SHORT COMMUNICATION

Mucocutaneous Leishmaniasis due to *Leishmania infantum* Infection

Kai-Philipp LINSE[1], Christian BOGDAN[2], Holger A. HAENSSLE[1#] and Ferdinand TOBERER[1#]
[1]Department of Dermatology, University Hospital Heidelberg, Heidelberg, and [2]Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene, Universitätsklinikum Erlangen und Friedrich-Alexander-Universität (FAU) Erlangen, Erlangen, Germany. E-mail: kai-philipp.linse@med.uni-heidelberg.de
[#]These authors contributed equally to this work.
Accepted May 23, 2022; Epub ahead of print May 23, 2022
Acta Derm Venereol 2022; 102: adv00748. DOI: 10.2340/actadv.v102.2321

Leishmaniasis is an infectious disease caused by protozoan parasites of the genus *Leishmania* which are transmitted between mammalian hosts by blood-sucking sand flies (1). There are at least 20 species of the genus *Leishmania*. Depending on the infecting species and the ensuing immune response, human infection may lead to cutaneous leishmaniasis (CL), mucocutaneous (MCL) or mucosal leishmaniasis (ML) or to systemic or visceral leishmaniasis (VL). MCL and ML are typical clinical manifestations of infections with parasites of *Leishmania* (*Viannia*) subgenus, which prevails in Central and South America, but can also result from infections with the *Leishmania* (*Leishmania*) subgenus in the Mediterranean area, the Middle and Far East and in Africa (2–4). We report here a rare case of mucocutaneous leishmaniasis due to *Leishmania infantum* infection.

CASE REPORT

A 77-year-old woman presented with a 5-month history of swelling and ulceration of the upper lip and hard palate (**Fig. 1**A). At the time of first manifestation, the patient received immunosuppressive medication consisting of the tumour necrosis factor (TNF)-antagonist etanercept and high-dose glucocorticoids because of a newly diagnosed rheumatoid arthritis. A microbial swab was positive for Herpes simplex virus type 1 (HSV1), but virostatic therapy with valaciclovir resulted in no significant improvement.

A punch biopsy of the upper lip was performed. Histopathological analyses demonstrated an ulceration and a pseudolymphomatous, lympho-plasmacellular infiltrate, as well as epithelioid cell granulomas. Immunohistochemistry was negative for HSV1/2, *Treponema pallidum*, latent membrane protein 1 (LMP1) and cytomegalovirus (CMV). No fungal elements were detected following Alcian-periodic acid-Schiff (Alcian-PAS) staining. Microscopy, microbial culture and a PCR-test were negative for mycobacteria species. The findings were consistent with a diagnosis of cheilitis granulomatosa (CG) accompanied by an atypically pseudolymphomatous reaction pattern (**Fig. 2**A), an assessment that was shared by an external histopathology reference centre. Additional

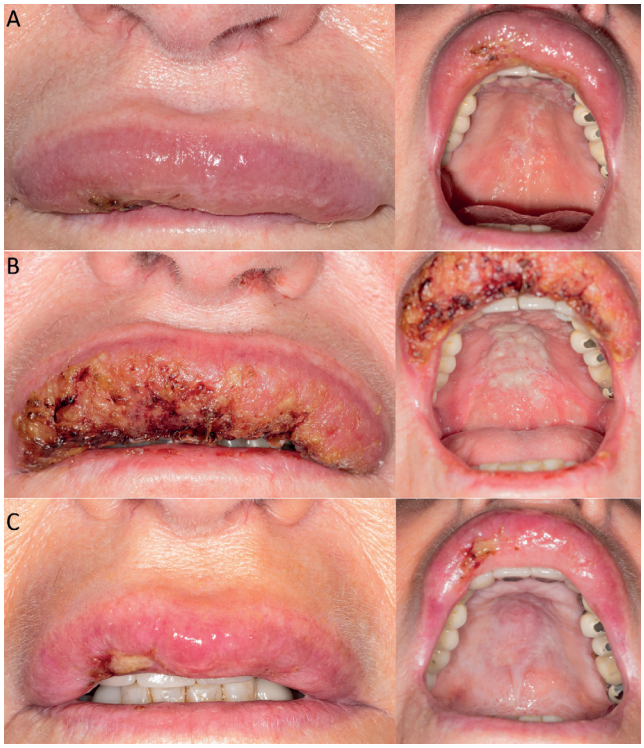

Fig. 1. Swelling and ulceration of the upper lip and hard palate. (A) Initial presentation. (B) Twelve weeks after initial presentation and before treatment with liposomal amphotericin B. (C) Follow-up 4 months after the end of therapy with liposomal amphotericin B.

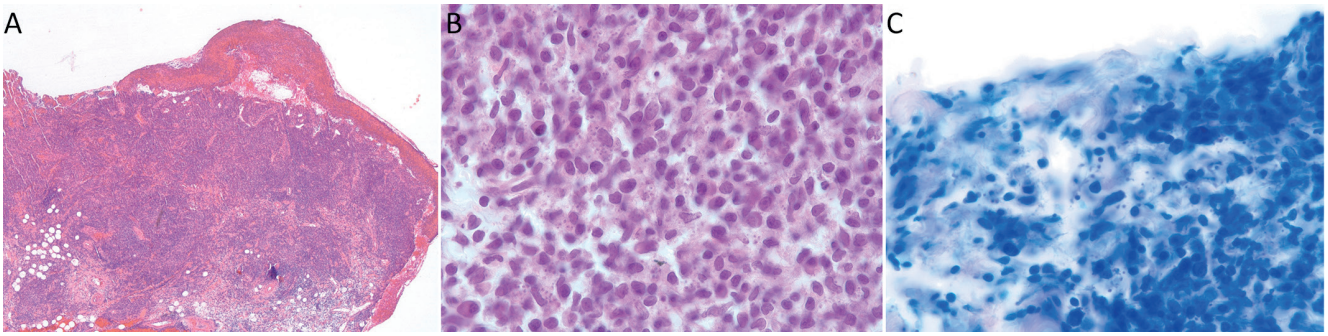

Fig. 2. (A) Ulceration with an underlying pseudolymphomatous dense infiltrate, consisting of lymphocytes and plasma cells as well as epithelioid cell granulomas (A: haematoxylin eosin staining (HE): original magnification ×25). (B and C) Histopathology of the second biopsy revealing numerous intracellular amastigotes (B: HE staining, oil immersion, original magnification ×630, C: Giemsa staining: original magnification ×630).

immunohistological analyses excluded a malignant lymphoma as an important differential diagnosis. Magnetic resonance imaging (MRI) of the facial skull and computed tomography (CT) of the thorax and abdomen revealed a maxillary sinusitis, but no further specific organic abnormalities.

The suspected CG was treated with various therapeutic regimens, including local triamcinolone injections, high-dose systemic glucocorticoids and systemic application of the janus kinase inhibitor (JAKi) upadacitinib. However, the swelling and ulceration of the upper lip and oral mucosa progressed despite the therapeutic immunosuppression (Fig. 1B). Therefore, 2 new biopsies of the upper lip and the hard palate were performed. Unexpectedly, haematoxylin and eosin-stained sections now showed numerous round-to-oval, non-encapsulated intracellular microorganisms suggestive of *Leishmania* amastigotes (Fig. 2B). Upon Giemsa staining, the nuclei of these amastigotes appeared reddish to purple (Fig. 2C). A diagnosis of mucocutaneous leishmaniasis (MCL) was made. Cytochrome b gene sequencing, as well as *Leishmania* mini-exon PCR and restriction-fragment-length-polymorphism analysis, identified *L. infantum* as the causative species. A detailed travel history of the patient revealed multiple stays in Southern Europe, Asia and North Africa over the past decades, but none in Central or South America. The patient did not recall any sand fly bites or skin lesions during or after her travel activities.

All immunosuppressive medications were stopped and systemic therapy with liposomal amphotericin B (cumulative dose 20 mg/kg body weight) was initiated. Follow-up examinations after 4 months showed significant clinical improvement (Fig. 1C).

DISCUSSION

Diagnosis of MCL can be very challenging. Due to its complex clinical presentations and polymorph histopathological features MCL can mimic infectious, malignant, and autoimmune diseases. The severity and clinical manifestations of MCL are quite variable. The lesions can be of polypoid, infiltrative, ulcerative or papulonodular nature. The most frequent locations are the oral cavity, the nose, the palate, the pharynx and the larynx (4).

Diagnosis of (mucocutaneous) leishmaniasis requires identification of the parasite by histopathology, culture and/or PCR; the latter represents the most sensitive diagnostic technique. Early diagnosis and prompt treatment are essential to prevent disfiguring lesions (5–7).

MCL most likely results from the local and/or haematogenous spread of the parasite after a bite by an infected sand fly, is accompanied by a strong immunopathology and affects both inhabitants and travellers of endemic zones (4, 6). The incubation period of MCL may be up to several years (2, 4, 8, 9). Immunosuppression is a predisposing factor for MCL, as it can either promote the transition from CL to MCL or cause reactivation of latent leishmaniasis with subsequent cutaneous or mucosal manifestation (8, 10, 11).

MCL is a characteristic disease manifestation, particularly in Central and South America, where the species *L. (V.) braziliensis* accounts for most cases. MCL due to *L. infantum* is rarely suspected, frequently leading to diagnostic delay or undue therapeutic procedures (4, 12).

In conclusion, MCL should be considered in the differential diagnosis of unclear mucosal and skin lesions, even without a history of sand fly bites, especially if the symptoms begin or clinical appearance worsens under immunosuppressive therapy. *L. infantum*, which is highly prevalent throughout the Mediterranean area, can cause a spectrum of leishmaniasis, including MCL in patients travelling to, or residing in, endemic areas (12).

The authors have no conflicts of interest to declare.

REFERENCES

1. Bañuls AL, Bastien P, Pomares C, Arevalo J, Fisa R, Hide M. Clinical pleiomorphism in human leishmaniases, with special mention of asymptomatic infection. Clin Microbiol Infect 2011; 17: 1451–1461.
2. Richter J, Hanus I, Häussinger D, Löscher T, Harms G. Mucosal Leishmania infantum infection. Parasitol Res 2011; 109: 959–962.
3. de Vries HJ, Reedijk SH, Schallig HD. Cutaneous leishmaniasis: recent developments in diagnosis and management. Am J Clin Dermatol 2015; 16: 99–109.
4. 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. J Infect 2011; 63: 76–82.
5. Burza S, Croft SL, Boelaert M. Leishmaniasis. Lancet 2018; 392: 951–970.
6. Handler MZ, Patel PA, Kapila R, Al-Qubati Y, Schwartz RA. Cutaneous and mucocutaneous leishmaniasis: differential diagnosis, diagnosis, histopathology, and management. J Am Acad Dermatol 2015; 73: 911–926.
7. Merino-Espinosa G, Corpas-López V, Díaz-Sáez V, Morillas-Márquez F, Tercedor-Sánchez J, Azaña-Defez JM, et al. Cutaneous leishmaniasis by Leishmania infantum: behind granulomatous lesions of unknown aetiology. J Eur Acad Dermatol Venereol 2018; 32: 117–124.
8. Bogdan C. Leishmaniasis in rheumatology, haematology and oncology: epidemiological, immunological and clinical aspects and caveats. Ann Rheum Dis 2012; 71: i60–i66.
9. Grant A, Spraggs PD, Grant HR, Bryceson AD. Laryngeal leishmaniasis. J Laryngol Otol 1994; 108: 1086–1088.
10. Jeziorski E, Dereure J, Mac Bullen G, Blanchet C, Ludwig C, Costes V, Rodiere M. Mucosal relapse of visceral leishmaniasis in a child treated with anti-TNFa. Int J Infect Dis 2015; 33: 135–136.
11. Tuon FF, Bombonatto GM, Roesler Battaglin E, Sakumoto MH, Amato VS, Abegao de Camargo R et al. Case report: reactivation of mucosal and cutaneous leishmaniasis in a renal transplanted patient. Am J Trop Med Hyg 2014; 91: 81–83.
12. 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: 54–56.