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CASE REPORT

Oral Leishmaniasis: diagnostic and therapeutic journey

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Abstract:

Leishmaniasis, caused by protozoan parasites, is a widespread infectious disease and a prominent example of neglected tropical diseases. Brazil is among the countries most severely affected by this condition globally. Mucocutaneous leishmaniasis rarely involves oral sites, presenting diagnostic challenges. This study explores a case of mucocutaneous leishmaniasis discussing clinical presentation, diagnostic process and treatment. An 85-year-old woman presented with a progressively enlarging, painful palatal ulcer. The patient had a history of treated tuberculosis and reported additional symptoms including breathing difficulties, nosebleeds, osteoarthritis, hearing loss, and insomnia. Initial biopsy showed ulcerated squamous epithelium and nodular granulomatous inflammation. Despite negative diagnostic tests for tuberculosis, syphilis, HIV, and viral hepatitis, sarcoidosis was initially considered but treatment was ineffective. Worsening symptoms later revealed structures consistent with *Leishmania sp.* amastigote forms, confirmed by immunohistochemistry, leading to a diagnosis of oral leishmaniasis. Treatment with liposomal amphotericin B resulted in successful management. The rarity of oral manifestations further complicates diagnosis, highlighting the critical role of dentists in conducting a thorough assessment, administering the correct treatment, and ensuring proper follow-up to guarantee patient compliance.

Keywords: Leishmaniasis, Mucocutaneous; Oral manifestations; Diagnostics; Case reports.

INTRODUCTION

Endemic in more than 98 countries and territories worldwide, leishmaniasis is a poverty-related infectious disease caused by protozoan parasites of the genus *Leishmania*[1,2]. *Leishmania* parasites are transmitted among mammalian hosts — such as humans, dogs, or rodents — via bites from female phlebotomine sandflies belonging to the genus *Lutzomyia*[2].

Leishmania infection is initiated by the bite of infected phlebotomine sandflies, typically on exposed regions of the skin. Subsequently, these promastigotes are phagocytosed by host cells. Following this initial phase, the parasites exhibit tropism for specific tissues, dictating the clinical manifestation of the disease[2-4]. The parasites may remain confined to the dermis, leading to cutaneous leishmaniasis, characterized by either nodular or ulcerative lesions[2,4]. However, in a subset of cases, the infection can progress to involve the delicate mucosal tissues of the upper respiratory tract, resulting in the disfiguring sequelae of mucocutaneous leishmaniasis. Alternatively, the parasites may disseminate systemically, targeting visceral organs, culminating in visceral leishmaniasis, a potentially life-threatening systemic disease that often presents without preceding or concurrent cutaneous involvement[2,3].

Mucosal involvement in leishmaniasis is uncommon and arises from hematogenous or lymphatic spread

Statement of Clinical Significance
Oral leishmaniasis is rare and poses a diagnostic challenge, especially in patients with complex histories and negative biopsies for amastigote forms. This highlights the dentist's key role in thorough evaluation, accurate treatment, and follow-up to ensure compliance and optimal outcomes.

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of amastigotes from the skin to the nasopharyngeal mucosa. Mucosal lesions can manifest as polypoid, infiltrative, ulcerative, or papulonodular formations[5]. Among the mucosal sites, the oral cavity is between the most commonly affected anatomical areas[6,7]. Diagnosing leishmaniasis can be highly challenging, and oral lesions may serve as the initial indicators of the disease. This paper presents an unusual case of mucosal leishmaniasis affecting the oral cavity and underscores the role of dentists in the diagnosis and treatment of this disease.

CASE REPORT

An 85-year-old Caucasian female patient attended the Stomatology Center in September 2018, complaining of "mouth sores". Intraoral examination revealed an ulcer with a yellowish background on the hard palate. The lesion, approximately 2.0×2.0 cm, displayed non-infiltrating characteristics with well-defined borders and non-pulsatile painful symptoms. Additionally, bleeding erythematous hyperplastic gingival lesions were observed in the region of superior anterior teeth (Figure 1). Comprehensive dermatological evaluation revealed no other visible or undiagnosed cutaneous lesions. The patient reported difficulties in breathing, nosebleeds, osteoarthritis in the upper and lower limbs, hearing loss, and insomnia. A history of tuberculosis, diagnosed and treated in 2013, was also noted. Cone beam computed tomography of the maxilla revealed a hypodense image associated with the roots of the upper right second molar and upper left canine, indicative of chronic periapical lesions. Atypical calcification in the medullary bone of the maxilla and thickening of the mucosa in the left maxillary sinus were also identified.

Based on the patient's medical history, multiple diagnostic tests were conducted, including Purified Protein Derivative (PPD) exams, rapid molecular tests, sputum smear microscopy, and tuberculosis culture, all of which yielded negative results, effectively ruling out tuberculosis. Rapid tests for syphilis, HIV, and viral hepatitis also returned negative results. To further investigate the palatal ulcer, an incisional biopsy was performed.

Histopathological analysis of the biopsy revealed an ulcerated squamous epithelium and nodular granulomatous inflammation. The inflammation was notably rich in lymphocytes and epithelioid cells, with some few Langhans-type giant cells present in the lamina propria (Figure 2A-D). Ziehl-Neelsen stain was negative for acid-fast bacilli and Periodic Acid–Schiff with diastase (PAS-D) was negative for fungi (Figure 2E-F). Given these clinicopathological findings, the diagnosis of sarcoidosis was suggested. To address the condition, the patient underwent a therapeutic trial with Doxycycline (100 mg 12/12h); however, there was no observed improvement in her clinical condition.

Due to the COVID-19 pandemic, the patient only returned to the stomatology service in 2021, with a significant worsening of her clinical condition. The lesions extended throughout the palatal mucosa, involving the hard and soft palate, maxillary gingiva and alveolar

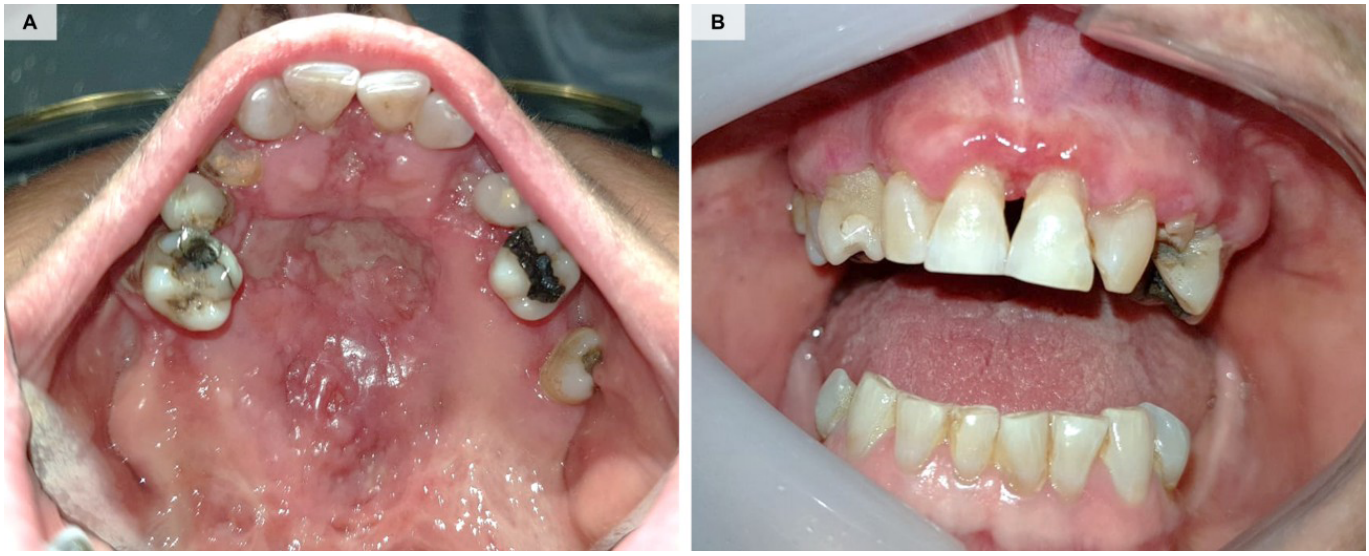

Figure 1. Illustrates the clinical features of the lesion in 2018. **(A)** A non-infiltrating ulcer with well-defined edges and a yellowish appearance on the hard palate. **(B)** Bleeding erythematous hyperplastic gingival lesions observed in the region of maxillary anterior region.

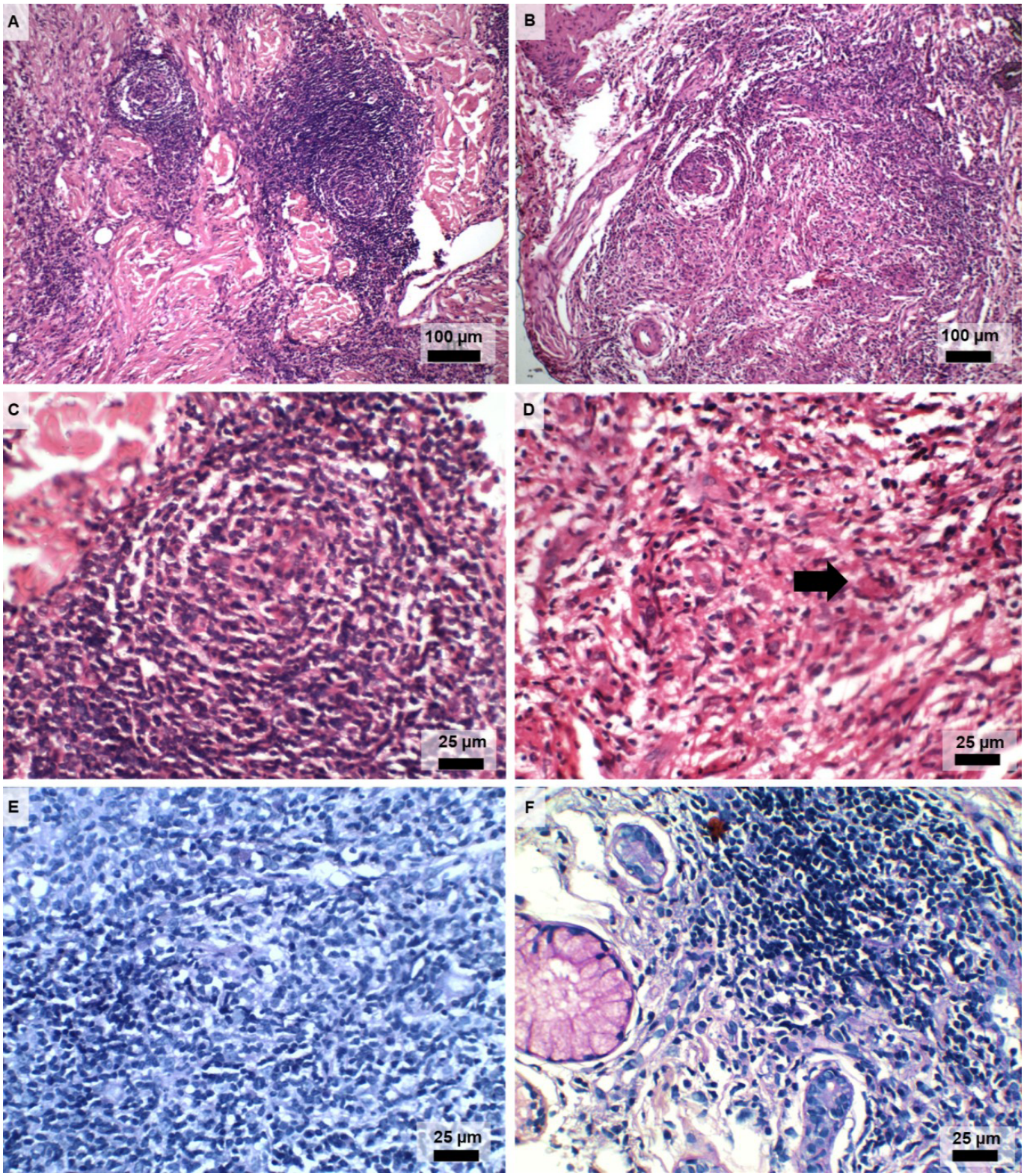

Figure 2. Photomicrographs of histological slides depict the key pathological features observed in the incisional biopsy. **(A–B)** Display an inflammatory infiltrate arranged nodularly within the connective tissue (HE, 40x/100x, respectively). **(C)** Illustrates inflammation consisting of lymphocytes, while **(D)** exhibits epithelioid cells (macrophages) and a few Langhans-type multinucleate giant cells (black arrow) (HE, 400x). **(E)** Ziehl-Neelsen and **(F)** PAS-D histochemical stains were negative for acid-fast bacilli and fungi, respectively (400 x).

ridge, and upper labial mucosa (Figure 3A). Another incisional biopsy of the palatal lesion was performed, and histological slides stained with hematoxylin and eosin (HE) revealed the oral mucosa showing pseudoepitheliomatous hyperplasia and ulceration of the lining squamous epithelium.

Within the lamina propria, non-caseating granulomas were evident, formed by condensations of lymphocytes surrounding epithelioid cells and occasional multinucleated giant cells. Moreover, some structures compatible with amastigote forms of *Leishmania sp.* were identified, both in the extracellular environment and the cytoplasm of macrophages and were confirmed by immunohistochemical reaction for anti-leishmanial antibody (1:100, ISCIII, Madrid, Spain) (Figure 3C–D). Stains including PAD-D, Grocott, and Ziehl-Neelsen were negative. The final diagnosis was Leishmaniasis.

The patient commenced treatment with miltefosine, but it was suspended shortly afterward due to the development of a skin rash. Subsequently, the use of liposomal amphotericin B was suggested resulting in excellent clinical outcomes (Figure 3E–F). Written informed consent was obtained for the publication of this case report, and patient management adhered to the principles outlined in the Helsinki Declaration.

DISCUSSION

Leishmaniasis, a globally prevalent infectious disease, stands as one of the most neglected tropical diseases[2]. Brazil is one of the most affected countries in the world[1,8]. The primary causative agent in mucosal-involved leishmaniasis is *Leishmania braziliensis*, leading to ulcerated and papulonodular lesions on the oral and nasal mucosa, alongside cutaneous lesions[6]. While mucosal leishmaniasis most commonly arises as a secondary complication following cutaneous involvement[5,6], the absence of any history of skin or other mucosal ulcers or scars in our case supports the oral cavity as the primary and sole site of clinical manifestation[6,7]. Although epistaxis is a common finding in mucosal and mucocutaneous forms of leishmaniasis, symptoms such as difficulty breathing and osteoarthritis are less frequently observed, typically occurring in more advanced or chronic cases[6,7]. The combination of these symptoms, along with the unusual presentation, was initially misleading and suggested a range of other potential conditions.

Although the initial radiographic findings were consistent with common odontogenic conditions, the later identification of atypical medullary bone calcifications and mucosal thickening in the maxillary sinus prompted consideration of a granulomatous or inflammatory etiology. Maxillary sinus mucosal thickening has been reported as a common CT finding in patients with leishmaniasis, supporting the relevance of this diagnosis in our case[9]. While medullary bone calcifications are not characteristic features of leishmaniasis, they may occasionally occur as a result of prolonged granulomatous inflammation in chronic or advanced cases[6].

The life cycle of Leishmania comprises two distinctive morphological stages: promastigote and amastigote. Promastigotes, the flagellated and motile stage, reside extracellularly within phlebotomine (of the genus *Lutzomyia*)[2]. These promastigotes are introduced into the dermis of mammalian hosts through the bite and hematophagous feeding of phlebotomine. Inside macrophages, promastigotes are phagocytosed, differentiate into amastigotes within phagolysosomes, multiply through simple division, and subsequently infect other mononuclear phagocytic cells[2]. The histopathological diagnosis of leishmaniasis is based on identifying a granulomatous inflammatory reaction containing amastigote forms, either extracellularly or within macrophages[8,10].

The diagnosis of oral leishmaniasis can be particularly challenging, especially when there is a scarcity of parasites in the biopsied lesion specimens, similarly, as was the case in this instance[10]. Although the oral biopsy revealed a typical non-calcifying granulomatous inflammation consistent with the pathological features of oral leishmaniasis, unequivocal identification of amastigote forms was not achieved in this occasion.

Furthermore, special stains for acid-fast bacilli and fungal organisms yielded negative results, excluding other granulomatous diseases such as tuberculosis, leprosy, and deep mycoses from the differential diagnosis[8,11]. Consequently, the possibility of sarcoidosis was considered as a diagnosis by exclusion, however, this possibility was ruled out due to the poor therapeutic response to doxycycline. In the second biopsy, amastigote forms of the parasite were conclusively identified in histological HE-stained sections and confirmed by immunohistochemical analysis using an anti-leishmania antibody. This ultimately led to the definitive diagnosis of leishmaniasis.

Despite arriving at the final diagnosis, initial treatment with miltefosine was discontinued due to the development of a skin rash. Adverse effects of treatment are one of the reasons for inadequate adherence to treatment plan, posing a significant obstacle to the effective

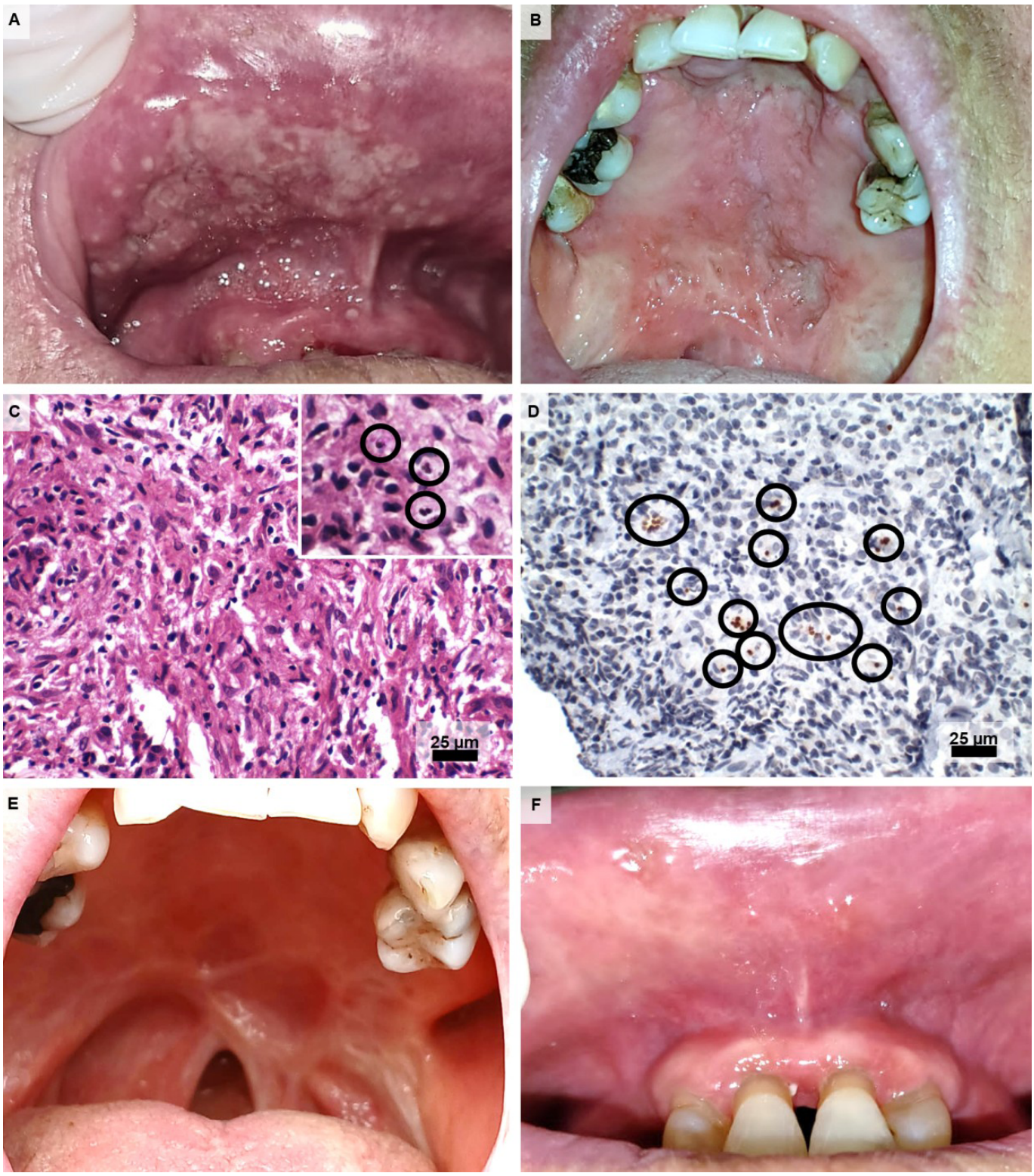

Figure 3. Clinical features of the lesion in 2020 indicating a deterioration in the clinical condition. **(A–B)** Multiple ulcerative lesions observed in the maxillary gingiva, alveolar ridge, and upper labial mucosa. **(C)** Epithelioid cells (HE, 400 x). In detail (1000 x) small structures compatible with amastigote forms of *Leishmania sp.* are identified. **(D)** Immunohistochemical positivity (highlighted in larger magnification) for anti-leishmania antibody (LSAB, 400 x). Clinical features of the lesion in April 2025 showing clinical remission of lesions on the palate, gingiva/alveolar ridge and labial mucosa **(E–F).**

management of mucocutaneous leishmaniasis[12]. Other factors contributing to poor adherence include complex treatment regimens, cultural and lay perceptions about the disease and its treatment, life stress, feelings of hopelessness and negativity and the prolonged duration of the lesions[12].

While the initial treatment was unsuccessful, the subsequent administration of liposomal amphotericin B led to excellent clinical outcomes and patient compliance. The mechanism of action of amphotericin B involves binding to ergosterol, a component of the protozoan cell membrane, to create a transmembrane channel, leading to the leakage of monovalent ions and subsequent cell death[13]. While nephrotoxicity is a major side effect of this anti-leishmanial drug, it has been successfully managed with liposomal amphotericin B, the pharmaceutical form employed in this case[13]. In fact, liposomal amphotericin B has proven effective in therapeutic and prophylactic against various fungal pathogens, including leishmania[14]. Notable advantages of this formulation include its ability to target the pathogen cell wall and distribute to infected tissues at levels exceeding the minimum inhibitory concentration for many pathogens. A systematic review conducted by Chivinski et al.[15] on the efficacy and safety of liposomal amphotericin B for 38 cases of cutaneous and mucosal leishmaniasis revealed a pooled cure rate of 87.0% (95%CI 79.0–92.0%), comparable to rates reported for other anti-leishmanial drugs. These findings underscore the fully satisfactory results achieved in the final stages of leishmaniasis treatment in the current case report.

This case highlights a rare presentation of mucosal leishmaniasis with three key distinctive features. First, unlike the typical secondary progression from cutaneous lesions, the absence of current or prior skin involvement established the oral cavity as the primary and sole site of manifestation — a rare finding in immunocompetent patients. Second, the initial clinical and histopathological features mimicked sarcoidosis, emphasizing the diagnostic challenges when amastigotes are scarce in biopsy specimens and reinforcing the need for multiple diagnostic strategies. Third, the patient experienced an adverse reaction to miltefosine, requiring a switch to liposomal amphotericin B, which resulted in successful treatment. Collectively, this case underscores the importance of clinical vigilance, broadened diagnostic consideration, and individualized treatment planning in managing atypical presentations of this neglected tropical disease.

CONCLUSION

In conclusion, the case underscores the diagnostic challenges presented by rare manifestations of disease, such as oral leishmaniasis, especially in elderly patients with complex medical histories. Despite initial diagnostic hurdles and ineffective treatments for suspected conditions like sarcoidosis, the identification of *Leishmania sp.* amastigote forms through immunohistochemistry led to a definitive diagnosis. Within leishmaniasis-endemic regions or in patients with relevant exposure history, the presence of ulcerative or granulomatous lesions warrants critical diagnostic consideration for leishmaniasis. Successful management with liposomal amphotericin B highlights the critical importance of accurate diagnosis and appropriate treatment in achieving positive clinical outcomes, particularly in the context of global health concerns surrounding neglected tropical diseases like leishmaniasis.

AUTHORS' CONTRIBUTIONS

SMSF: data curation, formal analysis, investigation. **CRRO:** data curation, formal analysis, investigation. **GMF:** data curation, formal analysis, investigation. **EMVA:** data curation, formal analysis, investigation. **IAPS:** investigation, methodology, writing – original draft. **ACBS:** investigation, methodology, writing – original draft. **JCMA:** investigation, methodology, writing – original draft. **NL:** investigation, methodology, writing – original draft. **CAS:** investigation, methodology, writing – original draft. **ERCR:** formal analysis, validation. **ROG:** formal analysis, validation. **RLCAJ:** formal analysis, project administration, supervision, validation, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: The study was conducted in accordance with ethical standards and was approved by the Institutional Ethics Committee (Protocol No. 25000.237810/2014-54).

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