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Co-occurrence of mucosal leishmaniasis caused by *Leishmania infantum* and mucosal-associated lymphoid tissue lymphoma☆

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Dear Editor

We present the case of a patient with a tongue leishmaniasis caused by *Leishmania infantum* retrospectively diagnosed concomitantly with a marginal zone lymphoma.

Leishmaniasis is caused by protozoan parasites from more than twenty different *Leishmania* species [1]. The vector, a female phlebotomine sandfly widely present worldwide, transmits parasites during blood feeding. Following parasite inoculation, most humans control parasite proliferation and become asymptomatic carriers. Immunosuppression in previously healthy subjects may favour leishmaniasis reactivation. However, cases of reactivation have also been described in immunocompetent patients. In Europe, the most prevalent leishmania species is *L. infantum*, which predominantly causes Visceral Leishmaniasis (VL) or Cutaneous Leishmaniasis (CL), Mucosal Leishmaniasis (ML), with or without concomitant VL caused by *L. infantum* has been reported sporadically [2].

Lymphomas involving the tongue are extremely rare and represent approximately 3% of all lymphomas involving the head and neck region. Extra-nodal marginal zone lymphoma of mucosal-associated lymphoid tissue lymphoma is a low-grade B-cell lymphoma that accounts for 7–8% of all B-cell lymphomas [3]. Just as *Helicobacter pylori* gastritis is a predisposing factor for gastric Marginal Zone Lymphoma (MZL), other microorganisms have been associated with site-specific extra-nodal marginal zone lymphomas based on strong, but not definitive evidence [3].

A 62-year-old man presented with a painful tongue in October 2021. He didn't report any travel abroad for the last 2 years and does not have any pet. He is living in a commune located in the Provence-Alpes-Côte d'Azur region, southern France. His medical history started in November 2020 when he consulted for a painful tongue swelling. Physical examination showed a swollen tongue with a large, circumscribed, and ulcerated yellow-white lesion. A lingual biopsy made it possible to diagnose of a marginal zone lymphoma through direct examinations and a compatible immunohistochemistry (CD20, CD79a positive and CD5, CD10, CD23, CD138, BCL6, CyclineD1 negative). Thus, the patient underwent four cures of rituximab and bendamustine from February 2021 to May 2021 and stopped because of toxic dermatitis. The clinical response was good. Complete lymphoma remission was confirmed with a Positron emission tomography scan in July 2021.

Another lingual biopsy has been taken in November 2021 for a recurrence of the tongue swelling. Briefly, formalin-fixed paraffin-embedded tongue biopsy was cut to 3 μm thickness and stained with hematoxylin-eosin-saffron. Special stains were used for detection of microorganisms, including periodic-acid Schiff, Giemsa, Grocott methenamine silver, and Ziehl-Neelsen acid-fast stains. First-line immunohistochemical analysis was performed by using antibodies directed against CD3, CD20, and Bcl-2. The patient was afebrile and had hepatosplenomegaly. Laboratory results showed low white blood cell count (PNN: 1.0 G/L and WBC: 1.7 G/L), C-reactive protein of 4.4 mg/l. The biopsy sample in November 2021 showed significant inflammatory reaction and many Leishman bodies (Giemsa stain) within the macrophages (see Fig. 1). Immunohistochemical exploration showed many reactive T cells, the absence of B cells and confirmed the absence of lymphomatous infiltration. Real-time PCR tests, targeting the kinetoplast minicircle gene, successfully detected *Leishmania* spp. [4] on both the second lingual biopsy and blood sample. Subsequent sequencing targeting both the ITS1 and ITS2 region of the rRNA gene found 99.7% identity with *L. infantum* (Genbank LR697137.1). Serological investigation remained positive for leishmaniasis on both ELISA (Bordier®, *Leishmania infantum,* France) and immunoblotting assays (LD-Bio Diagnostic®, France). The diagnosis of mucosal-visceral leishmaniasis was retained. Retrospectively, a molecular analysis with DNA detection of *L. infantum* was performed from the previous lingual biopsy (November 2020) and confirmed the diagnosis of leishmaniasis concomitant with a marginal zone lymphoma of the tongue.

The patient has been treated with intravenous liposomal amphotericin B (40 mg/kilograms), allowing to reach negative blood *Leishmania* sp. PCR in one month and clinical improvement after a 6-month follow-up.

☆ Informed and signed consent form was obtained from the patient.

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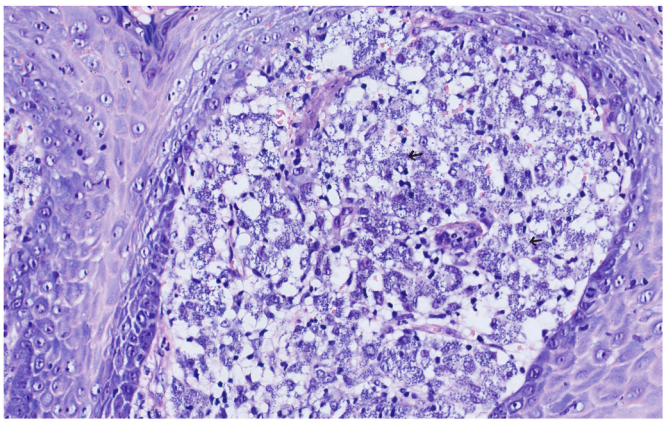

Fig. 1. Swelling tongue biopsy
Biopsy blade with Giemsa coloration x 25 with the C13220-21MDEU NanoZoomer® S360MD slide scanner system (Hammatsu photonics, Massy, France), Giemsa coloration; arrows point out amastigotes. Original magnification, X400.

Mucosal leishmaniasis (ML) caused by *L. infantum* usually involve the oral cavity including the tongue, intranasal mucosa, pharynx and larynx [5]. It remains a question if patients are infected as a site of inoculation or as a secondary localization through hematogenic parasite spread after an infected sandfly's bite. Notably, most patients with ML do not have a history of CL [5]. Although there has not been performed recent exhaustive seroprevalence surveys, many inhabitants of southern France are healthy carriers of *L. infantum*, especially in the Alpes-Maritimes region [6].

There is a possible correlation between leishmaniasis and MZL. Chronic antigenic stimulation by microbial agents has already been proposed as a possible pathogenic mechanism in marginal zone lymphoma. The parasites enter the spleen and activate macrophages of the marginal zone, inducing an interleukin-10-mediated permissive environment. Their sustained antigenic stimulation triggers polyclonal B-cell proliferation. This pathway is essential for controlling B-cell proliferation and its persistent activation is known to increase the risk of B cell malignancies.

In the case reported here, the patient with an initial diagnosis of MZL of the tongue, has been treated with rituximab and bendamustine, with a good clinical and imaging response, before the relapse of the tongue swelling and secondary diagnosis of leishmaniasis. However, both molecules increase the risk of lymphopenia. A serologic screening is already recommended for organ transplant recipients with potential exposure to *Leishmania* in patients [7]. But serological diagnosis of VL may be missed in immunocompromised patients and even more if treated with antibody production interfering drug such as rituximab. To overcome the low serology's sensitivity in immunocompromised patients, PCR tests on blood sample might be considered for leishmaniasis screening.

Clinicians should consider Leishmania infection in the differential diagnosis of marginal zone lymphomas. More specifically in patients living in or migrating from endemic countries, blood leishmania PCR and serology should systematically be tested before initiating immunosuppressive therapies. Further studies are needed to precise the role of leishmaniasis on marginal zone lymphoma development in endemic areas.

Authorship contributions

Hugues BEUDET: Took care of the patient; Collected the data; Wrote the manuscript.

Coralie L'OLLIVIER: Performed microbiological analysis; Wrote the manuscript.

Reda BOUABDALLAH: Took care of the patient; Reviewed the final manuscript.

Fabrice CAMPANA: Took care of the patient; Reviewed the final manuscript.

Anais BAGONCHY: Took care of the patient; Reviewed the final manuscript.

Hubert LEPIDI: Performed histological analysis; Reviewed the final manuscript.

Philippe PAROLA: Took care of the patient; Supervised the study; Reviewed the final manuscript.

Nadim CASSIR: Took care of the patient; Conceived and designed the analysis; Wrote the manuscript; Reviewed the final manuscript.

Declaration of competing interest

None.

Acknowledgment

None.

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