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Case report

Recurrent mucosal leishmaniasis of the epiglottis in an immunosuppressed patient

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SUMMARY

Leishmaniasis is a disease caused by the intracellular protozoan parasite *Leishmania* and are known more than 20 species(1) harmful for men. A 74-year-old man, with sarcoidosis treated with methotrexate and corticoid, was assessed, in 2021, by an ENT specialist due to dysphagia, dysphonia, and odynophagia with a 5-year evolution and progressive worsening. A biopsy of the right vocal cord and epiglottis was performed, and the histology demonstrated the presence of amastigotes in the tissues coloured by Giemsa making the diagnosis of Leishmaniasis. The patient was referred to the Infectious Diseases Department, with the diagnosis of mucosal leishmaniasis, and hospitalized for treatment with Liposomal Amphotericin B. The dysphagia and odynophagia improved and was discharged to Infectious Diseases Day hospital to continue treatment. He completed a total of 10 days of treatment and continued follow up in Infectious Diseases, Pneumology and ENT departments. During this time the patient stopped treatment with methotrexate but maintained deflazacort 6 mg per day. In 2023, the patient presented with worsening dysphonia and dysphagia. A new biopsy of the epiglottis was performed in the ENT department. *Leishmania* DNA was detected, and histology was compatible with Leishmaniasis of the left larynx. He was hospitalized in Infectious Diseases department and started treatment with Liposomal Amphotericin B. The patient completed a total of 10 days of treatment, and, by this time, the medical team decided to maintain suppressive therapy once a month with Liposomal Amphotericin B, until the patient present with a CD4 leucocyte count superior to 350/mm^3 . By the time of this article, the patient maintained follow up in the Infectious Disease department with monthly sessions of therapy.

Background

Leishmaniasis is a disease caused by the intracellular protozoan parasite *Leishmania* and are known more than 20 species [1] harmful for men. Humans, dogs and rodents act as reservoirs [2] and its transmission to humans is through the bite of an infected female phlebotomine sand-fly of the genus *Phlebotomus* in the Old World (Europe, Africa and Asia) and *Lutzomyia* in America [3]. *Phlebotomus perniciosus* and *P. ariasi* are the vector species in Portugal [4]. In the 80 ś there was proof of another form of transmission with great epidemiological importance through the sharing of infected needles and syringes in the community of intravenous drug users [5].

Leishmaniasis can present in different clinical forms: localized cutaneous (LCL) or diffuse cutaneous (DCL), mucocutaneous (MCL), and visceral (VL) also known as *kala-azar* or black fever [6]. Manifestations may differ according to the immunological state of the patient and characteristics of the parasite. Leishmaniasis incidence is higher in patients receiving chemotherapy or other immunosuppressant, or who are HIV positive. These patients also tend to have a worse prognosis and a greater chance of relapse [2].

Between 1999 and 2014 were diagnosed in Portugal 199 cases of visceral leishmaniasis (122 in immunosuppressed adults) and 27 cases of the cutaneous form. Even though there is no regional predilection for the occurrence of leishmaniasis, some regions present as hot spots for the infections, such as Alto-Douro, Lisbon and Algarve [5].

L. infantum is the responsible agent of VL in Europe with high endemicity in the Mediterranean basin where immunosuppression confers a higher risk of clinical disease due to this species. While visceral and cutaneous manifestations of *L. infantum* are quite common, mucosal presentation is rare and has been only sporadically described [6].

Mucocutaneous leishmaniasis is usually secondary to haematogenous spread after months or years of skin infection and can manifest as

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infiltrative, ulcerated or vegetative lesions in nose (most common site), pharynx, larynx and mouth [5]. If left untreated, mucosal lesions can leave sequelae, interfering in the swallowing, breathing, voice and speech processes that require rehabilitation. Treatment with prolonged antibiotic is the most effective therapy [7].

Case presentation

A 74 yo male patient living in the central region of Portugal, is observed, in March of 2021, in the emergency department due to dysphagia, dysphonia and odynophagia with 5 years of evolution and progressive worsening. Past medical history included pulmonary sarcoidosis medicated with methotrexate (15 mg once a week) and corticotherapy (deflazacort6 mg once a day). The patient worked in Germany in the industry of boats and in cleaning companies for over 40 years and returned to Portugal 8 years ago. He lived near a river and used water from a well to irrigate its backyard. He also owned two vaccinated dogs.

In the emergency department he was evaluated by an ENT specialist and a biopsy of a granulomatous lesion of the epiglottis and right vocal cord was performed after hospitalization. The biopsy revealed the presence of numerous *Leishmania* amastigotes by Giemsa stain in the vocal cord and epiglottis tissue, leading to the diagnosis of Leishmaniasis.

The patient was referred to the Infectious Diseases Department and was hospitalized for treatment. In the physical exam he had noticeable dysphonia and dysphagia.

Blood work at admission showed a low leucocyte (2.8 $\times 10^9$/L) and platelet (115 $\times 10^9$/L) count, a CD3 + /CD4 + of 106.0/mm^3 with a total of lymphocytes count of 410.0/mm^3 , and positive serology for *Leishmania* antibodies through indirect immunofluorescence (dilution of 1/1280), western blot and CLIA.

Bone marrow aspiration was also performed but the result was negative for amastigote forms and the abdominal ultrasound did not show any abnormality.

The medical team decided for treatment with Liposomal Amphotericin B 4 mg/kg daily on days 1–5, 10, 17, 24, 32 and 38 [8] considering that the patient was immunosuppressed.

The patient completed the first two series of treatment administration while hospitalized with significant improvement of dysphagia, odynophagia but still maintaining dysphonia. By the thirteenth day of treatment the patient was evaluated by ENT with improvement of the oedema and granulomatous lesions of the epiglottis and vocal cord. He was discharged by the fifteenth day and completed the rest of the treatment in the day hospital.

He maintained follow up in the Infectious Diseases department, ENT and Pneumology. During this time, and to reduce immunosuppression, methotrexate was suspended by the Pneumology assistant, maintaining deflazacort 6 mg per day.

In 2023, the patient presented with worsening dysphonia and dysphagia. The Infectious Diseases and ENT assistant decided to repeat a biopsy, that showed positivity for *Leishmania* DNA and histology conformed the diagnosis.

The patient, was again, admitted in the Infectious Diseases department, with the diagnosis of recurrent mucosal leishmaniasis and started a new course of Liposomal Amphotericin B 4 mg/kg daily.

Blood work presented, like in the first admission, a low leucocyte (2.8 $\times 10^9$/L) and platelet (74 $\times 10^9$/L) count, a CD3 + /CD4 + of 218.0/mm^3 with a total of lymphocytes count of 576.0/mm^3 , and positive serology for *Leishmania* antibodies through indirect immunofluorescence (dilution of 1/120), western blot and CLIA. The infectious diseases team opted to perform another bone marrow aspiration, but the result was negative for amastigote forms again.

During hospitalization, the patient completed a total of 6 days (days 1–5 and 10th) of treatment with slight improvement of dysphonia and resolution of dysphagia. He was discharged to day hospital and continued treatment for four more session (days 17, 24, 32 and 38th). Since the patient presented with low, CD3 + /CD4 + count, due to is immunosuppression, the medical team decided to maintain suppressive monthly therapy until the patient presents with a CD3 + /CD4 + count superior to 350.0/mm^3 [8].

By the time this work was written, he still maintained follow up in the Infectious Diseases department, with monthly treatments with Liposomal Amphotericin B.

Discussion

Leishmaniasis is rarely detected in an early stage and skin lesions usually appear three to ten weeks after inoculation and can spontaneously heal without treatment. In 3–5% of the cases, lesions may develop and emerge in mucosa by hematogenous spread [11]. This patient reported the beginning of symptoms 5 years prior to hospitalization. He was evaluated by several doctors, completing different courses of antimicrobial therapy but with no improvement.

Identification of the Leishmania species involved in this case was not performed. It is known that *L. infantum* is endemic in the Mediterranean Basin and *L. donovani* has been reported sporadically in different south European countries [3]. Cases of cutaneous leishmaniasis have been reported in Portugal in Douro, Tejo and Sado basins. It is estimated that 10 new cases of Leishmania are reported per year in Portugal and *L. infantum* is the main identified species [4]. In Germany, where the patient lived for 20 years, a study was performed analysing the number of cases of Leishmaniasis in a 2-year period. This study demonstrated a total of 70 cases with 47% contracted in European Mediterranean area and Portugal, and 22% in Mediterranean islands of Ibiza, Ischia, Majorca, Malta, Korfu and Sicily [9]. There is also evidence for the natural occurrence of sandflies in Germany, and cases of autochthonous origin have been confirmed [10]. It is not possible to determine where the patient was infected but considering the low number of autochthonous cases in Germany, and their crescent number in Portugal, being that the patient lived close to a river with two dogs, it is most likely that the infection site was the south European country.

Considering the patient was immunocompromised due to corticotherapy and methotrexate with CD3 +/CD4 + count of 106/mm^3 , the medical team opted for treatment with Liposomal amphotericin B according to the IDSA guidelines for patients with visceral/cutaneous Leishmaniasis receiving immunosuppressive therapy: Liposomal amphotericin B in dosage of 4 mg/kg/day IV on days 1–5, 10, 17, 24, 31 and 38 [8]. There are few published guidelines regarding the treatment of visceral, mucous or cutaneous leishmaniasis in non-HIV immunosuppressed patients, and so, the proposed course of action was based solely on the literature available at that time.

When the patient presented with recurrence of this disease, the medical team opted to treat with the same course of therapy but maintaining suppressive therapy as long as the patient presented with altered immunity.

It is known that immunocompromised patients with HIV, coinfected with leishmaniasis, have higher relapse rates and treatment failure occur more frequently. In a case report, from 2018, presenting a coinfected HIV/visceral leishmaniasis patient, the medical team opted for repeated administration daily for 5 days every 3 weeks, after treatment with a total cumulative dose of 40 mg/kg, to prevent relapse of the disease. This patient failed to maintain immunological recovery, so treatments where never suspended [11].

However, this case report shows an immunosuppressed patient due to high doses of corticosteroids and methotrexate therapy for a long period of time. Even after the suspension of methotrexate, he failed to obtain an immune recovery. The team's decision to maintain monthly courses of therapy was based in his CD3 + /CD4 + count and the reduced number of case reports of recurrence in non-HIV patients. Additionally, we present a patient who solely has recurrent mucous leishmaniasis, contrary to the 2018 case report which reports a

recurrence of cutaneous and visceral leishmaniasis.

Furthermore, a study published in 2010, regarding patients co-infected with HIV and Leishmaniasis suggested the term "active chronic visceral leishmaniasis", to describe a clinical entity where patients presented with persistence of *Leishmania* parasites in peripheral blood for several years, despite multiple rounds of curative treatment and long-term secondary prophylaxis with Liposomal amphotericin B. These patients presented with episodes of clinical, symptomatic disease and asymptomatic periods. The study suggested that the failure of immune recovery and other mechanisms, such as the absence of interleukin-2 and gamma interferon production, or the existence of parasite "sanctuaries", as potential causes for the recurrence of Leishmaniasis despite treatment [12]. Again, this differs from the case report, because in our patient, visceral leishmaniasis was excluded both times. Moreover, in the 2010 French study, most of the patients who are co-infected cannot elicit an immune recovery, being that most of the relapses happen with a CD3 + /CD4 + count below 200. In fact, the study mentions that no recurrence was observed in patients with more than 200 CD3 + /CD4 +, which vary from our own case, since the criteria of CD3 +/CD4 + < 200 is observed in the initial diagnosis, but not at the time of relapse (CD3 + /CD4 + count of 218).

This article intends to show a rare location of mucosal Leishmaniasis an its recurrence. As far as the authors know, there are few published texts or case reports of recurrence of this disease in non-HIV patients.

With the crescent use of immunosuppressive therapy for several conditions (ie. Sarcoidosis, rheumatoid arthritis, Crohn's disease) it is important to think of these rare pathologies, since it is easier for patients with altered immunity to be affected by one or more opportunistic organisms, as well as, have rare presentations and recurrences of the disease itself. It is also of crucial importance to understand that states of altered immunity can present similarly as patients living with HIV, which means that sometimes there is a need to use the same criteria of suppressive therapy with these kinds of patients.

Ethical approval

No ethics committee approval required.

Consent

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.

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Declaration of Competing Interest

The authors have no conflicts of interest.

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