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Title of the article

Mucocutaneous leishmaniasis must be included in the differential diagnosis of midline destructive disease: Two case reports.

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Abstract

Midline destructive lesions have multiple possible etiologies, which can be grouped into neoplastic, infectious or vasculitis-associated. The purpose of these case reports and literature review was to highlight the need to include mucocutaneous leishmaniasis in the diagnosis of midfacial lesions in any patient who has lived in *Leishmania* endemic areas because this entity meets all of the clinical criteria to be considered a form of midline destructive lesions. We present two cases of mucocutaneous leishmaniasis that occurred in a Bolivian native male immigrant and a European male traveler to Panama in which lesions were misdiagnosed as different midline destructive lesions with different causes (Wegener, vasculitis, and NK/T cell lymphoma). The conclusion of our work is that all patients with midline destructive lesions should undergo histological and molecular studies to evaluate for mucosal leishmaniasis, particularly patients whose clinical history suggests this possibility. In cases of uvular involvement, biopsy of this region might be a possible alternative to nasal biopsy.

Key Words: mucocutaneous leishmaniasis; midline destructive lesions.
Introduction

Midline destructive lesions (MDLs) have multiple possible etiologies and pose a diagnostic dilemma. Historically, MDLs have been known as “lethal midline granulomas” due to their high mortality. Another term that has been employed is “idiopathic midline granuloma”, which expresses ignorance about the lesions’ origin. Although this term is obsolete, many cases of MLDs remain idiopathic \(^1\). Other obsolete terms for MDLs include “polymorphic reticulosis” and “Stewart’s granuloma”.

MDLs commonly lead to ulcerative necrosis of the nasal mucosa in the cartilaginous septum area, which becomes perforated. Typically, the necrosis extends and progresses to the rest of the nasal cavity and sinus causing functional disturbances. Destruction by infiltration can progress to cause aesthetic alterations, particularly when the external nose and upper lip are affected and destroyed. The oral cavity and pharynx might also be affected depending on the etiology.

The three most common causes of MDLs are nasal extranodal NK/T lymphoma (NKTL), Wegener's granulomatosis and cocaine-induced midline destructive lesion (CIMDL). Other causes of MDLs are less common, but in general, the etiologies of MDLs can be grouped into neoplastic, autoimmune, infectious and unknown causes \(^{1,2,3}\). More generally, Barnes (2009) \(^4\) grouped the causes of MDLs into neoplastic, infectious or vasculitis-associated.

The differential diagnosis of MDLs is difficult because of the similarities of the presenting symptoms and common clinical features. Despite diagnostic improvements, the etiology occasionally remains unidentified \(^1\). However, prompt establishment of diagnosis is imperative for initiating the proper therapy. Unfortunately, misdiagnoses are not infrequent, and unnecessary harmful therapies are occasionally employed \(^{1,5,6}\).
Leishmaniasis comprises a cluster of diseases caused by a protozoan parasite that belongs to the genus *Leishmania*. In humans, there are three basic clinical forms of leishmaniasis: visceral, cutaneous, and mucocutaneous. Leishmaniasis is endemic in more than 80 countries in the New World (i.e., the Americas) and the Old World (i.e., Europe, Africa and Asia).

Mucocutaneous leishmaniasis is the result of the propagation of certain species of *Leishmania* parasites from the skin (cutaneous lesions) to the nasal mucosa, midfacial region and neighboring areas, such as the oral cavity, pharynx and upper respiratory tract, due to lymphatic or hematogenous dissemination. The mucosal and cutaneous forms of leishmaniasis are infrequently coeval. Indeed, mucosal leishmaniasis generally becomes clinically obvious years or decades after the cutaneous infection. This metastatic spread (skin to mucosa) is rare and is subject to parasitic factors, to the immunity of the host and perhaps even to geographical factors. Leishmania is transmitted by the bite of one of the 90 types of female phlebotomine sandflies that have been proven to be vectors of *Leishmania*. During blood meals, the sandflies inject promastigotes that are phagocytized by macrophages and transform into amastigotes, which multiply in infected cells. After metastatic dissemination, mucosal leishmaniasis results from infection of the macrophages in the nasal and oro-pharyngeal mucosa. Although the mucosal involvement of leishmaniasis is relatively uncommon, some studies have reported a 72.7% rate of mucosal compromise. Mucocutaneous leishmaniasis is more frequent in the New World than in the Old World. In Latin America, mucocutaneous leishmaniasis is known as Espundia and is caused by several *Viannia Leishmania* subgenera (i.e., *braziliensis*, *panamensis* and less frequently *amazonensis* and *guyanensis*). In the Old World, mucocutaneous leishmaniasis is rarely observed, is caused by *L. infantum*, *L. major* and *L. tropica* and affects elderly people and immunosuppressed patients.
The purpose of these case reports and literature review was to highlight the need to include mucocutaneous leishmaniasis in the diagnosis of MDL complexes in any patient who has lived in Leishmania endemic areas because this entity meets all of the clinical criteria to be considered a form of MDL.

Cases

Case 1: A 33-year-old male native Bolivian native immigrant who complained of nasal stuffiness, crusting and episodic epistaxis was admitted to the University Hospital of Valencia (Spain) in 2009. A diagnosis of vasculitis was made. We lack information about the clinical studies that led to this diagnosis. The patient was treated with oral prednisone over months and exhibited no evident improvement.

In July 2012, the patient moved to Bilbao (Spain) and was attended by the ENT Service of the University Basurto Hospital with the same symptoms and signs described above. The patient denied having a cocaine habit. Local examination revealed adherent nasal crusting and a large perforation of the nasal septum. The nasopharynx, palate, oropharynx and uvula exhibited diffuse inflammation. A complete blood cell count, biochemistry, respiratory viral and bacterial serology (including HIV), pANCA and cANCA and urinalysis were normal, with the exception of neutrophilia (82%), lymphopenia (12%) and elevated CRP (3.95 mg/dl). Computed tomographies of the face, neck, chest and abdomen were performed and were normal, with the exception of radiological images of a midline destructive lesion. Biopsies from the nasal cavities, nasopharynx and posterior wall of the oropharynx revealed inflammatory non-necrotizing granulomas with giant cells and vasculitis. Under the presumption of Wegener’s granulomatosis, the patient began treatment with cyclophosphamide, methotrexate and prednisone but experienced a worsening of symptoms and enlargements of the facial midline lesions; thus, another
biopsy from the nasopharynx was taken. Histological study of this specimen revealed extranodal T-cell lymphoma (NKTL), and chemotherapy consisting of CHOP cycles was applied. Despite this treatment, the patient’s condition worsened; the destruction spread over the nasal cavities, nasal ala, upper lip, nasopharynx and oropharynx. In the oral cavity, the soft palate and uvula suffered marked hypertrophy because the lesions were proliferative rather than destructive (Figure 1). Chemotherapy was discontinued, and the patient was re-evaluated. Under general anesthesia, new biopsies of the nasal cavities and the entire uvula were taken. Histologic studies confirmed mucosal leishmaniasis in the uvula but not in the nasal sample (Giemsa, PAS, and hematoxylin and eosin staining; Figure 2 A, B).

Under the diagnosis of mucocutaneous leishmaniasis, the patient was treated with intravenous liposomal amphotericin B over one month and exhibited a nearly complete remission of the mucosal lesions and significant improvement in his symptoms. Unfortunately, three months later, the patient suffered a leishmaniasis relapse that was manifested as new nasal and oral lesions. A pentavalent antimonial (Glucantime) was administered for one month with excellent results, and the patient was asymptomatic six months after the end of this treatment.

Case 2: A German 73-year-old male underwent functional endoscopic surgery on the right nasal cavity to treat presumed polyposis (in a private practice). During the postoperative period, the patient suffered nasal inflammation. Based on histopathological studies of surgical biopsies, he was diagnosed with and treated for a sinonasal aspergillosis infection with oral voriconazole, but the patient’s condition markedly worsened. Due to progressive deterioration of the right nasal cavity and the extension of the lesion to the nostril and upper lip, the patient was referred to the ENT Service of Miguel Servet (Zaragoza) Hospital for further evaluation. On admission, the patient
complained of a right nasal obstruction and pharyngeal and oral discomfort. On examination, an ulcer seated in the right nostril affecting the ala and columella was found to extend to the upper lip and philtrum. The skin close to the ulcer was congestive (Figure 3). Necrotic inflammation that included the septum was observed on nasal endoscopy. Sinonasal CT revealed the absence of the middle turbinates and bone defects on the floors of both nasal cavities (Figure 4). A 3-mm oronasal fistula with necrotic rims was present on the right side of the posterior hard palate. The soft palate and uvula exhibited proliferative hypertrophy and pale necrotic surfaces. To a lesser extent, the tonsils and their pillars exhibited similar appearances (Figure 5). The patient denied having a cocaine habit. The results of a complete blood cell count, erythrocyte sedimentation, a biochemistry panel, p-ANCA, c-ANCA, viral serology (including HIV) and urinalysis were normal. The CPR was 1.59 mg/dl. Microbiological studies of nasal endoscopic smears revealed positivity for only *Staphylococcus aureus*. Chest radiography and abdominal echography were normal. Two nasal biopsies were taken, but the results were inconclusive due to tissue necrosis and non-specific granulomatous inflammation; thus, an uvulectomy was performed under local anesthesia for an extensive histopathological analysis. The specimen was stained with Giemsa and hematoxylin and eosin, which revealed the presence of multiple histiocytes with intracellular inclusions consistent with *Leishmania amastigotes* (Figure 2 C, D).

Once the diagnosis was made, the patient was interviewed and recounted that he had been in Panama 24 months prior to the beginning of his nasal problems; however, he did not remember having any significant skin injuries related to mosquito bites. The patient responded to 30 days of intravenous liposomal amphotericin B treatment and exhibited marked improvement in the facial, nasal, oral and pharyngeal lesions. The oronasal
fistula closed spontaneously. The primary consequence was an unsightly scar on the right nostril and upper lip.

**Discussion**

The clinical presentation and evolution of mucocutaneous leishmaniasis is similar to that of midline destructive lesions (MDLs), particularly in the early and middle periods. Typically, nasal rhinorrhea and bleeding are the initial symptoms. Adherent bloody crusting covers the necrotic area and causes nasal obstruction. Thereafter, the cartilaginous septum is destroyed. Subsequently, leishmaniasis progresses through the nasal cavity and later to the oral cavity and pharynx. Mucosal leishmaniasis can appear anywhere in the oral cavity, although it most commonly occurs on the palate and can present clinically as an exophytic, nodular or ulcerated lesion that simulates a malignant neoplastic process \(^7\)\(^-\)\(^10\). The tissue of the upper lip and nostrils suffers thickening, followed by ulceration and finally destruction. The most evolved forms reach the entire upper aero-digestive territory, with the exceptions of the tongue and the midline facial, which can cause severe mutilation \(^7\)\(^,\)\(^10\). Mucocutaneous leishmaniasis does not spontaneously resolve, and without treatment, it can be fatal, typically due to infectious complications \(^7\).

The characteristics of the human host and the features of the parasite species responsible for the infection affect the clinical manifestations of the disease. The clinical manifestations range from asymptomatic exposure and self-healing skin ulcers to life-threatening, severe destruction of the nasal and oro-facial structures (i.e., mucocutaneous leishmaniasis) \(^11\)\(^-\)\(^13\).

Based on retrospective multicenter analysis, Davide et al. (2014) \(^14\) found that primary oral leishmaniasis primarily affects the tongue (57%) and that the most typical clinical
presentation is an exophytic lesion (69%). This study also provided a review of the literature that revealed that, in immunocompetent patients, the oral mucosa is the second most frequently affected site after the larynx in head-neck primary mucosal leishmaniasis. In the two male patients described in our report, the lesions affected the hard and soft palates and exhibited clinical presentations of mucosal ulcerations (1 of the 2 cases) and proliferative exophytic lesions (both cases), but the tongues were intact. However, our two reported cases of mucocutaneous leishmaniasis cannot be considered to be mucosal leishmaniasis with primary oral involvement because they were preceded by severe destruction of the naso-facial structures, which is the main difference between mucosal and mucocutaneous leishmaniasis.

Leishmaniasis is one of the world's most unattended diseases and chiefly affects poor populations; 350 million people, primarily in developing countries, are at risk for leishmaniasis, and 2 million new cases appear annually. The term "mucocutaneous leishmaniasis" is correctly applied to the New World tegumentary illness because most of these cases of mucocutaneous leishmaniasis occur in Latin America (i.e., Bolivia, Brazil and Peru). However, the global incidence of tegumentary leishmaniasis (including cutaneous and mucocutaneous leishmaniasis) is greater than 1.5 million new cases per year across 82 countries, and 90% of those cases are reported in Brazil, Peru, Afghanistan, Iran, Saudi Arabia and Syria. Travel and emigration result in the acquisition of leishmaniasis in places where it is endemic and result in clinical manifestations that occur later in other countries where the illness is poorly known. The largest European study of imported tegumentary leishmaniasis collected 223 cases over an 11-year period (1998-2009); 133 patients were diagnosed with New World tegumentary leishmaniasis, and 9% of these patients had mucocutaneous leishmaniasis. Only 32 patients were tested for human immunodeficiency virus infection, all of the results of which were negative. This
finding differs from the findings obtained for visceral leishmaniasis, for which HIV infection is an established risk factor 16. There is general agreement that the incidence of tegumentary leishmaniasis that is imported from endemic countries is gradually increasing across all of Europe 16,17. The numbers of observed cases have doubled in the Netherlands and tripled in the UK in the last decade 12.

Clinical diagnosis can be suspected if cutaneous leishmaniasis is observed or suspected at the time of mucosal presentation of the illness, but this circumstance is rarely observed. Skin and serology tests (e.g., IFAT and ELISA) are useful in cases of visceral leishmaniasis but are not reliable for mucosal disease, although a positive serology or a positive leishmanin skin test increases clinical suspicion 7,18,19. Leishmaniasis is confirmed by the identification of the parasites (in histological samples) or identification of the parasite DNA (by PCR techniques) in human tissues 19.

MDLs present a dilemma because the etiological diagnosis thereof is frequently imprecise. Anamnese, various clinical features and diagnostic studies (e.g., ANCA's serology, urinalysis and radiology) can be performed but only for diagnosis. One indicator of the value of these diagnostic tests is the fact that, in some cases of Wegener’s granulomatosis, more than 30% of the affected patients are ANCA-negative 20. In contrast, ANCA positivity can be present in cocaine-induced midline lesions 3,5. For these reasons, these studies are complementary to histological and immunohistochemical studies that constitute the primary diagnostic methods for MDLs. In contrast, mononuclear inflammatory infiltrates, necrotizing inflammation, granulomatous inflammation and vasculitic involvement can be observed in Wegener's granulomatosis, CIMDL and other MDLs such as mucosal leishmaniasis. Extensive nasal necrosis in biopsy samples further increases the difficulty of the histological diagnosis of lesions, and the final diagnosis requires multiples biopsies 6. Histological differentiation between
these diseases can be easy, difficult, or impossible depending on the stage of the illness, the quality of the clinical information delivered to the pathologist, the size of the biopsy and the number of sections inspected.  

The histopathology of mucosal leishmaniasis exhibits non-specific submucosal chronic inflammatory processes that might or might not be associated with non-necrotizing granulomatous reactions, and a small number of parasites are typically present, which makes diagnosis difficult even when Giemsa staining is employed. One histopathological study reported non-specific findings, such as the presence of lymphocytes, plasma cells, histiocytes and multinucleated giant cells. Other possible histopathological findings include vasculitis with or without fibrinoid necrosis and fibrin thrombi. In contrast, mononuclear inflammatory infiltrates, granulomatous inflammation and vasculitis can also be observed in Wegener's granulomatosis, CIMDL, NKTL, deep mycosis (due to Paracoccidioidomycosis or histoplasmosis) and other MDLs etiologies, which makes differential diagnosis problematic. Thus, a comprehensive search of amastigotes must be performed in histological preparations that are stained with H&E and Giemsa. Additionally, a full immunohistochemical battery should be performed to rule out lymphoma. In the two case reports presented, the sensitivity of the histopathological findings obtained from the uvular biopsy was higher than that of the findings obtained from the nasal biopsy. Amastigotes are scarce in mucosal lesions, but in our two presented cases, particularly case 2, the parasites were abundant in the uvular biopsies. Regarding mucocutaneous leishmaniasis, we have only two cases and thus cannot state with any confidence that the histological study of uvular biopsies is superior to that of nasal biopsies in terms of diagnostic efficacy, but our findings are not negligible; thus, this hypothesis should be tested in future studies.
A more sensitive method for proving the presence of mucosal leishmaniasis in tissue specimens is the demonstration of Leishmania DNA by molecular methods, such as PCR techniques \(^1,12\), but these studies are rarely included in the differential diagnosis of MDLs unless there is an epidemiological reason to suspect leishmaniasis is present.

Our report includes studies of two patients with mucosal leishmaniasis whose clinical presentations were consistent with MDLs. Indeed, our two patients met the American College of Rheumatology diagnostic criteria \(^24\) for Wegener’s granulomatosis because they presented with nasal and oral inflammation and histologic granulomas. Both patients were incorrectly diagnosed and treated for Wegener's granulomatosis and NKTL. Therapeutic failure and the progression of the mucosal leishmaniasis were necessary to cause the reconsideration of the diagnoses, the detection of mucosa leishmaniasis, and the application of successful treatments.

Mucocutaneous leishmaniasis causing midfacial destruction and involvement of the oral cavity exhibits clinical behaviors that are identical to those of other causes of MDLs (e.g., Wegener’s granulomatosis, cocaine-induced midline destructive lesions, NKTL and others). In developed countries where mucocutaneous leishmaniasis is rare and unfamiliar to occidental physicians, this disease is highly likely to be considered an MDL that is not related to zoonosis. The main contribution of our work is as follows: mucocutaneous leishmaniasis is one of the possible causes of MDLs. Our experiences with the presented cases and our mistakes support this assertion. Therefore, for any patient with a suspicion of MDL, it seems reasonable to determine whether there are reasons to suspect leishmaniasis, and when such suspicions are present, practitioners should proceed to specific studies for the diagnosis of mucocutaneous leishmaniasis (i.e., the demonstration of parasite DNA by PCR techniques).
Various medications can be used to treat mucocutaneous leishmaniasis, including pentavalent antimonials (30-100% cure rate), intravenous amphotericin B deoxycholate (80-90% cure rate), and miltefosine (58-83% cure rate)\(^7\).

In conclusion, for any patient with a suspected MDL, it seems reasonable to investigate whether an epidemiological reason to suspect leishmaniasis is present, and if so, the practitioner should proceed to specific studies for the diagnosis of mucocutaneous leishmaniasis (e.g., the demonstration of parasite DNA by PCR techniques).

**Bibliography**


**Figure Legends**

Figure 1. Patient 1. Surgical exposure of the uvula. White gauze was placed behind the uvula to clarify the appearance of the mucosal surface. The uvula had a proliferative hypertrophic appearance. A self-retaining mouth gag holding the endotracheal tube is shown in the foreground.

Figure 2. Histopathological findings from the uvular biopsies. A. (Patient 1) Chronic inflammatory process in the submucosa highlighting the presence of abundant histiocytes (H&E 10 x). B. (Patient 1) Presence of amastigotes in the cytoplasm of some histiocytes (H&E 40 X). C. (Patient 2) Basophilic histiocytic proliferation in the corium and submucosa (H&E 20 x). D. (Patient 2) An abundance of amastigotes can be observed in the cytoplasm of most of the histiocytes (Giemsa 40 x).

Figure 3. Patient 2. A necrotic ulcer affecting the right nostril, upper lip and philtrum. The skin adjacent to the ulcer exhibited inflammatory reddening.

Figure 4. Patient 1. Coronal CT scan showing the partial absence of the middle turbinates and partial occupations of the maxillary sinus (*) and the anterior ethmoid sinus (x). On
the floors of both nasal cavities, areas of bone lysis (arrows) can be observed and are more evident on the right side, which exhibited a punctate oronasal fistula on clinical inspection. Note the ulcerative process in the septum (arrowhead).

Figure 5. Patient 2. Clinical photograph showing the oral cavity and pharynx. The uvula is hypertrophied. The uvula and the adjacent soft palate exhibit whitish necrotizing surfaces that are interrupted by areas of congestive proliferation.