treated with intravenous meglumine antimoniate (20 mg per kg/day) for four weeks. On the 17th day of treatment, he started to complain of mild to moderate arthralgias and myalgias. A transient elevation of amylase – 82 (13-53 U/L) and liver enzyme levels - AST-66 (0-34 U/L); ALT-72 (10-49 U/L); GGT-272 (<73 U/L); Alkaline-phosphatase- 231 (45-129 U/L) - were observed. No electrocardiographic abnormalities were detected. The minor side events associated with meglumine antimoniate did not necessitate discontinuation.

In the early post-treatment period, there was clinical improvement with significant regression of the mid face plaque. However, we could identify residual erythema of the affected area (Figure 1b). During the follow-up period one year later, there was no sign of recurrence.

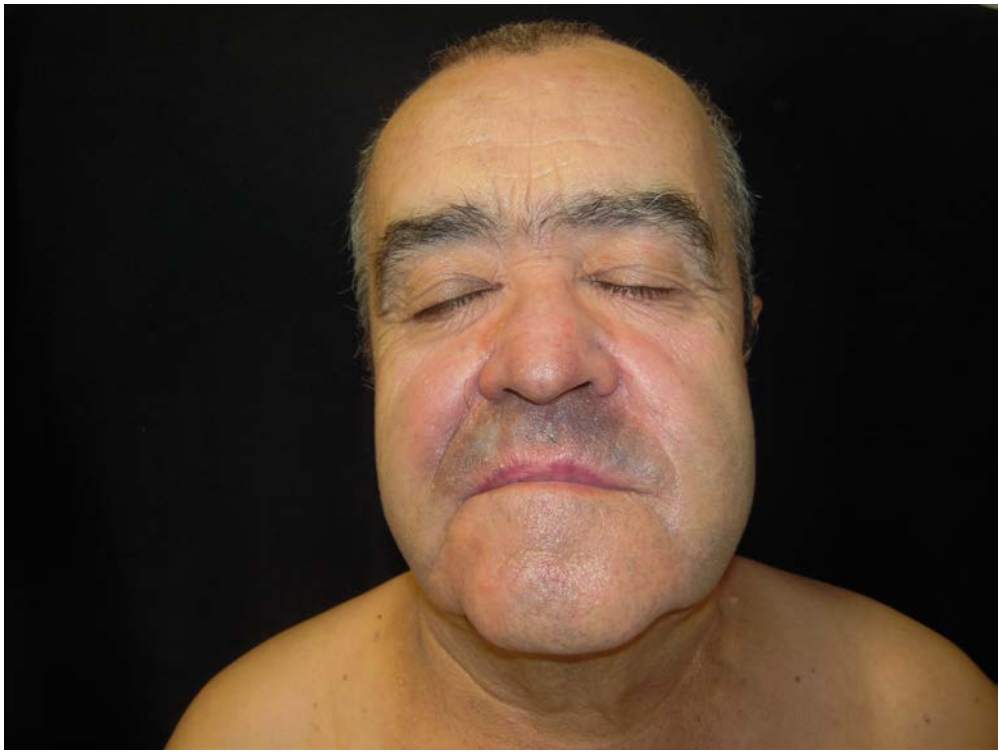

Figure 1b: Significant regression of mid face plaque

Discussion

Cutaneous leishmaniasis commonly involves the exposed areas of the body and can appear in the form of papules, nodules, plaques, or ulcers. In rare cases, it may appear as paronychia or in annular, zosteriform, chancriform, whitlow, lupoid, erysepeloid, or sporotrichoid variants, making this infection a great imitator with a broad differential diagnosis [4, 5].

The present case should be classified as cutaneous leishmaniasis by mucosal inoculation [6]. This entity must be differentiated from secondary mucosal involvement and mucocutaneous leishmaniasis. This last entity occurs in the majority of the cases in Central and South America, and is caused by *L. braziliensis*. The correct classification is relevant owing to the diversity of evolution and prognosis of these three clinical patterns. Our patient has type 2 diabetes mellitus. Three atypical cases of cutaneous leishmaniasis by *L. major* were also reported in diabetic patients [7]. Diabetes mellitus can compromise T cell response and contribute to the extension and atypical presentation of the infection and predisposition to superinfection seen in leishmaniasis patients [7].

The risk factors for leishmaniasis are immunologic, socio-economic, and environmental. In Portugal, there have only been published 59 cases of cutaneous leishmaniasis in humans [8]. However, a national canine survey reported a high prevalence of leishmaniasis (12.54%) in the southern region of Portugal [9].

The Portuguese population harbors two main genotypes of *Leishmania infantum*: genotype A, correlated with HIV positive immunocompromised patients and genotype B, more frequent in immunocompetent patients. Our patient had genotype B, which is in accordance with this hypothesis [10].

There are no established guidelines for the treatment of cutaneous leishmaniasis. The treatment depends on the immune status of the host, the area of the body involved, and the different susceptibility of the *Leishmania* species. The majority of lesions are self-healing, leading to flat atrophic scars. However, it is currently accepted that lesions should be treated in order to reduce the residual scar and recovery time, and to avoid the transmission of the parasite. Systemic treatments should be used in patients with: multiple (>5) or large lesions (>4cm), a lack of response to topical treatment, evidence of loco-regional spread, immunosuppression, and cosmetic and functionally impaired lesions [11].

Pentavalent antimonials remain as first line treatment for all forms of Leishmaniasis [12, 13]. The recommended dose for cutaneous leishmaniasis is 20 mg of pentavalent antimonial per kg/day for 20-28 days, which can be given intravenously or intramuscularly [13]. The intra-lesional administration of pentavalent antimony is a good therapeutic option in some forms of cutaneous leishmaniasis, depending on the number, localization, and extension of the lesions. With this approach, we can increase drug concentration in the lesions, reduce systemic side effects and costs, and obtain good esthetic results [13]. The molecular and cellular mechanisms of action of antimonials are not well understood, but it is supposed that they may act by inhibiting glycolysis and fatty acids β-oxidation in the amastigotes of the parasite [14]. Liposomal amphotericin B is another option. Its mechanism of action is attributed to ergosterol binding, leading to membrane permeability and modification of the

osmotic balance of the parasite [14]. Some authors consider that pentavalent antimonials should be replaced by this treatment, which has fewer side effects [11], whereas others consider that amphotericin B has no place in cutaneous non-complicated leishmaniasis because of the simplicity and cost of the alternative options [6]. Liposomal amphotericin B is administered intravenously at a dose of 1 to 1.5mg/kg/day for 21 days or 3mg/kg/day for 10 days [11]. In some countries, it is the first line treatment reserved for severe forms of leishmaniasis, such as mucosal and visceral leishmaniasis and HIV co-infected patients. Pentamidine is also a second line treatment option. The recommended dose is 2-3mg/kg on alternate days; 4 to 7 injections in total [6].

Because systemic therapy with meglumine antimoniate has been effective in all patients with presumptive cutaneous leishmaniasis by *L. infantum* [2] and mucosal involvement is difficult to treat, we chose to treat our patient with intravenous meglumine antimoniate for 4 weeks; good results with minor adverse effects were achieved. This case illustrates the need for an accurate and rapid diagnosis of cutaneous leishmaniasis in rural areas of the Iberic region.

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