Medical Imagery

Painful and swollen tongue: mucosal leishmaniasis due to *Leishmania infantum*

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A B S T R A C T

Background: Leishmaniasis is a parasitic disease caused by different *Leishmania* species. *L. infantum* is found in the Mediterranean area. It usually causes visceral or cutaneous leishmaniasis, but rarely mucosal leishmaniasis (ML).

Methods: A 62-year-old man with metastatic non-small-cell lung carcinoma visited the outpatient clinic because of a painful and swollen tongue. Initially, oral candidiasis was suspected and patient was unsuccessfully treated accordingly. Subsequently, a biopsy from the tongue was taken.

Results: Histology of the tongue biopsy showed an inflammation with histiocytes and *Leishmania* amastigotes. Molecular analysis determined these parasites as *L. donovani* complex. Based on the patient’s travel history, ML caused by *L. infantum* was diagnosed.

Conclusion: ML is an unusual presentation of *L. infantum*. ML is not only caused by *Leishmania* species endemic in Latin America, but also should be considered in the differential diagnosis for European patients. A biopsy of the affected location is needed to confirm the diagnosis.

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Introduction

Most mucosal leishmaniasis (ML) cases are caused by *L. braziliensis* which is endemic in Latin America (Burza et al., 2018; World Health Organization, 2010). In Europe, the most prevalent *Leishmania* species is *L. infantum*, which predominantly causes visceral leishmaniasis (VL) or cutaneous leishmaniasis (CL) (Burza et al., 2018; World Health Organization, 2010). However, localized ML in absence of concomitant VL or CL caused by *L. infantum* has been reported sporadically (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guddo et al., 2005; Hammami-Ghorbel et al., 2015; Mohammadpour et al., 2017; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013). As the lesions mimic other diseases, the correct diagnosis is often delayed (Aliaga et al., 2003; Hammami-Ghorbel et al., 2015). In this report, we present an ML case due to *L. infantum* and provide an overview of the literature regarding the diagnosis, affected localizations and treatment of ML by *L. infantum*.

Case

A 62-year-old man presented with a painful and swollen tongue in May 2020. His medical history included metastatic non-small-cell lung carcinoma (NSCLC) in March 2018. Initially, he had been treated with radiotherapy combined with four courses of carboplatin and pemetrexed, which was followed by maintenance therapy with pemetrexed. In September 2019, he developed progressive NSCLC and was treated with nivolumab as second line therapy for eight months. Four months after nivolumab was initiated, the patient developed toxicodermatosis due to nivolumab. He was treated with prednisolone 40 milligram per day, which was tapered in two months.

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At presentation, the complaints of the tongue had been present for 18 months. Under the suspicion of oral candidiasis, the patient had been treated several times with antifungals over the course of time. After the treatment with prednisolone, the abnormalities of the tongue worsened and were progressively painful (figure 1). The patient lost six kilograms of weight due to decreased appetite and oral pain. Moreover, the patient experienced difficulties in speech because of the thickness of his swollen tongue. Physical examination at presentation showed a swollen tongue with yellow-white lesions and ulcerations. The patient did not have fever or hepatosplenomegaly. Laboratory results showed normal blood cell counts, C-reactive protein of 25 mg/l and erythrocyte sedimentation rate of 36 mm/h. As the patient did not improve on antifungal therapy, the patient was referred to a dental surgeon for further examination. A biopsy from the edge of the tongue was taken. Histomorphology showed multilayer squamous epithelium with increased presence of histiocytes. CD1a staining was positive and showed micro-organisms suspected for Leishmania species. Additional molecular analysis by real-time polymerase chain reaction (PCR) confirmed the presence of Leishmania species in the biopsy tissue. DNA sequence analysis determined the Leishmania species as part of the L. donovani complex, which comprises two species: L. donovani and L. infantum. The rK39 rapid immunochromatographic-serological test was positive, while Leishmania PCR on blood was negative. Because the patient had no travel history outside Europe and frequently travelled to Spain and Italy, an L. infantum infection was diagnosed. Since the patient did not have any characteristics for VL and only had mucosal lesions, the patient was diagnosed with ML due to L. infantum. Subsequently, the patient was treated with liposomal amphotericin-B (LAmB) 3 milligrams/kilogram on day 1 to 5, 14 and 21. The complaints and abnormalities of the tongue improved significantly after treatment (figure 1).

Discussion

Leishmaniasis is an infectious disease caused by different Leishmania species that are transmitted by phlebotomine sand flies (Burza et al., 2018; World Health Organization, 2010). In Europe, the most prevalent Leishmania species is L. infantum (Burza et al., 2018; World Health Organization, 2010). L. infantum affects predominantly immunocompromised patients and children and mostly causes VL which is characterized by fever, weight loss, pancytopenia and hepatosplenomegaly, or CL which is characterized by a single nodule that can develop into an ulcer (Burza et al., 2018; World Health Organization, 2010). Our patient presented with ML due to L. infantum without prior history of VL or CL. Mucosal involvement in absence of concomitant visceral or cutaneous disease is rarely seen in L. infantum infections, but has been reported sporadically (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Hammami-Ghorbel et al., 2015; Mohammadpour et al., 2017; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013). This is in contrast to ML due to L. braziliensis, in which CL progresses to ML in a small part of the patients (Burza et al., 2018; World Health Organization, 2010). However, L. braziliensis is only endemic in Latin America, while L. infantum is endemic in the Mediterranean area (Burza et al., 2018; World Health Organization, 2010).

The scarcity of ML in Europe makes its diagnosis difficult. The presentation is often mistaken for another infection, malignancy or even auto-immune disease. As seen in our patient, there was a delay of 18 months in the diagnosis. Such delays were also observed by Aliaga et al. and Hammami et al., who reported delays with a mean of 13 months (range 3 weeks to 4.5 years) and of 6.9 months (range 2 to 36 months), respectively (Aliaga et al., 2003; Hammami-Ghorbel et al., 2015). To diagnose ML, a biopsy of the affected location is of utmost importance. Almost all known cases of ML, including our own patient, were diagnosed by histological examination of a biopsy in which Leishmania amastigotes were found (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013). A positive PCR on the biopsy was found in most of the cases (Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Gaspari et al., 2020; Guzzo et al., 2005; Mohammadpour et al., 2017; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013), also in a small number of cases in which the histological examination was negative or not performed (Cobo et al., 2016; Faucher et al., 2011; Mohammadpour et al., 2017; Patel et al., 2017).
In a part of cases, additional tests such as serology or Leishmania PCR on blood were performed (Aliaga et al., 2003; Cobo et al., 2016; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Patel et al., 2017; Richter et al., 2011). Serology was positive in most of the patients (Aliaga et al., 2003; Cobo et al., 2016; Faucher et al., 2011; Franco et al., 2015; Guzzo et al., 2005; Patel et al., 2017; Richter et al., 2011), while Leishmania PCR on blood was negative in the small number of tested patients (Faucher et al., 2011; Franco et al., 2015; Richter et al., 2011). Therefore, serology can help in diagnosing ML, but histological examination with or without Leishmania PCR on biopsy remains the cornerstone to diagnose ML.

ML due to L. braziliensis starts typically on the nostrils or lips and can progress to deeper mucosa, which can cause severe mutilations if untreated (Burza et al., 2018; World Health Organization, 2010). In contrast, L. infantum seems to favour other initial locations, such as the oral cavity (palatum, gingiva or tongue), intranasal mucosa, pharynx and larynx (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013). As most patients do not have a history of VL or CL, it remains a question if the lower parts of the upper respiratory tract (e.g. pharynx, larynx) are infected as a site of inoculation or as a secondary localization.

Our patient was treated successfully with LAmb. The two most reported treatment regimens for mucosal leishmaniasis due to L. infantum consisted of LAmB (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Gaspari et al., 2020; Guzzo et al., 2005; Richter et al., 2011; Stoeckle et al., 2013) or meglumine antimoniate (Aliaga et al., 2003; Cobo et al., 2016; Faucher et al., 2011; Franco et al., 2015; Hammami-Ghorbel et al., 2015; Mohammadpour et al., 2017; Neumayr et al., 2012; Stoeckle et al., 2013). Varying doses and durations of both treatments were observed. Both treatments seemed successful in most cases, but some patients relapsed (Cocuzza et al., 2013; Faucher et al., 2011; Gaspari et al., 2020; Richter et al., 2011; Stoeckle et al., 2013) and some patients switched or discontinued treatment because of side effects (Aliaga et al., 2003; Cobo et al., 2016; Faucher et al., 2011; Hammami-Ghorbel et al., 2015; Neumayr et al., 2012). As no controlled studies have been performed, an evidence based treatment guideline is still lacking.

VL due to L. infantum is mainly observed in immunocompromised patients or children (Burza et al., 2018; World Health Organization, 2010). Our patient had been treated with chemotherapy for NSCLC. The first complaints started during this therapy. However, the complaints worsened during treatment with a high dose of corticosteroids, indicating that the lowered immune status was important in developing ML in this patient. Although ML is relatively frequently found in immunocompromised patients, it has been reported in immunocompetent patients without prior medical history (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Hammami-Ghorbel et al., 2015; Mohammadpour et al., 2017; Neumayr et al., 2012; Richter et al., 2011). There seems to be no difference in clinical presentation (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Hammami-Ghorbel et al., 2015; Mohammadpour et al., 2017; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013) or treatment between immunocompromised and immunocompetent patients (Aliaga et al., 2003; Cobo et al., 2016; Cocuzza et al., 2013; Faucher et al., 2011; Franco et al., 2015; Gaspari et al., 2020; Guzzo et al., 2005; Hammami-Ghorbel et al., 2015; Mohammadpour et al., 2017; Neumayr et al., 2012; Patel et al., 2017; Richter et al., 2011; Stoeckle et al., 2013).

In conclusion, ML is a rare and unusual clinical presentation of an L. infantum infection, but should be considered when a patient has prolonged unexplained mucosal complaints without other diagnosis, and has travelled or stayed in the Mediterranean area in the past. A biopsy of the affected location should be taken to confirm or exclude the diagnosis.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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**Ethical Approval statement**

The patient provided consent for the publication of his clinical details.

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**References**


