CLINICAL PRACTICE ARTICLE

REVISED Orofacial manifestations of mucocutaneous leishmaniasis: a case series from Brazil [version 4; peer review: 2 approved]

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Abstract
Dentists play a fundamental role in the early diagnosis of oral leishmaniasis. Although these lesions are rare at oral mucosa, this is one of the manifestations sites of the disease This study reports seven clinical cases of orofacial mucocutaneous leishmaniasis. All had leishmaniasis diagnosis confirmed by laboratory tests, with orofacial involvement. 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 dentist. In two reported cases, there were unspecific biopsy results. This series of cases highlights the importance of a multidisciplinary approach in the diagnosis and treatment of oral and perioral leishmaniasis. Patients with atypical lesions, originating from or living in endemic regions, should be investigated for leishmaniasis. These procedures could avoid delays in diagnosis and decrease the risk of disease dissemination.

Keywords
Leishmaniasis, Mucocutaneous, Diagnosis, Oral, Dental Care

Open Peer Review

Reviewer Status ✓ ✓

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version 1 29 May 2019	✗ report	

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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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Author roles: Falcão GGVSC: Investigation, Writing – Original Draft Preparation; **Lins-Kusterer L**: Conceptualization, Writing – Review & Editing; **Leite-Ribeiro PM**: Investigation, Writing – Review & Editing; **Sarmento VA**: Conceptualization, Supervision, Writing – Review & Editing

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REVISED **Amendments from Version 3**

The most important amendments include:

In Case 7
We insert, in the text, that PCR analysis was not performed by the hospital laboratories. We just accepted the results presented by the patient in the consultation.

In the Discussion
Paragraph 4
We changed the sentence "Leishmaniasis should be considered in immunocompromised patients" for the sentence "Unusual manifestations as DisL or purely oral Leishmaniasis should be considered in immunocompromised patients".

Paragraph 10
The authors excluded the references and the paragraph, containing some controversial literature findings of the local treatment of leishmaniasis.

Any further responses from the reviewers can be found at the end of the article

Introduction

Leishmaniasis is a parasitic disease caused by several species of the protozoan genus *Leishmania*[1]. It is a widely dispersed disease, being endemic in 98 countries, including Brazil. Leishmaniasis classification encompasses different clinical forms[2]; mucocutaneous leishmaniasis is a chronic form of infection[3] that may manifest in the mucosa after months or years of latency[4].

The mucosal involvement of leishmaniasis is uncommon, mainly in immunocompetent individuals[5]. The lymphatic or hematogenous dissemination of amastigotes may occur from the skin to the nasal, oropharyngeal, laryngeal and/or tracheal mucosa. Delayed diagnosis[3,6] and development of primary lesion in the oral mucosa and in the head and neck region can cause dysphagia, dysphonia and dyspnoea[3].

The diagnosis of mucocutaneous leishmaniasis can be difficult[7]. In older lesions, few parasites are usually detected by microscopy or culture and the clinical aspect may resemble neoplasia[1,8]. Orofacial symptoms depend on the localization of the lesions and may include nasal obstruction, difficulties in swallowing, mucosal bleeding and/or hoarseness[8]. 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[9].

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 >150mg/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 cephalexin was initiated (1g/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

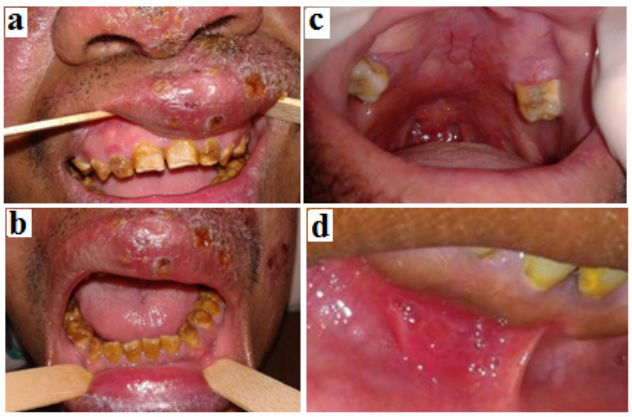

Figure 1. Oral examination evincing poor oral health status and amelogenesis imperfecta reported at Case-1 (**a** and **b**); Infiltrative lesion on hard, soft palate and uvula reported at Case-2 (**c**); Ulcerated lesions in the lower lip frenulum, reported at Case-3 (**d**).

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/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 hepatoxicity. 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, HIV – negative, with no other concomitant infections, 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 brasiliensis*. 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 discharge one month later with complete remission of lesions.

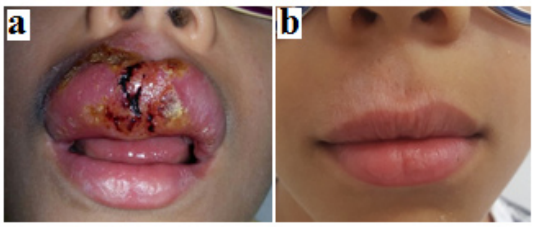

Figure 2. Hyperemic and pruritic lesion on the upper lip, reported at Case-4 (**a**); Aspect of the upper lip one month later, evidenced remission of lesion (**b**).

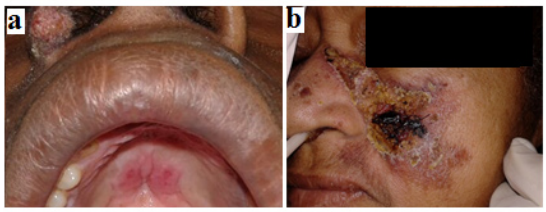

Figure 3. Ulcerated oral lesions in hard palate reported at Case-5 (**a**). Leishmaniasis lesion in the left malar region reported at Case-6 (**b**).

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 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-crusty 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. The PCR analysis was perfomed in a laboratory outside the hospital. 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-bluish 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 was referred to an oncology center. The patient has not yet returned for evaluation as they are receiving antineoplastic treatment outside our hospital.

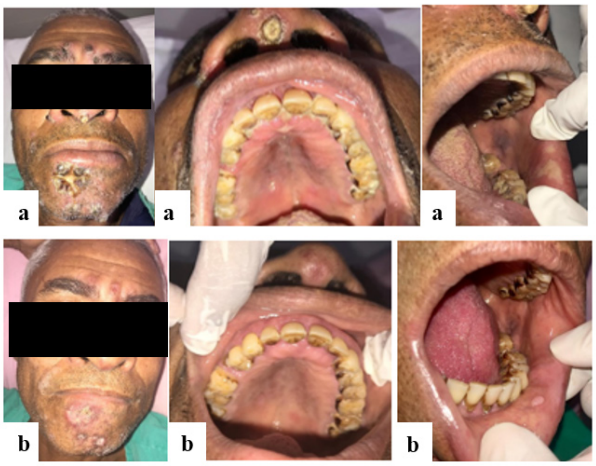

Figure 4. Ulcerated lesions in face, marginal gingiva, palate, and labial mucosa, before (**a**) and after treatment with liposomal amphotericin B (**b**) reported at Case-7.

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[1] 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[10]. 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[11,12]. In one case reported, the patient had severe psychological consequences due to facial deformity, reinforcing the importance of early diagnosis and appropriate therapy.

Unusual manifestations as DisL or purely oral Leishmaniasis should be considered in immunocompromised patients[13–16]. 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[1,15–19]. 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[20] or be transmitted by a transplanted organ[21]. Control of cutaneous leishmaniasis depends on case management, early detection and appropriate treatment[22]. 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, probably associated with immunossupression and therapeutic failure with inadequate treatment suspension or suboptimal doses.

Oral lesions of leishmaniasis are rare; however, oral mucosa may be one of the manifestations sites of the disease. In this context, the dental surgeon plays a fundamental role in the early diagnosis of oral lesions of leishmaniasis[3]. 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[1,7,23]. In our reported cases, we had two unspecific biopsy results.

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. Due to the granulomatous ulcerated aspect of leishmaniasis lesions, squamous cell carcinoma and deep fungal infections, such as paracoccidioidomycosis and histoplasmosis, are differential diagnoses. In the reported cases, negative biopsies and cultures for these mycoses, and the absence of malignant neoplasia in histological sections, followed by the cure of lesions treated with amphotericin, in patients with confirmed skin leishmaniasis lesions by Montenegro reaction or PCR, confirmed that the all described lesions were oral manifestations of leishmaniasis.

There is no specific standardization for mucocutaneous leishmaniasis therapy[17,22]. 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[9].

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 and the dental surgeon must be aware of the diverse clinical forms of leishmaniasis. Cases of orofacial mucosa leishmaniasis are rare, but we should be aware of them during oral examination. We agree that our report may contribute to a better dental evaluation and early diagnosis of cases of oral leishmaniasis.

Conclusions

The present study highlights the importance of a multidisciplinary approach in the diagnosis and treatment of orofacial leishmaniasis. Patients that travelled or live in endemic regions and presenting atypical lesions should be investigated for leishmaniasis. This could avoid delays in diagnosis and decrease the risk of the disease dissemination.

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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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 4

Reviewer Report 30 September 2020

https://doi.org/10.5256/f1000research.29234.r71901

✔ **Braulio Valencia**
Viral Immunology Systems Program (VISP), Kirby Institute, The University of New South Wales, Kensington, Australia

Nothing to comment.

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 confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 22 June 2020

https://doi.org/10.5256/f1000research.26813.r65109

? **Braulio Valencia**
Viral Immunology Systems Program (VISP), Kirby Institute, The University of New South Wales, Kensington, Australia

Observation case 6: it's up to the editors consider if this case is suitable to be incorporated or not

in the field of dentistry or oral health. In the lack of oral involvement, there is no rationale to include this case.

Observation case 7: if a confirmatory PCR was performed, authors must clearly state this PCR was based on a sampling obtained from the oral lesion. Due to this is a DisL case, PCR sample could be obtained from any of the more accessible samples.

Observation paragraph 4: the sentence "Leishmaniasis should be considered in immunocompromised patients" is unclear (it is assuming any Leishmaniasis, even localised cutaneous Leishmaniasis should be ....). "Unusual manifestations as DisL or purely oral Leishmaniasis should be considered in immunocompromised patients" is probably more accurate and supported by their findings.

Observation regarding therapy: again, references 17 and 21 are case reports. The authors must familiarise with evidence-based recommendations as the one provided in the prior review. Local treatment is exclusively recommended to localised cutaneous leishmaniasis. It's a wrong and dangerous recommendation to suggest local therapies are suitable for the treatment of mucosal leishmaniasis.

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 confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Aug 2020

Viviane Sarmento, Federal University of Bahia, Salvador, Brazil

Dear Reviewer,

We appreciate your comments and made some changes to the manuscript. In case 7, the PCR analysis was performed in a laboratory outside the hospital. Unfortunately, it was not possible to identify exactly where the sample was collected for PCR analysis. We added this information.

In relation to paragraph 4, we have changed the phrase “Leishmaniasis should be considered in immunocompromised patients” by the phrase “Unusual manifestations as DisL or purely oral leishmaniasis should be considered in immunocompromised patients”.

Regarding therapeutics, we chose to exclude the references and the paragraph from the discussion about the controversial findings in the literature regarding the local treatment of leishmaniasis.

Thank you very much.
The authors

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 11 May 2020

https://doi.org/10.5256/f1000research.25383.r62518

Elismauro Francisco Mendonça
Department of Oral Medicine (Oral Pathology), Dental School, Federal University of Goiás, Goiânia, Brazil

This paper is very interesting. It is well written and with scientific evidences. This lesion has clinical diagnosis very complex and the criteria used by the authors was well discussed in the paper.

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

Yes, the authors have showed for each case presented the investigation methods including diagnostic tests, as well as, the treatment. Although in some cases there was recurrence the lesion after protocol treatment, we believe that economic condition of the patients might contribute to unsuccessful treatment. Other point is the access to public health system in the country nor always favorable. In addition, the authors have discussed this aspect and limitations.

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

The discussion section was well presented , however would be interesting the authors to include which is the best scientific evidence for treatment in the actual moment? For example, glucantinme or anphotericin ? Or other?

Is the case presented with sufficient detail to be useful for other practitioners?

Yes, but in my opinion in the discussion section the authors should emphasize the high index of recurrence associated to treatment protocol used and comorbidities. Maybe the protocol treatment was not followed by the patient as prescribed by medical team.

Is the background of the case's history and progression described in sufficient detail?

Yes, the cases are well presented and clinical history can be easily followed by the reader.

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

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

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the conclusion balanced and justified on the basis of the findings?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 21 April 2020

https://doi.org/10.5256/f1000research.25383.r62403

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Braulio Valencia
Viral Immunology Systems Program (VISP), Kirby Institute, The University of New South Wales, Kensington, Australia

The following observations have not been addressed:

1. Case 6: This is purely a DisL case. Due to the lack of oral involvement, this case is eminently of the dermatology or infectious diseases fields.

2. Case 7: as in case 6, no substantial evidence was provided to assume oral involvement. Authors described "we accessed the PCR laboratory test", but it's not clear where was this sample obtained. Partial improvement of the oral lesion after AMB is not conclusive to assume the parasitic etiology.

3. Paragraph 4: there is no reasonable evidence suggesting MCL is generally associated with VL or immunosuppression. All references supporting this statement (11-19) are case reports informing unusual clinical presentations. It's highly recommended to authors review https://doi.org/10.1016/B978-0-323-55512-8.00104-6 for a better understanding of the pathobiology and risk factors of MCL.

4. Paragraph 8 and 9: authors must review the therapeutic section of https://doi.org/10.1016/B978-0-323-55512-8.00104-6 to understand how differently pure mucosal lesions and cutaneous lesions are treated. In the context of oral leishmaniasis, the suggestion of topical therapy for mucosal lesions is unacceptable.

These are significant imprecisions which, if not addressed, are going to generate a deficient review.

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

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

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the conclusion balanced and justified on the basis of the findings?
Yes

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 confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 May 2020

Viviane Sarmento, Federal University of Bahia, Salvador, Brazil

Dear reviewer,

Thank you for your considerations about the paper entitled "Orofacial manifestations of mucocutaneous leishmaniasis: a case series from Brazil". Each point will be discussed below:

Case 6: This is purely a DisL case. Due to the lack of oral involvement, this case is eminently of the dermatology or infectious diseases fields.

We appreciate your considerations. However, we would like to highlight that we have proposed to report, not only cases with oral involvement, but also mucocutaneous leishmaniasis on the face, because the dentist also evaluates this area. Therefore, case 6 fits the pre-established criteria.

2. Case 7: as in case 6, no substantial evidence was provided to assume oral involvement. Authors described "we accessed the PCR laboratory test", but it's not clear where was this sample obtained. Partial improvement of the oral lesion after AMB is not conclusive to assume the parasitic etiology.

Thank you for your comments. Case 7 was first diagnosed with mucocutaneous leishmaniasis by the Monte Negro test, performed in the patient's city of origin. The patient was referred to the hospital for treatment. However, the treatment with amphotericin was only initiated after PCR confirmation.

3. Paragraph 4: there is no reasonable evidence suggesting MCL is generally associated with VL or immunosuppression. All references supporting this statement (11-19) are case reports informing unusual clinical presentations. It's highly recommended to authors review https://doi.org/10.1016/B978-0-323-55512-8.00104-6 for a better understanding of the pathobiology and risk factors of MCL.

There are reports of cases of leishmaniasis with the involvement of the oral mucosa in patients with immunosuppression (HIV, transplant patients), but this does not associate the disease with such risk factors. We decided to change in the text to the following sentence: Leishmaniasis should be considered in immunocompromised patients.

4. Paragraph 8 and 9: authors must review the therapeutic section of https://doi.org/10.1016/B978-0-323-55512-8.00104-6 to understand how differently pure mucosal lesions and cutaneous lesions are treated. In the context of oral leishmaniasis, the suggestion of topical therapy for mucosal lesions is unacceptable.

Thanks for your comments. However, according to the cited reference concerning local therapy, the "experience with local therapy for New World CL is limited, as local therapy was long considered unsuitable, especially in those patients infected with L. (V.) Braziliensis or L. (V.) panamensis because of the potential risk of ML and the expectation that systemic treatment could prevent metastasis and mucosal involvement. However, systemic treatment does not guarantee the prevention of later ML. World CL."

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 04 November 2019

https://doi.org/10.5256/f1000research.20884.r55589

Braulio Valencia
Viral Immunology Systems Program (VISP), Kirby Institute, The University of New South Wales, Kensington, Australia

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 Leishmaniasis[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[4] 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

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2. El-Hassan A, Zijlstra E: 2. Mucosal leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2001; **95**: S19-S26 Publisher Full Text
3. Aronson N, Herwaldt BL, Libman M, Pearson R, et al.: Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH).*Am J Trop Med Hyg*. 2017; **96** (1): 24-45 PubMed Abstract | Publisher Full Text
4. Magill A: Leishmaniasis. 2013. 739-760 Publisher Full Text

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.