Orofacial manifestations of mucocutaneous leishmaniasis: a case series from Brazil [version 1; peer review: 1 not approved]

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Abstract
The dental surgeon plays a fundamental role in the early diagnosis of oral leishmaniasis, since oral mucosa may be the primary site of the disease manifestation. This study reports seven clinical cases of orofacial mucocutaneous leishmaniasis. All had mucocutaneous leishmaniasis with oropharyngeal involvement confirmed by laboratory tests. Five out of the seven cases were males, and in four cases, patients had associated comorbidities. Late diagnosis was observed, resulting in treatment delay and increased hospitalization stay. One patient had severe psychological consequences due to facial deformity. The lack of differential diagnosis due the great variability of clinical presentation of the lesions and frequent unspecific histopathology represent a challenge for the dental surgeon. In two reported cases, there were unspecific biopsy results. The multidisciplinary approach plays an important role in orofacial leishmaniasis diagnosis and treatment. Leishmaniasis should be investigated in case of atypical and persistent lesions in patients from endemic regions. This recommendation may avoid diagnosis delays and decrease dissemination of the disease.

Keywords
Leishmaniasis, Mucocutaneous, Diagnosis, Oral, Dental Care

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Any reports and responses or comments on the article can be found at the end of the article.
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Introduction

Leishmaniasis is a parasitic disease caused by several species of the protozoan genus *Leishmania*. It is a widely dispersed disease, being endemic in 98 countries, including Brazil. Leishmaniasis classification encompasses different clinical forms; mucocutaneous leishmaniasis is a chronic form of infection that may manifest in the mucosa after months or years of latency.

The mucosal involvement of leishmaniasis is uncommon, mainly in immunocompromised individuals. The lymphatic or hematogenous dissemination of amastigotes may occur from the skin to the nasal, oropharyngeal, laryngeal and/or tracheal mucosa. Delayed diagnosis and development of primary lesion in the oral mucosa and in the head and neck region can cause dysphagia, dysphonia and dyspnoea.

The diagnosis of mucocutaneous leishmaniasis can be difficult. In older lesions, few parasites are usually detected by microscopy or culture and the clinical aspect may resemble neoplasia. Orofacial symptoms depend on the localization of the lesions and may include nasal obstruction, difficulties in swallowing, mucosal bleeding and/or hoarseness. Destructive lesions of the mucosa contain few parasites, with high levels of tumor necrosis factor (TNF) suggesting an unmodulated immune response with increased production of proinflammatory cytokines responsible for tissue damage.

In this study we report seven clinical cases of orofacial mucocutaneous leishmaniasis from Brazil.

Case reports

This study included seven patients admitted to Edgard Santos University Hospital, Federal University of Bahia, Brazil. All patients had a confirmed diagnosis of mucocutaneous leishmaniasis with oropharyngeal involvement and no visceral involvement, confirmed by laboratory tests. This study was approved by the Ethics and Research Committee of Edgard Santos University Hospital, CAAE 93381518.7.000.0049. All patients (or parents/guardians) provided written informed consent for the publication of their medical data and images.

Case 1

Male, 24-years-old, Caucasian, unemployed, from Tancredo Neves, State of Bahia, Brazil, was admitted to the University Hospital, in January 2012, presenting diffuse bullous lesions on the body, osteoarthritis of the distal interphalangeal joints and proteinuria 399 mg/day (reference value >150 mg/day). He was diagnosed with systemic lupus erythematosus (SLE) and treated with mycophenolate mofetil (MMF). The starting dose for MMF was 0.5 g per day and it was increased up to 1 g per day intravenously. In 2014, two years after SLE diagnosis, he was hospitalized, presenting with ulcerated-painless-skin lesions on the face, upper lip, scalp, neck, upper and lower limbs. Oral examination evidenced crusty upper lip lesions, poor oral health status and amelogenesis imperfecta (Figure 1a and 1b). He developed secondary infection associated with fever, and antibiotic therapy with cephalaxin was initiated (1 g/day) and a maintenance dose of prednisone (5 mg/day intravenously). On the third day, biopsies were performed on the left nasal mucosa and on the right lower limb lesions. The diagnosis of disseminated leishmaniasis was confirmed (positive PCR and Montenegro intradermal test). Liposomal amphotericin B was introduced on the fourth day of hospitalization at a dose of 150 mg/day up to a maximum dose of 2,400 mg. The patient treatment was followed-up for six months, and lesions were observed to have healed. One month later, during the follow-up for SLE, we observed new development of ulcerated skin lesions on the face and on the upper and lower right limbs. Blisters and fever were absent and the recurrence of disseminated leishmaniasis was confirmed. Few weeks later, the patient was admitted for treatment of new lesions, presenting with erythema, diffuse facial edema, lymphadenopathy and ulcerated and pustular lesions. Patient was treated with liposomal amphotericin B at a cumulative dose of 3,050 mg and followed-up until complete remission of the lesions. Currently, patient is under maintenance treatment for SLE.

Case 2

In July 2013, 53-year-old male, Caucasian, unemployed, from Mundo Novo, State of Bahia, Brazil, attended to the Stomatology Clinic at University Hospital, presenting with pain, nasal obstruction, and complaints of odynophagia and dysphagia. Physical examination showed painful, hyperemic and friable lesion in the right nasal cavity, associated with infiltrative lesion on the hard and soft palate, and uvula (Figure 1c). We observed ulcerated lesion on the left eyebrow and right eye with seropurulent secretion, a small ulcer on the lower eyelid, on the lobe of the right ear and a lesion in the malar region. The patient was admitted for diagnosis and treatment of disseminated skin lesions. A biopsy of the palate lesions revealed a non-specific erosive chronic inflammatory process. The patient was HIV negative and positive for Montenegro reaction. Treatment with amphotericin B was initiated at a dose of 150 mg/d up to a maximum dose of 2,410 mg. Lesions regressed after drug treatment and oral treatment was initiated during hospitalization. We removed dental foci without any intercurrence. One month later, the patient was
discharged. However, in August 2013, in outpatient medical consultation, the lesions were observed in nasal mucosa and palate. He was followed up in the outpatient clinic and treatment with glucantime 20 mg/kg/day was prescribed for one month. The follow-up period was eight months, and the result was negative.

Case 3
Female, 31 years old, Caucasian, unemployed, from Salvador, State of Bahia, was diagnosed (Montenegro positive test) with American Tegumentary Leishmaniasis in October, 2011. The patient was treated with Glucantime, 20 mg/kg/day for 30 days. A lesion in her back region was partially healed. In 2012, two episodes of recurrence occurred and restarted treatment with Glucantime in January and May. In a third recurrence episode (August, 2012), due to the maintenance of the lesion, a lesion biopsy was performed and *Leishmania braziliensis* was diagnosed. Treatment with amphotericin B was initiated at a dose of 250 mg/d up to a maximum dose of 2,400 mg, resulting in wound healing. In 2013, the patient was admitted with submandibular lymphadenopathy and ulcerated lesions in the lower lip frenulum (Figure 1d), gingiva, nasal septum and in the back region. She was hospitalized for diagnosis and treatment of lesions with liposomal amphotericin B. Due to persistence of the lesions, HIV serology was performed. The patient was HIV positive and antiretroviral therapy was started (efavirenz 600mg, tenofovir 300mg, lamivudine 300mg, per day, one tablet containing the three drugs). Excisional biopsies of oral lesions were performed with unspecific result. Microbiological analysis for fungi was negative. Two months later, the patient was discharged and a maintenance dose of liposomal amphotericin B (150 mg/day) was prescribed.

Case 4
In 2017, an eight year-old Caucasian male from Salvador, Bahia, Brazil, presented with a hyperemic and pruritic lesion on the upper lip which had persisted for six months. Patient was treated with acyclovir cream, 5%, 5 times/day and cefadroxil (50 mg/kg/day) for seven days, with no response. He presented worsening of the lesion and Montenegro intradermal examination was performed (Figure 2a). The patient was positive for *American Tegumentary Leishmaniasis*. Treatment with glucantime (10 mg/kg/day) for 20 days was initiated. After three days of treatment, the patient developed vomiting episodes, intermittent fever, diarrhea, hypoglycemia, dark urine, and began developing a reaction of cardiotoxicity and hepatotoxicity. Treatment with liposomal amphotericin B was initiated (3 mg/kg/day for 5 days, followed by 3 mg/kg). One month later, patient was discharged with remission of the lesion (Figure 2b). Two months later, the patient was admitted at University Hospital with a new, erythematous and ulcerated lesion on the upper lip lesion, lymphadenopathy, and facial edema. Therapy with amoxicillin 250 mg (1g/day) and amphotericin B (100 mg/day) for 10 days was started. Patient is currently in psychological follow-up due to trauma caused by facial disfiguration and difficulty in returning to social life. Patient maintained outpatient follow-up and did not present with recurrence of the lesion.

Case 5
In 2008, a male, 30 years old, Caucasian, unemployed, presented with an isolated nodulation in the right leg and he was diagnosed with Tegumentary leishmaniasis. The patient was treated with Glucantime (10 mg/kg/day for 20 days), achieving complete healing of the lesions. In 2014 the patient presented a papule in the inferior eyelid of the right eye. Patient was PCR positive for *Leishmania braziliensis*. Lesions progressively appeared in different body surfaces such as the chest, abdomen, back, feet, and mouth. Ulcerated oral lesions were present in the hard palate, as well as the left and right jugal mucosa (Figure 3a).

Progression of disease was associate with fever, headache and weight loss. Treatment with glucantime (20 mg/day) for 30 days followed by treatment with amphotericin B at a cumulative dose of 1.5 to 2 g, 50 mg/day. Patient developed acute renal failure secondary to the use of amphotericin B. Treatment was replaced by the liposomal form at a dose of 100 mg/day and patient was discharged one month later with complete remission of lesions.

Case 6
Female, 59 years old, Caucasian, unemployed, with diabetes, hypertension, congestive heart failure, chronic renal disease and paraparesis secondary to Human T-cell leukemia virus type 1 (HTLV-1) infection. In June 2012, patient presented with a papule lesion in the left malar region with late ulceration and increasing in size (Figure 3b). After 15 days, another lesion developed in the right knee. Patient was positive for Montenegro intradermal test and diagnosed with mucocutaneous leishmaniasis and was admitted in the University Hospital in September 2012. Patient developed hyperkalemia and, after stabilization of renal function, treatment with liposomal amphotericin B (100 mg/day) was introduced. One day after, the patient developed another

Figure 2. Hyperemic and pruritic lesion on the upper lip, reported at Case-4 (a); Aspect of the upper lip one month later, evidenced remission of lesion (b).

Figure 3. Ulcerated oral lesions in hard palate reported at Case-5 (a). Leishmaniasis lesion in the left malar region reported at Case-6 (b).
episode of renal dysfunction and therapy was discontinued. Five days later, therapy was reintroduced, alternating with dialysis. The culture examination of the malleolar lesion was performed, being positive for *Proteus vulgaris* and hemoculture was positive for *Staphylococcus aureus*. In October 2012, patient was transferred to intensive care unit and developed multiple organ failure, dying two weeks later.

**Case 7**

Male, 59 years old, mixed ethnicity, unemployed, previously healthy, reported the appearance of an erythematous-crustey lesions in the mental protuberance region, evolving in two months to other parts of the body such as frontal and occipital regions, nasal septum, ears, hands, and lower limbs. Oral cavity clinic-examination showed scattered ulcers on the face, lower labial mucosa, and on the left lip commissure, pseudomembrane on the marginal gingiva, and an exophytic nodule in the left labial mucosa (Figure 4). Patient was Montenegro intradermal test positive and was admitted at the University Hospital in December 2018. After admission, we observed enlarged lymph nodes of hard consistency in the left inguinal region, and an extensive melanocytic lesion in the left plantar region. The lesion was irregular, presenting an area of hyperkeratosis with a grey-blush center. The patient was biopsied and the diagnostic hypothesis of melanoma was confirmed. We requested laboratory and imaging tests for melanoma staging. After seven days, we accessed the PCR laboratory test and initiated therapy with intravenous liposomal amphotericin B 50 mg at the dose of 200 mg/kg/day for 15 days (Figure 4). Diagnostic confirmation of melanoma resulted in the excision of the melanocytic lesion with left inguinal lymphadenectomy. Patient referred to an oncology center. The patient has not yet returned for evaluation as they are receiving antineoplastic treatment outside our hospital.

**Discussion**

Five out of the seven cases were males from Brazil’s endemic regions. Four cases had associated comorbidities (SLE, HIV, HTLV infection and melanoma). A multicenter case series study with seven patients presenting oral leishmaniasis reported higher frequency of oral lesions in males (86%), tongue (57%) with predominance of exophytic lesions (85%). In our case series, patients were predominantly males with ulcerated lesions in the lips.

The Montenegro reaction is a diagnosis test of high sensitivity, low cost and minimally invasive. Serological tests, such as immunoenzymatic assays and indirect immunofluorescence, show variation in their results depending on the applied technique and disease classification. In our series of cases, late diagnosis was observed resulting in treatment delay and extension of hospitalization stay.

Facial involvement of leishmaniasis is a serious complication, since it can lead to disfiguration and be potentially fatal. In one case reported, the patient had severe psychological consequences due to facial deformity, reinforcing the importance of early diagnosis and appropriate therapy.

Mucosal leishmaniasis is generally associated with visceral leishmaniasis or immunocompromised individuals. In immunocompetent patients, primary and exclusive mucosal involvement in the head and neck region is uncommon; lesions affecting the buccal mucosa exclusively are even rarer. In our series of cases, four cases (57.1%) presented some level of immunological deficiency.

Leishmaniasis is difficult to treat, and may present with spontaneous reactivation or be transmitted by a transplanted organ. Control of cutaneous leishmaniasis depends on case management, early detection and appropriate treatment. We observed cases of adverse drug reactions during treatment and protocol changes were necessary during the course of treatment. We also observed frequent recurrence of lesions due to inadequate treatment suspension or suboptimal doses.

The dental surgeon plays a fundamental role in the diagnosis of oral leishmaniasis. The great variability of clinical presentation of the lesions and frequent unspecific histopathology represent a challenge in regard to differential diagnoses. The dental surgeon can contribute to early diagnosis of mucosal lesions, since oral mucosa may be the primary site of the disease manifestation.

Although histopathological techniques describe the inflammatory infiltrate associated to leishmaniasis, they present low diagnostic specificity. The granulomatous aspect of lesions in later stages of cutaneous infection of leishmaniasis hampers histopathological analysis, since few parasites can be found in these lesions. In our reported cases, we had two unspecific biopsy results.

There is no specific standardization for mucocutaneous leishmaniasis therapy. The cases we reported were submitted to different therapeutic plans, adjusted to each patient. In our case series, all patients received systemic treatment for...
mucocutaneous leishmaniasis, because of this disease well-known resistance. Alternative topical treatment includes use of ointment, cryotherapy, and intralesional injection with antimonials. Multiple and large lesions compromising the face are less suitable for local therapy. The treatment of mucosal leishmaniasis are still based on case reports."}

The treatment of lesions involving the lip depends on clinical presentation, type of the leishmaniasis. Treatment comprises of intralesional injections, systemic treatment, or a combination of the two. Treatment for large intraoral lesions involves incisional biopsy for diagnosis and use of systemic medication. In the case of small intraoral lesions (5 to 10 mm), excision is recommended, and the patient should be monitored to confirm whether systemic therapy is necessary. In our cases, all patients were treated with systemic medication. We presented a case with primary and exclusive lesion on the lip. Local treatment was not administered, and the patient is under follow-up.

Our findings present some limitation. First, the few cases reported are not a representative population sample, limiting any possible inference. Due to socioeconomic reasons, patients living far from Salvador are not accessible for a close follow-up and dental care. Diagnosis based on oral biopsies are very limited far from Salvador are not accessible for a close follow-up and are not a representative population sample, limiting any possible inference. The variation in the clinical presentation of leishmaniasis diagnosis and decrease the risk of its dissemination.

Conclusions
The multidisciplinary approach in the diagnosis and treatment of orofacial leishmaniasis is highlighted in this case series. We recommend leishmaniasis investigation in the case of patients living in endemic regions and presenting atypical and persistent lesions. Following this recommendation may avoid delays in leishmaniasis diagnosis and decrease the risk of its dissemination.

Differential diagnosis of mucosal lesions should include mucosal leishmaniasis. The variation in the clinical presentation of leishmaniasis and its ability to mimic different diseases represent a challenge for disease diagnosis. The dentist may play an important role in the early diagnosis of orofacial leishmaniasis.

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

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The author(s) declared that no grants were involved in supporting this work.

References


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The scope of this article is to provide essential clues about orofacial manifestations of mucocutaneous leishmaniasis. Considering the target readers are Dental Surgeons, this manuscript has several imprecision's and inaccurate messages which need to be corrected.

Abstract section:
- The affirmation that "oral mucosa may be the primary site of the disease manifestation" is contradictory with the discussion and findings of this report as well as the existent and well-characterised clinical description of MCL. Almost all cases (except case 4) were manifested as disseminated Leishmaniasis with a significant and predominant cutaneous involvement. In the discussion section, paragraph four, line 5, authors state that primary and exclusive oral mucosa involvement is exceptionally uncommon. Then, what is described in the abstract is contradictory.

- Regarding that "All had mucocutaneous leishmaniasis with oropharyngeal involvement" is also incorrect. Due to the lack of detail in cases 5-7, it is not possible to accept these cases are definitively MCL. Case 6 is not a case of MCL; then, it needs to be removed from this article.

Introduction section:
- Paragraph 2, line 1-2: It's not clear if authors suggest that MCL is particularly frequent in immunosuppressed individuals. This affirmation is highly dependent on the prevalence of immunosuppressive comorbidities (as HIV). Considering that immunosuppressive conditions are not highly prevalent in endemic areas (except some African or Asian regions), this affirmation is inaccurate. Mucosal involvement in new-world Leishmaniases ranges from 5-20%\(^1\) Then, in any case, this affirmation is not correct or requires clarification.

- Paragraph 2, line 5-6: development of primary lesions in oral mucosa is very infrequent and mainly described in old-world Leishmaniases\(^2\) OR in individuals with immunosuppressive
conditions (4/7 cases in this report). For this reason, authors must consider changing the scope (title as well?) of this review from orofacial manifestations of MCL to atypical manifestations of leishmaniasis among immunosuppressed individuals.

**Case reports:**

○ Case 1: more than MCL, this is a case of disseminated leishmaniasis (DisL) in an immunosuppressed individual. Here the predominant mucosal involvement appears to be nasal (no details are provided regarding the degree of nasal involvement), and the oral involvement is confined to the upper lip involvement. This is unusual even in immunosuppressed individuals, considering that lips, gums, tongue, and hard palate are extremely infrequent in new-world MCL\(^3\).

○ Case 2: again, this is a case of DisL in an immunocompetent individual. Here the mucosal involvement is more typical, but an HIV seronegative status is not enough to classify the patient as immunocompetent. A better characterisation of this individual is required.

○ Case 3: again, another case of DisL in an immunocompromised patient. It's recommended to improve the quality of picture 1d. As mentioned before gums are unusual in new-world MCL. MCL is not commonly associated with lymphadenopathy. Both findings, and in the absence of parasitologic or histologic characterisation of the oral lesion makes it essential to consider other infectious diseases, importantly in an HIV-seropositive individual.

○ Case 4: this case is MCL, but the pathophysiology is different from the prior cases. Here, more than a lymphatic/hematologic dissemination, what generated the MCL was a direct inoculation on the lip or a skin inoculation close to a mucosal structure. This case is clearly, utterly different from the rest and hard to classify as an unusual manifestation or among immunosuppressed individuals.

○ Case 5: again, another DisL in an apparently immunocompetent patient. No details were provided here regarding the HIV serologic status or other potential sources of immunosuppression.

○ Case 6: again, another DisL in an immunosuppressed individual. In this case, there is not any oral or mucosal involvement (only cutaneous lesions are described). Then, this case must be removed from the report.

○ Case 7: there is a lack of evidence to catalogue this case as MCL. Besides the facial cutaneous lesions (only localised cutaneous leishmaniasis?), lesions described in the oral mucosa are unusually located, and an alternative explanation must be considered (metastatic melanoma?). It's not clear where the sample for PCR was obtained. With this unclear clinical and parasitological description, it's inaccurate to define the case as MCL.

**Discussion:**

○ Paragraph 3, lines 1-2: MCL is potentially fatal, mainly when larynx or trachea are affected. From that scenario, it's incorrect to describe them as a facial involvement.

○ Paragraph 4, lines 1-2: as suggested in the first observation of the introduction section, authors are suggesting MCL is generally associated with VL or immunosuppression. That is probably acceptable in the context of Sudanese MCL; however, this is not the epidemiological context of the study. Regarding immunosuppression, as discussed in the
same observation, due to the lack of coexistence between Leishmaniasis and immunosuppressive conditions, there is not any evidence supporting this affirmation. The references used to support this statement are case reports which were not designed to measure the prevalence of MCL among immunosuppressed individuals.

- Paragraph 5, lines 6-7: the high rate of recurrences observed in these cases are not necessarily related to therapeutic issues. Immunosuppression is probably the primary determinant of therapeutic failure.

- Paragraph 6, lines 6-8: again, this affirmation is contradictory with the findings of this report. Only one case was purely a "primary" MCL, in the rest, the predominant manifestation was the development of disseminated cutaneous lesions.

- Paragraph 8, lines 5-6: the reason why systemic therapy was administered in all these cases is that systemic treatment is the only standard therapeutic regimen for MCL (not due to resistance issues). For a better understanding of current therapeutic recommendations, authors must review citation four and update reference 9.

- Paragraph 9: no local therapy is currently recommended for MCL. This information must be improved or removed.

**Conclusions:**
- Paragraph 2: what other infections must be considered as a differential diagnosis among oral lesions?

**References**

**Is the background of the cases' history and progression described in sufficient detail?**
Partly

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
Partly

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**
Partly
Is the conclusion balanced and justified on the basis of the findings?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Infectious and Tropical Diseases, Neglected Tropical Diseases, New-World Leishmaniases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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