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Oral leishmaniasis: A scoping review

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Abstract
Introduction: Leishmaniasis is a sandfly-borne infection caused by the Leishmania parasite, produces localized and diffuse cutaneous manifestations, it can also manifest intra- and extraoral.
Objective: To analyze the literature on Leishmaniasis, particularly its diagnosis, epidemiology, treatment and manifestations.
Methodology: Articles on the subject published in PubMed and Google Scholar databases were analyzed, with emphasis on the last 5 years. The search was performed using Boolean logical operators "AND, OR and NOT." It was conducted using the words, "Leishmaniasis", "diagnosis", "epidemiology", "treatment", "systemic manifestations", "oral manifestations".
Results: The gold standard test for diagnosing Leishmaniasis is Giemsa-stained tissue smear microscopy, although culture on invasive specimens, loop-mediated isothermal amplification technique, and PCR are also used. This neglected tropical disease is a significant global health concern, affecting 98 countries and territories across four continents with an estimated 1 to 2 million new cases and 70,000 deaths annually. Treatment options are limited, with pentavalent antimony as the primary drug and additional agents like miltefosine, amphotericin B, paromomycin, and pentamidine available. Cutaneous manifestations vary widely, ranging from simple nodules and skin discoloration to extensive, ulcerated, and papulonodular lesions often involving the oral mucosa.
Conclusions: Leishmaniasis is a systemic parasitic disease significantly impacting oral health. Oral manifestations include nodules, discoloration, plaques, ulcers, and papulonodular lesions, potentially affecting mastication, swallowing, and speech.

Keywords: Leishmaniasis, protozoan, Leishmania braziliensis, oral manifestations, epidemiology, diagnosis, treatment

1. Introduction
Cutaneous leishmaniasis (CL), a vector-borne infection, is caused by the protozoan parasite Leishmania, the vector of which is the female sand fly [1]. This parasite is the causative agent of the human disease complex called leishmaniasis [2].
Cutaneous leishmaniasis is described as "the great mimic" due to its ability to mimic various types of dermatoses [3]. It causes chronic skin disease with lesions that heal with scarring, leaving those affected with some disfigurement [4]. Leishmaniasis is classified into different forms, including cutaneous leishmaniasis and visceral leishmaniasis. This specific categorization provides information on the different clinical presentations of the disease [5]. Cutaneous leishmaniasis lies in its clinical complexity, diverse geographic impact, and significant public health consequences.
The comprehensive approach needed to address this disease involves both specific medical interventions and broader efforts to address social and environmental factors that contribute to its spread. Therefore, in this work, we review the literature on Leishmaniasis, a sandfly-borne infection caused by the Leishmania parasite, particularly its diagnosis, epidemiology, treatment, and manifestations.

2. Materials and Methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT, with the keywords: "Leishmaniasis", "cutaneous leishmaniasis", "diagnosis", "epidemiology", "treatment", "systemic manifestations", "oral manifestations". The keywords were used individually, as well as each of them related to each other.

3. Results and Discussion

3.1 Epidemiology

Leishmania spp. are protozoan parasites transmitted by sand flies that cause leishmaniasis in humans and animals [6]. The disease is influenced by environmental, migratory and climatic factors. Wild or peridomestic animals, primarily rodents or dogs, serve as reservoirs [7]. To date, 53 species have been identified, though some remain controversial. Among these, 20 species infect humans and cause leishmaniasis [8].

It is one of the seven most important tropical diseases in the world [9]. It is ranked among the world's seven most important tropical diseases [9] and is endemic in over ninety countries [10]. With approximately 1 to 2 million new cases and 70,000 deaths annually, it is one of the deadliest neglected tropical diseases [9]. Epidemiological data estimate roughly 0.2 to 0.4 million visceral leishmaniasis cases and 0.7 to 1.2 million cutaneous leishmaniasis cases occurring each year [11].

Dogs are considered the primary reservoir for human infection with *L. infantum*. Canine leishmaniasis is a significant zoonosis endemic in over 70 countries across southern Europe, North Africa, the Middle East, Central Asia, China, South America, the United States, and Canada [12]. It has been demonstrated that leishmaniasis epidemics can emerge at any time in conflict zones and adjacent regions with a previous history of the disease [13].

Among the 53 identified *Leishmania* species, 20 infect humans, placing leishmaniasis among the seven most critical tropical diseases in more than 90 countries. With an annual incidence of 1 to 2 million new cases and 70,000 fatalities, it is a deadly tropical disease often overlooked.

3.2 Diagnosis

Cutaneous and *Mucocutaneous leishmaniasis* represents a diagnostic challenge also in endemic regions [14]. The gold standard test for diagnosis involves demonstration of the parasite by microscopy of Giemsa-stained tissue smears, but this option is not always available, and its sensitivity varies [15].

Culture is also used on invasive specimens, such as spleen, bone marrow or lymph node aspirates, or liver biopsy. Although these tests are highly specific, their sensitivity is not perfect, with the best performance in spleen aspirates (93%-99%) followed by bone marrow aspirate/biopsy (53%-86%). Lymph node aspiration has acceptable sensitivity (53%-65%) [16].

The impression and spread method is used, which is fast, inexpensive and relatively sensitive, in this method, the biopsy specimen is placed between two glass slides and pressure is applied in the center, which spreads the cells and tissue on both surfaces of the slides. The spreads are then dried, fixed in methanol, stained with Giemsa, and examined microscopically using a 100× oil immersion lens [17].

The loop-mediated isothermal amplification technique (LAMP) demonstrates high sensitivity and specificity compared to microscopy and PCR methods. A key advantage of LAMP, shared with other molecular methods, is its ability to use minimally invasive or noninvasive samples, such as blood. LAMP is now considered a suitable diagnostic test for prevalence studies, epidemiological investigations in humans and animals, as well as in diagnosis, especially for immunocompromised patients, and possibly for monitoring therapeutic success [18]. CL positivity is high in the Bajau tribal district area and is confirmed by detection of Leishmania amastigotes in blood collected from their lesions [19].

Although microscopy of Giemsa-stained tissue smears is the gold standard diagnostic method, its availability and sensitivity can vary. Invasive procedures such as culture and tissue aspiration are alternative options, but their sensitivity is imperfect. The print-and-spread method provides a rapid and inexpensive approach. The loop-mediated isothermal amplification (LAMP) technique is notable for its high sensitivity and specificity.

3.3 Treatment

Several treatments exist, although the evidence supporting the available options for cutaneous leishmaniasis is weak [20]. Treatment of these poorly understood infectious diseases is often limited to ineffective, expensive and toxic therapies, such as SbV used for leishmaniasis patients [21]. Currently, there is only one drug designed specifically for the treatment of leishmaniasis (pentavalent antimony), and it causes hepatotoxicity in patients and resistance in the parasite species over time. Other drugs, such as miltefosine, amphotericin B (AmB), paromomycin and pentamidine [22].

Miltefosine has shown resistance, is expensive and not available in many endemic countries [23]. WHO indicates that developing new treatments is a priority [24].

Immunotherapy has focused on the induction of an effective immune response to rapidly control the disease. Recent studies have indicated that a single dose of a suitable therapeutic vaccine induces a rapid and long-lasting recovery in patients and dramatically reduces drug toxicity and the emergence of resistance [25]. Its low cost, limited side effects and lack of possibility of developing resistance make it a valuable option, especially for infectious diseases with chemotherapy-related problems [26].

Current drug or vaccine therapy is not a perfect therapeutic way to eradicate leishmaniasis. More research is needed to develop an effective therapeutic vaccine [27].

There are still gaps in state-of-the-art treatments to be explored [28]. Research on leishmaniasis treatment and potentially vaccination against the disease is still ongoing [29]. Immunomodulators, nanotechnology and drug repurposing are the future of leishmaniasis treatment [30].

Pentavalent antimony, the primary drug used to treat leishmaniasis, causes hepatotoxicity and has developed resistance. Miltefosine is another option, but it also faces resistance issues and has limited geographical availability. Immunotherapy, particularly therapeutic vaccines, shows promise in mitigating toxicity and resistance. However, further research is necessary. Innovative approaches, such as immunomodulators and nanotechnology, hold the potential to revolutionize treatment.

3.4 Manifestations

They range from asymptomatic infections to lesions in cutaneous (Cutaneous leishmaniasis), mucosal (*Mucocutaneous leishmaniasis*) or visceral organ areas (Visceral leishmaniasis), depending on the species and host characteristics [31]. In addition, diagnosis can sometimes be complicated due to atypical manifestations and associations with other pathologies [32].

Cutaneous disease is the most common manifestation and is further subdivided into localized cutaneous disease and diffuse cutaneous disease. Localized skin lesions often have an incubation period of 2 to 4 weeks, at which time an asymptomatic papule, multiple papules or nodules appear at the site of inoculation. These lesions increase in size and transform into well-demarcated ulcers with a raised violaceous border and rupture of the epidermis. These lesions often heal spontaneously in 2 to 5 years (Depending on the species) with a depressed secondary scar. Diffuse cutaneous leishmaniasis also begins as a painless nodule but may progress to involve the entire skin surface. It has a predilection for the face, ears, and extensor surfaces such as the knees and elbows. Nasopharyngeal and oral mucosal invasion may be seen in up to one-third of patients. Progressive disease may result in leonine facies [33].

Cutaneous leishmaniasis primarily manifests in two forms: localized and diffuse. The localized variant is characterized by papules that develop into ulcers, typically healing spontaneously within 2-5 years. In contrast, the diffuse form progresses rapidly, affecting extensive areas such as the face and joints. This severe form can even involve the nasopharyngeal and oral mucosa.

3.4.1 Systemic manifestations

Leishmaniasis is a neglected vector-borne tropical disease that manifests as visceral leishmaniasis, CL and *Mucocutaneous leishmaniasis* [34]. In CL, a heterogeneous disease characterized by a variety of cutaneous manifestations ranging from simple nodules, skin discoloration, plaques to extensive disseminated forms, the parasites are found in the dermal layers of the skin [35].

Mucosal disease is due to hematogenous or lymphatic spread and often occurs after resolution of skin lesions. The oral and nasal mucosa are preferentially affected, although ulcerative involvement may extend to the vocal cords and tracheal cartilage, but bony structures are not involved. Mucosal disease can be severe and life-threatening [33].

The most frequent renal complications of parasitic diseases are acute kidney injury, glomerulonephritis and tubular dysfunction [36].

CL presents a diversity of skin manifestations, ranging from simple nodules to extensive disseminated forms. The mucocutaneous variant, resulting from hematogenous or lymphatic spread, primarily affects the oral and nasal mucosa and can be severe, even life-threatening. Additionally, this parasitic disease can lead to renal complications such as acute kidney injury, glomerulonephritis, and tubular dysfunction

3.4.2 Oral manifestations

Mucosal involvement by leishmaniasis is infrequent and results from hematogenous or lymphatic spread of amastigotes from the skin to the nasal, oropharyngeal, laryngeal, and/or tracheal mucosa. Additionally, very few cases with isolated mucosal lesions have been described. These lesions typically appear as erythema and ulceration or as plaques, papules, and/or exophytic nodules, commonly involving the hard or soft palate and tongue. However, they can affect any location, such as the lip, uvula, gingiva, tonsil, and retromolar region [37].

The dentist plays an important role in the diagnosis of this disease due to the involvement of the oral mucosa, particularly when it affects the buccal region, the posterior portion of the palate, and the tongue. *Leishmania braziliensis* is the most common etiological agent in leishmaniasis with mucosal involvement [38].

Cutaneous leishmaniasis caused by *L. panamensis* can spread to the nasopharyngeal mucosa and present with various skin lesions. Several studies have reported cases with mucosal involvement and specific lesion characteristics [39]. Scaly plaques, crusts, and scars have been observed on the facial skin and lips, with a solitary nodule reported at the junction of the hard and soft palate [40].

It has been reported that the nasopharyngeal and oral mucosa are invaded in up to one third of patients [33]. In one reported case, a patient presented with a single chronic nodular skin lesion on the left cheek for approximately 1 year. Histopathologic analysis of this lesion revealed nodular infiltrates of lymphocytes and histiocytes containing intracellular oval amastigotes, consistent with cutaneous leishmaniasis [41].

Analysis of the literature revealed that, in immunocompetent patients, the oral mucosa is the second most frequently affected site in the head and neck region, with the tongue being the most commonly involved area within the oral cavity [42].

Oral manifestations of mucosal leishmaniasis typically present as erythema, ulceration, plaques, papules, or exophytic nodules, often affecting the palate, tongue, lips, and posterior buccal mucosa. In severe cases, the disease can extend to the nasopharyngeal, oropharyngeal, laryngeal, and/or tracheal mucosa.

4. Conclusions

Leishmaniasis, a neglected tropical disease, affects more than 90 countries and is one of the 7 most deadly diseases, with 1 to 2 million new cases annually. Diagnosis uses tests such as Giemsa microscopy and advanced methods such as isothermal amplification (LAMP). Treatment has limitations with drugs such as pentavalent antimony and miltefosine. Leishmaniasis has diverse manifestations, from localized to diffuse, also affecting the oral and nasopharyngeal mucosa.

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