ISOLATED LARYNGEAL LEISHMANIASIS IN A 55-YEAR-OLD MAN WITH DYSPHONIA AND RHEUMATOID ARTHRITIS: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

We describe a case of isolated laryngeal leishmaniasis in an 55-year-old smoker, treated with steroids for rheumatoid arthritis, in the absence of concomitant visceral or cutaneous localizations. Clinical presentation was dominated by dysphonia. Laryngeal biopsy revealed the presence of Leishmania amastigotes, which were characterized by species-specific polymerase chain reaction as L. donovani parasites. In endemic areas, Leishmania infection may present with atypical localizations and it has to be considered as a possible cause of laryngeal symptoms, especially in subjects with known immunosuppressive diseases or under treatment with immunosuppressive drugs.

***Key words**: Laryngeal lesion, Leishmania, Leishmaniasis, Rheumathoid arthritis.*

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Introduction

Leishmania spp. are sandfly-transmitted protozoa causing a spectrum of diseases in humans[1,2]. Three main clinical syndromes are described: visceral, cutaneous and mucosal leishmaniasis[1]. Mostly in Latin America, Leishmania (L.) braziliensis may be responsible for a severe mucous membrane involvement extended from the nose and oral cavity towards pharynx and larynx[2]. In the Mediterranean Basin, L. donovani and L. infantum have been shown to cause occasionally localized mucosal disease in the absence of any concomitant visceral or cutaneous involvement[3,4].

Atypical mucosal localizations of Leishmania with variable clinical presentations are rare among immunocompetent individuals[3], whereas they have been reported in immunodeficient patients, such as those infected with human immunodeficiency virus type 1 (HIV-1), as well as organ transplant recipients and individuals on immunosuppressive therapies[4-17]. Mucosal leishmaniasis may result from lymphatic or haematogenous spread of the parasites. In the respiratory tract, descending invasion from oral or nasal mucosa may occur, leading to a destructive disease.

Here, we describe a case of laryngeal leishmaniasis in a 55-year-old smoker, with a recent diagnosis of rheumatoid arthritis (RA) treated with steroids, who presented with dysphonia. Moreover, we review other published cases of isolated laryngeal leishmaniasis in immunocompromised subjects.

Methods

We report a case of isolated laryngeal leishmaniasis in an immunocompromised patient who presented to the Division of Infectious Diseases of the Garibaldi-Nesima Hospital of Catania. Furthermore, we review 13 case reports from 10 articles[4,9-17] (Table 1).

Age	Sex	Nation	Comorbidities	Lesion site	Lesion description	Signs and symptoms	Diagnosis	Leishmania spp.	Therapy	Outcome
52	M	Spain	Asthma (treated with corticosteroids), nose polyps, smoke	Larynx	…..	Weight loss, cough, odynophagia, dysphonia	Histological Anti-leishmania antibodies	…..	Meglumine antimoniate (20 mg/kg/day) for 28 days	Clinical recovery
64	F	United Kingdom	Asthma (treated with corticosteroids), diabetes and hypertension	Larynx	Ulcerative lesion	Hoarseness	Histological	…..	Paromomycin (ineffective), amphotericin B (3 mg/kg/day) for a month	Clinical recovery
50	M	France	Scleroderma (treated with corticosteroids)	Larynx	…..	Dysphonia	Histological	…...	Meglumine antimoniate	Clinical recovery
52	F	Malta	Diabetes, hypertension, asthma (treated with corticosteroids), smoke	Right vocal cord	Nodular lesion	Hoarseness and dysphagia	Histological Anti-leishmania antibodies	…..	Sodium stibogluconate (850 mg/day) for 28 days	Clinical recovery
62	M	United Kingdom	Asthma (treated with corticosteroids)	Larynx	Edema and erythema	Hoarseness	Histological	L. *donovani*	Sodium stibogluconate (20 mg/kg/day) for 21 days	Clinical recovery
48	M	Portugal	HIV infection, radiochemoterapy for oral carcinoma	Left vocal cord	Irregular burgeoning lesion	Dysphonia, dysphagia and dyspnea	Histological anti-leishmania antibodies	…..	Meglumine antimoniate (20 mg/kg/day) for 28 days	Clinical recovery
29	M	Spain	HIV infection, smoke, alcohol	Epiglottis, hypopharyn, larynx	Swelling and reddening with ulcerations covered by grey exudate	Hoarseness, odynophagia, dysphagia, dyspnea, weight loss	Histological	…..	Meglumine antimoniate (20 mg/kg/day) for 5 weeks	Clinical recovery
30	M	Spain	HIV infection	Right vocal cord	Ulcerative lesion	Hoarseness	Histological Anti-leishmania antibodies	L. *donovani*	Meglumine antimoniate (850 mg/day) for 20 days	Clinical recovery, VL after nine months
35	M	France	HIV infection	Vocal cords	Ulcerative lesion	Dysphonia	Histological	L. *infantum*	Meglumine antimoniate (850 mg/day)	Clinical recovery
40	M	France	HIV infection	Larynx	Polypoid lesion	Dysphonia	Histological Anti-leishmania antibodies	L. *infantum*	Meglumine antimoniate (20 mg/kg/day) for 14 days	Clinical recovery, VL after two years
65	F	United Kingdom	Diabetes, hypertension, asthma (treated with corticosteroids), peripheral neuropathy, probable previous cutaneous leishmaniasis	Vocal cords	Leukoplakia aand polypoid granulation	Hoarseness	Histological	L. *infantum*	Liposomal amphotericin B	Clinical recovery
64	F	United Kingdom	Diabetes, hypertension, asthma (treated with corticosteroids)	Vocal cords	Edema, granulations and ulcerations of both vocal cords	Hoarseness	Histological	…..	Aminosidine (14 mg/kg daily) for 17 days, with no clinical improvement	Partial clinical recovery
84	M	United Kingdom	Chronic obstructive pulmonary disease (treated with corticosteroids)	Left vocal cord	Edema and erythema	Hoarseness and dysphagia	Histological	L. *donovani*	Liposomal amphotericin B (3 mg/kg/day) for 5 days, repeated on day 14 and 21	Clinical recovery
55	M	Italy	GERD, Rheumatoid Arthritis treated with corticosteroids and diclofenac, smoke, alcohol, previous VL, previous mycrolaryngoscopic surgery for Reinke's edema	Vocal cords	Edema, whitish patches, leukoplakia	Dysphonia and globus sensation	Histological Anti-leishmania antibodies	L. *donovani*	Liposomal amphotericin B (3 mg/kg/day) for 7 days, then once a week for 5 weeks	Clinical recovery

Table 1: Features of 14 cases of isolated laringeal leishmaniasis in immunocompromised subjects.

Other articles were discarded because they did not meet the following criteria: 1) full description of the case; 2) absence of any other mucosal lesion; 3) access to English full text. Patients were considered immunocompromised in presence of known immune compromising factors, such as HIV infection, corticosteroid therapy and malignancies.

Case report

In September 2010, a 55-year-old man presented with a two-month history of progressive dysphonia and globus sensation. He denied dyspnea, dysphagia, cough or sputum production. The patient was taking lansoprazole for gastroesophageal reflux disease (GERD) and he was receiving prolonged courses of high-dose steroids, hydroxychloroquine and diclofenac since January 2009 for the treatment of RA. He had been smoking 20 cigarettes a day for 20 years and drinking about 30 milliliters of alcohol daily. At the age of 45, he had developed visceral leishmaniasis (VL), which had been treated with amphotericin B. When he was 47, he had undergone microlaryngoscopic surgery because of bilateral Reinke's edema.

Neither lymphadenopathies nor other abnormal findings were detected on head and neck examination. The liver was slightly enlarged. Laboratory investigations, including complete blood cell count, serum biochemical studies and urinalysis, were all within the normal range, with the exception of augmented erythrocyte sedimentation rate (ESR) (33 mm/h), C reactive protein (58.8 mg/l) and lactate dehydrogenase (482 UI/l). HIV test was negative, as well as Mantoux intradermal reaction. Cardiological evaluation and chest radiograph were

unremarkable. Flexible laryngoscopy showed a swollen vocal cord on the right side with an irregular surface and a white patch on its middle third. On the left side, some areas of mild leukoplakia were described between the middle and anterior third of the vocal cord (Fig.1). Histological examination of laryngeal specimens showed the presence of non-necrotizing granulomatous inflammation in the subepithelium, with lymphocytes, granulocytes and many histiocytes. Giemsa staining showed cytoplasmic inclusions within histiocytes, which were suggestive of Leishmania amastigotes. Serological test for Leishmania was positive with a titer of 1/640. L. donovani was detected by polymerase chain reaction (PCR). Bone marrow biopsy was negative for Leishmania parasites. The patient was treated with liposomal amphotericin B at a dose of 3 mg/kg/per day for seven days and, subsequently, 3 mg/kg once a week for 5 weeks, obtaining a complete clinical and endoscopic recovery.

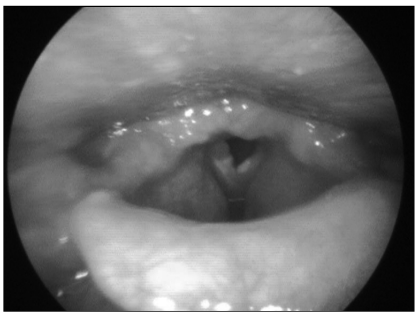

Fig. 1: Flexible laryngoscopy showed a swollen vocal cord on the right side with an irregular surface and a white patch on its middle third. On the left side, some areas of mild leukoplakia between the middle and anterior third of the true vocal cord.

Review of published works and discussion

In our review of the literature, we considered fourteen cases[4,9-17] (Table 1): median patient age was 52 years (Interquartile range 42-64), ten (72%) were men. Five patients (37%) came from the United Kingdom, three (21%) each from France and Spain, one (7%) each from Malta, Portugal and Italy. Four patients (29%) had travelled to countries where leishmaniasis is endemic, mainly in the Mediterranean basin. Immunodeficiency was related to HIV infection in five cases (37%). Nine patients (63%) were taking steroids, in the majority of cases for the treatment of asthma. Six patients (43%) complained of dysphonia, eight subjects (57%) had hoarseness. Less common symptoms were dysphagia, odynophagia and globus sensation. Histological examination was essential to diagnose leishmaniasis, as parasites were visualized in the biopsy specimens in all cases, usually with Giemsa stain. Anti-leishmania antibodies were positive in six cases (43%). Identification of Leishmania spp. was possible in 50% of patients: L. donovani was isolated in four cases (29%), L. infantum in three cases (21%).

Seven patients (50%) received meglumine antimoniate, generally at a dose of 20 mg/kg/day; in two cases (14%) sodium stibogluconate was administered, whereas in four cases (29%) patients were treated with liposomal amphotericin B. Twelve patients (86%) achieved cure; two patients (14%) developed visceral leishmaniasis, respectively nine and twenty-four months after treatment for laryngeal leishmaniasis.

The presence of dysphonia in a smoker with GERD, taking steroids for RA, certainly needs a thorough investigation. In differential diagnosis, cancer and infections have to be ruled out; laryngoscopy, with histological evaluation of laryngeal biopsies, represents the best approach to reach the correct diagnosis. In our case, laryngeal biopsy revealed the presence of inclusions within the cytoplasm of histiocytes. The detection of L. donovani by PCR, along with a positive serology test, led to the diagnosis of laryngeal leishmaniasis.

In recent years an increase in visceral and mucosal leishmaniasis has been observed in patients with immunodeficiency, such as patients undergoing organ transplantation or immunosuppressive therapy, patients with malignancies or HIV infection[4-17]. In our case, the patient was receiving steroids, hydroxychloroquine and diclofenac for the treatment of RA. The immunosuppressive role of these agents is well known and could have led to Leishmania reactivation with laryngeal localization. Analogously, reactivation of latent diseases, such as tuberculosis, hepatitis B virus and herpes viruses, is a critical issue in patients treated with new biological drugs, i.e. tumor necrosis factor-alpha inhibitors, so that pre-treatment screening and monitoring are essential[18-20]. Considering the widespread use of biological drugs for the treatment of several immune-mediated diseases (i.e. psoriasis, RA) and the capability of Leishmania to reactivate, it is critical for physicians to keep into account the possibility of mucosal or even visceral leishmaniasis to occur when using these drugs.

The pathogenesis of isolated laryngeal leish-

maniasis is still unclear: Aliaga et al. suggested that the lower temperature of the upper airways may favor the survival of some Leishmania strains[4].

In asthmatic patients, long-term use of inhaled steroids may cause local immunosuppression. For homosexual individuals, veneral transmission of Leishmania has also been hypothesized[12].

Unfortunately, no standardized protocols are available for the treatment of laryngeal leishmaniasis, because of the limited number of cases observed so far. Both pentavalent antimonials and liposomal amphotericin B seem to be effective but available evidence does not allow to recommend any specific protocol in terms of both dosage and duration of treatment. Follow up is important in the management of laryngeal leishmaniasis since local or visceral relapses may occur[3,13,14].

In conclusion, although rare, leishmaniasis has to be suspected in all patients presenting with laryngeal symptoms, especially if they are immunocompromised or they have lived or travelled to endemic areas. Healthcare providers should be aware of this clinical entity in order to avoid misdiagnose or delayed diagnose.

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