

Visceral leishmaniasis in patients with lymphoma

Case reports and review of the literature

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Abstract

Introduction: Non-HIV-related visceral leishmaniasis (VL) is becoming increasingly prevalent in nontropical countries because of the increasing number of patients with chronic diseases and the development of immune-modulating drugs.

Patient concerns: Case 1 is a 60-year-old male patient of Senegalese origin presented with weight loss, lymphadenopathy, anemia, and elevated lactate dehydrogenases. Case 2 is a 46-year-old male patient of Algerian origin, with a negative HIV serology presented with cutaneous lesions.

Diagnosis: Patient 1: The diagnosis of stage IV lymphocytic lymphoma (LL) was confirmed by an inguinal nodal biopsy in 2013. Patient 2: The diagnosis of T-cell lymphoma was made in 2003.

Interventions: Patient 1 received 5 cycles of bendamustine and rituximab followed by a complete remission. Patient 2 was initially treated with >10 different treatments followed by 8 different chemotherapy regimens due to the disease progression.

Outcomes: Patient 1: In 2017, after a follow-up of 4 years, the patient presented with fever, lymphadenopathy, splenomegaly, and pancytopenia in the setting of hemophagocytic syndrome. The initial diagnosis was a relapse of lymphoma and the patient was treated with ibrutinib. His status worsened, and *Leishmania* DNA was detected by polymerase chain reaction (PCR) on the blood and bone marrow aspirates. Ibrutinib was stopped. Amphotericin B treatment induced a complete clinical remission and clearance of *Leishmania* DNA from the blood.

Patient 2: In 2017, after a follow-up of 14 years, the patient presented with fever, lymphadenopathy, hepatosplenomegaly, pancytopenia with hemophagocytic syndrome, and an increase in the tumor skin lesions. A skin biopsy was taken from the face and the patient. A careful reexamination of the skin biopsy revealed the presence of *Leishmania* bodies. He was treated with 40 mg/kg liposomal amphotericin B leading to a regression of the clinical symptoms and negativation of the blood PCR.

Conclusions: This case study shows that VL may be a diagnostic challenge in patients with lymphoma. Reactivation or primary infection should be considered in the differential diagnosis. The purpose of this study is to remind clinicians to think of VL in patients with systemic symptoms that could be misdiagnosed as a progression of the underlying lymphoma.

Abbreviations: DNA = deoxyribonucleic acid, HIV = human immunodeficiency viruses, HL = Hodgkin lymphoma, LL = lymphocytic lymphoma, SMZL = splenic marginal zone lymphoma, T-PLL = T cell prolymphocytic leukemia, VL = visceral leishmaniasis.

Keywords: diagnostic challenge, lymphoma, negative HIV status, visceral leishmaniasis

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CT, MB and AM share last authorship.

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1. Introduction

Visceral leishmaniasis (VL) is a vector-borne parasitic disease caused by a group of protozoa belonging to the *Leishmania* genus. The parasites are transmitted to humans via the bite of the phlebotome and predominantly target the reticuloendothelial system. VL is endemic in tropical and subtropical areas, including the Mediterranean basin. International travelling has caused an increase in leishmaniasis cases in nonendemic countries, making the recognition of this infection important. Non-HIV-related VL is becoming increasingly prevalent in nontropical countries because of the increasing number of patients with chronic diseases and the exponential development of immune-modulating drugs for the treatment of auto-immune, inflammatory, and neoplastic diseases, especially hematological malignancies.^[1,2] VL is a life-threatening condition usually presenting with hepatosplenomegaly, chronic fever, weight loss, and pancytopenia. We present a case series and review of 11 cases of VL in the setting of lymphoid malignancy, including 2 original cases. In 7 of these cases, the clinical presentation was misleading and mimicked that of a progression of the underlying lymphoma and led to the use of chemotherapy or targeted treatment of the lymphoma.

2. Materials and methods

We present 2 original cases and a review of the literature. Patients have provided informed consent for the publication of their cases. All the procedures were performed in accordance with the principles expressed in the Declaration of Helsinki. According to the French legislation, ethical approval was not required for this observational, noninterventive study.

Using the PubMed database, we searched all the case reports of VL associated with lymphoma since 1988 (older available case report). The MeSH terms used for the search were: «leishmaniasis», «visceral leishmaniasis», «lymphoma», «Hodgkin lymphoma» and «chronic lymphocytic leukemia». The search was limited to studies performed in humans, published in English or French. We selected publications on the basis of their title and abstract. We screened the references of all case reports and reviewed additional cases. Other primary or secondary causes of immunodeficiency, mucosal and mucocutaneous leishmaniasis^[3,4] were excluded from the analysis. We extracted data from the relevant articles, including patient demographics and a detailed medication history. We documented the clinical features of the VL and of the lymphoma, including fever, weight loss, splenomegaly, skin involvement, biological parameters, histology, treatments received, and evolution.

3. Case reports

3.1. Case 1

A 60-year-old male patient of Senegalese origin presented with weight loss and lymphadenopathy. The biological analysis showed anemia (11 g/dL), elevated lactate dehydrogenases, and an IgGκ monoclonal gammopathy. A sternal puncture found a lymphocytic infiltration of the bone marrow.

The computed tomography (CT) scan revealed lymphadenopathy and splenomegaly. The diagnosis of stage IV lymphocytic lymphoma (LL) was confirmed by an inguinal nodal biopsy. He received 5 cycles of bendamustine and rituximab followed by a complete remission. This treatment was complicated by several infectious complications due to hypogammaglobulinemia.

Four years later, the patient presented with fever, lymphadenopathy, splenomegaly, and pancytopenia in the setting of hemophagocytic syndrome. The initial diagnosis was a relapse of the hematological disease and the patient was treated with ibrutinib. His status worsened, and a second bone marrow aspiration was performed. *Leishmania* DNA was detected by PCR on the blood and bone marrow aspirates. A diagnosis of *L. infantum* visceral infection was made.

The patient reported travels in Gambia, Burkina Faso, Mali, and Mauritania. His HIV status was negative. Ibrutinib was stopped. Amphotericin B treatment induced a complete clinical remission and clearance of *Leishmania* DNA from the blood.

3.2. Case 2

A 46-year-old male patient of Algerian origin and with a negative HIV serology, presented with a primary cutaneous peripheral T-cell lymphoma, not otherwise specified. He was initially treated with topical steroids, PUVA therapy, interferon, bexarotene, methotrexate, followed by 8 different chemotherapy regimens due to the disease progression. Fourteen years after the initial diagnosis, he presented hemophagocytic syndrome, and an increase in the tumor lesions of the face (Fig. 1). He was then erythrodermic with splenomegaly, multiple cutaneous tumors, and fever. He was treated with systemic corticosteroids and a new line of treatment with liposomal doxorubicin. A careful reexamination of the skin biopsy performed revealed abnormally frequent histiocytes and the presence of *Leishman* bodies. *Leishmania* amastigotes were visualized on the bone marrow aspirate and *Leishmania infantum* DNA was detected by PCR in the blood and skin.^[5] The patient reported yearly travels to Algeria. He was treated with 40 mg/kg liposomal amphotericin B leading to a regression of the clinical symptoms and negativation of the blood PCR. Several relapses occurred requiring a maintenance treatment with amphotericin B.

4. Review of the literature

We identified 11 case reports of VL in the setting of lymphoma. In 2 patients, the diagnosis of lymphoma was infirmed^[6,7] and there was a final number of 9 patients with coexistent VL and lymphoma (Table 1).

The median age of the patients was 56 years (range, 19–72). Eight patients were males and 1 female.

The HIV status was negative in all patients. Five patients were Europeans (Italy, Germany), 1 was Brazilian, and 1 was Japanese, the origin was unknown for the last 2 patients. Travels were reported in 4 patients (Iraq and Afghanistan, n = 1; China, n = 1; Mediterranean basin, n = 1; Spain, n = 1). There were no reported data about insect bites. The hematological malignancies were Hodgkin lymphoma (HL, n = 2),^[8,9] splenic marginal zone lymphoma (SMZL, n = 2),^[10,11] follicular cell lymphoma (n = 1),^[12] lymphoplasmocytic lymphoma (n = 1),^[13] chronic lymphocytic leukemia (n = 1),^[14] angioimmunoblastic T lymphoma (n = 1),^[11] and T-cell prolymphocytic leukemia (T PLL, n = 1).^[15] All the patients had received cytotoxic chemotherapy except for the patient with T-cell prolymphocytic leukemia.^[15] VL developed at the time of the diagnosis of lymphoma in 2 patients,^[8,15] before in 2^[8,9] and during the course of the disease in the others.

Clinical signs and symptoms included splenomegaly in 8 patients, lymphadenopathy in 6 patients, fever in 5, weight loss in

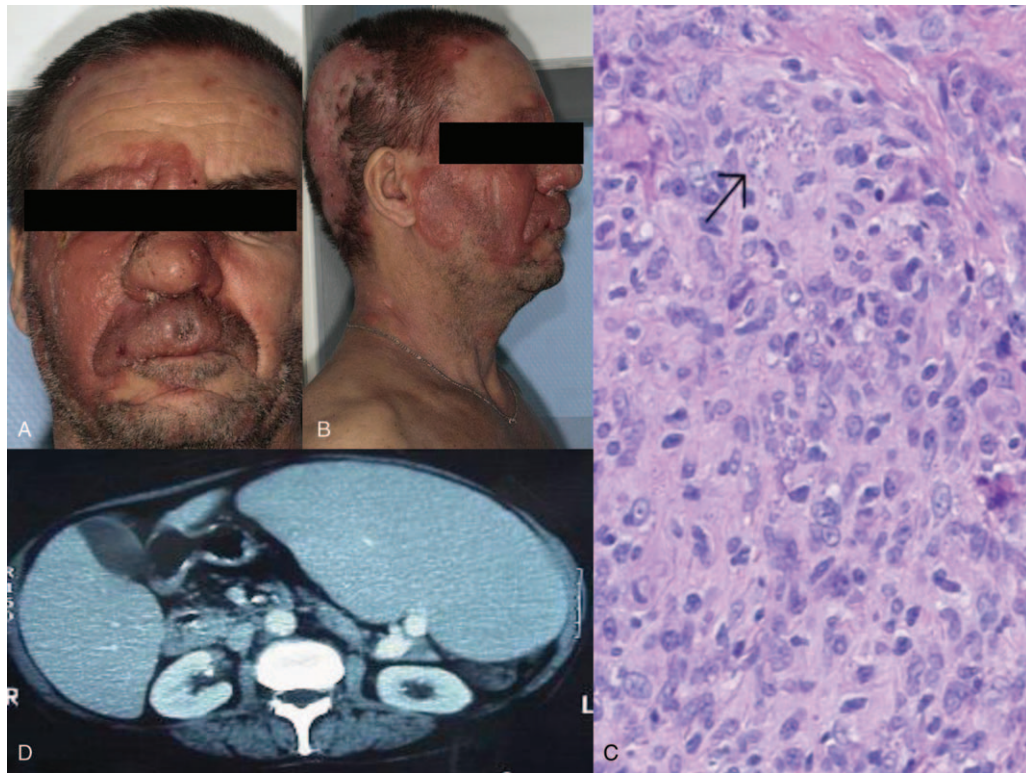


Figure 1. Clinical, histological, and radiological signs in a patient with cutaneous T-cell lymphoma and associated cutaneous and visceral leishmaniasis. (A, B) Clinical pictures of patient 2 with cutaneous T-cell lymphoma and associated cutaneous and visceral leishmaniasis, before treatment with amphotericin B. (C) Histology of the right cheek skin biopsy in the same patient. Hematoxylin-eosin, $\times 40$ magnification. Histiocytes with *Leishmania* bodies (arrow) and lymphoma cells were coexistent on the same skin biopsy. (D) Transversal section of the computed tomography scan at the time of visceral leishmaniasis diagnosis, showing the existence of a splenomegaly.

3, and skin manifestations in 2 patients (maculopapular rash and skin darkening).

Medullary infiltration was present in 7 patients, pancytopenia in 4 patients. There was no associated hemophagocytic syndrome.

The parasitic species was *Leishmania infantum* ($n=5$), and not specified in 4 cases. The diagnosis was based on medullary puncture ($n=6$), presence of *Leishmania* in the peripheral blood smear ($n=2$) or on histology (liver biopsy, $n=1$), serology ($n=3$), blood PCR ($n=3$), tissue PCR (kidney biopsy, $n=1$). VL was mistaken as lymphoma progression in 5 patients.

The median follow-up after diagnosis was 22.8 months.^(1–72)

Treatments of VL included systemic amphotericin B ($n=8$), pentamidine ($n=1$), antimonium ($n=1$). The outcome was a complete remission in 4 patients with negatiation of the PCR, 2 clinical complete remission of VL (with no control of the PCR), 2 patients died at last follow-up.

5. Discussion and conclusion

Here, we report 11 cases of VL in patients with lymphoid malignancies, including 7 cases in which VL was misdiagnosed as a progression of the underlying hematological malignancy. The expected increase in the number of international travelers and migrants, and global warming in the next decades, suggest that such cases will become more and more frequent. VL can be the result of a parasite reactivation during episodes of immune

suppression, or of a recent infection after travel to endemic countries. Reactivation seems rather unlikely given the number of VL cases relative to the large number of immunocompromised patients born in endemic areas. Both our patients had recently traveled to endemic areas. Clinicians should thus be aware of the symptoms of VL and consider it in the differential diagnosis in patients with hematological malignancies. Coexistence of lymphoma and leishmaniasis in the same node was described in 2 patients with Hodgkin lymphoma.^[6,7] Cytokines released by recruited regulatory T cells may inhibit the immune responses to the parasite, facilitating the growth of both the tumor and parasite within the same tissue. The clinical symptoms (splenomegaly, fever, weight loss) and laboratory abnormalities (pancytopenia) are often nonspecific. Serological diagnosis of VL may be delayed or missed in patients treated with drugs that interfere with antibody production (rituximab).^[10] Rituximab is known to impair both antibody production and the TH2 cytokine responses by abolishing antigen presentation by B-cells, while enhancing both the number and the activity of regulatory T cells.^[10] Thus, blood or medullary PCR may be helpful in the diagnosis of VL and in the disease follow-up. The parasite species was *L infantum* (when specified), consistent with the fact that others species like *L major* do not disseminate.^[16]

In 2 patients from the literature, SMZL developed after years of VL infection.^[8,9] There is a possible correlation between the 2 conditions because chronic antigenic stimulation by microbial agents has been proposed as a possible pathogenic mechanism in

Table 1

Clinical characteristics and evolution of 9 patients with lymphoma and visceral leishmaniasis from the literature.

Article	Sex	Age	Lymphoma	Clinical manifestations	Marrow infiltration	Hematological treatments	Diagnosis of visceral leishmaniasis	Recent travel	Species	Leishmaniasis serology	Leishmaniasis on BM	Leishmaniasis treatment	Cytopenias: evolution	Blood Leishmania PCR: evolution	Evolution
Casabianca et al. Seronegative visceral leishmaniasis with relapsing and fatal course following rituximab treatment. <i>Infection</i> . 2011;39(4):375–8.	M	72	Follicular lymphoma	Splenomegaly and lymphadenopathy	Yes	Rituximab and polychemotherapy	After the diagnosis of lymphoma	No	Infantum	Negative	Yes	Ampho B	Persistent pancytopenia	Negativation and relapse	CR, then relapse—deceased
Cencini et al. Atypical clinical presentation of visceral leishmaniasis in a patient with non-Hodgkin lymphoma. <i>Eur J Haematol</i> . 2015;94(2):186.	M	60	Lymphoplasmacytic lymphoma	Splenomegaly and pancytopenia	Yes	Rituximab and bendamustine	ND	NA	NA	NA	Yes	Ampho B	Regression	NA	CR
Orlandi et al. Visceral leishmaniasis mimicking Richter transformation. <i>Leuk Lymphoma</i> . 2014;55(12):2952–4.	M	56	Chronic lymphocytic/leukemia	Splenomegaly and lymphadenopathy	Yes	Rituximab and polychemotherapy, alemtuzumab	After the diagnosis of lymphoma	NA	NA	NA	Yes	Ampho B	Regression	NA	Partial remission, then relapse
Domingues et al. Coexistence of leishmaniasis and Hodgkin's lymphoma in a lymph node. <i>J Clin Oncol</i> . 2009;1027(32):e184–5.	M	15	Hodgkin lymphoma	Weightless, fever, lymphadenopathy	None	Polychemotherapy	After the diagnosis of lymphoma	NA	Infantum	NA	Yes	Ampho B	Regression	Negativation	CR, then relapse, and second CR
Evers et al. Visceral leishmaniasis clinically mimicking lymphoma. <i>Ann Hematol</i> . 2014;93(5):665–7.	M	57	Splenic marginal zone lymphoma	Splenomegaly and pancytopenia	Yes	Splenectomy	Before the diagnosis of lymphoma	Spain	Infantum	Positive	Yes	Ampho B	Regression	Negativation	CR
Vase et al. Development of splenic marginal zone lymphoma in a HIV-negative patient with visceral leishmaniasis. <i>Acta Haematol</i> . 2012;128(1):20–2.	M	60	Splenic marginal zone lymphoma	Fever, splenomegaly and pancytopenia	Yes	Splenectomy and rituximab	Before the diagnosis of lymphoma	Mediterranean basin	Infantum	NA	NA	Ampho B	Regression	Negativation	CR
Osakwe et al. Visceral leishmaniasis with associated immune dysregulation leading to lymphoma. <i>Mil Med</i> . 2013;178(3):e386–9.	M	50	Angioimmunoblastic T cell lymphoma	Fever, splenomegaly, lymphadenopathy, maculopapular rash	Yes	Rituximab and polychemotherapy	After the diagnosis of lymphoma	Iraq, Afghanistan	NA	NA	NA	Ampho B	NA	NA	NA
Magnan et al. Visceral leishmaniasis associated with Hodgkin's disease: diagnostic difficulties. <i>Rev Pneumol Clin</i> . 1991;47(4):188–91.	F	19	Hodgkin lymphoma	Weight loss, fever, splenomegaly, lymphadenopathy and anemia	Yes	Polychemotherapy	Simultaneous	NA	NA	Positive	Yes	Meglumine and thiopeptamidine	Regression	NA	CR
Liao et al. Concomitant T-cell prolymphocytic leukemia and visceral leishmaniasis: a case report. <i>Medicine</i> (Baltimore). 2016;97(38):e12410.	M	50	T-cell prolymphocytic leukemia	Weight loss, fever, splenomegaly, skin lymphadenopathy, skin darkening and pancytopenia	NA	NA	Simultaneous	China	Infantum	NA	Yes	Antimonium and Ampho B	NA	NA	Deceased
Case 1	M	60	Lymphocytic lymphoma	Weight loss, lymphadenopathy, splenomegaly, anemia	Yes	Rituximab and bendamustine	After the diagnosis of lymphoma	Gambia	Infantum	Positive	Yes	Ampho B	Regression	Negativation	CR
Case 2	M	46	PTCL NCS	Fever, lymphadenopathy, splenomegaly, pancytopenia	Yes	8 different chemotherapy	After the diagnosis of lymphoma	Algeria	infantum	NA	Yes	Ampho B	Regression	Negativation	CR then relapse

CR = complete response; F = female; M = male; NA = not available; VL = visceral leishmaniasis.

MZL. *Helicobacter pylori* infection has been involved in the pathophysiology of gastric MZL. The parasites enter the spleen and activate macrophages of the marginal zone, inducing an interleukin-10-mediated permissive environment.^[17] This sustained antigenic stimulation triggers polyclonal B-cell proliferation. This pathway is essential for controlling B-cell proliferation^[18] and its persistent activation is known to increase the risk of B cell malignancies.

In conclusion, *Leishmania* infection should be considered in the differential diagnosis of lymphoma progression in patients living in or migrating from endemic countries, presenting with fever of unknown origin, and a blood *Leishmania* PCR systematically performed in suspicious cases.

Author contributions

Original drafting of the manuscript: GK, AdM

Study supervision: SBr, CT, MBag, AdM

Acquisition and analysis of data: GK, MDVP, CRW, MBat, ML, JDB, SH, SBe

Critical review of the manuscript and final approval: all authors

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