

Received: 2017.10.16  
Accepted: 2018.01.31  
Published: 2018.05.01

e-ISSN 1941-5923  
© Am J Case Rep, 2018; 19: 512-516  
DOI: 10.12659/AJCR.907584

# Leishmania in a Patient with Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia

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Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Patient:** Male, 73  
**Final Diagnosis:** Leishmania  
**Symptoms:** Fever  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Oncology

**Objective:** Unusual clinical course  
**Background:** Leishmaniasis is a parasitic infection spread by the bite of infected sand flies that are usually present in the Middle East, Africa, and some parts of Asia and Europe. Leishmaniasis manifests in 3 different forms: Visceral (also known as Kala Azar), which is the most serious type; cutaneous, which is the most common type; and mucocutaneous. The symptoms of this infection range from a silent infection to fever, enlargement of the liver and spleen, weight loss, and pancytopenia.  
**Case Report:** In this case report, we discuss a 73-year-old man known to have chronic lymphocytic leukemia (CLL), presenting with unremitting fever and who to our surprise was found to have Kala Azar.  
**Conclusions:** Early diagnosis and treatment are very important in treating visceral leishmaniasis. While the conventional treatment in immunocompromised patients is liposomal amphotericin B, our patient responded to corticosteroids.

**MeSH Keywords:** General Surgery • Laparoscopes • Medical Oncology

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/907584>

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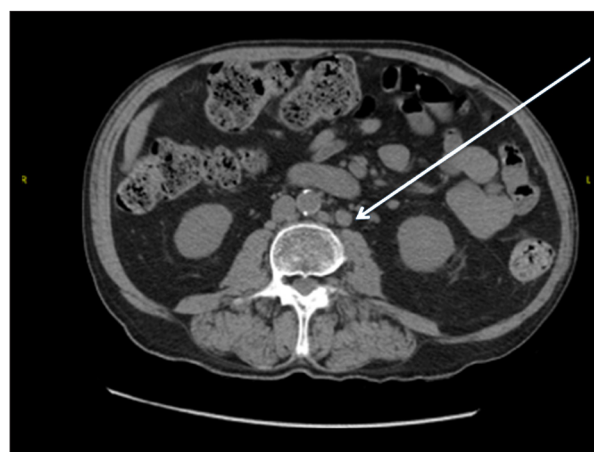
## Background

Leishmaniasis is a condition caused by an intracellular infection from protozoans of the genus *Leishmania*. Rodents and canines are the reservoirs for the protozoans, and the vector is the phlebotomine sand fly. Humans play the role of the host [1]. Depending on the *Leishmania* species and the host immune response, 3 clinical forms of Leishmaniasis may develop: cutaneous, visceral, and mucocutaneous [2]. Leishmaniasis is endemic in about 90 countries; at least 12 million people are reported to be infected worldwide, and 400 000 new cases are reported each year [3]. Visceral leishmaniasis presents as a systemic disease with symptoms such as weight loss, skin lesions, fever, anemia, leukopenia, lymphadenomegaly, and hepatosplenomegaly [4]. However, these symptoms most often develop several months or even years after the primary infection. The manifestation of leishmaniasis in the form of superficial lymph node enlargement is known to occur in the Mediterranean countries, Africa, and China [3]. Here, we report the case of a 73-year-old man with a history of chronic lymphocytic leukemia who presented for non-remitting fever. A laparoscopic para-aortic lymph node dissection was done and biopsies revealed visceral leishmaniasis.

## Case Report

A 73-year-old Italian man, known to have chronic lymphocytic leukemia (for more than 14 years) and benign prostatic hyperplasia, presented due to a 30-day history of non-remitting fever, diaphoresis, and weight loss. He was known to be pancytopenic, with a documented positive Coombs test. He had been living in Spain and within the last 10 years had only travelled to Lebanon and Italy. He had no sick contacts, drank 1 glass of wine daily, and smoked 15 cigarettes a day. He denied IV drug use and other substance abuse. His past medical history revealed that he had a left ureteral stone treated by ureterolithotomy. In addition, he had a disc herniation repair and a previous fine-needle aspiration of the thyroid showing a colloid nodule. On medication review, he was taking Prednisone 30 mg for 2 weeks as treatment for hemophagocytic syndrome, which was diagnosed in Spain, with which he reports mild improvement of his symptoms. He was also taking Omnic (a proton pump inhibitor) 0.4 mg, as well as ciprofloxacin, acyclovir, and fluconazole to cover possible infectious agents due to persistence of fever in his immunocompromised state.

On physical exam, the patient was found to be fatigued and sweating. There were a few lesions noted in the throat. In addition, a distended abdomen and hepatosplenomegaly were noted. Initial labs noted an ANC of 756, hemoglobin of 9.5, and platelets at 24 000.

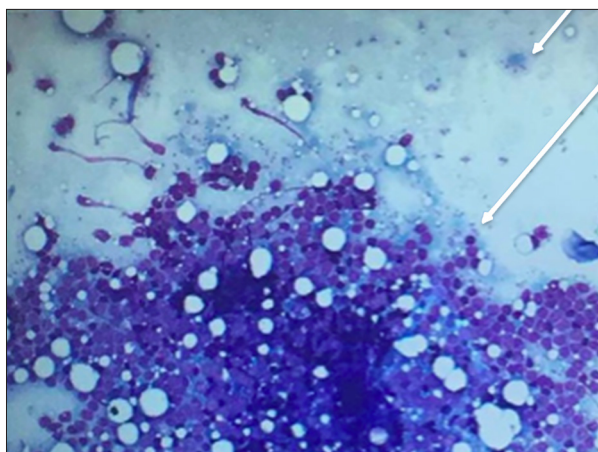


**Figure 1.** CT scan showing the para aortic lymph node enlargement (arrow).

Two units of platelets were transfused, followed by another 2 units on the following day. A chest X-ray was done, which showed completely normal results. A CT scan was performed of the neck, chest, abdomen, and pelvis, without contrast, which revealed multiple bilateral cervical lymph nodes with splenomegaly measuring 17 cm. No hepatomegaly or focal liver lesions were seen, but a 2-cm dilation of the portal vein was noted. Furthermore, multiple ilio-hypogastric lymph nodes were noted to be extending from the renal level to the iliac bifurcation. The largest of these were of the paraspinal and para-aortic subgroups, measuring 1.2 cm in the shortest axis (Figure 1). The patient was started on a course of IV solumedrol at 250 mg BID as treatment for a suspected Richter's transformation or possible suboptimally treated hemophagocytic syndrome. He responded to the steroids and dramatically improved symptomatically. Two weeks after the course of steroids was started, laparoscopy was scheduled to biopsy the affected lymph nodes and finalize the diagnosis. During the operation, surgeons noted difficulty in discerning the lymph nodes from the surrounding tissue. Two para-aortic lymph nodes and 1 mesenteric lymph node were removed. The first 2 were sent to pathology and the latter to culture. The pathology report for the para-aortic lymph node stated: "The structure of the lymph node is totally disorganized, with prominence of histiocytes. CD5-, CD23-, and CD 79A-positive, consistent with CLL. The histiocytes are positive for CD68 and studded with numerous parasitic-like organisms, morphologically suggestive of leishmania."

Vitals were stable at day 1 post-op, with a total fluid intake of 2000 mL and total output of 1300 mL.

He was started on a diet of clear fluids. On day 2 post-op, the patient had 1 recorded episode of fever (38.6°C), which resolved on its own. The patient received 1 packed red blood cell transfusion, after which his vital signs were normal. His ANC at this time was 3731.



**Figure 2.** Bone marrow biopsy showing Leishmania bodies (arrows). Giemsa stain, 100x.

Ten days following the surgery, a bone marrow aspiration was performed from the posterior-superior iliac crest. The pathology report was as follows: "The aspirate shows the presence of all hematopoietic cells, although decreased in number. Leishmania bodies are easily seen inside macrophages. CD20 is positive in lymphoid aggregates. CD5, CD23, and CD79 are positive and consistent with small B cell proliferation (CLL)." (Figure 2).

Upon pathological demonstration of leishmania bodies, the patient was immediately started on liposomal amphotericin B and his symptoms improved. AmBisome was given via IV at a dose of 5 mg/kg once daily for 5 days, followed by 1 dose weekly for 3 weeks. Following treatment, the patient returned to Spain, making follow up difficult.

## Discussion

Visceral Leishmaniasis, also known as kala-azar or black fever, is the most severe form of leishmaniasis and can affect the liver, spleen, bone marrow, and lymph nodes. This disease is caused by protozoan parasites that are of the *Leishmania* genus. If left untreated, affected patients often die, especially those younger than 2 or older than 45 years of age, and those that are malnourished [1]. Symptoms are usually related to the affected organs mentioned above. Hepatosplenomegaly, fever, fatigue, malaise, and weight loss are often among the presenting signs and symptoms [5]. Visceral leishmania is often indolent; the parasite resides in the mononuclear phagocytic system until symptoms eventually show, and it may take several months or even years for this to occur. Hepatomegaly is less frequently encountered than splenomegaly (which occurs earlier) [6]. The rate of growth of the spleen is related to the rate of progression of the disease. The longer the duration of time, the more significant the splenomegaly. It can be so severe that the spleen reaches the hypochondrium. Death

arises due to predisposition to infection that results from the attack of these parasites on the immune system (phagocytic system) and not due to the infection itself [6]. The incidence of leishmaniasis is correlated well with socioeconomic status. Poor housing and unsanitary conditions, such as open sewage and lack of waste management, are thought to increase the resting and breeding sites and thus promotes access of the sandfly to humans. In addition, diets lacking in protein, iron, vitamin A, and zinc are also associated with increased risk of leishmania. Furthermore, leishmaniasis has been shown to be climate-sensitive, being affected by changes in rainfall, temperature, and humidity. Therefore, global warming and land degradation can affect the epidemiology and transmission of leishmania in many ways [5]. There also exists an association between leishmaniasis and certain medications, especially TNF-alpha antagonists. Although published data on this topic are scarce, many case reports point out this association between TNF-alpha antagonists and leishmania [7].

Visceral leishmaniasis can coexist with different types of cancers, including chronic lymphocytic leukemia and non-Hodgkin's lymphoma. As a result of this and the similar presenting symptoms, patients with visceral leishmaniasis are often investigated for underlying malignancy [3], as was the case with our patient. They often undergo lymph node biopsies and pathology/culture, which usually reveals the true diagnosis.

Two species of *Leishmania* cause visceral leishmaniasis. The species commonly found in East Africa is *L. donovani* and the species found in Europe, North Africa, and Latin America is *L. infantum* (*L. chigasi*). Diagnosis is often made by detecting amastigotes in a bone marrow or splenic aspirate. Serologic testing, when performed, assesses the immune system response and does not rely on detecting the parasite itself [1].

The treatment of choice for visceral leishmaniasis is amphotericin B, preferably the liposomal formulation as it is associated with less renal toxicity and other adverse effects. Studies suggest that optimal tissue levels can be achieved with an initial dose of at least 5 mg/kg [8]. The FDA-recommended regimen is 3 mg/kg on days 1 to 5, 14, and 21 [9]. Other available treatment options include the pentavalent antimonial drugs such as sodium stibogluconate and meglumine antimoniate, which are still widely used, but not as first-line monotherapy [10]. The 2 newest drugs available for treatment of visceral leishmania are paromomycin and miltefosine. Miltefosine, which was approved by the FDA for use in adults in 2014, is the first oral treatment for this disease and has a cure rate of about 95%. [6]. The indication for miltefosine is visceral leishmaniasis due to *leishmania donovani* or cutaneous leishmaniasis due to *leishmania braziliensis*, *leishmania guyanensis*, or *leishmania panamensis*. However, this medication is currently still in clinical trials [11].

The above case is interesting due to the background of CLL, which shifted the differential diagnosis more towards that of a malignant cause. Richter's syndrome, the transformation of a CLL/SLL to a more aggressive subtype of lymphoma, was considered in this patient as it is often characterized by the appearance or worsening of B symptoms, an increase in LDH, or enlargement of lymph nodes in a patient with a long-standing CLL [12]. The comorbidity of cancer among visceral leishmaniasis patients is very uncommon. In our case, the patient had in fact been pancytopenic for a long time, which caused him to be vulnerable to infection. The duration of the leishmania infection is unknown, so one could argue the possibility that the chronic pancytopenia was due primarily to the infection, with an apparent worsening due to administration of steroids. However, in this case it was a paradoxical improvement in symptoms that was noted with steroid administration. It is thus important to keep infectious causes as a differential for patients seemingly presenting with worsening of lymphoma. Infection with visceral leishmania was confirmed in this case, as the patient was found to have the parasite within lymph nodes in the retroperitoneal and mesenteric regions. Furthermore, the parasite was also found within histiocytes in the bone marrow, which is the criterion standard for the diagnosis of visceral leishmania [13]. A splenic aspirate was not done in order to avoid performing further invasive procedures on a patient with pancytopenia (especially due to the thrombocytopenia). The spleen, however, was enlarged and likely contained the parasite as well.

The finding of visceral leishmaniasis on biopsy was unexpected. The infection was likely picked up during his prior visits to Lebanon, which is considered an endemic country. Interestingly, the incidence of both cutaneous and visceral leishmaniasis have gone up significantly in Lebanon since 2012 due to the massive influx of Syrian refugees into the country, which correlates with the onset of the patient's symptoms [14]. In addition, another aspect of this case that was unusual was the apparent drastic response to corticosteroid therapy. The response of this patient to the 2-week course of prednisone was puzzling, as corticosteroids are well known to depress immunity, leaving patients less able to clear infections. Steroids are therefore an indirect causative agent for this infection and do not improve an already present infection [15]. The steroids were introduced because of a diagnosis of hemophagocytic syndrome made in Spain, prior to arrival at our institution. Hemophagocytic syndrome involves excess inflammation due to abnormal activation of immune cells. Diagnosis is made either by molecular identification of associated gene mutations or clinically by the presence of at least 5 of the following 8 findings:

1. Fever  $\geq 38.5^{\circ}\text{C}$ ,
2. Splenomegaly,
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood),

- a. Hemoglobin  $< 9 \text{ g/dL}$ ,
- b. Platelets  $< 100\,000/\text{microL}$ ,
- c. Absolute neutrophil count  $< 1000/\text{microL}$ ,
4. Hypertriglyceridemia (fasting triglycerides  $> 265 \text{ mg/dL}$ ) and/or hypofibrinogenemia (fibrinogen  $< 150 \text{ mg/dL}$ ),
5. Hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver,
6. Low or absent NK cell activity,
7. Ferritin  $> 500 \text{ ng/mL}$ ,
8. Elevated soluble CD25.

However, it is important to remember that due to high mortality, treatment is often started even if criteria are not completely met [16]. Our patient met 3 of the 8 criteria, which is not unusual. However, the patient, although slightly improved, was not completely recovered following steroid administration. Another possibility is that the patient's steroid use may have caused adrenal suppression, which was improved when IV steroids were initiated. This, however, is unlikely as the patient was only on his home prednisone for 2 weeks duration. There is great need for increased awareness of the incidence of visceral leishmaniasis and the need to be more aggressive in the early treatment and detection, as patients may have devastating results if left untreated and undiagnosed. Although it can be a difficult diagnosis to make, as symptoms often overlap with those seen in lymphoma, it should be maintained as a differential diagnosis, especially in patients with the above-mentioned symptoms.

## Conclusions

Visceral Leishmania, the most severe manifestation of leishmaniasis, can present with infiltration of a variety of organs and structures, including the liver, spleen, bone marrow, and lymph nodes. Interestingly, this form of leishmaniasis can coexist with many forms of cancer, including hematologic malignancies, a fact that can complicate the diagnosis. Here, we reported a case of visceral leishmania in a patient with a baseline of chronic lymphocytic leukemia. The presence of enlarged lymph nodes in the setting of this baseline malignancy prompted an investigation focused on malignancy (i.e., Richter transformation) as the cause of his symptoms. This case not only illustrates an uncommon and unexpected presentation of leishmaniasis masked by malignancy, but also provides an important reminder to maintain a high index of suspicion for these protozoan infections, especially in endemic areas, even in the setting of malignancy. Any delay in the diagnosis and treatment of visceral leishmania can be severely detrimental for the prognosis of such patients.

## Conflicts of interest

None.

## References:

1. Chappuis F, Sundar S, Hailu A et al: Visceral leishmaniasis: What are the needs for diagnosis, treatment and control? *Nat Rev Microbiol*, 2007; 5: 873–82
2. Jayasena W, Abeygunasekara P, Jayasundara J: Visceral leishmaniasis: A hidden killer? *Medico-Legal Journal of Sri Lanka*, 2014; 1: 37–41
3. Rahim A, Moniruzzaman M, Khan FI, Rahman MM: Visceral leishmaniasis with generalized involvement of lymph nodes in a 55-year-old woman: A case report. *J Sci Found*, 2014; 10: 80–84
4. Ramos RA, Ramos CA, Santos EM et al: Quantification of *Leishmania infantum* DNA in the bone marrow, lymph node and spleen of dogs. *Rev Bras Parasitol Vet*, 2013; 22: 346–50
5. World Health Organization. Leishmaniasis. Fact sheet [series online]. 2017 Apr. [cited 2016 Oct 16]; Available from: URL: <http://www.who.int/mediacentre/factsheets/fs375/en/>
6. Piscopo TV, Mallia Azzopardi C: Leishmaniasis. *Postgrad Med J*, 2007; 83(976): 649–57
7. Zanger P, Gabrysch S: Leishmaniasis in the era of tumor necrosis factor alpha antagonist therapy – a research agenda for Europe. *Euro Surveill*, 2013; 18(30): 20542
8. Adler-Moore J, Proffitt RT: AmBisome: Liposomal formulation, structure, mechanism of action and pre-clinical experience. *J Antimicrob Chemother*, 2002; 49: 21–30
9. Meyerhoff A: U.S. Food and Drug Administration Approval of AmBisome (Liposomal Amphotericin B) for Treatment of Visceral Leishmaniasis. *Clin Infect Dis*, 1999; 28(1): 42–48; discussion 49–51
10. Murray HW: Treatment of leishmaniasis in 2004. *Am J Trop Med Hyg*, 2004; 71: 787–94
11. Sindermann H, Engel KR, Fischer C et al: Oral Miltefosine for leishmaniasis in immunocompromised patients: Compassionate use in 39 patients with HIV infection. *Clin Infect Dis*, 2004; 39(10): 1520–23
12. Parikh SA, Kay NE, Shanafelt TD: How we treat Richter syndrome. *Blood*, 2014; 123: 1647–57
13. Sundar S, Rai M: Laboratory diagnosis of visceral leishmaniasis. *Clin Vaccine Immunol*, 2002; 9: 951–58
14. Saroufim M, Charafeddine K, Issa G et al: Ongoing epidemic of cutaneous leishmaniasis among Syrian refugees, Lebanon. *Emerg Infect Dis*, 2014; 20: 1712–15
15. Pittalis S, Nicastrì E, Spinazzola F et al: *Leishmania infantum* leishmaniasis in corticosteroid-treated patients. *BMC Infect Dis*, 2006; 6: 177
16. Jordan MB, Allen CE, Weitzman S et al: How I treat hemophagocytic lymphohistiocytosis. *Blood*, 2011; 118: 4041–52