Laryngeal leishmaniasis in a HIV-positive patient: A case report and review of the literature

VIVIANA FISICARO[1*], EDOARDO CAMPANELLA[1*], ANDREA MARINO[2], ALESSANDRO GUARNERI[1], ALESSANDRO FRANZÒ[1], EUGENIA PISTARÀ[1], SERENA SPAMPINATO[1], ALESSANDRO BANDIERA[1], VINCENZO BOSCIA[2], BENEDETTO MAURIZIO CELESIA[2], GIOVANNI BARTOLONI[3], BRUNO CACOPARDO[2] and GIUSEPPE NUNNARI[2]

[1]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, I-98124 Messina; [2]Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, ARNAS Garibaldi Hospital, University of Catania, I-95122 Catania; [3]Department of Anatomy, Diagnostic Pathology, Legal Medicine Hygiene and Public Health, University of Catania, I-95123 Catania, Italy

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Abstract. Laryngeal leishmaniasis represents an infrequent manifestation of mucosal leishmaniasis, and even rarer is the coexistence of mucosal and visceral relapse. The present study describes the case of the simultaneous occurrence of relapsing mucosal and visceral leishmaniasis in a patient infected with human immunodeficiency virus (HIV) who was under secondary prophylaxis with liposomal amphotericin B. The clinical manifestations, diagnostic approaches employed and the treatment regimen implemented are described herein. Furthermore, the present study discusses the implications of the co-infection between leishmaniasis and HIV on the host immune response and the management strategies employed for relapsing forms. Emphasizing the necessity for the prompt initiation of targeted treatment to enhance clinical outcomes, the present study underscores the critical importance of maintaining a heightened level of suspicion for laryngeal leishmaniasis relapse in individuals with HIV exhibiting persistent laryngeal symptoms.

Introduction

Leishmaniasis is a neglected tropical disease caused by an obligate intracellular, vector-borne protozoan parasite belonging to the Trypanosomatidae family. The disease manifests in three primary phenotypic categories: Cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML) and visceral leishmaniasis (VL). The genus *Leishmania* encompasses a total of 22 species (1), each species displays specific geographical preferences, host-related factors and characteristic symptoms (2).

In people living with human immunodeficiency virus (HIV; PLWH), cutaneous, mucosal and visceral manifestations can be caused by any of the *Leishmania* species that infect humans (3). Moreover, in patients with HIV infection, the manifestations of leishmaniasis may differ from HIV-negative individuals, with different localizations and unique organ involvement, due to both the *Leishmania* characteristics and the peculiarity of HIV (4,5).

Leishmania and HIV share the same host cell targets and the synergistic interaction between these two diseases can contribute to the progression of both conditions, potentially attributed to the persistent activation of the immune system (6-8).

In PLWH, achieving the complete eradication of *Leishmania* is a rare occurrence, and the possibility of relapse, involving different organs, exists. Consequently, identifying predictive factors for leishmaniasis relapse has garnered significant attention (3,9,10).

The present study describes the case of an individual infected with HIV who experienced a rare simultaneous occurrence of relapsing mucosal and visceral leishmaniasis, highlighting the significance of the prompt suspicion and recognition of the disease, as well as the challenges in the differential diagnosis. Additionally, the implications of HIV-coinfection on the pathogenesis, the clinical manifestations, treatment strategies and prophylaxis measures employed for leishmaniasis are discussed.

Case report

A 58-year-old male patient with HIV presented at the Emergency Department of ARNAS Garibaldi Hospital

Correspondence to: Dr Andrea Marino, Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, ARNAS Garibaldi Hospital, University of Catania, Via Palermo 636, I-95122 Catania, Italy
E-mail: andrea.marino@unict.it

*Contributed equally

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(Catania, Italy), reporting a 6-month history of dysphonia and breathing difficulties. He also mentioned experiencing fever (up to 38˚C) in the past month. His medical history included HIV infection since 1996 and the current use of antiretroviral therapy with dolutegravir and doravirine. He was a smoker (~20 cigarettes daily) and had asthmatic bronchitis for which he used inhaled steroids. He had a previous case of visceral leishmaniasis in 2011 and had been on secondary prophylaxis with liposomal amphotericin B at a dose of 4 mg/kg every 4 weeks.

Upon a physical examination, he displayed mobile right-sided laterocervical lymphadenopathies measuring over a centimeter, which were firm and non-tender. Hepatosplenomegaly was also noted. Blood tests revealed a CD4 lymphocyte count <200 cells/mm^3, an HIV viral load <20 copies/ml, a white blood cell count of 2,100/mm^3, a red blood cell count of 3,800,000/mm^3, a hemoglobin level of 8.7 mg/dl, a platelet count of 75,000/mm^3 and a B2-microglobulin level of 10 mg/dl (Table I).

Following a neck ultrasound which revealed enlarged lymph nodes, a subsequent computed tomography scan confirmed these findings in the bilateral laterocervical regions, as well as in multiple mesenteric, external iliac and para-aortic locations (Fig. 1). PET/CT imaging indicated significant metabolic activity with abnormal tracer accumulation in various lymph node regions and nodules in the mesenteric area.

Indirect laryngoscopy identified hyperplastic lesions on the anterior and middle thirds of the left true vocal cord. Biopsies of the vocal cord and right supraclavicular lymph node revealed lymphomonocytic inflammation and phagocytic activity against *Leishmania* parasites, respectively (Fig. 2).

With these results, a diagnosis of simultaneous ML and VL relapse was made. Treatment commenced with liposomal amphotericin B at 4 mg/kg/day for 5 days, followed by a dose on the 10th day and four more doses every 7 days.

Following treatment, the patient's condition significantly improved, with resolution of dysphonia and breathing difficulties. Hematological parameters also improved (Table I). He was discharged after the sixth dose of liposomal amphotericin B and completed the treatment course as an outpatient. Secondary prophylaxis continued every 4 weeks as scheduled.

Discussion

Human leishmaniasis displays a range of clinical manifestations, which can be categorized into three main phenotypic types: CL, ML and VL. ML, in particular, refers to the engagement of mucous membranes in the upper respiratory tract, spanning from the inner walls of the nostrils to the larynx, as well as the oral cavity. This condition is caused by *Leishmania* spp., particularly New World species, such as *L. braziliensis* (11).

ML can manifest concurrently with or before CL or VL (12). In the Mediterranean area, ML is primarily caused by species within the *Leishmania donovani* complex, notably *Leishmania infantum* (2,13). Visceral leishmaniasis can affect various internal organs, particularly those belonging to the reticuloendothelial system, including the spleen, liver, lymph nodes and bone marrow, leading to pancytopenia with high risk of bleeding and severe infections (14,15).

In the case described herein, a diagnosis of laryngeal leishmaniasis was made in an individual living with HIV who suffered a relapse of VL despite receiving secondary prophylaxis for leishmaniasis. Laryngeal involvement is rare, occurring for only 1% of cases, as indicated by Cincurá *et al* (16). This discovery renders the present case unique, being the first documented occurrence of laryngeal involvement concurrent with a relapse of VL. Although instances of sequential mucosal relapse in VL have been reported, such occurrences are exceedingly uncommon (17,18).

Patients with ML frequently present with chronic nasal symptoms, including nasal discharge, ulcerations and epistaxis. Over time, these symptoms tend to exacerbate and can lead to complications like dysphagia and dysphonia, as observed in our patient, due to the gradual deterioration of soft tissues (2,13,19,20).

The mechanism through which *Leishmania* reach the mucous membranes remains a topic of ongoing debate. Three potential pathways have been proposed. Firstly, ML can arise due to the direct extension of contiguous facial skin lesions, as notably observed in cases of *L. major* infection. Another possible explanation for mucous membrane involvement is the direct inoculation of parasites into the mucosa through sand fly bites, particularly in the context of oral and nasal localizations. Lastly, lymphatic or hematogenous dissemination is considered a feasible route, especially in instances of *L. infantum* leishmaniasis, which typically lacks preceding skin manifestations (13).

Immunodeficiency significantly heightens susceptibility to leishmaniasis. In individuals with a robust immune system, the protective response against *Leishmania* is characterized by a Th1 cytokine profile, which confers resistance against infection and inhibits disease progression (21). Conversely, susceptibility to *Leishmania* infection and unfavorable outcomes are linked to a Th-2 cytokine response (22,23). In the context of HIV infection, there is a Th1/Th2 shift provoked by HIV, resulting in unconventional and widespread manifestations (13). The interplay between HIV and leishmaniasis can synergistically exacerbate the advancement of both conditions, possibly due to the chronic activation of the immune system (7,24,25).

Of note, PLWH who maintain higher CD4$^+$ counts tend to experience lower rates of relapse (9). Secondary prophylaxis holds significant importance in managing leishmaniasis. It has been observed that the relapse rate of VL in patients with CD4$^+$ counts <200, who receive monthly secondary prophylaxis, is comparable to that of patients with higher CD4$^+$ counts who do not receive such prophylaxis. The occurrence of relapse not only worsens immunosuppression, but also accelerates the progression of HIV disease. This heightened susceptibility to opportunistic infections can lead to severe consequences, including adverse outcomes and even mortality (26). Consequently, implementing secondary prophylaxis is crucial for mitigating the risk of relapse and its detrimental effects in individuals with both HIV and VL (27). However, although these occur at a lower rate, relapses in patients receiving secondary prophylaxis are frequently reported (27-29), as demonstrated in the case in the present study.

Considerable attention is being directed towards identifying variables that could act as predictors of leishmaniasis relapse, aiding clinicians in identifying PLWH who are at a

Table I. Laboratory findings (reference range) taken at the initiation of liposomal amphotericin B therapy, at the time of hospital discharge and at the end of therapy.

Parameter	At the initiation of liposomal amphotericin B therapy	At the time of hospital discharge	At the end of liposomal amphotericin B therapy
Hemoglobin, g/dl (13.6-17.2)	8.7	9.3	9.5
RBC, 10^6 cells/mmc (4.3-5.7)	3.8	4.1	3.99
WBC, cells/mmc (4,000-10,000)	2,100	4,300	2,100
Neutrophils, % (40-75)	50.3	69.2	45
Lymphocytes, % (25-50)	38.5	22.6	42.3
Platelets, cells/mmc x10^3 (150-400)	75	90	86
AST, UI/l (15-35)	16	11	11
ALT, UI/l (15-35)	6	9	6
Creatinine levels mg/dl (0.6-1.3)	1.07	1.28	1.40
C-reactive protein, mg/dl (0.01-0.5)	2.34	0.33	8

RBC, red blood cell count; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

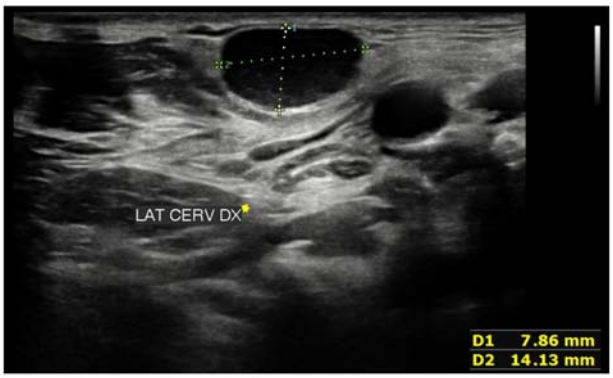

Figure 1. Neck ultrasound illustrating enlarged lymph nodes.

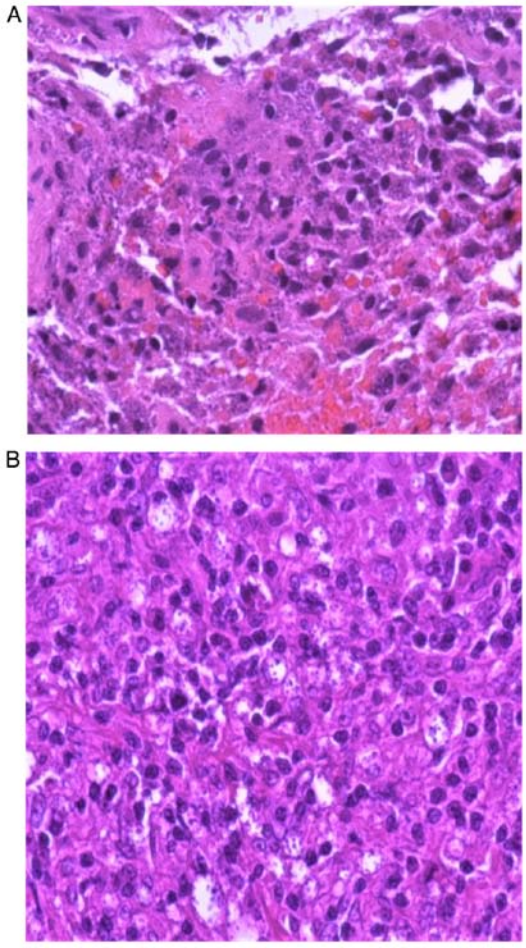

Figure 2. (A) Histological examination of vocal cord biopsy stained with hematoxylin and eosin (x60 magnification). The image reveals the presence of actively phagocytic histiocytes with *Leishmania* amastigotes within the lamina propria, in the context of extensive stromal amyloid degeneration. (B) Histological examination of the excisional biopsy of lymph node stained with hematoxylin and eosin (x60 magnification). The image reveals the presence of epithelioid granulomatous lymphadenitis, with evidence of phagocytes exhibiting abundant phagocytic activity towards *Leishmania* parasites.

higher risk. Cota *et al* (9) demonstrated that factors, such as the absence of $CD4^+$ cell count improvement during follow-up, $CD4^+$ counts <100 cells/ml at the onset of primary VL, the lack of secondary prophylaxis, and a history of previous VL relapse could potentially serve as predictive indicators for relapse. Similarly, Takele *et al* (10) suggested that lower $CD4^+$ T cell counts, a decreased production of IFN-γ and elevated levels of PD1 expression on $CD4^+$ T-cells could potentially be indicative markers of an increased risk of relapsing disease. An elevation in lactate dehydrogenase (LDH) levels is a useful marker for cell necrosis in such infections (30).

It has been postulated that local mucosal immunosuppressive factors, such as tobacco smoke, systemic or inhaled corticosteroid therapy and upper respiratory diseases can facilitate the development of ML (13,31,32) Fare clic o toccare qui per immettere il testo. The patient in the present study was a smoker and received inhaled steroids to manage asthmatic bronchitis (3).

Numerous studies have delved into the potential role of *Leishmania* RNA viruses (LRVs) in the pathogenesis of ML. These viruses are capable of infecting specific *Leishmania*

species, particularly *Leishmania braziliensis* and *Leishmania guyanensis*. Recent research carried out in murine models has revealed a close association between the presence of LRVs and the severity of infection. This association leads to modifications in the host's immune response to the parasite and is considered a significant virulence factor contributing to the development of ML. Indeed, when comparing the percentage of ML samples that tested positive for LRVs with those that were negative, the presence of the virus has been found to significantly exacerbate the disease (33,34).

Following the Infectious Diseases Society of America (IDSA) guidelines (3), diagnosing leishmaniasis involves identifying *Leishmania* amastigotes in tissue samples. Obtaining tissue aspirates or biopsy specimens is highly recommended for performing smears, histopathology, parasite culture and molecular testing. For VL, bone marrow aspiration is the preferred diagnostic source. Nonetheless, other potential sources, such as the liver, enlarged lymph nodes and whole blood can also be utilized. In the case described herein, the diagnosis of VL was established via a lymph node biopsy. For ML, it is advised that individuals at risk undergo a comprehensive assessment for mucosal symptoms as part of their initial evaluation. These individuals should be promptly referred to a specialist for an otorhinolaryngological (ORL) examination, which typically involves fiber-optic endoscopy. This comprehensive approach ensures early detection and appropriate management for those vulnerable to ML. This approach, involving ORL examination, is effectively highlighted in the case described herein as well. As shown in the present study, a microscopic confirmation is the preferred technique to ensure an accurate diagnosis of relapse. A positive result from a non-quantitative PCR assay may not definitively confirm or exclude the possibility of relapse.

As regards treatment, liposomal amphotericin B is the preferred regimen for VL, regardless of the patient's immune status. However, in immunocompromised individuals, the dosage regimen requires higher daily doses, an increased administration frequency and a greater cumulative total dose. Evaluating the response to anti-leishmanial treatment relies mainly on clinical criteria, eliminating the need for microscopic confirmation in patients who display swift clinical improvement. For clinically apparent ML, systemic anti-leishmanial therapy is advised to prevent both morbidity (e.g., disfigurement) and mortality (e.g., from respiratory obstruction or aspiration pneumonia). Additionally, the IDSA guidelines recommend considering prophylactic corticosteroid therapy for individuals with laryngeal/pharyngeal disease at increased risk of respiratory obstruction. The treatment for ML primarily involves lipid formulations of amphotericin B, particularly liposomal amphotericin B, with cumulative total doses varying from ~20 to 60 mg/kg. Notably, a strong association exists between clinical parameters and microscopic responses in cases of ML. It is crucial to emphasize that relapse in patients treated with amphotericin formulations signifies immunological failure rather than drug failure or resistance development. Hence, although data on this approach are limited, managing such patients with the same drug, possibly at higher doses or for extended periods of time, could be considered. Finally, according to the IDSA guidelines, initiating secondary prophylaxis with an effective anti-leishmanial drug is recommended after completing the initial treatment course. The most suitable agent and regimen, however, remain undetermined definitively. Periodic parenteral liposomal amphotericin B use (3-5 mg/kg every 3-4 weeks) has shown reduced relapse rates. Nonetheless, the risk of relapse persists, as observed in the patient described herein who experienced relapses of both VL and ML despite receiving secondary prophylaxis. As outlined by the IDSA guidelines, discontinuing secondary prophylaxis could be considered for individuals who lack evidence of active *Leishmania* infection, provided their CD4 cell counts have remained between 200-350 cells/mm^3 for at least 6 months. It should be noted that even in such cases, instances of relapse have been reported (3,35).

In conclusion, the present study underscores the significance of maintaining a vigilant mindset towards the relapse of VL and ML in a patient with HIV infection who previously experienced VL, even when receiving secondary prophylaxis. In the case of ML, the early recognition of symptoms can significantly improve the well-being and survival rates of patients, taking into consideration that smoking and inhaled steroids may play a critical role in disease development. As symptoms tend to be non-specific, it is crucial for physicians to consider the possibility of this coinfection and include ML in the differential diagnosis, distinguishing it from carcinoma, other malignant tumors, and granulomatous diseases.

Nevertheless, further research is warranted to gain a deeper understanding of the risk factors associated with leishmaniasis relapse and to devise more efficient diagnostic and preventive approaches (36). Early treatment has proven to enhance patient outcomes, and therefore, investing in comprehensive studies will facilitate the development of improved strategies for diagnosis and prevention.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors (VF, EC, AM, AG, AF, EP, SS, AB, VB, BMC, GB, BC and GN) contributed to the study conception and design. VF, EC and AM were involved in the conceptualization of the study. EC was involved in the methodology of the clinical case. AG, AF, EP, SS, AB, GB, VB and BMC were involved in analyzing the patient's data., VB, SS and AM were involved in data curation. VF and EC were involved in the writing and preparation of the original draft. AM was involved in the writing, reviewing and editing of the manuscript., GB, GN and BC supervised the study. All authors have read and

agreed to the published version of the manuscript. BC and GN confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient described herein.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of his data and any related images.

Competing interests

The authors declare that they have no competing interests.

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