International Journal of Infectious Diseases 97 (2020) 204–207

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

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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ARTICLE INFO

Article history:
Received 25 March 2020
Received in revised form 29 May 2020
Accepted 1 June 2020

Keywords:
Mucocutaneous leishmaniasis
Combination therapy
Aerosolized liposomal amphotericin B
Pentamidine
Recurrent leishmaniasis
Chronic kidney disease

ABSTRACT

Introduction: Mucocutaneous leishmaniasis (MCL) is a complication of tegumentary leishmaniasis, causing potentially life-threatening lesions in the ear, nose, and throat (ENT) region, and 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, and type-2 diabetes mellitus was referred for severe relapsing MCL acquired in Argentina. ENT examination showed severe diffuse pharyngolaryngeal 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 four courses of liposomal amphotericine B (L-AmB) and two courses of miltefosine over a 2-year period, the patient presented recurrence of symptoms a few months after the end of each course.

After the patient was referred to us, a combined treatment was started with intravenous pentamidine 4 mg/kg on alternate days for 10 doses, followed by one dose per week for an additional seven doses, intralesional meglumine antimoniate on the nasal lesion once per week for six 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 temporarily worsened, and the addition of insulin was required to maintain glycemic compensation 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 treatment of choice for MCL, they are relatively contraindicated in cases of chronic kidney disease.The required dose adjustment in cases of impaired renal function is unknown, therefore the use of alternative drugs is recommended. This case was resolved with combination treatment, including aerosolized L-AmB, which had never been used before for MCL.

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https://doi.org/10.1016/j.ijid.2020.06.003

Introduction

Leishmaniasis is a parasitic disease caused by protozoa of the genus *Leishmania*, transmitted by the bite of infected sand flies (WHO, 2010). Mucocutaneous leishmaniasis (MCL) is a severe manifestation endemic in South America caused by species of the subgenus *Viannia*, mainly *Leishmania braziliensis* and *Leishmania panamensis* (WHO, 2010).

MCL can occur in up to 40% of inappropriately treated patients with leishmaniasis caused by *L. braziliensis*, several months to years after the appearance of skin lesions (Solomon et al., 2019).

Nose, palate, pharynx, and larynx are the most frequent localizations for MCL, where mucosal lesions may present with edematous swelling, which conceals the underlying granulation tissue; involvement of the cartilage in the epiglottis and the arytenoids may occur, and can lead to deformity of these structures with the risk of permanent sequelae (Lessa et al., 2007).

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

Case report

Shortly 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 a course of antibiotic treatment and the patient underwent a biopsy in another centre. Histological examination showed the presence of lymphoplasma cellular inflammation, with the presence of giant cells. The patient did not receive any specific treatment. From February 2016, the patient was hospitalized several times due to the onset of dyspnoea, leading to the subsequent identification of pharyngeal, laryngeal, and nasal lesions, which were biopsied. The histological 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/mL (cut-off >11 EU/mL).

A diagnosis of MCL was made and the patient received four cycles of intravenous therapy with L-AmB (3 mg/kg on days 1–5 and 10; total dose 72 mg/kg) followed by three cycles of oral miltefosine (50 mg three times a day for 28 days) over a 2-year period. While the skin lesion resolved, mucosal lesions relapsed within a few weeks or months after each cycle of therapy, leading to recurrence of dyspnoea and dysphonia — symptoms that were treated with local steroid administration. Eventually, the treatment course with miltefosine was discontinued due to progressive impairment of the patient's renal function.

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

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

A swab from the nostril lesion, followed by polymerase chain reaction (PCR), gave a positive result for *Leishmania* genus, with a positive immunofluorescence antibody test (IFAT) 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 6 days of incubation. The strain was subsequently identified as belonging to *L. (V.) braziliensis* following ITS1 and hsp70 PCR-RFLP analysis, and hsp70 sequencing (Van der Auwera and Dujardina, 2015).

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 alongside a short cycle of intravenous methylprednisolone and repeated ENT examinations of the airways' patency (Figure 1G). 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 30 days after admission and continued the treatment as an outpatient. During the first month of treatment, blood samples were collected, and blood amphotericin levels were measured, demonstrating low concentrations of this drug (<0.15 mg/L).

Three months after the beginning of treatment the patient developed progressive worsening of renal function, with serum creatinine values up to 3 mg/dL (eGFR 22 mL/min), leading to the suspension of drug administration. Moreover, long-term addition of insulin glargine, 8 UI subcutaneously at night, to oral antidiabetic treatment was required to maintain glycemic compensation. Renal function gradually returned to the pretreatment values 1 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 outpatient follow-up. Serological tests were stably negative after 3 months of treatment. Thirteen months after the initiation of treatment the patient was asymptomatic and ENT examination did not show any lesions or inflammation (Figure 1B, D and F).

Discussion

A standardized treatment for MCL has yet to be defined, with the current guidelines suggesting that the 'choice of antileishmanial agent, dose, and duration of therapy for persons with MCL should be individualized' (Aronson et al., 2017).

Systemic pentavalent antimonials are the first-choice drug for the treatment of MCL (Aronson et al., 2017; Gradoni et al., 2017). However, antimonials are relatively contraindicated in cases of chronic kidney disease due to the risk of drug accumulation (Kip et al., 2018), their dose-dependent toxicity (Da Justa Neves et al., 2009), and the subsequent risk of cardiac toxicities (Sundar and Chakravarty, 2013).

Miltefosine and L-AmB are also commonly used (Aronson et al., 2017; Gradoni et al., 2017); however, in this case, the previous administration of these drugs achieved only temporary benefits, with subsequent relapses of MCL as well as serious side effects.

These limitations led to the use of second-line drug combination therapy with intravenous pentamidine, oral azole, aerosolized L-AmB, and intralesional meglumine antimoniate. A similar drug combination had previously been shown to successfully treat a case of relapsing visceral leishmaniasis (Rybniker et al., 2010).

Intravenous pentamidine represents a valid alternative to first-line drugs (Lai A Fat et al., 2002), demonstrating an efficacy comparable to pentavalent antimonials both in cases of systemic (Tuon et al., 2008) and intralesional use (Soto et al., 2016).

In this case, in order to obtain adequate control of the disease at the level of the mucous membranes of the upper

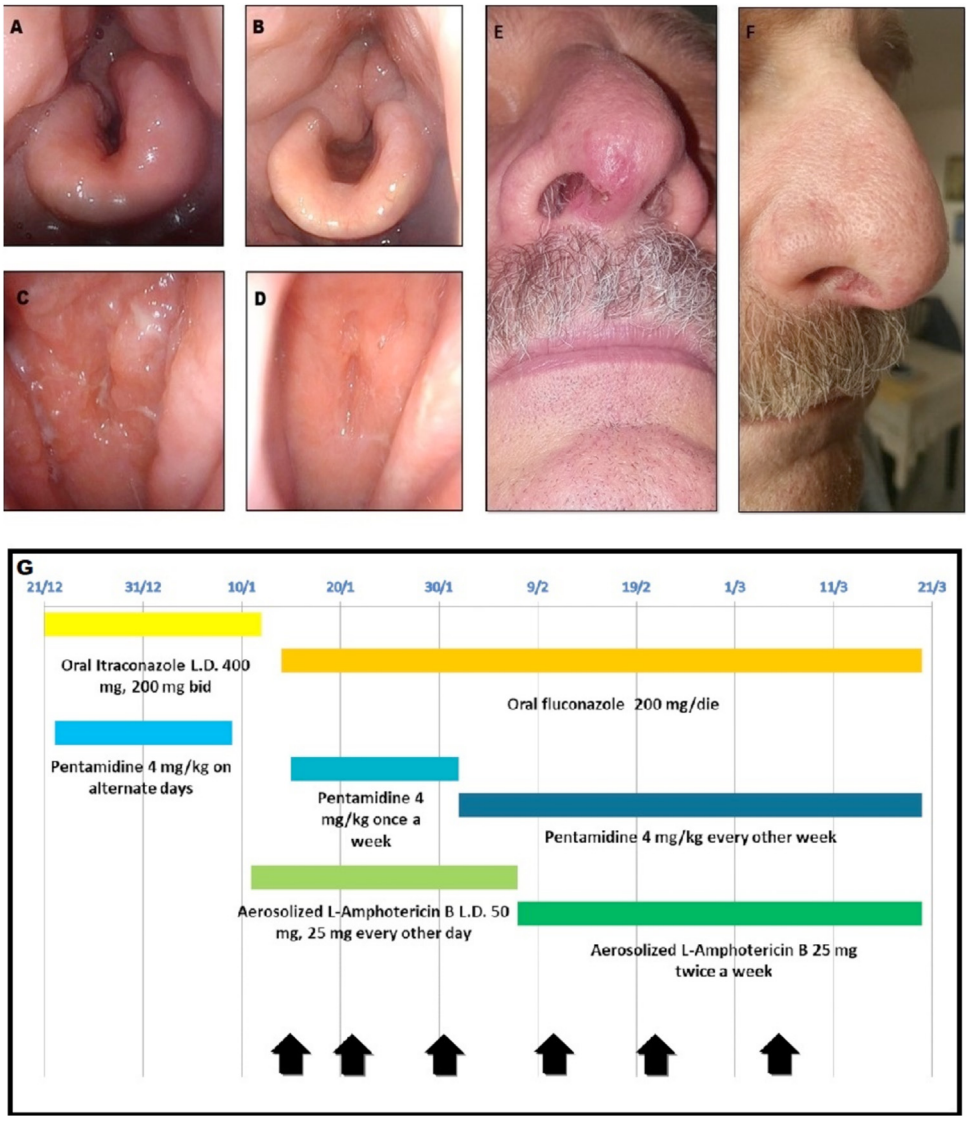

Figure 1. Infiltrative lesions caused by *Leishmania braziliensis* in the larynx (A), in the nasopharynx (C), and in the right nostril (E) before treatment. The larynx (B), the nasopharynx (D), the right nostril (F) after 12 weeks of treatment. (G) Treatment timeline, with dosages of antiprotozoal drugs. From 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 four doses, then i.v. pentamidine 4 mg/kg every other week for three 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, then 25 mg twice a week for 41 days. Black arrows: intralesional meglumine (1.5 g/5 mL); administration 1 mL per dose.

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 for L-AmB had already been evaluated for the treatment and prophylaxis of pulmonary aspergillosis in an immunodepression subset (Xia et al., 2015). It has been widely observed that this route of administration is accompanied by major localization of the drug in the lung and in the digestive system, thus limiting systemic exposure and the risk of nephrotoxicity (Xia et al., 2015). 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 with the i.v. formulation and the optimal deposition of the drug in the upper respiratory tract, this 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.

Funding

This article has been supported by funds of "Ministry of Education, University and Research (Italy) Excellence Departments 2018-2022" Project for the Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data and materials are available online, with the sources reported in the references.

References

Aronson N, Herwaldt BL, Libman M, Pearson R, Lopez-Velez R, Weina P, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg 2017;96:24–45.

Da Justa Neves DB, Caldas ED, Sampaio RNR. Antimony in plasma and skin of patients with cutaneous leishmaniasis — relationship with side effects after treatment with meglumine antimoniate. Trop Med Int Health 2009;14: 1515–1522.

Gradoni L, López-Vélez R, Mokni M. Manual on case management and surveillance of the leishmaniases in the WHO European Region. World Health Organ. Reg. Off. Eur.; 2017.

Kip AE, Schellens JHM, Beijnen JH, Dorlo TPC. Clinical pharmacokinetics of systemically administered antileishmanial drugs. Clin Pharmacokinet 2018;57: 151–176.

Lai A Fat EJSK, Vrede MA, Soetosenojo RM, Lai A Fat RFM. Pentamidine, the drug of choice for the treatment of cutaneous leishmaniasis in Surinam. Int J Dermatol 2002;41:796–800.

Lessa MM, Andrade HL, Castro TWN, Oliveira A, Scherifer A, Machado P, et al. Mucosal leishmaniasis: epidemiological and clinical aspects. Braz J Otorhinolaryngol 2007;73:843–7.

Rybniker J, Goede V, Mertens J, Ortmann M, Kulas W, Kochanek M, et al. Treatment of visceral leishmaniasis with intravenous pentamidine and oral fluconazole in an HIV-positive patient with chronic renal failure — a case report and brief review of the literature. Int J Infect Dis 2010;14:.

Solomon M, Sahar N, Pavlotzky F, Barzilai A, Jaffe CL, Nasereddin A, et al. Mucosal leishmaniasis in travelers with *Leishmania braziliensis* complex returning to Israel. Emerg Infect Dis 2019;25:642–8.

Soto J, Paz D, Rivero D, Soto P, Quispe J, Toledo J, et al. Intralesional pentamidine: a novel therapy for single lesions of Bolivian cutaneous leishmaniasis. Am J Trop Med Hyg 2016;94:852–6.

Sundar S, Chakravarty J. Leishmaniasis: an update of current pharmacotherapy. Expert Opin Pharmacother 2013;14:53–63.

Tuon FF, Amato VS, Graf ME, Siqueira AM, Nicodemo AC, Amato Neto V. Treatment of New World cutaneous leishmaniasis — a systematic review with a meta-analysis. Int J Dermatol 2008;47:109–24.

Van der Auwera G, Dujardina JC. Species typing in dermal leishmaniasis. Clin Microbiol Rev 2015;28:265–94.

WHO. Control of the leishmaniases: WHO TRS N°949 report of a meeting of the WHO Expert Committee. . p. 22–6.

Xia D, Sun WK, Tan MM, Zhang M, Ding Y, Liu ZC, et al. Aerosolized amphotericin B as prophylaxis for invasive pulmonary aspergillosis: a meta-analysis. Int J Infect Dis 2015;30:e78–84.