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Review

Ear, nose and throat manifestations of mucocutaneous Leishmaniasis: a literature review

Francesca Marra, Maria Celeste Chiappetta, Vincenzo Vincenti

Unit of Audiology and Pediatric Otorhinolaryngology, Department of Clinical and Experimental Medicine, University of Parma – Parma, Italy

Summary. Leishmaniasis comprises a group of diseases caused by a protozoan parasite belonging to the genus Leishmania and transmitted by the bite of infected female sand flies. Leishmaniasis is endemic in 88 countries and causes significant morbidity and mortality worldwide. Phenomena such as globalization and human migration, as well as the increased volume of international travel have extended its prevalence in developed countries. In addition, the incidence of leishmaniasis as an opportunistic disease has increased in recent years because of the growing number of patients with immune depression secondary to chronic illness, neoplasm, transplant and HIV infection, thereby constituting a public health problem. In humans, there are three possible clinical syndromes of leishmaniasis: cutaneous, mucocutaneous and visceral. Mucocutaneous disease is due to extension of local skin disease into the mucosal tissue via direct extension, bloodstream or lymphatics. Lesions interest mainly the oral and nasal mucosa and occasionally the laryngeal and pharyngeal mucosa. If not recognized and adequately treated, MCL may disfigure the patient because of the chronic local destruction of tissue of the nose, pharynx and palate. Because of the invariable involvement of the areas pertaining otorhinolaryngologists, it is important for ENT specialists and family physicians to have awareness of this condition and its clinical manifestations, particularly in presence of a history positive for travel to endemic areas. If mucocutaneous leishmaniasis is suspected, otorhinolaryngologic examination is very helpful in establishing a correct diagnosis, preventing inappropriate treatment.

Key words: Leishmaniasis, ear, mose, throat

Introduction

Leishmaniasis comprises a group of diseases caused by a protozoan parasite belonging to the genus Leishmania; the disease is transmitted by the bite of infected female sand flies and humans are considered incidental hosts (1).

Human infection by pathogenic leishmanial species causes diverse chronic infections of the skin and viscera and is present in both the Old (Far and Middle East, Central Western and Eastern Europe and Africa) and New (Central and South America) Worlds (2). In humans, there are three possible clinical syndromes of leishmaniasis: cutaneous, mucocutaneous and visceral.

Cutaneous Leishmaniasis (CL) is caused by several species: Leishmania major and tropica in the Old World and Leishmania mexicana, amazoniensis, guyanensis, panamensis and braziliensis in Central and South America (3). It is the least severe form of disease and presents as singular ulcerative or nodular lesions at or near the site of insect exposure.

Visceral disease (VL), known as kala-azar, results from the proliferation of parasites within the reticuloendothelial system of the liver, spleen and bone marrow, with subsequent progressive hepatosplenomegaly and bone marrow suppression (4). This is a fatal, systemic disease.

Mucocutaneous disease (MCL), known as espundia, is caused by L. braziliensis, L. Amazonensis, L. pa-

namensis (New World) and L. infantum (Old World); it can be due to extension of local skin disease into the mucosal tissue via direct extension, bloodstream or lymphatics (5). Lesions interest mainly the oral and nasal mucosa and occasionally the laryngeal and pharyngeal mucosa (6). If not recognized and adequately treated, MCL may disfigure the patient because of the chronic local destruction of tissue of the nose, pharynx and palate.

Due to the frequent involvement of the abovementioned districts, otorhinolaryngologic examination has an important role in the differential diagnosis. Boaventura et al. (7) proposed an algorithm for MCL diagnosis and stated that otorhinolaryngologic examination, as the first step in evaluation of suspect MLC cases, may avoid incorrect diagnosis and prevent inappropriate and toxic treatment. Thus, it is important for otorhinolaryngologists to have awareness of this condition, particularly in presence of a history positive for travel to endemic areas. This review will focus on ENT manifestations and clinical markers of MCL in order to familiarise otorhinolaryngologists and family physicians with the different clinical pictures and the diagnostic procedures in this condition.

Materials and methods

Using the key words "mucosal leishmaniasis", and "ear", "nose", "throat" and "larynx" we searched the medical literature through the electronic database MEDLINE (National Library of Medicine, Bethesda, MD), for relevant articles, case reports and free texts on the ENT manifestation of leishmaniasis.

The review of the medical literature identified studies reporting more than one hundred cases of localized ENT manifestations.

Discussion

According to the World Health Organization, leishmaniasis is endemic in 88 countries of Central and South America, the Middle East and some regions of Africa and Europe (8) and causes significant morbidity and mortality worldwide. Indeed, phenomena such as globalization and human migration, as well as the increased volume of international travel have extended its prevalence in developed countries (9). In addition, the incidence of leishmaniasis as an opportunistic disease has increased in recent years because of the growing number of patients with immune depression secondary to chronic illness, neoplasm, transplant and HIV infection, thereby constituting a public health problem (10). In humans, there are three possible clinical syndromes of leishmaniasis: cutaneous, mucocutaneous and visceral.

MCL is a serious clinical form of the human leishmanial infection and it is known to be a potential sequela of CL resulting from hematogenous or lymphatic spread from cutaneous lesions or via direct extension from the primary infected site on the skin. Cutaneous lesions consist of papules, ulcerations or infiltration, often unresponsive to antibiotics or steroids (11). The time period between cutaneous lesions and mucosal involvement varies from months to years after skin lesions have healed. Clinical manifestations are dependent on infecting species and host factors such as age, genetics, immunocompetence (12). The species mainly responsible for the mucosal form of the disease are: L. braziliensis, panamensis and amazoniensis in the New World; L. infantum, donovani, aethiopica and tropica in the Old World (12).

Although oral cavity, pharynx, and larynx may be involved, the nasal mucosa is the site most frequently interested; lesions have been described as red, whithish, or violaceous lesions, consisting of granular swelling or polypoid, nodular or ulcerate lesions (11). Pathologically, the main characteristic is the presence of a diffuse inflammatory infiltrate in the chorion, composed of a mixture of lymphocytes, macrophages and plasmacells (11).

The favourite sites for manifestations of this disease are the cartilaginous nasal septum and the anterior portions of the nasal fossae, including the vestibule, the lower turbinates and the floor of the nose (12). Initial signs are erythema and edema of the involved mucosa. Nodules of the mucosa eventually develop, followed by ulcerations, often covered with a mucopurulent exudate, and granulomatous-like lesions. These usually lead to destruction and perforation of the nasal septum (13). The skin of the nose may be thickened,

swollen and hyperemic, with consequent increase of the nasal pyramid volume. As the disease progress, patients begin to present a leishmaniotic facies known as the "tapir nose" as a consequence of severe tissue destruction. The most frequent clinical symptoms are nasal obstruction, serous and crusted rhinorrea, discomfort, and epistaxis. In order to better characterise the severity of the disease as well as to judge response to therapy, Lessa et al. (14) classified nasal disease in 5 stages based on both appearance and localization of lesions (table 1). The differential diagnosis includes malignancies, rhinophyma, traumatic septal perforation or drug use, necrotizing vasculitis, tertiary syphilis, and other granulomatous diseases such as paracoccidioidomycosis, leprosy, tuberculosis and rhinosporidiosis (5,12,15).

Oral and oropharyngeal lesions usually appear as ulcerations in lips, tongue, tonsils, hard and soft palate and they may present also as exophytic, nodular, and indurated lesions (4). The mucosal lesions of pharynx may cause edema particularly in the uvula, tonsillar pillars and the posterior wall of pharynx. Granulation tissue permeates the mucosal findings and the increase of this tissue may deform completely the anatomical structures of the palate and the posterior pharynx; this process may lead to a significant stenosis in the transition between oropharynx and rhinopharynx (12).

Palatinal pain, gingival bleeding and painless cervical adenopathies may be noted; other symptoms are dysphagia and odynophagia (16). A differential diagnosis should be made with malignant disease such as lymphoma, squamous cell carcinoma or Kaposi's sarcoma and also with other conditions such as syphilis, tuberculosis, mycosis, herpes simplex virus and cytomegalovirus infection, blastomycosis and paracoccidioidis (10).

Similar to the pharynx, laryngeal mucosal lesions present the same type of fine granulous tissue that, with increased inflammation, involves the mucosa, the epiglottis and may extends to the laryngeal vestibule and the vocal folds; during this phase dysphonia is always present (17). Involvement of the cartilage in the epiglottis and the arytenoids may occur as in the cartilagineous septum to a greater or lesser degree, resulting in perichondritis which make swallowing very painful. Usually patients have a history of persistent dysphonia, dyspnea, hoarseness and odynophagia (18). A direct laryngoscopy may show vocal cord irregularity with arytenoid and epiglottis swelling and erythema (19).

In the differential diagnosis it may be considered laryngeal tumor, aspecific granulomatous laryngitis, TBC-related laryngitis, laryngitis related to Histoplasma infection, extra-nodal Natural Killer-cell lymphoma (20).

MCL usually does not affect the ears; however, involvement of the rhinopharynx can lead to Eustachian tube dysfunction with consequent otitis media with effusion. Conductive hearing loss, tinnitus and dysacusis are the major complaints in such cases (12).

Even if rarely, the ears can be involved in cutaneous leishmaniasis. The review of the literature showed three cases of primary cutaneous lesions of the ear, characterized by edema and diffuse hyperaemia of the external ear, erythematous and ulcerated areas on the helix, the antihelix or the external auditory canal, without involvement of the tympanic membrane; symptoms include intense pruritus and painful swelling of the involved areas (8,21-22).

The differential diagnosis of ulcerative auricolar lesions includes bacterial, fungal, atypical mycobacterial or tubercular infections, lymphoproliferative disorders or neoplasms (22).

MCL is a parasitic disease with a broad spectrum of possible manifestations that has to be considered in the differential diagnosis in a variety of clinical settings, especially in patients with immunodeficiency or who live in or travel to endemic regions (23); thus, a multidisciplinary approach involving otolaryngology, histopathology, internal medicine and infectious diseases is desirable. Apart from possible underlying diseases, laboratory findings are usually unremarkable. MCL diagnosis is based on the clinical examination and histopathological analysis obtained from the biopsy of the lesions. However, all granulomatous lesions

Table 1. Clinical staging system for patients with mucosal leishmaniasis (14)

Stage	Nasal clinical findings
1	Nodulation without ulcerations
2	Superficial ulcerations
3	Deep ulcerations
4	Septum perforation
5	Destruction of nasal architecture and altered facial structure

look very similar in the histophatological analysis and differentiation is only possible by the morphological characterization of the parasite. An immunohistochemical evaluation is based on the use of anti-Leishmaniasis polyclonal antibody. There is also the Montenegro skin test which consists of the intradermal injection of Leishmaniasis antigen in the inner portion of the arm: this test indicates contact with the parasite, but does not differentiate whether the disease is active or whether the patient has been treated.

The treatment for MCL is based mainly on pentavalent antimonials, amphotericin B and pentamidine; in order to minimize injection-associated complications, different oral drugs, such as ketoconazole, miltefosine and paromomycin, have been recently proposed (9).

Conclusions

MCL can lead to serious sequela, however, early diagnosis can prevent complications. Pathologists and clinicians should be aware of this unusual clinical entity so that diagnosis will not be delayed. Therefore, MCL should be included in the differential diagnosis of patients with nasal, oropharyngeal, and laryngeal symptoms unresponsive to medical treatment, especially if they have a history of travel in endemic areas or present immunodeficiency. If a characteristic cutaneous or mucocutaneous lesion with edema, erosion and/or granulomatous aspect is detected, a complete otorhinolaryngologic examination should be performed. Complementary exams such as intradermal DTH skin test, serology, histopathology should be also performed. Otorhinolaryngologic examination, as the first step in evaluation of suspect MCL cases, may avoid incorrect diagnosis, preventing inappropriate treatment.

References

1. Mcgwire BS, Satoskar AR. Leishmaniasis: clinical syndromes and treatment. QJ Med 2013, doi: 10.1093/qjmed/hct116.
2. Santangeli L, Mc Cluney NA, Hathorn I, Shakeel M, Anderson C. Leishmaniasis presenting to the otolaryngologist: a rare but important cause of persistent hoarseness. J Laryngol Otol 2009; 123: 1181-1183.
3. Clayton R, Grabczynska S. Mucocutaneous leishmaniasis presenting as facial cellulitis. J Laryngol Otol 2005;119:567-569.
4. Daneshbod Y, Oryam A, Davarmanesh M et al. Clinical histopathologic, and cytologic diagnosis of mucosal leishmaniasis and literature review. Arch Pathol Lab Med 2011;135:478-482.
5. Pereira Diniz JL, da Rocha Costa MO, Goncalves DU. Braz J Otorhinolaryngol 2011; 77 (3): 380-384.
6. Marsden PD. Mucosal leishmaniasis due to Leishmania (Viannia) Braziliensis in Tres Bracos, Bahia – Brazil. Rev Soc Bras Med Trop 1994;27(2):93-101.
7. Boaventura VS, De Oliveira JGS, Costa JML et al. Short report: the value of the otorhinolaryngologic exam in correct mucocutaneous leishmaniasis diagnosis. Am J Trop Med Hyg 2009; 81(3): 384-386.
8. Khorsandi-Ashtiani MT, Hasibi M, Yazdani N et al. Auricular leishmaniasis mimicking squamous cell carcinoma. J Laryngol Otol 2009; 123:915-918.
9. Amato VS, Tuon FF, Bacha HA, Neto VA, Nicodemo AC. Mucosal leishmaniasis. Current scenario and prospects for treatment. Acta Tropica 2008;105:1-9.
10. Pellicioli AC, Martins MA, Sant'ana Filho M, Rados PV, Martins MD. Leishmaniasis with oral mucosa involvement. Gerodontology 2012; 29: e1168-c1171, doi: 10.1111/j.1741-2358.2011.00512.x.
11. Aliaga L, Cobo F, Mediavilla JD et al. Localized mucosal leishmaniasis due to Leishmania infantum. Clinical and microbiologic findings in 31 patients. Medicine 2003; 82 (3)147-158.
12. Lessa MM, Lessa HA, Castro TWN, et al. Mucosal leishmaniasis: epidemiological and clinical aspects. Rev Bras Otorrinolaringol 2007; 73 (6): 843-847.
13. Virgilio GR, Hale BR. A case of mucocutaneous leishmaniasis. Otolaryngol Head Neck Surg 2005; 132:800-801.
14. Lessa HA, Lessa MM, Guimaraes LH, et al. A proposed new clinical staging system for patients with mucosal leishmaniasis. Trans R Soc Trop Med Hyg 2012, 106 (6): 376-381.
15. Bacciu A, Buzio C, Giordano D et al. Nasal polyposis in Churg-Strauss syndrome. Laryngoscope 2008;118(2):325-329.
16. Miliàn MA, Bagan JV, Jimenez Y, Perez A, Scully C. Oral Leishmaniasis in a HIV-positive patient. Report of a case involving the palate. Oral Diseases 2002; 8:59-61.
17. Oryan A, Shirian S, Tabandeh MR, Hatan GR, Kalantari M, Daneshbod Y. Molecular, cytological, and immunocytochemical study and kDNA sequencing of laryngeal Leishmania Infantum infection. Parasitol Res 2013; 112: 1799-1804.
18. Di Lella F, Vincenti V, Zennaro D et al. Mucocutaneous Leishmaniais: report of a case with massive involvement of nasal, pharyngeal and laryngeal mucosa. Int J Oral Maxillofac Surg 2006;35: 870-872.

19. Casero R, Laconte L, Fraenza L, Iglesias N, Quinteros Greco C, Villablanca ML. Leishmaniosis laringea recidivante: un caso inusual en un paciente inmunocompetente tratado con corticoides. Revista Argentina de Microbiologia 2010;42:118-121.
20. Teemul TA, Lima MG, Williams J, Lester SE. Laryngeal leishmaniasis: case report of a rare infection. Head and Neck 2013 - doi 10.1002/HED.
21. Dos Santos da Silva M, Telles de Sousa R, Batista da Silva E, et al. Primary lesion of mucocutaneous leishmaniasis simulating external otitis. Braz J Otolaryngol 2012,78(5):137.
22. Tarkan O, Cetik F, Uzun S. Auricular cutaneous leishmaniasis mimicking neoplastic disease. J Laryngol Otol 2012,126:821-824.
23. Bogdan C. Leishmaniasis in rheumatology, haematology and oncology: epidemiological, immunological and clinical aspects and caveats. Ann Rheum Dis 2012;71(Suppl II):i60-i66.

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Correspondence:
Vincenzo Vincenti, MD
Unit of Audiology and Pediatric Otorhinolaryngology,
Department of Clinical and Experimental Medicine,
University of Parma,
Via Gramsci 14 – 43126 Parma, Italy
Tel.:+39-0521-703204
Fax: +39-0521-290157
Email: vincenzo.vincenti@unipr.it