Visceral leishmaniasis and lymphoma: a rare and dangerous couple

Nicola Battino, Antonio Pisano

Complex Operative Unit of Internal Medicine, ASL Sulcis-Iglesiente, "CTO" Hospital, Iglesias (SU), Italy

ABSTRACT

Leishmaniasis is a parasitic disease caused by protozoa of the genus *Leishmania*. The vectors are hematophagous (blood-feeding) dipterans of various genera, with humans serving as accidental definitive hosts and, in some cases, as reservoirs. Visceral leishmaniasis more often affects immunocompromised individuals, in whom the protozoan invades and replicates within the host's macrophages, evading innate and cell-mediated immune responses. We describe the case of a 54-year-old male patient who had not traveled to endemic areas. He presented with progressive asthenia associated with persistent fever, which had been treated at home with nonsteroidal anti-inflammatory drugs and oral betamethasone. During hospitalization, he developed cytopenia and hepatosplenomegaly. Bone marrow biopsy revealed the presence of *Leishmania* and intravascular large B-cell lymphoma. When faced with cases of fever of unknown origin, clinicians should also investigate opportunistic infections. An underlying condition causing immunosuppression may not be clear, and corticosteroids often alter hematological values, thus masking a hematological disease.

Correspondence: Nicola Battino, Complex Operative Unit of Internal Medicine, ASL Sulcis-Iglesiente, "CTO" Hospital, Iglesias (SU), Italy.
E-mail: nicola.battino@libero.it

Key words: visceral leishmaniasis, intravascular large B-cell lymphoma, hepatosplenomegaly, cytopenia.

Contributions: both authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: the patient agrees to the publication of the case report.

Availability of data and materials: all data underlying the findings are fully available

Funding: none.

Received: 25 October 2024.
Accepted: 1 November 2024.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2025; 19:1843
doi:10.4081/itjm.2025.1843

Introduction

Leishmaniasis is a vector-borne parasitic disease caused by a group of protozoa belonging to the genus *Leishmania* (Table 1). The parasites are transmitted to humans through the bite of the sandfly and predominantly affect the reticuloendothelial system. There are three forms of the disease: cutaneous, mucosal, and visceral forms (discussed in our case). In Europe, the only autochthonous etiological agent of the visceral form is *Leishmania infantum*. Approximately 300,000 new cases of visceral forms are reported annually, with 90% of cases occurring in Bangladesh, Brazil, Ethiopia, India, Nepal, South Sudan, and Sudan. The estimated number of deaths from visceral leishmaniasis each year is about 20,000-50,000, making it the second deadliest tropical disease.

HIV co-infection is common, as immunosuppression facilitates the progression of the infection, while the association with hematological diseases is rarer. The onset of symptoms is usually insidious, with a slow appearance of malaise, fever, weight loss, and splenomegaly (with or without hepatomegaly) over a period of weeks or months.[1] Bone marrow invasion can lead to pancytopenia, with hemorrhagic diathesis requiring transfusions of concentrated red blood cells and platelets.

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 25% of NHL cases.[2] In Europe, the incidence is about 4.92 cases per 100,000 people per year.[3]

At diagnosis, around 40% of patients have stage I or II disease. However, the majority (about 60%) present with stage III/IV disease. Bone marrow involvement occurs in up to 42% of cases, which indicates a poorer prognosis,[4] with survival being less than one year if untreated.[5]

The diagnostic category of DLBCL is heterogeneous in terms of morphology, genetics, and biological behavior. In the 2017 World Health Organization classification, numerous clinicopathologic entities are recognized as

separate diagnostic categories. Intravascular large B-cell lymphoma (ILCL) is a rare subtype of large B-cell lymphoma characterized by the proliferation of lymphoma cells within the lumen of small blood vessels, particularly capillaries and post-capillary venules, without an obvious extravascular tumor mass or circulating lymphoma cells in peripheral blood. The true incidence of ILCL is unknown.

In 2020, Kalmi *et al*. published a review that identified 11 cases of visceral leishmaniasis in patients with newly diagnosed or known lymphoma from 1988 to 2020.[6]

The cytokines released by recruited regulatory T-cells may inhibit immune responses to the parasite, facilitating the growth of both the tumor and the parasite within the same tissue.

Case Report

We describe the case of a 54-year-old man, with no known chronic illnesses, admitted for persistent fever lasting three months, with peaks reaching 39°C, chills, and night sweats. He had taken nonsteroidal anti-inflammatory drugs and corticosteroids at home without benefit.

Upon admission, the patient was in fair general condition, with normal hemodynamic parameters. Physical examination did not reveal any significant abnormalities, particularly in the hypochondriac organs, which were normal, a finding confirmed by a total-body computed tomography (CT) scan conducted at admission that also ruled out infectious foci or tumor masses.

Hematological tests showed mild neutrophilic leukocytosis with a preserved leukocyte formula, modest normocytic anemia (9.6 g/dL), elevated inflammatory markers (C-reactive protein 7.8 mg/L, erythrocyte sedimentation rate 120), slight elevation of transaminases and γ-glutamyl transferase, hypoalbuminemia, and hyperferritinemia (1337 ng/mL).

Empirical broad-spectrum intravenous antibiotic therapy with β-lactam and quinolone was initiated, but febrile episodes persisted, and the patient's general condition deteriorated. *Klebsiella pneumoniae* was isolated from the sputum culture, leading to the administration of meropenem instead of the β-lactam. Further cultures (blood cultures, urine cultures) were performed without isolating any pathogens, and serological tests returned negative results for toxoplasma, *Rubella*, cytomegalovirus, Epstein Barr virus, *Borrelia*, *Brucella*, *Rickettsia*, *Leishmania*, and *Legionella*. Nucleic acid testing on a nasopharyngeal swab was also negative for adenovirus, coronavirus, Middle East respiratory syndrome, metapneumovirus, rhinovirus, influenza A, influenza A/H1, influenza A/H3, influenza B, parainfluenza virus types 1-4, respiratory syncytial virus, *Bordetella pertussis* and *parapertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*.

Microscopic examination of the peripheral blood smear confirmed the instrumental findings of the complete blood count and did not reveal parasites such as protozoa or plasmodia. The quantiferon test was negative.

Clinical conditions did not improve despite therapy, and after the 10th day of hospitalization, anemia, thrombocytopenia, elevated transaminases, and lactic dehydrogenase levels appeared (Table 2).

The new clinical finding was hepatosplenomegaly, confirmed by a follow-up CT scan, which also revealed right basal pneumonia. The whole-body fludeoxyglucose-18 positron emission tomography scan detected increased glucose metabolism in the liver and spleen, widespread hypermetabolic activity in the bone marrow compartment, and hyperfixation of the radiotracer in the pulmonary parenchymal consolidation of the right lower lobe.

Bone marrow aspiration showed a degree of dysplasia in the lymphocytic lineage, but no parasites were visualized.

Finally, a bone marrow biopsy revealed the presence of ILCL with a concomitant *Leishmania* infection.

Liposomal amphotericin B therapy was initiated, resulting in the remission of the fever. After treating the infection, the patient was enrolled in the therapeutic protocol for lymphoma.

Discussion

The complete diagnosis was established through a bone marrow biopsy after 20 days of hospitalization and

Table 1. Geographical locations of Leishmania species

Species	Geographical locations
L. donovani	India, Sub-Saharan Africa, China, Pakistan
L. infantum	Mediterranean area, Middle East, North and Sub-Saharan Africa, Balkans, China
L. major	Middle East, Africa, India, China
L. tropica	Middle East, India, Southern Europe, Southwest Asia
L. aethiopica	Etiopia, Kenya, Yemen
L. chagasi	South America
L. venezuelensis	Venezuela
L. mexicana	Mexico, Central America, Texas, Oklahoma
L. amazonensis	Amazon Basin, Brazil
L. braziliensis	South America
L. peruviana	Peru and Argentina (Altiplano)
L. guyanensis	Northern Amazon, Guyana
L. panamensis	Panama, Costa Rica, Colombia

over 3 months since the onset of the fever. The pancytopenia associated with hepatosplenomegaly, which appeared later, the negative serology for *Leishmania*, and the absence of superficial and deep lymphadenopathies contributed to the diagnostic delay.

In cases of fever of unknown origin, the clinician must consider every possible diagnosis: infections (accounting for 25% to 50% of cases), connective tissue diseases (10% to 20% of cases), neoplasms (5% to 35% of cases), and other pathologies (15% to 25% of cases). It is essential to note how these percentages can vary in different geographical regions.[7]

It is crucial to emphasize the dangers of prescribing corticosteroids without a definitive diagnosis, as they can mask the clinical picture and hematochemical values and create immunosuppression if used for a prolonged period. Among infections, opportunistic pathogens such as mycobacteria, fungi, and parasites should be investigated, and clinicians should not stop at the negative results of serological tests or polymerase chain reaction amplification tests.

There are various serological tests for human leishmaniasis, both quantitative and qualitative. The most used tests (direct immunofluorescence, enzyme-linked immunosorbent assay, and western blot) have medium to high specificity and sensitivity (70-98%), particularly the western blot. Bone marrow aspirates are generally safer than splenic aspirates, and in one study, the sensitivity of bone marrow examination was found to be proportional to the time spent examining the smear (66% and 92% at five minutes and one hour, respectively).[8]

Histopathological diagnosis requires the visualization of amastigotes, which are spherical or ovoid bodies measuring 1 to 5 microns in length and 1 to 2 microns in width. Amastigotes are usually found inside macrophages but can also be seen outside the cells. In our case, it was necessary to perform a bone marrow histopathological examination to arrive at the correct diagnosis.

Visceral leishmaniasis enters the differential diagnosis with malaria, which can present with a similar clinical picture. However, our patient had not traveled to endemic areas, and the search for plasmodium was negative. Among fungi, *Histoplasma capsulatum* can cause an acute infection with fever, hepatosplenomegaly, and pancytopenia in the context of immunosuppression. Other parasitic infections that were ruled out include extraintestinal amebiasis and schistosomiasis, both of which are considered in the differential diagnosis of fever and hepatosplenomegaly.

Another condition that was investigated was hemophagocytic lymphohistiocytosis (HLH), an aggressive syndrome with high mortality characterized by excessive immune activation, with the absence of normal downregulation by activated macrophages and lymphocytes. Infection is a common trigger in both genetically predisposed and sporadic cases. Our patient met four diagnostic criteria for HLH:[9] fever, splenomegaly, cytopenia, and ferritin >500 ng/mL. Bone marrow histopathology ultimately ruled out this diagnosis as well.

Visceral leishmaniasis unrelated to HIV is becoming increasingly common in non-tropical countries due to the growing number of patients with chronic diseases and the development of immunomodulatory drugs.[1] In our case, the histological study of the bone marrow revealed the coexistence of large B-cell lymphoma and leishmania, a rare association. The aforementioned 2020 review reminds physicians to consider visceral leishmaniasis in patients with new systemic symptoms that might be mistakenly diagnosed as the progression of an underlying lymphoma when known.[6] Visceral leishmaniasis is described in the literature as an opportunistic infection in other hematological malignancies such as acute myeloblastic leukemia and chronic myeloid leukemia.[10]

Conclusions

In conclusion, our case, though rare, highlights the importance of investigating opportunistic infections even in HIV-negative patients. Immunosuppression not linked to HIV infection may present more subtly, as in the case of intravascular lymphoma. Additionally, an infectious diagnosis should not be ruled out after negative serology, as our case demonstrates that sometimes more invasive investigations are necessary. Lastly, it is important to note that the use of corticosteroids without a specific diagnosis, besides contributing to immunosuppression, can mask hematochemical values, as it happened with our patient, delaying the onset of cytopenia, which led us to perform a bone marrow biopsy.

Table 2. Alterations in blood values during hospitalization.

	1° day	10° day	16° day	24° day
Hgb	9.6	7.0	7.1	7.2
Rbc $\times 10^6$mcL	3.08	2.30	2.35	2.38
Mcv	92.5	90.4	86.8	85.3
WBC $\times 10^3$ mcL	12.55	8.40	5.97	5.86
PLT $\times 10^3$ mcL	210	140	84	57
AST	45	104	57	347
ALT	43	96	69	150
LDH	306	309	322	

HgB, hemoglobin; Rbc, red blood cells; Mcv, mean corpuscular volume; WBC, white blood cells; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase.

References

1. Jeronimo SMB, de Queiroz Sousa A, Pearson RD. Leishmaniasis. In: Guerrant RL, Walker DH, Weller PF, eds. Tropical infectious diseases: principles, pathogens and practice. 3rd ed. Philadelphia, PA, USA: Saunders Elsevier; 2011.
2. World Health Organization. WHO Classification of tumours of haematopoietic and lymphoid tissues. 2017. Available from: https://www.iarc.who.int/news-events/who-classification-of-tumours-of-haematopoietic-and-lymphoid-tissues-2/.
3. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116:3724-34.
4. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press; 2017.
5. Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. CA Cancer J Clin 2010;60:393-408.
6. Kalmi G, Vignon-Pennamen MD, Ram-Wolff C, et al. Visceral leishmaniasis in patients with lymphoma: Case reports and review of the literature. Medicine 2020;99:e22787.
7. Wright WF, Betz JF, Auwaerter PG. Prospective studies comparing structured vs nonstructured diagnostic protocol evaluations among patients with fever of unknown origin: a systematic review and meta-analysis. JAMA Netw Open 2022;5:e2215000.
8. Da Silva MRB, Stewart JM, Costa CH. Sensitivity of bone marrow aspirates in the diagnosis of visceral leishmaniasis. Am J Trop Med Hyg 2005;72:811-4.
9. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
10. Prasad Sah S, Rijal S, Bhadani PP, et al. Visceral leishmaniasis in two cases of leukemia. Southeast Asian J Trop Med Public Health 2002;33:25-7.