Laryngeal Leishmaniasis: A Neglected, Emerging Disease in Northern Italy

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Summary: Leishmaniasis represents an emerging public health issue in Mediterranean countries. The incidence of this condition has progressively risen in Northern Italy due to the growing number of immunocompromised people and probably due to climate changes. We hereby describe a case of relapsing laryngeal leishmaniasis in a female immunocompetent patient, presenting as aspecific chronic laryngitis. She was affected by severe asthma treated by inhaled steroid therapy, likely responsible for the parasite's diffusion through a *locus minori resistentiae*. The aspecific clinical presentation led to a delayed diagnosis and the lack of guidelines for the treatment caused multiple relapses. Biopsies of laryngeal lesions in the follow-up were performed by operative flexible videolaryngoscopy, thus avoiding general anesthesia and reducing associated healthcare costs. The aim of this report is to underline the diagnostic and therapeutic challenges that patients with this condition face and to present what is, to the best of our knowledge, the first application of prophylactic aerosolized pentamidine for relapsing laryngeal leishmaniasis.

Key Words: Leishmaniasis–Larynx–Italy–Vocal folds.

INTRODUCTION

Leishmaniasis is a disease caused by obligate intracellular protozoan parasites of the genus *Leishmania*, transmitted by phlebotomine sandflies.[1] *Leishmania* parasites are responsible of a broad range of clinical manifestations, with cutaneous, mucocutaneous, visceral involvement depending on the leishmania species and immune response of the patient.[2] Over 20 species of the parasite may affect both humans and animals,[3] the two most frequent being *L donovani* and *L infantum*, the former having an anthroponotic transmission, the latter having a zoonotic transmission.

Mucosal Leishmaniasis is a rare condition that commonly presents in association with cutaneous Leishmaniasis,[4] it arises from hematogenous or lymphatic dissemination of the parasites from the skin to the mucosa of the upper respiratory tract, but the site of infection is generally undetectable. This condition typically evolves over time and can remain clinically silent for many years, causing an intense inflammatory reaction and tissue damage, with only sparse amastigote forms in the affected tissue.[5]

We hereby describe the diagnostic and therapeutical workup of a female patient affected by mucosal leishmaniasis localized to the larynx presenting with chronic dysphonia. We aim to raise awareness on this condition which represents an emerging public health issue with relevant diagnostic and therapeutic challenges.

CASE REPORT

A 56-year-old woman presented in April 2021 for chronic dysphonia lasting for a year. She was referred to our laryngological service by her phoniatrician and her voice therapist after a 12-month rehabilitative treatment with a diagnosis of dysfunctional dysphonia. The patient was a nonsmoker, had a BMI of 39 and was affected by severe asthma treated by inhaled corticosteroids (fluticasone propionate 500 mcg twice a day). She had no other comorbidities and no history of cutaneous lesions. Flexible high-definition videolaryngoscopy showed a relevant swelling of the right laryngeal ventricle and severe right polypoid corditis in what looked as Reinke's edema (Figure 1). Due to the persistent voice disorder with no improvement from voice therapy, phonosurgical treatment was proposed. The ventricle "pseudo-eversion" was removed in general anesthesia under suspension direct microlaryngoscopy with Digital Acublade carbon-dioxide laser (Figure 2). The procedure was well tolerated, albeit a very limited voice improvement was achieved. Surprisingly, the histopathological examination revealed the presence of a large number of microorganisms, referable to *Leishmania* amastigotes, in the subepithelial connective tissue of the specimen. Polymerase chain reaction (PCR) as well as a western blot serologic assay performed on the excised tissue confirmed the diagnosis of laryngeal leishmaniasis.

The patient was referred to the infectious disease specialists, who administered intravenous liposomal amphotericin: 250 mg for five consecutive days, followed by three administrations once a week, with partial improvement of dysphonia. Four months later, due to persistence of dysphonia and of inflammation of the larynx a second vocal fold biopsy was taken under flexible videolaryngoscopy.

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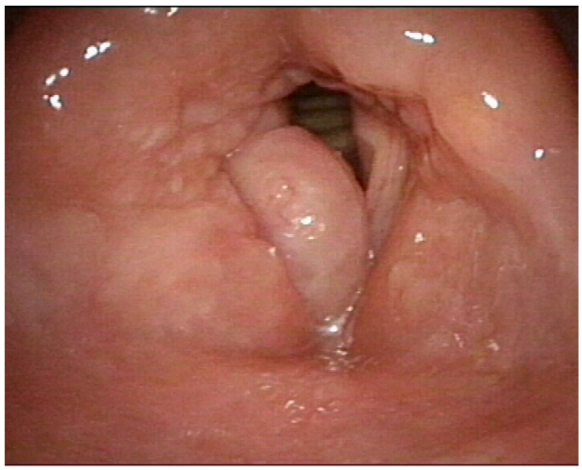

FIGURE 1. Video-laryngoscopic appearance at first presentation of the described patient in April 2021. The whole larynx is inflamed, over the right vocal fold there is hypertrophic tissue mimicking a ventricular prolapse, partially obstructing the glottic lumen. A granular appearance of the mucosa on the ventral face of the arytenoids and the false vocal fold can be appreciated.

Histology showed persistence of leishmania parasites, thus a second course of liposomal amphotericin 250 mg for 5 days (cumulative dose: 1250 mg) was prescribed with complete clinical and endoscopic recovery (Figure 3), with a mild, rapidly reversible increase of creatinine.

However, 1 month later the patient began to complain of respiratory obstruction and dysphonia, the videolaryngoscopic assessment showed slightly swollen false cords and an irregular surface of the right hypoglottic region. A third endoscopic biopsy confirmed persistence of Leishmania infection.

At this time treatment was changed to intravenous pentamidine isethionate (300 mg/day three times a week for a total of eight). The drug was well tolerated without any adverse effects and partial remission of symptoms. At the end of treatment, videolaryngoscopy showed a normal

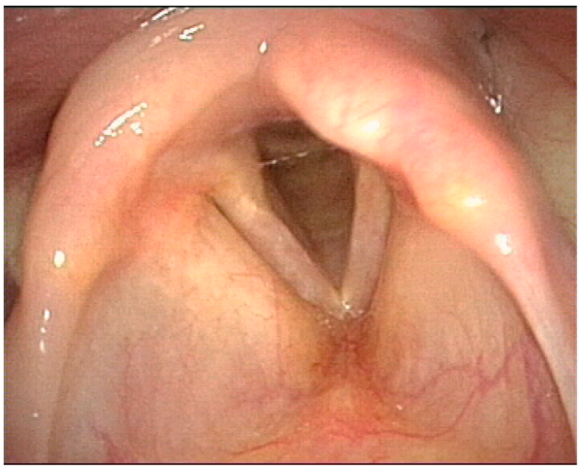

FIGURE 3. After liposomal amphotericin treatment the larynx has regained a normal aspect and the patient is asymptomatic.

appearing larynx; a fourth office-based biopsy showed no persistence of the disease.

A year later, in March 2023, the patient complained of a progressive, although mild, deterioration of voice quality and of recurrence of voice fatigue; the endoscopic laryngeal assessment (Figure 4) showed again a swollen, hyperemic left vocal fold which raised the suspicion of a relapse of Leishmaniasis, confirmed by a fifth biopsy showing positive histology and PCR for *Leishmania* spp. Therefore a second cycle of intravenous pentamidine was administered, with partial dysphonia improvement. The endoscopic follow-up showed the persistence of inflammation of vocal cords (more pronounced on the left), suggestive for Leishmania recurrence. Thus, infectious disease specialists prescribed aerosol pentamidine 300 mg once a month.

After four administrations complete remission of symptoms was observed and the laryngoscopy, performed in December 2023, showed complete resolution of the inflammation.

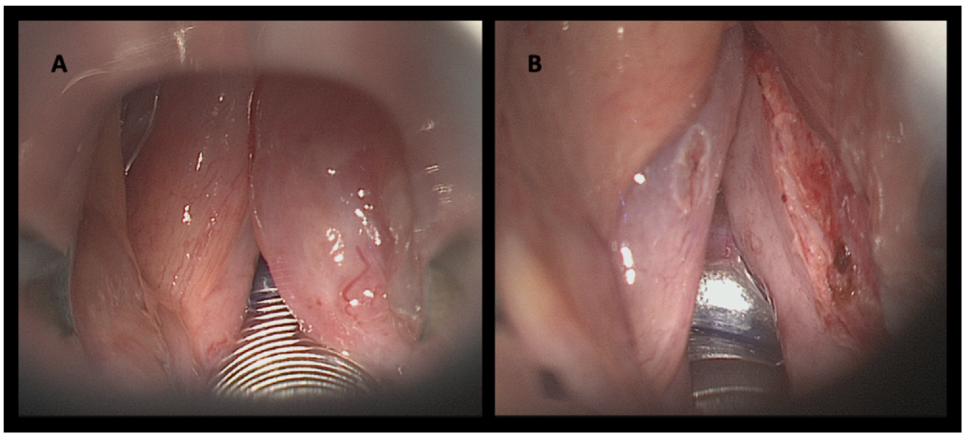

FIGURE 2. At the end of the surgical procedure the right exuberant tissue overlying the vocal fold has been excised by CO_2 laser and a small biopsy has been taken on the left vocal fold. **A.** Intraoperative view before and **B.** after surgery.

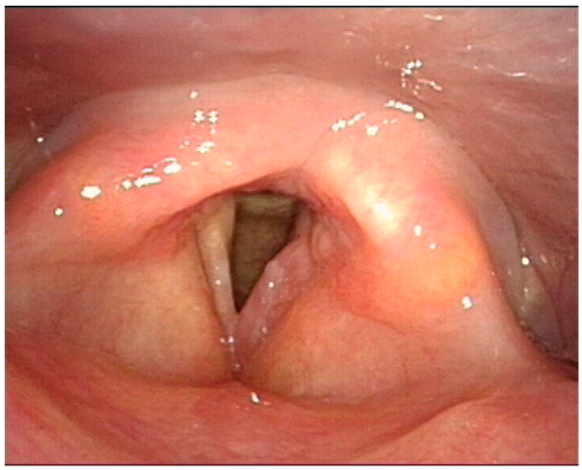

FIGURE 4. Recurrence of Leishmaniasis over the left vocal fold in March 2023.

After an interdisciplinary discussion, it was decided to continue with secondary prophylaxis with monthly aerosol of pentamidine for at least 12 months.

DISCUSSION

Historically, in Italy, the highest incidence of leishmaniasis was found along the Tyrrhenian coast, in the southern peninsular regions, and in the main islands. In the last 20 years a northward spread of both zoonotic and human infection has been reported as the result of climate changes paralleling vectors diffusion, development time, biting rate and parasite replication,[6] but also resulting from the move of infected dogs from southern kennels to the northern regions.[7]

The described patient did not travel in endemic areas, but frequently spent holidays in Liguria, an Italian region known to be endemic for *L infantum*, that can cause cutaneous and less frequently mucosal and visceral leishmaniasis. The risk of dissemination of leishmania to mucosal tissues depends on multiple factors such as the interaction of the parasite with the host's immune system. Leishmania genetic characteristics can also influence tissue tropism and intrinsic virulence.[8]

In previous reports[9,10] laryngeal leishmaniasis has been mainly observed in males and in immunocompromised patients, particularly those affected by comorbidities including HIV, diabetes, and use of immunosuppressive drugs. The increase of immunocompromised population in Europe has led to a raise of cases with mucosal involvement, especially for *L infantum* infection.[11] In our patient a peculiar risk factor for the development of Leishmaniasis was the chronic use of inhaled corticosteroids; according to Roberts et al,[10] they can create a local immunosuppression in the larynx, thus favoring the arousal of an organ-confined disease in patients who otherwise could have had only a transient subclinical infection.

The main symptoms associated with laryngeal leishmaniasis - dysphonia, dyspnea, and dysphagia[9] - are nonspecific, and so are the laryngeal lesions that can mimic many inflammatory or neoplastic conditions. Histologic diagnosis of mucosal leishmaniasis is based on the demonstration of *Leishmania* amastigotes in tissue lesions; histology has good sensitivity (50–100%) and specificity (> 95%). RT-PCR detects the presence of *Leishmania* DNA either in culture or tissue specimens with high sensitivity (around 100%).[12]

No national guideline for the treatment of leishmaniasis in Italy has been released.[1] Liposomal amphotericin B (L-AMB) is considered the drug of choice for the treatment of mucosal and visceral leishmaniasis in high-income countries, although its use is off-label in Italy where the only drug registered for the treatment of leishmaniasis is intravenous pentamidine. In a recent review of the literature, pentamidine isethionate showed a cure rate equivalent to L-AMB, with likely severe, although infrequent, side effects.[13] Other treatment options are systemic pentavalent antimony compounds and oral miltefosine that show higher toxicity and lower efficacy, respectively.[7]

Despite receiving adequate intravenous antiparasitic treatment, laryngeal lesions relapsed after 1 year from the last course.

The recurrence of Leishmaniasis despite treatment is common in immunosuppressed subjects, particularly when no immune recovery is achieved.[14] In the present experience, in view of the unfeasibility of interrupting topic steroids treatment, we borrowed the prophylactic schedule with aerosolized pentamidine from the Pneumocystis jirovecii pneumoniae. To our knowledge, no other reports on this approach have been reported in leishmaniasis therapy, as only few experiences exist with aerosolized liposomal amphotericin B.[15] The rationale is particularly robust in the case of laryngeal leishmaniasis due to the expected effective local concentration of the drug that may lead to a clinical response reducing the risk of systemic side effects. We believe this innovative strategy might be considered when underline predisposing conditions to recurrence of leishmaniasis could not be removed.

CONCLUSION

Laryngeal leishmaniasis is a condition that provides many clinical and therapeutic challenges, due to nonspecific symptoms and lesions. In consideration of the important changes in the epidemiology and geographical distribution of Leishmaniasis, clinicians ought to be aware of this condition to avoid delayed diagnosis and improper treatment.

When predisposing factors are present, laryngeal leishmaniasis recurrences should be expected even after apparent normalization of the laryngoscopic findings. Therefore, long-term clinical follow-up, possibly by high-definition videolaryngoscopy, and appropriate prophylaxis are necessary. Furthermore, the possibility to obtain laryngeal biopsies by flexible videolaryngoscopy allows to avoid repeated general anesthesia to confirm the suspect of

recurrence of this insidious parasitic disease. Inhaled pentamidine seems to be a promising tool to avoid relapses but treatment guidelines are still missing and are needed to help clinicians in facing this challenging disease.

Consent to participate

Written informed consent was obtained from the patient.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest/competing interests.

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