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Medical Imagery

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

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ABSTRACT

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.

Introduction

Most mucosal leishmaniasis (ML) cases are caused by *L. brazilliensis* 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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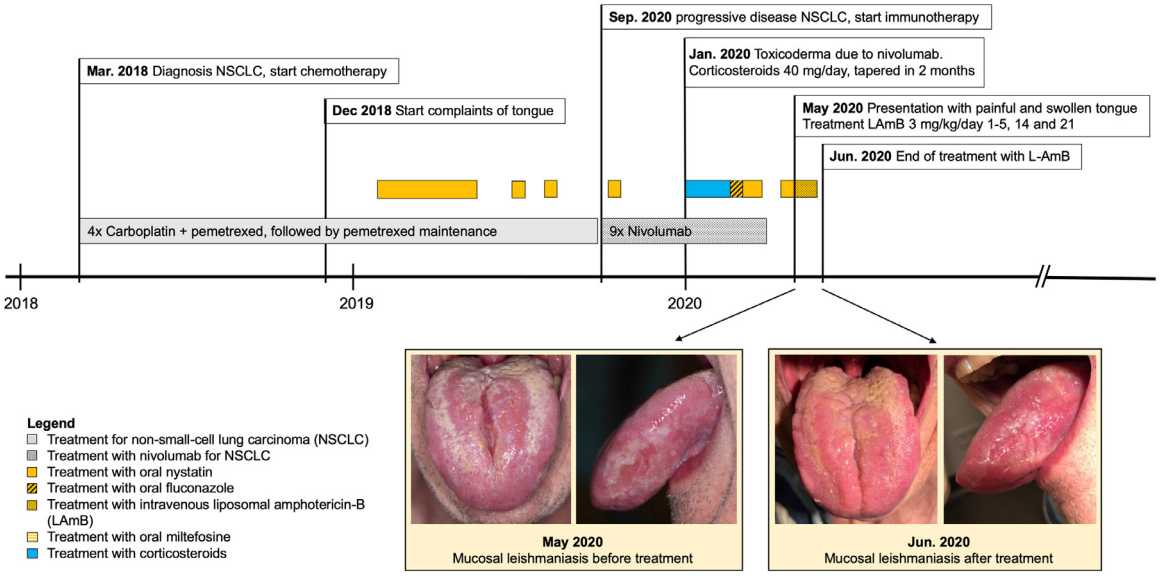

Figure 1. Timeline of developments in a patient with mucosal leishmaniasis due to *L. infantum*.

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 immunochromotographic-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; 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). This is in contrast to ML due to *L. brazilliensis*, in which CL progresses to ML in a small part of the patients (Burza et al., 2018; World Health Organization, 2010). However, *L. brazilliensis* 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; Guddo 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; Guddo 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; Guddo 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; Guddo 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. brazilliensis* 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; Guddo 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; Guddo 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; Guddo 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; 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) 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; 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).

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 case details.

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References

Aliaga L, Cobo F, Mediavilla JD, Bravo J, Osuna A, Amador JM, et al. Localized mucosal Leishmaniasis due to Leishmania (Leishmania) infantum clinical and microbiologic findings in 31 patients. Medicine 2003;82(3):147–58. doi:10.1097/00005792-200305000-00001.

Burza S, Croft SL, Leishmaniasis Boelaert M. The Lancet 2018;392:951–70. doi:10.1016/S0140-6736(18)31204-2.

Cobo F, Rodríguez-Granger J, Gómez-Camarasa C, Sampedro A, Aliaga–Martínez L, Navarro JM, et al. Localized mucosal leishmaniasis caused by Leishmania infantum mimicking cancer in the rhinolaryngeal region. Int J Infect Dis 2016;50:54–6. doi:10.1016/j.ijid.2016.08.003.

Cocuzza S, Strazzulla A, Pinzone MR, Cosentino S, Serra A, Caltabiano R, et al. Isolated Laryngeal Leishmaniasis in Immunocompetent Patients: An Underdiagnosed Disease. Case Rep Infect Dis 2013;2013. doi:10.1155/2013/165409.

Faucher B, Pomares C, Fourcade S, Benyamine A, Marty P, Pratlong L, et al. Mucosal Leishmania infantum leishmaniasis: Specific pattern in a multicentre survey and historical cases. Journal of Infection 2011;63(1):76–82. doi:10.1016/j.jinf.2011.03.012.

Franco AP, Gamo Villegas R, Pinedo F, Caro-Gutiérrez D, López-Estebaranz JL. Mucosal leishmaniasis of the tongue caused by Leishmania infantum in an immunocompetent woman. International Journal of Dermatology 2015;54(1):e39–41. doi:10.1111/ijd.12567.

Gaspari V, Zaghi I, Macrì G, Patrizi A, Salfi N, Locatelli F, et al. Autochthonous cases of mucosal leishmaniasis in Northeastern Italy: Clinical management and novel treatment approaches. Microorganisms 2020;8(4):588. doi:10.3390/microorganisms8040588.

Guddo F, Gallo E, Cillari E, La Rocca AM, Moceo P, Leslie K, et al. Detection of Leishmania infantum kinetoplast DNA in laryngeal tissue from an immunocompetent patient. Human Pathology 2005;36(10):1140–2. doi:10.1016/j.humpath.2005.07.006.

Hammami-Ghorbel H, Ben Abda I, Badri T, Chelbi H, Fenniche S, Mokhtar I, et al. Mucosal leishmaniasis of the lip: An emerging clinical form in Tunisia. Journal of the European Academy of Dermatology and Venereology 2015;29(6):1212–15. doi:10.1111/jdv.12580.

Mohammadpour I, Motazedian MH, Handjani F, Hatam GR. Lip leishmaniasis: A case series with molecular identification and literature review. BMC Infectious Diseases 2017;17(1):96. doi:10.1186/s12879-016-2178-7.

Neumayr ALC, Walter C, Stoeckle M, Braendle N, Glatz K, Blum JA. Successful treatment of imported mucosal leishmania infantum leishmaniasis with miltefosine after severe hypokalemia under meglumine antimoniate treatment. Journal of Travel Medicine 2012;19(2):124–6. doi:10.1111/j.1708-8305.2011.00572.x.

Patel TA, Scadding GK, Phillips DE, Lockwood DN. Case report: Old world mucosal leishmaniasis: report of five imported cases to the hospital for tropical diseases, London, United Kingdom. American Journal of Tropical Medicine and Hygiene 2017;97(4):1116–19. doi:10.4269/ajtmh.17-0162.

Richter J, Hanus I, Häussinger D, Löscher T, Harms G. Mucosal Leishmania infantum infection. Parasitology Research 2011;109(3):959–62. doi:10.1007/s00436-011-2356-x.

Stoeckle M, Holbro A, Arnold A, Neumayr A, Weisser M, Blum J. Treatment of mucosal leishmaniasis (L. infantum) with miltefosine in a patient with Good syndrome. Acta Tropica 2013;128(1):168–70. doi:10.1016/j.actatropica.2013.07.002.

World Health Organization. Control of the leishmaniases. World Health Organization Technical Report Series 2010:22–6.