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Case report

Visceral leishmaniasis in Kosovo: A case of misdiagnosis and diagnostic challenges

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ABSTRACT

Introduction: Visceral leishmaniasis (VL) is a parasitic disease caused by various Leishmania species and is a potentially life-threatening condition. The disease is highly endemic in several regions, including the Balkans, yet information regarding its prevalence in Kosovo is limited.

Case presentation: In this case presentation, a 62-year-old man was admitted to a hospital in Kosovo due to a persistent high fever, and after extensive evaluations and treatments, he was diagnosed with fever of unknown origin (FUO) and transferred to a hospital in Turkey. An abscess of the psoas muscle caused by MRSA was found, however, pancytopenia persisted despite antibiotic treatment. Six months later, the patient was hospitalized again due to fever, chills, and night sweats. Microscopic examination and serological tests revealed the presence of Leishmania infantum in the bone marrow. Liposomal amphotericin B treatment resulted in a significant improvement in the patient's condition.

Discussion: The diagnosis of VL can be challenging, and it can easily be misdiagnosed as other diseases, resulting in diagnostic delays and potentially fatal outcomes. In endemic regions such as the Balkans, it is crucial for physicians to be aware of this infection to avoid misdiagnosis or diagnostic delay. Early diagnosis and prompt treatment of VL are essential in preventing morbidity and mortality.

Conclusion: This case highlights the significance of considering VL as a possible diagnosis in patients presenting with febrile illnesses accompanied by pancytopenia and splenomegaly, especially in endemic regions.

Introduction

Visceral leishmaniasis (VL), also known as kala-azar, is a parasitic disease caused by different Leishmania species that vary by geographical area. In European-acquired infections, *L. infantum* is the only species found to cause VL. The transmission of the parasite occurs through blood-feeding female sandflies, which are mainly found in southern European countries, primarily those of the Mediterranean basin. Despite its prevalence, leishmaniasis is relatively neglected in Europe and not a priority for public health agencies. Epidemiological data on leishmaniasis are mainly available from southwestern Europe, with scarce and outdated information available from southeastern Europe, particularly the Balkan region [1].

The Balkans are a significant leishmaniasis region, and the epidemiological situation of leishmaniasis and other zoonoses in the Balkans is not well-characterized due to challenging circumstances prevailing in recent decades. Although VL is a notifiable disease in almost all Balkan countries, a reporting system is lacking. Physicians (and veterinarians) often lack knowledge and experience in diagnosing leishmaniasis, leading to underreporting and inaccurate data. *Leishmania infantum* is the primary causative agent of human VL and CL in the Balkans [2].

Currently, leishmaniasis is suspected to be highly endemic in Kosovo, particularly in recent years, but there is no reporting system in place, and only a few publications are available [1]. There are no reports of human leishmaniasis in Kosovo, except for Austrian soldiers testing positive for antibodies after being stationed in Kosovo and other Balkan countries [3].

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The symptoms caused by this protozoa infection are diverse. Although many Leishmania infections are asymptomatic, three clinical syndromes can be identified: cutaneous leishmaniasis (CL), mucosal leishmaniasis (mL), and visceral leishmaniasis (VL). The incubation period varies from a few weeks up to six months and sometimes years. VL can be fatal if left untreated due to the disease itself or from infectious or hemorrhagic complications. However, VL may also behave asymptomatically or as a latent infection and become manifest after years in case of the development of immunodeficiency of any etiology [4].

The classical manifestations of advanced disease include irregular and prolonged fever, cachexia (malnutrition being both a risk factor for and a sequela of visceral leishmaniasis), hepatosplenomegaly (with splenomegaly usually predominant and the spleen sometimes massive), anemia, leukopenia, thrombocytopenia, occasionally associated with bleeding, hypergammaglobulinemia (mainly IgG, from polyclonal B cell activation), and hypoalbuminemia [5].

The clinical diagnosis of VL is challenging because its presentation overlaps with other infections like typhoid fever, tuberculosis, brucellosis, malaria, or some hematologic malignancies [4][5][6][17]. Diagnosis can be confirmed through direct demonstration of Leishmania in tissue specimens or cultures or by serologic testing. Further diagnostic options have arisen, such as rapid diagnostic kits and polymerase chain reaction (PCR) tests. In general, the use of multiple diagnostic approaches is recommended to increase the likelihood of a positive result [6].

Liposomal amphotericin B (LAMB) is currently the recommended first-line antileishmanial drug based on available efficacy data from different VL endemic regions of the world. Antimonials are still effective in all VL endemic regions, except in the Indian subcontinent, where parasite susceptibility to antimonials has decreased. Miltefosine is the only available oral antileishmanial drug to date, while paromomycine is another alternative antileishmanial agent [4].

Case presentation

In April 2022, a 62-year-old man was admitted to the Department of Infectious Diseases at the University Clinical Centre in Pristina due to a high fever that had been initially intermittent and later on had become persistent for two weeks prior to hospitalization. The patient had been seen by several physicians, including a family physician, gastroenterologist, pulmonologist, and urologist, but the cause of the high fever could not be identified.

On admission, the patient had a fever of 38.5 °C and slightly enlarged spleen. Blood tests were performed and showed the following results: erythrocyte sedimentation rate (ESR) = 5 mm/h, leukocytes = 4.0 × 10^9/L, erythrocytes = 4.02 × 10^{12}/L, hemoglobin = 11.5 g/dL, platelets = 123 × 10^3/mm^3, hematocrit = 31.3 %, C-reactive protein (CRP) = 54.9 mg/dL, procalcitonin (PCT) = 0.35 ng/mL (< 0.25), serum albumin = 44.1 g/L (34–54), direct bilirubin = 2.85 μmol/L (< 5.1), total bilirubin = 9.4 μmol/L (< 20.5), aspartate aminotransferase (AST) = 25 UI/L (8–33), alanine aminotransferase (ALT) = 43 UI/L (4–36), gammaglutamyl transferase (GGT) = 153 UI/L (5–40), lactate dehydrogenase (LDH) = 288 U/L (105–333), D-dimer = 16 (0.5), PT = 10.5 s (11–15), INR = 0.98 (< 1.1), PTT = 30 s (24–39), TT = 16 s, anti CCP = 7.0 U/mL (< 500), C3 = 100 mg/dL (80–178), C4 = 19 mg/dL (12−42), IL 6 = 13.9 pg/mL (< 5.90), CK-MB = 35 ng/mL (< 25), AFP = 13.24 IU/mL < 40), CEA = 2.06 ng/mL (< 10), Anti ENA = negative, ANA = negative, ANCA = negative, Anti DSDNA = 4.58 IU/mL (< 30), PSA = 1.50 ng/dL (< 4.1), Fr PSA = 0.123 ng/dL (< 0.87), FrT3 = 4.6 pg/mL (1.5–6.0), T4 = 11.61 μg/dL(4.5–12.5), TSH = 2.29 mIU/mL (0.4–4.5).

Several serologic tests were also performed, including Leptospira IgM/IgG, Lyme Borreliosis IgM/IgG, Wright, Widal,TORCH, HBsAg and Anti HCV. All results were negative except for Toxoplasma IgG and Rubella IgG, which were positive. The patient also underwent additional examinations, including lumbar puncture, bone marrow aspiration, urine culture, blood culture, smear of peripheral blood, QuantiFERON TB gold test, echocardiography, bone scintigraphy, and CT scans of the brain, head, chest, abdomen, and pelvis. However, except of QuantiFERON TB gold test which was positive, and splenomegaly (170 mm) on CT scan of the abdomen, none of other tests revealed any other pathological findings.

Due to the positive result of the QuantiFERON TB gold test and the lack of any other identifiable cause for the patient's fever, treatment with four antituberculous drugs was started. However, this treatment had to be interrupted after several weeks due to severe toxic hepatitis.

During the patient's two-month stay at the hospital, laboratory tests demonstrated a progressive multilineage cytopenia and increased values of inflammation markers, despite several courses of different antibiotics used as single agents or in combination (ceftriaxone, gentamycin, vancomycin, meropenem, azithromycin, and levofloxacin) (Table 1). The patient was subsequently discharged from the department at the end of June 2022 and referred for further treatment abroad with a diagnosis of fever of unknown origin (FUO).

The patient was admitted to the LIV Hospital Vadi Haematology Department in Istanbul, Turkey, on June 26, 2022, where examinations revealed splenomegaly and pancytopenia. Abdominal MRI showed an abscess in the left psoas muscle with dimensions of 68 × 45 mm, which expanded the muscle. The material provided by the abscess biopsy revealed MRSA, which was eventually drained. After six days on antibiotics (Tigecycline), the patient became afebrile, and acute phase inflammatory reactants regressed to normal levels. The antibiotic was given for three weeks, but the patient's pancytopenia persisted throughout the follow-up period, until July 19, 2022.

The biopsy material from the bone marrow taken in Kosovo was reexamined in the Istanbul hospital, and the findings were interpreted as bone marrow findings secondary to infection, medications, and immune system-mediated pathologies. 18-FDG-PET (18-fluorodeoxyglucose positron emission tomography) showed a prominent spleen with involvement of the liver and bone marrow. A diagnostic splenectomy was recommended, but the patient declined the procedure.

In January 2023, six months after hospitalization in Istanbul, the patient was hospitalized for the third time, this time at the University Clinical Centre in Pristina, Haematology Department, due to fever, chills, weight loss, and night sweats. Repeated tests showed persistent anemia/pancytopenia, and peripheral blood smear examination was again without pathological changes. Abdominal and pelvic scan revealed an enlarged spleen and liver. Repeated puncture of the bone marrow was performed, and light microscopic examination of a Giemsa-stained bone marrow specimen finally revealed the presence of amastigotes of *Leishmania infantum* within the macrophages (Fig. 1).

The microscopic findings were corroborated by a positive serological test for Leishmania IgG = 2.783 (IgG cut-off 0.481). As a result, the patient was referred to the Department for Infectious Diseases of the University Clinical Centre in Pristina for further assessment and management. Treatment with liposomal amphotericin B (LAMB) 1.5 mg/kg/day for 14 days was administered to the patient. Following the treatment, the patient's fever subsided, and their overall health condition improved. The laboratory results obtained three weeks after the treatment indicate a significant improvement (Table 1).

Discussion

Visceral leishmaniasis (VL) is a severe parasitic disease that, if left untreated, can result in death. Due to its clinical presentation, the disease can be easily mistaken for other diseases of hematological, malignant, autoimmune, or other etiology. In cases where underlying diseases are present, VL may be misdiagnosed as a progression of an existing condition [5]. Therefore, physicians in endemic regions, such as the Balkans, should be aware of this infection to avoid possible misdiagnosis or diagnostic delays, as was the case with our patient.

Although Kosovo is considered a European country with low endemicity for leishmaniasis [3], the border with Albania, which has medium

Table 1
Hematological lab results timeline.

	First Admission[a], April, 2022	Discharge[a], June 2022	Second admission[b], June–July 2023	Third admission[c], January, 2023	Fourth admission[a], February, 2023	Outpatinet[d], March, 2023
ESR (mm/h)	5	70	77		100	76
Leukocytes ($\times 10^9$/L)	4.0	3.6	2.1	1.8	2.2	5.6
Erythrocytes ($\times 10^{12}$/L)	4.02	2.54	3.31	3.95	3.05	4.48
Hemoglobin (g/dL)	11.5	6.3		8.8	7.8	12.5
Platelets ($\times 10^3$/mm^3)	123	100	165	74	140	192
Hematocrit (L %)	31.3	18.2	27.2		21.9	
CRP (mg/dL)	54.9	69.5	51.4	41	31.3	3.6
PCT (ng/dL)	0.35	0.35		0.24		
Albumin/ serum (g/L)	44.1	28.7	31.0	25.7	28.5	
AST (U/L)	25	93	56	25	13	33
ALT (U/L)	43	278	48	45	34	26
GGT (U/L)	153	120	121			
LDH (U/L)	288	750	258	334	310	
D-dimer	16	2.1			1.7	0.67

ESR – erythrocyte sedimentation rate, CRP – C reactive protein, PCT – pro calcitonin, AST – aspartate amino transferases, ALT – alanine amino transferases, GGT – gamma glutamyl transferases, LDH – lactate dehydrogenases.

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[d] Outpatient, three weeks after discharge.

and high endemicity for leishmaniasis [3], and the massive movements of the population of Kosovo for holidays and work in this country throughout the year, make infection very possible. This indicates that all cases with fever, splenomegaly, and pancytopenia/anemia in Kosovo should be investigated for VL at the very beginning of these conditions.

The incubation period for VL can vary from a few weeks to a few years, while the onset is typically insidious and progresses slowly with various signs and symptoms overlapping with the features of other infectious diseases, as described in other case presentations [5,6] and VL studies [7]. In our case, the incubation period was probably short because the laboratory results on the patient's hospital admission did not show deviations from the reference values. The case presented shows the extent of suffering experienced by the patient and his family, as well as the financial expenses they were subjected to until the final diagnosis of the disease, which can be prevented in the future in similar cases only by increasing the degree of suspicion for this disease, especially in endemic regions, whenever fever, splenomegaly, and pancytopenia/anemia are present.

A practical problem that can worsen the condition of hosts infected with leishmania is the secondary infection caused by bacteria [8]. The course of the disease in our case was complicated by an abscess of the psoas muscle caused by MRSA. Although we specifically did not find any case described with VL and abscess of the psoas muscle, studies for secondary bacterial infections, such as sepsis, bronchopneumonia, perineal abscess, otitis media, UTI, GI infections, skin infections [7,9–13], and even the ICD lead infection [14], are frequent and are a consequence of immunosuppression caused by VL. The most frequently isolated etiological agents are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Klebsiella species*, *E. coli*, *Salmonella species*, Shigella species, Enterobacter species, etc., depending on the site of secondary infection and the presence or absence of HIV coinfection [7,9–14].

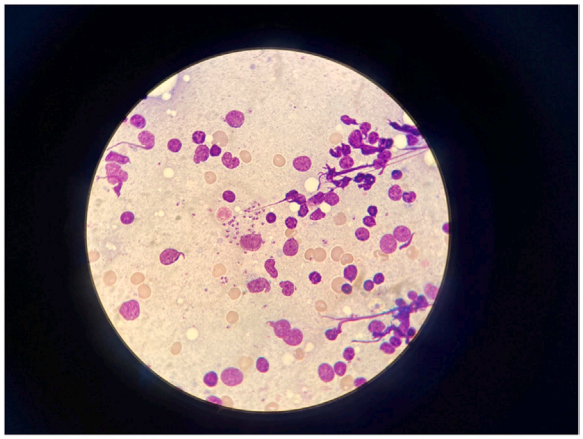
Coinfection among leishmaniasis and other infectious diseases is common among the natural population, especially in the endemic areas of the disease. It depends on environmental factors, vector availability, host-parasite interactions, and, above all, geographical boundaries. A variety of infections coexist with leishmaniasis, such as HIV, leprosy, tuberculosis, schistosomiasis, Covid-19, etc., and the prevalence is different in different parts of the world. The impacts of coinfections are observed in immunopathogenesis, clinical manifestation, diagnosis, and therapeutic response [15–18].

The case presented herein involves a misdiagnosis of tuberculosis (TB) infection due to a positive QuantiFERON TB gold test. As a result of this test, anti-TB treatment was initiated, which was ultimately determined to be unnecessary and resulted in life-threatening toxic hepatitis. The duration of this incorrect treatment lasted several weeks before being halted. Although coinfection of leishmania with tuberculosis is possible [18], it is more likely that the misdiagnosis was due to desperate attempts to identify the cause of fever, hepatosplenomegaly, and pancytopenia/anemia. The potential causes of a false positive QuantiFERON TB gold test include chronic medical conditions, other mycobacteria, environmental mycobacteria, use of tuberculosis antigen tubes with issues, or use of a low conversion cut-off [19,20]. No studies confirm the false positive result of the QuantiFERON TB gold test in VL. In the presented case, the incorrect technical procedure for testing or a low conversion cut-off may be the reason for the false positive test. This must be considered when evaluating patients with FUO who lack clear epidemiological or clinical evidence of TB infection.

Conclusion

The case presented highlights the diagnostic challenges associated with visceral leishmaniasis (VL), which can lead to incorrect diagnosis and treatment, or a diagnosis of secondary bacterial infection that is mistaken as the primary cause of the clinical condition. These challenges can result in dangerous delays in proper diagnosis and treatment, causing significant suffering for the patient and their family, as well as financial expenses. In endemic regions such as the Balkans, physicians should be aware of this disease to avoid misdiagnosis or diagnostic delays. It is necessary to increase awareness among physicians about the presence of VL, and for public health institutions in Kosovo to take appropriate measures to ensure accurate reporting.

a.



b.

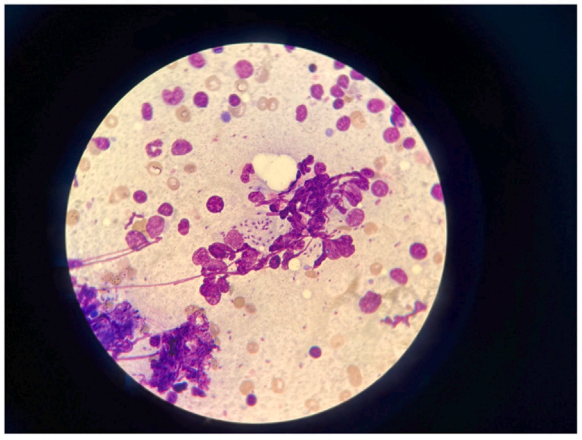


Fig. 1. Light-microscopic examination of an M-Giemsa-stained bone marrow specimen showing macrophages containing multiple Leishmania amastigotes (a,b).

CRediT authorship contribution statement

Tolaj Ilir: Conceptualization, Writing – original draft, approving final version. **Murati Mehmet:** Data curation, Writing – review & editing. **Gashi Hatixhe, Berisha Fjorda, and Gashi Visar:** Investigation, Visualization. **Shala Nexhmedin:** Writing – review & editing. **Fejza Hajrullah:** Supervision.

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Ethical approval

YES.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest

The authors declare no conflict of interest.

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