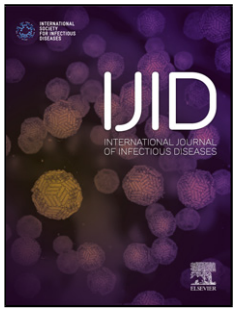

Refractory mucocutaneous leishmaniasis resolved with combination treatment based on intravenous pentamidine, oral azole, aerosolized liposomal amphotericin B and intralesional meglumine antimoniate

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Highlights

- Comorbidities limit treatment options in tegumentary leishmaniasis
- Combination therapy should be considered in relapsing mucocutaneous leishmaniasis
- We report the use of aerosolized liposomal amphotericin B as add-on treatment for refractory mucosal lesions

Abstract

Introduction: Mucocutaneous leishmaniasis (MCL) is a complication of tegumentary leishmaniasis causing potentially life-threatening lesions in the ear, nose and throat (ENT) district, most commonly due to *Leishmania (Viannia) braziliensis*. We report a case of relapsing MCL in an Italian traveler returning from Argentina.

Case description: A 65-year-old Italian male patient with chronic kidney disease, arterial hypertension, prostatic hypertrophy, type-2 diabetes mellitus was referred for severe relapsing MCL acquired in Argentina. ENT examination showed severe diffuse pharyngo-laryngeal edema and erythema partially obstructing the airways. A nasopharyngeal biopsy revealed a lymphoplasmacytic inflammation and presence of *Leishmania* amastigotes, subsequently identified as *L. (V.) braziliensis* by hsp70 PCR-RFLP analysis and sequencing. Despite receiving 4 courses of liposomal amphotericine B (L-AmB) and two courses of miltefosine in a two-years period, the patient presented recurrence of symptoms few months after the end of each course.

After the patient was referred to us, a combined treatment was started with intravenous pentamidine 4mg/kg on alternate days for 10 doses followed by one dose per week for additional 7 doses, intralesional meglumine antimoniate on the nasal lesion once per week for 6 doses, oral azoles for three months, and aerosolized L-AmB on alternate days for three months.

The treatment led to regression of mucosal lesions and respiratory symptoms. Renal function temporary worsened and addition of insulin was required due to maintain glycemic compensation also after pentamidine discontinuation.

Conclusions: This case highlights the difficulties in managing a life-threatening refractory case of MCL in an Italian traveler with multiple comorbidities. Even though parenteral antimonial derivatives are traditionally considered the first choices for treatment of MCL, they are relatively contraindicated in case of chronic kidney disease, therefore dose adjustment in case of impaired renal function is unknown and the use of alternative drugs is recommended. This case was resolved with combination treatment including aerosolized L-AmB which was never used before for MCL.

Keywords:

Mucocutaneos leishmaniasis. Combination therapy. Aerosolized liposomal amphotericin-B. Pentamidine. Recurrent leishmaniasis. Chronic kidney disease

Introduction:

Leishmaniasis is a parasitic disease caused by protozoa of the genus *Leishmania*, transmitted by the bite of infected sand flies [1]. Mucocutaneous leishmaniasis (MCL) is a severe manifestation endemic in South America caused by species of the subgenus *Viannia*, mainly *L. braziliensis* and *L. panamensis*[1].

MCL may occur in up to 40% of inappropriately treated patients with leishmaniasis caused by *L. braziliensis*, several months to years after the appearance of the skin lesion[2].

Nose, palate, pharynx and larynx are the most frequent localization of MCL where mucosal lesions may present with edematous swelling which conceal the underlying granulation tissue; involvement of the cartilage in the epiglottis and the arytenoids may occur and determine deformity of these structures with the risk of permanent sequelae[3].

We report a case of MCL in a traveler with multiple comorbidities which was refractory to several course of first- and second-line treatment highlighting the challenge in balancing the need for an effective therapy and the drug-related adverse reactions.

Case Report:

Short following a vacation in Argentina in May 2015, a 65-year-old Italian male patient with chronic kidney disease, arterial hypertension, benign prostatic hypertrophy and type-2 diabetes mellitus developed an ulcerated skin lesion on the right leg on the site of an insect bite. The lesion did not improve after some course of antibiotic treatment and the patient underwent a biopsy in another centre. Histological examination showed the presence of linfo-plasmacellular inflammation with the presence of giant cells. The patient did not receive any specific treatment. Since February 2016, the patient was hospitalized several times due to the onset of dyspnoea, leading to the subsequent identification of pharynx, larynx and nasal lesions, which were biopsied. The histologic pattern was similar to that of the skin lesion, moreover intracellular *Leishmania* amastigotes were also identified. Leishmaniasis serology was also positive with a titer of 17.6 Elisa Units (cut off > 11 EU).

The diagnosis of MCL was made and the patient received four cycles of intravenous therapy with L-AmB (3mg/kg on day 1-5 and 10, total dose 72mg/kg) followed by three cycles of oral miltefosine (50mg tid for 28 days) in a two-year period. While the skin lesion resolved, mucosal lesions relapsed within few weeks or months after each cycle of therapy determining dyspnoea and dysphonia, symptoms which were treated also with local steroid administration. Eventually, the treatment course with miltefosine was discontinued due to progressive impairment of the patient renal function.

Due to the worsening of the disease, he was referred to our unit in December 2018 for a re-evaluation.

By the time of admission, he presented dyspnea, dry cough, dysphagia for solid foods and almost complete aphonia. On physical examination it was observed the presence of an ulcerated lesion on the right nostril (figure 1, panel E). Serum creatinine was 2.13 mg/dL (eGFR 33.3 mL/min). The patient underwent to tele-laryngoscopy showing the presence, in the entire pharynx and in the larynx up to the glottal plane, of diffuse infiltrative mucosal lesions consisting of infiltrating irregular tissue which determined a marked reduction in the air passage (figure 1, panel A, C). Bilateral lung infiltrates suggesting aspiration pneumonia were also revealed by the chest CT scan.

Lesion swab from the nostril lesion showed positivity at the polymerase chain reaction (PCR) for *Leishmania* genus and immunofluorescence antibody test (IFAT) was positive at a titer of 1:640 (cut off =1:80). Cultures seeded with biopsy material from the pharynx lesion were strongly positive for *Leishmania* promastigotes after only six days of incubation. The strain was subsequently identified as belonging to *L. (V.) braziliensis* by ITS1 and hsp70 PCR-RFLP analysis and hsp70 sequencing[4].

Given the clinical history of multiple relapses and renal failure, a combined treatment with oral itraconazole (subsequently substituted with fluconazole), intravenous pentamidine, aerosolized L-AmB and intralesional infiltration of meglumine antimoniate in the nostril lesion was prescribed initially along with a short cycle of intravenous methylprednisolone and repeated ENT examinations of the airways' patency (figure 1, panel G).Intravenous therapy with pentamidine was initially administered every other day and discontinued after 10 doses due to the onset of presyncope symptoms, generalized malaise and dyspnea.

The patient was discharged thirty days after admission and continued the treatment as outpatient. During the first month of treatment, blood samples were collected, and amphotericin was dosed demonstrating low concentrations (<0.15 mg/l).

Three months after the beginning of treatment the patient developed progressive worsening of the renal function, serum creatinine values up to 3 mg/dL (eGFR 22 mL/min) imposed the suspension of the drug administration. Moreover, long term addiction of glargine insulin 8 UI subcutaneously at night to oral antidiabetic treatment was required to maintain glycemic compensation. Renal function gradually returned to the pre-treatment values one year after discontinuation of treatment.

The patient underwent strict endoscopic monitoring which showed the progressive improvement of mucosal lesions throughout the hospital stay and during the outpatient follow-up. Serological tests were stably negative after 3 months

of treatment. Thirteen months after the initiation of treatment he was asymptomatic and ENT examination did not show any lesions or inflammation (figure 1, panel B, D, F).

Discussion:

A standardized treatment for MCL has yet to be defined and the current guidelines suggest that the "choice of antileishmanial agent, dose, and duration of therapy for persons with MCL should be individualized"[5].

Systemic pentavalent antimonials are the first-choice drug for the treatment of the MCL [5,6]. However, antimonials are relatively contraindicated in case of chronic kidney disease due to the risk of drug accumulation[7], their dose-dependent toxicity[8] and the subsequently risk of cardiac toxicities [9].

Miltefosine and L-AmB are also commonly used [5,6], however, in this case, the previous administration of those drugs determined temporarily benefit followed by relapses of MCL and serious side effects.

These limitations oriented to the use of second-line drug, combination therapy with intravenous pentamidine, oral azole, aerosolized L-AmB and intralesional meglumine antimoniate. A similar drug association successfully treated a case of relapsing visceral leishmaniasis[10].

Intravenous pentamidine represents a valid alternative to first line drugs[11], demonstrating an efficacy comparable to the pentavalent antimonials both in case of systemic[12] and intralesional use[13].

In this case, in order to obtain adequate control of the disease at the level of the mucous membranes of the upper respiratory tract, but in a context of disseminated involvement of the larynx and pharynx which posed particular difficulties for topical administration of antimonials, it was decided to add aerosolized L-AmB. This administration route of L-AmB has already been evaluated for the treatment and prophylaxis of pulmonary aspergillosis in immunodepression subset[14]. It has been widely evaluated that this route of administration is accompanied by a major localization of the drug in the lung and in the digestive system thus limiting the systemic exposition and the risk of nephrotoxicity[14]. To our knowledge this is the first case of administration of aerosolized L-AmB for the treatment of MCL. Given the fewer side-effects in comparison to the i.v. formulation and the optimal deposition of the drug in the upper respiratory tract it may represent a valid addition to a systemic drug in difficult to treat patients with MCL and extensive pharyngeal and laryngeal involvement, however further studies are needed to establish its efficacy.

Declarations

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Conflicts of interest: the authors declare that they have no conclicts of interest

Ethical approval: not applicable

Consent to participate: not applicable

Consent for publication: not applicable

Availability of data and material: all data and material are available online and the sources are reported in the references

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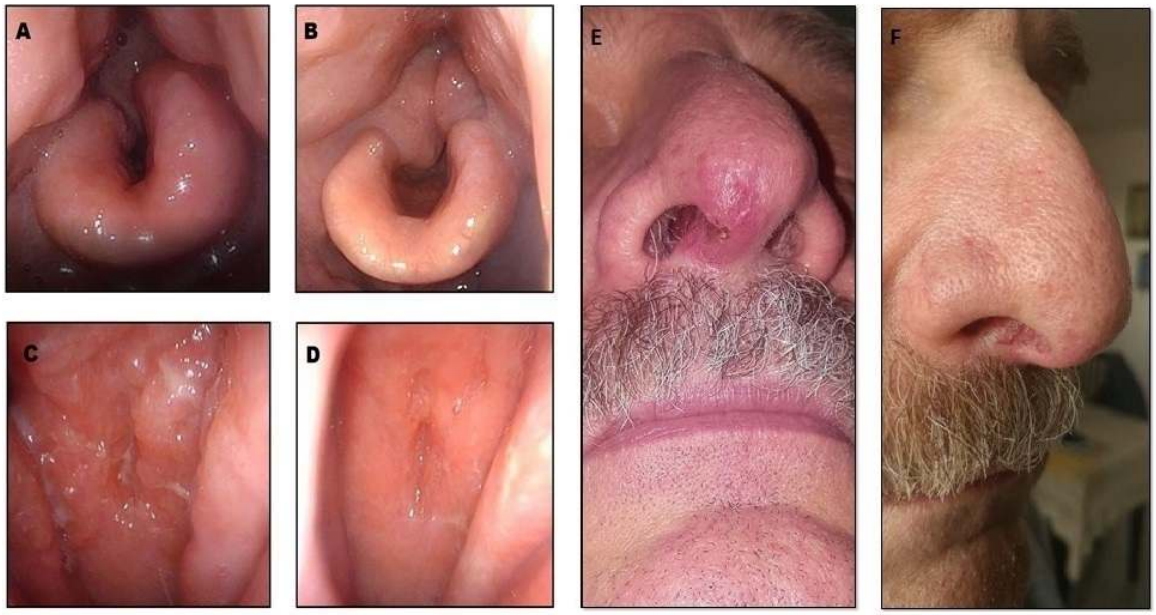
Figure 1. Infiltrative lesions caused by *Leishmania braziliensis* in the larynx (panel A), in the nasopharynx (panel C) and in the right nostril (panel E) before treatment. The larynx (panel B), the nasopharynx (panel D), the right nostril (panel F) after 12 weeks of treatment.

Treatment timeline with dosage of antiprotozoal drugs (panel G). From the top to the bottom: Oral itraconazole with a loading dose of 400 mg followed by 200 mg twice a day for 22 days. Oral fluconazole 200 mg/die once a day for 65 days. Intravenous (i.v.) pentamidine 4 mg/kg on alternate days for 10 doses followed by i.v. pentamidine 4 mg/kg once a week for 4 doses, then i.v. pentamidine 4 mg/kg every other week for 3 doses (total 17 doses). Aerosolized L-amphotericin B with a loading dose of 50 mg, followed by 25 mg every other day for 27 days, the 25 mg twice a week for 41 days. Black arrows: intralesional meglumine (1,5g/5mL) administration 1mL per dose.rative lesions caused by *Leishmania braziliensis* in the larynx (A) and in the nasopharynx (C) before treatment. The larynx (B) and the nasopharynx (D) after 12 weeks of treatment.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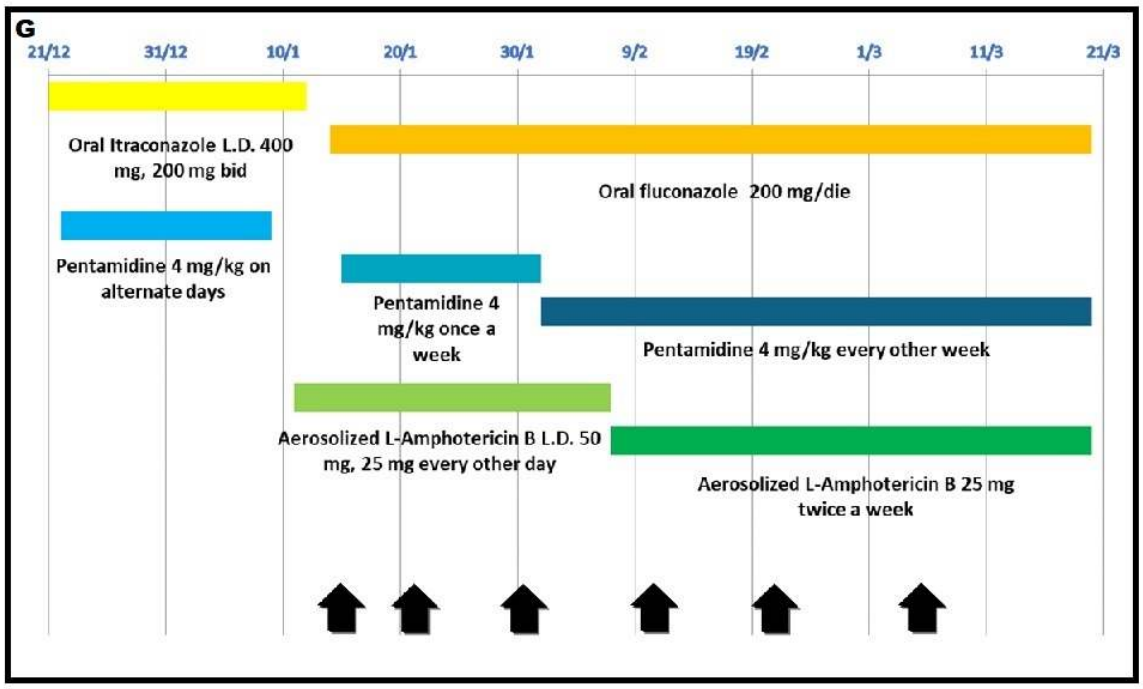
G
21/12
31/12
10/1
20/1
30/1
9/2
19/2
1/3
11/3
21/3
Oral Itraconazole L.D. 400 mg, 200 mg bid
Oral fluconazole 200 mg/die
Pentamidine 4 mg/kg on alternate days
Pentamidine 4 mg/kg once a week
Pentamidine 4 mg/kg every other week
Aerosolized L-Amphotericin B L.D. 50 mg, 25 mg every other day
Aerosolized L-Amphotericin B 25 mg twice a week

Highlights

- Comorbidities limit treatment options in tegumentary leishmaniasis
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- We report the use of aerosolized liposomal amphotericin B as add-on treatment for refractory mucosal lesions