Dermatologic and otorhinolaryngologic manifestations in Leishmaniasis

Manifestações dermatológicas e otorrinolaringológicas na Leishmaniose

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Summary

Introduction: Leishmaniasis is an extremely important parasitic disease as regards epidemiology, and, in such a disease, man is an occasional host to the Leishmania protozoon. Some of the major clinical, visceral and integumentary features are the mucocutaneous ways that can harm face and upper airways and even cause deforming lesions, leading to a functional impairment.
Objective: Review the main dermatologic and otorhinolaryngologic manifestations in leishmaniasis.
Methods: It was based on the Virtual Health Library (BVS), by entering the following keywords: Leishmaniasis, mucocutaneous leishmaniasis, nasal mucosa, and nose. References dated from 1999 to 2008 have been regarded.
Final Comments: It is about a zoonosis, in which the human being is an occasional host attacked by Lutzomya or Phlebotomus insects that are, in turn, infected by the Leishmania parasite, and the early diagnosis of a leishmania-related lesion is essential, especially when a nasopharyngeal impairment is evident, with a view to preventing deformities or functional harms. The evaluation of cutaneous and/or mucosa lesions and the accurate definition of leishmaniasis diagnosis given by either dermatologists or otorhinolaryngologists enables the proper treatment to be implemented and the subsequent reduction in the disease dissemination.
Keywords: leishmaniasis, mucocutaneous leishmaniasis, nasal mucosa, nose.

Resumo

Introdução: A leishmaniose é uma parasitose de grande importância epidemiológica na qual o homem é um hospedeiro acidental do protozoário do gênero Leishmania. Dentre as principais apresentações clínicas, visceral e tegumentar, encontram-se as formas mucocutâneas, que podem acometer a face e as vias respiratórias superiores, podendo ocasionar lesões deformantes, com prejuízo funcional.
Objetivo: Revisar as principais manifestações dermatológicas e otorrinolaringológicas da leishmaniose.
Método: Utilizou-se como base de dados a Biblioteca Virtual em Saúde (BVS), sendo utilizadas as palavras chave: leishmaniose, leishmaniose mucocutânea, mucosa nasal e nariz. Foram consideradas as referências datadas de 1999 a 2008.
Comentários Finais: Trata-se de uma zoonose, na qual o ser humano é um hospedeiro acidental, acometido após a picada de insetos dos gêneros Lutzomya ou Phlebotomus, infectado pelo parasita da espécie Leishmania e cujo diagnóstico precoce de lesão leishmaniótica é imprescindível, especialmente quando há comprometimento nasofaríngeo, objetivando a prevenção de deformidades ou prejuízos funcionais. A avaliação de lesões cutâneas e/ou mucosas com a definição precisa do diagnóstico de leishmaniose, seja por dermatologistas ou por otorrinolaringologistas, favorece a implantação do tratamento adequado e, por conseguinte, permite a redução da disseminação da doença.
Palavras-chave: leishmaniose, leishmaniose mucocutânea, mucosa nasal, nariz.

Introduction

Leishmaniasis is regarded by the World Health Organization as one of the five most relevant endemic infectious-parasitic diseases and public health problem worldwide (1). It is an infectious chronically-evolving disease caused by a *Leishmania* protozoon, which can appear to have a clinical visceral, cutaneous, mucocutaneous, mucous and rarely diffuse form (2).

Risk factors for the development of mucous leishmaniasis are as follows: Presence of lesions above the pelvis, large cutaneous ulcers and inadequate treatment of cutaneous leishmaniasis (3).

The objective of this study is to review the main dermatological and otorhinolaryngological manifestations of leishmaniasis.

Method

The literature's review was performed in a 5-month period by reading scientific articles published between 1999 and 2008, and the following keywords were entered: leishmaniasis, nasal mucosa and nose. It was based on the Virtual Health Library (BVS) database.

Literature's review

The first iconographic records of cutaneous leishmaniasis belong to the pre-Inca Peruvian and Ecuadorian ceramics (years 400-900 A.D.). In the Old World (Asia, Africa and Europe), the written reports of the disease date back to the 1st century A.D. (4).

Over one thousand years later, in 1903, the agent of the disease is first described and separately by Leishman and Donovan. The disease was visceral leishmaniasis and its agents were the species that is presently known as *Leishmania donovani* (4).

Historic findings suggest that American Tegumentary Leishmaniasis (ATL) had already attacked the American population before the contact with the European and African. It is assumed that it was originated in Western Amazon in archeological times by way of human migrations, after arriving at the high wilderness and, subsequently, the hot interandine lands, by the Bolivian and Peruvian borders with Brazil (5).

Leishmaniasis is regarded by the World Health Organization as one of the five most relevant endemic infectious-parasitic diseases and public health problem worldwide (1). It is estimated that the world prevalence of leishmaniasis is 12 millions, impacting 80 countries and an estimated ratio of 400,000 new cases of the disease every year (3)

In Brazil, the highest prevalence throughout the American continent is found, estimating 65,000 new cases every year. Leishmaniasis is the second most common parasitic disease around the world, estimating 600,000 new cases every year (6).

In the 1980's, ATL was noticed in 19 Federal Unities and its geographical expansion was verified when, in 2003, the autochthony was confirmed in all the Brazilian states. A wide diffusion is noticeable and, in some areas, there is an intense concentration of cases, while in others cases are isolated (7).

In the American continent, there are currently 11 renowned dermotropic species of *Leishmania* causative of human disease and 8 species described only in animals. However, in Brazil, 7 species have been identified, 6 of the subgenus *Viennia* and 1 of the subgenus *Leishmania* (8).

The word leishmaniasis refers to the infection of vertebrate hosts by the protozoa of the genus *Leishmania*, which, like other trypanosomoatids of the *Kinetoplastida* order characteristically show an extranuclear DNA in its cytoplasm in a mitochondrial organelle, the kinetoplast. This genus is characterized by showing two evolving forms during its biological cycle in the host organisms: Amastigote, which is a mandatory intracellular parasite in vertebrate, and promastigote, being developed in the digestive tube of the invertebrate vectors or in axenic culture (3).

It is primarily a zoonotic infection of wild animals and, more rarely, in domestic animals, including marsupial, carnivore, and also primate, and man is an accidental host. All *Leishmania* species are transmitted by the bite of female mosquitoes called phlebotominae, belonging to genera *Lutzomyia* and *Phlebotomus*, and this transmission is made by the inoculation of these promastigote forms on the skin of the vertebrate host (5).

The transmission classically resulted from the bite of an insect, the called vector insect. This insect, also called sandfly, belongs to the Old Worlds at the genus *Phlebotomus* in the New World at the genus *Lutzomyia* (4).

It is a chronically-evolving infectious disease that can appear to have a clinical visceral, cutaneous, mucocutaneous, mucous and rarely diffuse form (2).

Man acquires the infection when contacting the florestal areas where there is an enzootic observation for the different species of *Leishmania* (9).

ATL is an infectious, chronic, non-contagious disease caused by *Leishmania* protozoan, whose main species are *Leishmania (Vienna) braziliensis*, *Leishmania (Vienna) guyanensis* and *Leishmania (Leishmania) amazonensis* (5). In men, the incubation period is around 2 months, but there can be shorter periods (2 weeks) and longer periods (2 years) (8).

In the American continent, there are currently 11 renowned dermotropic species of Leishmania causative of human diseases and 8 species described only in animals (7.8). However, in Brazil, 7 species have been identified - 6 in the subgenus *Viannia* and 1 in the subgenus *Leishmania*. The 3 main species are:

- ***Leishmania (Leishmania) amazonensis*** - spread through the primary and secondary Amazon forests (Amazonas, Pará, Rondônia, Tocantins, and southeast of Maranhão), mainly in areas of blackwater and whitewater-inundated forests. Its presence is widened to the Northeast (Bahia), Southeast (Minas Gerais and São Paulo) and Midwest (Goiás);
- ***Leishmania (Viannia) guyanensi*** - apparently restricted to the Amazon Basin (Amapá, Roraima, Amazonas and Pará) and reaching both Guianas. It is mainly found in non-flooded forests, in areas that are not flooded during rainy periods;
- ***Leishmania (Viannia) braziliensis*** - it is widespread from the south of Pará to the Northeast, reaching the mid-south of the country and some areas of the Eastern Amazon as well. In Amazon, the infection is usually found in non-flooded areas. As to the subgenus *Viannia*, there are other recently described *Leishmania* species: *L. (V) lainsoni*, *L. (V) naiffi*, with a few human cases in Pará; *L. (V) shawi*, with human cases found in Pará and Maranhão.

More recently, the species *L. (V.) lainsoni*, *L. (V.) naiffi*, *L. (V.) lindenberg* and *L. (V.) shawi* were identified in the North and Northeastern regions (8).

Over 200 men-pathogenic Leishmania species are described. Until the 1990's, the classification of these species was based on essentially clinical and geographical criteria, taking into consideration on one hand the distinction between the Old World and the New World, and on the other hand the clinical forms of the disease (4).

The major clinical ATL manifestations can be defined as:

1) Cutaneous Lesions: The disease mostly appears to be only one ulcerative lesion with usually painless elevated borders as a frame. The bottom is granular, with or without exudation. Normally, the located and disseminated forms respond satisfactorily to the traditional therapy. In the diffuse form considerably less frequent, lesions are papular or nodular, deforming and very severe, becoming widespread in the corporal surface and it can resemble Virchowian leprosy. The diffuse form usually develops badly because it does not respond satisfactorily to the therapy.
2) Mucous Lesions: mucous ATL features is mostly secondary to cutaneous lesions. Nasal cavities are most frequently impaired, followed by pharynx, larynx and oral cavity. Therefore, the most common complaints about nasal impairment are obstruction, epistaxis, rhinorrhea and crusts; in pharynx, odynophagia; in larynx, hoarseness and cough; in oral cavity, mouth wound. At the clinical exam, infiltration, ulceration, drilling of the nasal septum, ulcero-vegetative lesions, ulcer-crustose lesions in nasal cavity, ulcerodestructive lesions can be observed in the mucosa.

Mucous leishmaniasis (LM) is a form of Tegumentary leishmaniasis associated with *L. braziliensis, L. panamensis* and, less frequently, with *L. amazonensis* (11).

In Brazil, the leishmaniatic nature of cutaneous and nasopharyngeal lesions was first confirmed only in 1909 by Lindenberg, who found forms of Leishmania identical to *Leishmania tropica* (Wright, 1903) from the leishmaniasis in the Old World, in cutaneous lesions of individuals working in the wilderness of the countryside of the State of São Paulo (9).

The early diagnosis of mucous lesion is essential to achieve a more effective response to the therapy and avoid deforming and/or functional sequels (2).

The manifestations of mucous diseases comprise pillar and uvula impairments having an increase in volume, hyperemia, rugosities and superficial ulcers (12).

It is estimated that 3-5% of Cutaneous Leishmaniasis (CL) cases develop a mucous lesion. The classic ML form is secondary to the cutaneous lesion (10). Usually, it appears after LC is clinically cured, with an insidious commence and a scarce symptomatology. In most cases, ML results from chronically-evolving CL and it is cured without a treatment or with an inadequate treatment. Patients having multiple cutaneous lesions, extensive lesions and lesions developing for more than one year, located about the waist, are the highest risk group to develop metastasis to mucosa (8).

The presentation of the clinical form with exclusive lesions of laryngeal and tracheal mucosa is relatively uncommon (2).

The clinical presentation shows a polymorphism and the severity scope of the signals and symptoms is also variable, although the distinct clinical presentations are somewhat corresponding to the different species of the parasite (7).

It mostly impairs the male gender and the age groups that are normally higher than CL, what is probably due to its secondary complication feature. Most ML patients show a scar indicating a previous CL. Others show cutaneous and mucous lesions simultaneously. Some ML individuals do not show a CL-indicating scar. It is supposed that in these cases lesion was transitory. In some cases, mucous lesions occur as a result of the extension of the adjacent (contiguous) cutaneous lesion and there are also those cases in which the lesion starts in the exposed submucosa, such as lip. Lesion is usually painless and starts in the anterior, cartilaginous nasal septum, near the nasal introit, and it is therefore easily viewed (8).

The mucous leishmaniasis believed to be usually caused by a hematogenic dissemination of the leishmaniasis inoculated in the skin for nasal mucosa, oropharynx, palates, lips, tongue, larynx and, exceptionally, trachea and upper respiratory tract. More rarely, ocular conjunctiva and mucosa of genital organs and anus can be attacked. Skin lesions near the natural orifices can as well invade mucosa contiguously (8).

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The diagnosis of these lesions is extremely important to avoid disfiguring and/or mutilating cicatrizations abnd the distinction of this lesion in wide-ranging diagnoses (13).

The nasal mucosa is the favorite place for lesions having as a consequence nasal obstruction, epistaxis, granuloma in the anterior nasal septum and, subsequently, drilling of the nasal septum and downfall of the nasal tip. Other impaired places by order of frequency are larynx - edematous infiltration, granulation and fibrosis - and larynx - granuloma leading to dysphonia (11).

In the mucosa exam, erythema, infiltration, erosion and ulceration with a granulosa bottom can be observed. If there is a secondary infection, lesions can appear to be recovered by mucopurulent exudates and crusts (8).

Some individuals prematurely cure the lesion, sometimes without consulting a doctor. Others keeps lesion for months in activity and the cicatrization process is slow. This phenomenon can be explained by rapidly or slowly establishing a specific immune response effective in eliminating the parasite (7).

There can also be a mucous lesion without a primary skin lesion (15% of cases). In this last situation, an abortive primary lesion is believed to have happened. In 1% of mucous lesion cases, manifestations can only occur in larynx. Evidences suggest that, among CL patients developing ML, 90% happen within a 10-year term. Among these, 50% occur in the first 2 years after cutaneous lesions are cicatrized. The etiologic agent causative of ML in the country is *L. (V.) braziliensis*, however there are cases mentioned in literature which are related to *L. (L) amazonensis* and *L. (V.) guyanensis* (8).

Leishmaniasis cure is not sterile, it has been possible to isolate likely parasites of ATL scars in individuals who have been cured for years, such a fact is proven in experimental studied by using animal MODELS. This phenomenon could explain the appearance of late regressions as well as the appearance of the disease in immunosuppressed patients, as in the case of AIDS (Acquired Immunodeficiency Syndrome) (7).

This type of the disease is characterized by a strongly positive Montenegro's Intradermal Reaction (MIDR), yet its parasitology is difficult to be confirmed, and for showing a difficult therapeutic response, requiring higher doses of drugs, regressing more frequently (7.5%) than the cutaneous form (4.3%). It is also more susceptible to complications, mainly infectious, and it can lead to death in 1% of the cases. Examining the mucosa in patients with cutaneous leishmaniasis is suggested, because first mucous lessons are usually symptomatic (7,8).

Mucous leishmaniasis is presented under the following clinical forms:

- **Late mucous form** - it is the most common one. It can appear several years after the cutaneous form is cicatrized. Classically, it is associated with multiple cutaneous or long-lasting lesions, spontaneous cures or insufficient CL treatments.
- **Mucous form with an undetermined background** - when ML is clinically isolated, it is not possible to detect any other evidence of previous CL. Such forms would probably be associated with subclinical infections or small lesions, not ulcerative, rapidly evolving and that would have been overlooked, without leaving noticeable scars.
- **Simultaneous mucous form** - when the mucous lesion happens at a distance, but simultaneously with the active cutaneous lesion (not contiguous to the natural orifices).

- **Contiguous mucous form** - resulting from the direct propagation of a cutaneous lesion, located near natural orifices, to the mucosa of digestive airways. The cutaneous lesion can be active or cicatrized at the time of diagnosis.
- **Primary mucous** – happens, occasionally, by the bite of the vector on the mucosa or submucosa of lips and genitals (7,8).

For many authors, the nasal cavity is the preferably impaired location in nearly all the mucous leishmaniatic lesions. Some hypotheses try to clarify this preference. The direct contact is considered, i.e., the individual touches the primary cutaneous lesion and then they itch their nose, disseminating it to the mucosa or by contiguous cutaneous lesions. However, very few cases were reported with this type of transmission (5).

In a study by Fornazieri, 2008: inside the nasal impairment, the most common symptoms and signals were the septal drilling (50%), ulcer in nasal mucosa (50%) and epistaxis (31,2) (11).

In mucous lesions, paracoccidioidomicosis, virchowian leprosy, Rhinoscleroma, sarcoidosis, frambesia, tertiary syphilis, medium facial granuloma and neoplasias must be excluded (9).

The laboratory diagnosis of leeishmaniasis is primarily constituted in three exam groups: parasitological, immunological and molecular (Polymerase Chain Reaction - PCR) (7,8).

The parasitological exam is the most specific method to diagnose leishmaniasis at laboratories. It comprises parasitic researches in tissues or organs that are supposedly infected by: 1) direct exam, 2) culture or 3) PCR (4).

The biopsy must be made with a 4-7 mm diameter punch, or by wedge, using a bistoury. In ulcerative lesions, lesion border must be preferred, which usually shows an in tumescent and hyperemic aspect. When parasites are present, they are in intracytoplasmatic vacuoles of macrophages or in intercellular spaces, usually isolated. The surety diagnosis by histopathology is only given when the parasite is identified in the tissues (10).

Montenegro's Intradermal Reaction is founded on the visualization of the late cellular hypersensitivity response. It usually remains positive after the treatment or cicatrization of the cutaneous lesion spontaneously treated or cured, and it can be negative in weakly-reacting and early-treated individuals.

Other serological tests detect circulating anti-*Leishmania* antibodies in the patients' sera with usually low titles. ELISA (Enzyme-Linked Immunosorbent Assay) is not commercially available yet, and its use is restricted to research. In ulcerative lesions by *L. (V.) braziliensis*, sensitivity to the test of Indirect Immunofluorescence (IIF) is around 70%, in the first year of the disease; whereas in lesions by *L. (V.) guyanensis*, sensisitivity is lower (7).

The differentiated diagnosis is made with paracoccidioidomicosis, squamous cell carcinoma, basal cell carcinoma, lymphomas, rhinophima, rhinosporidiosis, entomophthoromycosis, Virchowian leprosy, tertiary syphilis, traumatic or drug-induced septal drilling, allergic rhinitis, sinusitis, sarcoidosis, Wegner's granulomatoses and other more infrequent diseases (7, 8).

The pentavalent antimoniates are indicated to treat all kinds of tegumentary leishmaniasis, although the mucous and mucocutaneous forms require more attention because they show more slow responses and a higher likelihood of retrocession. With an intention to standardizing the therapeutic outline, the WHO recommends that the doses of this antimoniate is calculated in mg/SbV/Kg/day, SbV what means a pentavalent antimoniate. In all the forms of mucous impairment, the recommended dose is 20mg/SbV/Kg/day (maximum of 3 ampoules per day), during 30 consecutive days. If there is not a full cicatrization within 12 weeks after the end of the treatment, the outline must be repeated only once. In case there is no response, use one of the drugs that are second in choice (10).

The antimoniate - N- metylglucamine, is commercially shown at a 5 ml bottle containing 405mg pentavalent antimoniate and each ml has 81 mg SbV. In case there is no satisfactory response to the treatment by the pentavalent antimoniate, the drugs of second in choice are Amphotericin B and Pentamidine (10).

Discussion

Leishmaniasis is a very epidemiologically relevant parasitosis in South America, epsecially in Brazil. Devastation of forest enables the human begins to have a higher contact with infected wild animals, as well as a higher contagion of domestic animals by vector insects.

Some of its main clinical forms are the cutaneous and mucous ones, and they can occur simultaneously. The impairment of nasal cavities is the most common ATL form. The identification of painless lesions, which can be unique, with a granulosa bottom, with or without exudation and an infiltrating, ulcerative or crustose aspect, must make the professional doctor investigate the likelihood of leishmaniatic disease.

Considering that mucous lesions can be secondary to cutaneous lesions, it can be affirmed that the early diagnosis of cutaneous Tegumentary Leishmaniasis allows for a proper treatment and reduces the chances of esthetic or functional damages. It is essential to understand that the mucous leishmaniasis, in its most frequent presentation - the impairment of nasal cavities - has a simple observation, because the nasal septum damage is easily noticeable.

Conclusion

It is about a zoonosis, in which the human being is an occasional host attacked by *Lutzomya* or *Phlebotomus* insects that are, in turn, infected by the *Leishmania* parasite, whose early diagnosis of a leishmania-related lesion is unforeseeable, especially when a nasopharyngeal impairment is present, therefore, intended to prevent deformities or functional harms. The evaluation of cutaneous and/or mucosa lesions and the accurate definition of leishmaniasis diagnosis given by either dermatologists or otorhinolaryngologists enables the proper treatment to be implemented and the subsequent decline in the disease dissemination.

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