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Review Article

Cutaneous leishmaniasis: an underdiagnosed entity in the first contact

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ABSTRACT

Leishmaniasis is a chronic, vector-borne parasitic disease caused by a flagellated protozoan of the genus *Leishmania*, which has more than 20 species. Usually, it is a disease that affects the tropical and subtropical populations of the world. The disease is transmitted through the bite of female mosquitoes of the genus *Lutzomyiaen* and *Phlebotomusen*. The clinical presentation and its manifestations are variable, they are affected by the species and immunological state of the host. Generally, three main types are distinguished: the most frequent presentation and with the best prognosis is cutaneous leishmaniasis (CL), the second is known as mucocutaneous leishmaniasis (MCL), and the third presentation is visceral leishmaniasis, which puts endanger the life of the person presenting it. Leishmaniasis is related to various risk factors, including: poverty, malnutrition, migration, and inadequate housing conditions; in addition, people who work in rural areas, such as farmers, farmers, or the military in endemic areas, are at greater risk of suffering a bite by a transmitting mosquito. Due to its variable manifestations and greater affectation in poor areas, it is a pathology that is normally overlooked. The objective of this review is to define and differentiate the most frequent types of presentation as well as their cutaneous manifestations, and to provide extensive information on diagnostic methods. Briefly, general information on the pathology and treatment of these lesions will be provided.

Keywords: Skin, Dermatology, Infection, Leishmaniasis

INTRODUCTION

Leishmaniasis infections can be seen in nearly 90 countries, and on every continent in the world except Australia and Antarctica. The world health organization estimates that the annual incidence of leishmaniasis is around 600,000 to 1 million cases, of which between 50,000 and 90,000 belong to the visceral presentation.[1]

Most CL diagnoses occur in South America, the Mediterranean basin, the Middle East, and Central Asia. Most VL cases occur in Brazil, East Africa, and India, while CML occurs mainly in Brazil, Bolivia, Ethiopia, and Peru. The most affected population are children and young adults under 20 years of age.[2]

ETIOLOGY

Leishmaniasis is a parasitic, vector-borne disease. Its main route of transmission is zoonotic, but cases of human-to-human transmission have also been reported through contaminated needles, transfusion, or congenital infection. It is caused by a flagellate protozoan of the genus *Leishmania*, which has more than 20 species.[3]

The parasite enters the vector female sandfly mosquito through blood feeding from an infected reservoir mammal, in this blood are macrophages with amastigotes. Within the mosquito intestine, the amastigote differentiates into its flagellated form called the promastigote, which replicates and adheres to the epithelium. Subsequently, when the mosquito feeds on another mammal, the parasite is injected into the bloodstream, where in its promastigote form it will infect new macrophages and transform back into an amastigote.[4]

CLINICAL MANIFESTATIONS

Leishmaniasis causes a spectrum of manifestations. There are three main forms of clinical presentation, which are:[5] CL, which has three presentations: localized, diffuse, post-kala-azar, MCL and visceral leishmaniasis, also called kala-azar.

The range of clinical manifestations can be attributed to the variability in the virulence of the parasite and the host's immune response.[5]

Cutaneous leishmaniasis

Localized CL

Cutaneous leishmaniasis should be considered as a differential diagnosis in patients with a history of living in endemic areas or a history of travel to an endemic region, one to six months before the lesion appears. The incubation period is days, weeks, or even months. A papule forms at the parasite inoculation site, which typically progresses to a plaque or nodule with a tendency to ulcerate.[6]

It frequently appears in exposed sites, such as the face or extremities, where the vector has the greatest opportunity to access.

The primary lesion is usually a single one, but if there are multiple mosquito bites, multiple lesions may occur. Later, these indurated nodules usually ulcerate from their center, and a brown crust (firmly attached to the base) will cover the ulcer and the area of infection. The most distinctive clinical feature of CL is the appearance of firm, sloping margins with a prominent central crater in the ulcer, called a volcanic ulcer, which may include sporotrichoid, verrucous, zosteriform, psoriasiform, eczematous, and erysipeloid features.[7]

These features may help differentiate CL from other causes of chronic ulceration. Over the next 3 to 18 months, the lesion may eventually heal, depending on the specific species. It is estimated that up to 10% of cases of CL progress, become chronic, and exhibit more severe clinical features. An example is the chiclero ulcer, an ulcerated lesion that appears on the auricle of gum collectors from the chicle tree in Mexico and Central America. CL is not life-threatening, but it can lead to substantial cosmetic morbidity, social stigma, and psychological effects.[8]

Diffuse CL

It is a rare syndrome that occurs mainly in the context of infection by *L. L. aethiopica*, *L. L. mexicana* and *L. L. amazonensis* although it has been described in other new world species, especially in the context of acquired immunodeficiency syndrome (AIDS).[9]

Generally, they have a defect in the cell-mediated immune response, and are anergic to the leishmania antigen, where low IFN-γ and TNF-α levels are present, which contribute to the understanding of their immunopathology and their treatment. It starts as a lesion localized that does not ulcerate, with spread of amastigotes to macrophages from other areas of the skin. Soft nodules or plaques form on the face and extensor limb surfaces but may affect the entire body. The lesions contain numerous parasites and can severely affect the face, giving it a leonine appearance, analogous to lepromatous leprosy.[10]

Post-kala-azar CL

This type of skin involvement is a sequel to visceral leishmaniasis caused by *L. donovani* and occasionally by *L. infantum*, especially in immunosuppressed patients. It usually occurs within six months to one or more years after treatment but can occur up to 20 years later.[11]

However, in HIV-infected patients, skin lesions may coincide with and even precede visceral leishmaniasis. A well-known finding that led to the name kala-azar (which means black fever in Hindi), is skin hyperpigmentation, which is believed to be the result of hormonal disturbances.[11]

This sign has been described in 9.88% of patients with visceral leishmaniasis and has recently been associated with increased production of adrenocorticotropic hormone. In addition, it may present skin-colored nodules or verrucous papules, which predominantly affect the face and may extend to the rest of the body. In immunosuppressed patients, it is more frequent and severe; the form of presentation may be atypical, with nodular lesions that are not always they affect the face, and greater abundance of the parasite in the lesions. Preservation of sensation in the lesional skin helps distinguish it from leprosy.[12]

MUCOCUTANEOUS LEISHMANIASIS

Most cases are caused by *L. braziliensis*, although it can also be caused by *L. amazonensis*, *L. guyanensis*, and *L. panamensis*. Mucosal involvement may coexist with skin involvement or appear after its resolution, even years later. The route of dissemination can be hematic or lymphatic. The most frequently affected mucous membranes are the nasal and oral, although the lesions can extend to the oropharynx and larynx, with possible involvement of the cartilage and vocal cords. MCL is a potentially fatal and highly disfiguring condition due to destruction of oro-nasopharyngeal mucosa and cartilage, occasionally affecting the larynx and leading to aspiration pneumonia.[13]

DIAGNOSIS

The diagnosis can be presumptive or definitive. The clinical characteristics of the disease are key to the presumptive diagnosis. The first and most critical step in diagnosis is for physicians to consider CL when faced with a painless, ulcerative lesion with a thick granulomatous background, with indurated, violaceous edges, and with a duration of more than four weeks, which should raise clinical suspicion. In addition, that relevant epidemiological data that allow suspicion in people from the community, the place of origin of the patient or trips to endemic areas be taken into account, which must always be confirmed by means of parasitological and immunological tests.[14]

Dermoscopy can help the presumptive diagnosis, since it will help the clinician, where he can observe: erythema (100%); vascular structures, including polymorphic vessels (40.2%), hairpin vessels (39.4%) and arboriform vessels (38.6%); scab (70.1%), and erosion or ulceration (44.1%). Less frequent, but more characteristic, are the yellowish-white teardrop structures (42.5%) and the burst pattern of white stars. Direct smear: it is the most widely used laboratory method, especially in endemic areas. It is a simple and inexpensive test that is placed with Giemsa stain and then examined with direct microscopy.[15]

Its main objective is to achieve the observation of amastigotes in a clinical sample, which establishes the diagnosis, either from a direct smear from a needle aspirate, a skin cleft smear, a biopsy or cultured material. Given the limited sensitivity of any of these tissue sampling approaches, a combination is recommended. Amastigotes can be observed microscopically inside or outside of macrophages. They are round or oval structures, 2-4 µm in diameter, with a characteristic nucleus and kinetoplast; the cytoplasm stains pale blue with Giemsa, and the kinetoplast appears as a purple bar. Preparation of a skin lesion for sampling is simple but key. The lesion should be prepared as follows:[16]

Clean the lesion thoroughly with soap and water, rinse with water. Blot dry with gauze, removing any residual betadine, if used. If appropriate, debride a portion of the overlying exudate or eschar to clean the ulcer base. This is generally painful and local anesthesia should be considered. Limit bleeding because it can confuse the smear. If culture of parasites is planned, a sterile technique should be used. Full-thickness skin punch biopsies should not be the first diagnostic procedure for CL, both because of their more invasive nature and because they may be less efficient.

Histopathological analysis of a biopsy

It is not a routine method, unless there is doubt about the diagnosis or you want to rule out other diagnostic possibilities. For histopathology, the biopsy should be performed with a scalpel or a 4-mm punch, which includes subcutaneous cell tissue, and must be fixed in formalin. Histologically, non-specific ulceration, pseudoepitheliomatous hyperplasia and a mixed inflammatory infiltrate can be observed, and specifically, the presence of amastigotes inside the dermal macrophages, which occurs in 50-70% of biopsies.[17]

Parasitological culture

The material is obtained by aspiration or biopsy, which must be crushed before inoculation into the culture medium. Cultures should be kept at 23°C and become positive between 3-30 days, the usual being 7-15 days. The sensitivity is around 60%-70%. The disadvantages are that temperature-controlled incubation systems and inverted microscopes are required.[17]

The gold standard medium for culture is Novy-MacNeal-Nicolle with positive results in one to three weeks, or Schneider Drosophila medium, which gives positive results in one week.[17]

Serologic

Several serologic assays are available, including direct, agglutination test, ELISA, immunofluorescence, and western blot. These antibody detection techniques share a high sensitivity for acute visceral disease but are not strictly specific for the early stage of the disease. Antibodies slowly decline after cure and are also present in a number of asymptomatically infected individuals, making it impossible to differentiate between current and past infection. Likewise, it can present cross-reactivity with other antibodies, such as those of Chagas disease, therefore, the serological results must be interpreted in the context of the clinical history. Furthermore, several of these trials are not available in endemic areas.[17]

Montenegro test

The antigen is injected intradermally and the reading is done after 48-72 hours. It depends on a delayed type IV hypersensitivity and is prepared with dead Leishmania promastigotes; the rate varies by geographic area. It is

considered positive if there is a papule or an erythematous plaque greater than 5 mm and it means that the patient's T lymphocyte recognizes the parasite antigen, due to having been exposed to it, which occurs if the patient has the disease. It is negative in diffuse CL, in active visceral leishmaniasis and in post-kala-azar leishmaniasis. There is no difference between current and past infection, its main utility is epidemiological.[17]

PCR

Leishmania parasites that cause CL can now be genotyped with PCR techniques to detect leishmania DNA. PCR-based methods are considered more specific and can detect current infections. PCR offers a rapid, highly sensitive, specific diagnostic modality and provides a specific treatment for Leishmania species.[17]

TREATMENT

For the management of CL, different factors must be taken into account, such as the immune status of the host, the location, the species and the severity of the infection. CL can be classified as simple and complex, leading to conservative management or local treatment in the first, and systemic treatment in the second.[18]

Simple or uncomplicated CL

Simple or uncomplicated CL is defined as that caused by Leishmania species when there is a low risk of mucosal involvement, without obvious mucosal involvement, located in areas with no cosmetic compromise, or lesions that are already developing. healing spontaneously at the time of diagnosis. Likewise, when it is a single lesion or few lesions, or a small lesion (less than 1cm), in an immunocompetent host.[18]

Complex CL

This is the name given to all cases of CL caused by *L. braziliensis* and *L. infantum*, in immunocompromised patients, with previous local treatment failure and a recurrent or diffuse presentation. There are mucocutaneous manifestations, subcutaneous nodules and large regional adenopathies, with ≥5 lesions of > 1 cm or a single lesion of >5 cm, located in areas with cosmetic compromise and not accessible to local treatment. Locations on the face, ears, fingers or toes, skin covering the joints or genitals should be considered for systemic treatment.[18]

Topical treatment

Cryotherapy: liquid nitrogen applied for 15 to 20 seconds to the lesion 1-2 mm outside the lesion. It is recommended three times per session every three weeks until the lesion heals. It can be considered in pregnant patients or other people with contraindications to systemic therapy.[18]

Thermotherapy: local anesthesia is required. Heat at 50°C is applied for 30 seconds to the lesion 1-2 mm outside the lesion. Produces second degree burns.

Sodium stibogluconate or meglumine antimonate, 0.2-0.5 ml can be applied intradermally (5 sites/lesion at 0.1 ml/cm^2) every three to seven days (up to five sessions). Its use is recommended for three weeks or prior completion of treatment if healing has already occurred.[18]

Topical paromomycin: apply to the BID lesion for 20 days. It is appropriate for simple ulcerative lesions and effective for *L. L. major* and *L. V. panamensis*. Poor responses in *L. aethiopica* infections. Not recommended if there is lymphocutaneous involvement systemic treatment.[18]

Toral treatment

Azoles: The efficacy of this treatment is limited and failure is common (up to 50%). Ketoconazole has been used at 200 to 600 mg/day, and itraconazole at 200-400 mg/day, for 1 to 2 months.

Miltefosine: It is a phosphatidylcholine analogue. The dose is 1.5-2.5 mg/kg daily for 28 days; it is well tolerated.[18]

Parenteral treatment

Pentavalent antimonials: they are the mainstay of therapy due to their high success rate and the toxicity associated with the use of other medications. It has been the best drug for more than 50 years as first-line therapy. Sodium stibogluconate or meglumine antimonate remains the first-choice treatment for CL in most countries. Doses are described as 10-60 mg/kg, with a standard dose of 20 mg/kg administered intramuscularly over 10-20 days, or until healed.[19]

Its presentation is in 5 ml ampoules, corresponding to 405 mg of pentavalent antimony each mL, therefore, 81-85 mg/mL of pentavalent antimony. Generally, two intramuscular ampoules are indicated for 20 days. It is recommended not to administer more than three ampoules in a single application in adults. If complete healing is not achieved in a period of 12 weeks after the end of the parenterally administered treatment, the scheme should be repeated, extending to 30 days. Adverse effects include a local reaction, abdominal pain, myalgia, arthralgia, fever, chills, headache, phlebitis, anorexia, nausea and vomiting.[20]

CONCLUSION

Leishmaniasis is a public health problem worldwide and in Mexico. It is a chronic parasitic disease, transmitted by mosquitoes that is caused by a flagellated protozoan of the genus *Leishmania*, which has more than 20 species. The genus *Phlebotomus* is the most common vector of

transmission and the genus *Lutzomyiael. Leishmania panamensis* is responsible for about 95% of cases, and *L. braziliensis* for the remaining 5%.

Usually, it is a disease that affects the tropical and subtropical populations of the world. Therefore, it is essential for doctors in the region and the rest of the country to know the clinical manifestations, suspect the diagnosis of leishmaniasis and be able to address the pathology in time to prevent possible complications from it.

Most of the patients who present this disease are victims of poverty, and live in inadequate and unsanitary conditions, even in areas far away from adequate medical care.

For the prevention of this disease, it is of vital importance to educate the population at risk, so that they can avoid being bitten by the mosquito or seek early attention when they already present it. Leishmaniasis is divided into three main types, according to its manifestations. clinical: CL, MCL and visceral leishmaniasis. It is possible to conclude that knowing the clinical manifestations of each type is of vital importance.

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