Case Report / *Olgu Sunumu*

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# Evaluation of Four Cases of Visceral Leishmaniasis

## Dört Visseral Layşmanyaz Olgusunun Değerlendirilmesi

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**Abstract**

Visceral leishmaniasis (VL), kala-azar is a vector-borne disease caused by over 20 obligatory intracellular protozoan species of the *Leishmania* genus. In Türkiye, it is sporadically seen in the Aegean, Mediterranean, and Central Anatolian regions, particularly in pediatric age groups. Due to migration, war, economic challenges, and social or cultural influences, patients from different geographies are also being monitored in our healthcare facilities. VL-associated hemophagocytic lymphohistiocytosis (HLH) is one of the life-threatening complications. This case series evaluated initial symptoms, clinical findings, laboratory results, and outcomes of four pediatric patients diagnosed with VL at our hospital between 2021-2024. All patients were male and aged between 3 months and 17 years. The most common findings were fever, splenomegaly, pancytopenia, and elevated liver function tests. VL diagnosis was confirmed by clinical findings and the detection of *Leishmania* in bone marrow aspirates using at least one of the methods available at our hospital: serological tests, rapid diagnostic kits, and polymerase chain reaction testing. Two patients were referred from Syria. All patients were treated with liposomal amphotericin B, and one patient died due to HLH. Given the geographical location of Türkiye, VL should be considered in patients with fever, hepatosplenomegaly, and cytopenia/pancytopenia.

**Keywords:** Hemophagocytic lymphohistiocytosis, pediatric, visceral leishmaniasis

**Öz**

Visseral layşmanyaz (VL), kala-azar, *Leishmania* cinsinin 20'den fazla zorunlu hücre içi protozoon türünün neden olduğu vektör kaynaklı bir hastalıktır. Türkiye'de, özellikle pediyatrik yaş gruplarında, Ege, Akdeniz ve Orta Anadolu bölgelerinde sporadik olarak görülmektedir. Göç, savaş, ekonomik zorluklar ve sosyal veya kültürel etkiler nedeniyle, farklı coğrafyalardan gelen hastalar da sağlık tesislerimizde takip edilmektedir. Visseral layşmanyaz ile ilişkili hemofagositik lenfohistiyositoz (HLH), yaşamı tehdit eden komplikasyonlardan biridir. Bu olgu serisi, 2021-2024 yılları arasında hastanemizde VL tanısı konulan dört pediyatrik hastanın ilk semptomlarını, klinik bulgularını ve laboratuvar sonuçlarını değerlendirmiştir. Tüm hastalar erkekti ve yaşları 3 ay-17 yaş arasındaydı. En sık görülen bulgular ateş, splenomegali, pansitopeni ve karaciğer fonksiyon testlerinde yükselme idi. Visseral layşmanyaz tanısı, klinik bulgular ve hastanemizde mevcut olan serolojik testler, hızlı tanı kitleri ve polimeraz zincir reaksiyonu testlerinden en az birinin kullanılmasıyla kemik iliği aspiratlarında *Leishmania* saptanmasıyla doğrulandı. İki hasta Suriye'den sevk edildi. Tüm hastalar lipozomal amfoterisin B ile tedavi edildi ve bir hasta HLH nedeniyle öldü. Türkiye'nin coğrafi konumu göz önüne alındığında, ateş, hepatosplenomegali ve sitopeni/pansitopeni olan hastalarda VL düşünülmelidir.

**Anahtar Kelimeler:** Hemofagositik lenfohistiyositoz, pediyatrik, visseral leishmaniazis

## Introduction

Visceral leishmaniasis (VL), kala-azar, is a zoonotic parasitic infection caused by particular *Leishmania* species, which is transmitted to humans by infected female sandflies of the genus *Phlebotomus*. Infected sandflies spread it, and it is commonly observed in tropical and subtropical regions such

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as North Africa, South America, and East Asia (1). The onset of symptoms is generally subacute, insidious, and slowly progressive, rarely acute. Clinical findings include fever, weight loss, splenomegaly, hepatomegaly, pancytopenia (more frequently anemia and thrombocytopenia), elevated liver enzymes, and hypoalbuminemia. The most serious, potentially fatal complications of VL are disseminated intravascular coagulation and hemophagocytic lymphohistiocytosis (HLH). Diagnosis in a child clinically suspected of VL (fever with splenomegaly, hepatomegaly, weight loss, pancytopenia, and hypergammaglobulinemia or laboratory findings such as hemophagocytic syndrome) is confirmed by direct demonstration of *Leishmania* in tissue samples or cultures, or through serological tests (2). Migration, wars, economic difficulties, long journeys, and social or cultural influences facilitate the emergence and spread of infectious diseases (3). VL treatment is challenging due to factors including drug toxicity, resistance, epidemiological variability, and, importantly, a lack of evidence-based data for the pediatric population (4). Our case series underscores the need for further research to improve the understanding and management of VL in pediatric patients.

## Case Report

### Case 1

An 11-year-old male patient presenting with abdominal pain, fever, hepatosplenomegaly, and pancytopenia was referred with a preliminary diagnosis of hematologic malignancy. It was learned that the patient had arrived from Syria about a month prior. Physical examination revealed a pale appearance, a 2/6 systolic murmur over the heart, a liver extending 4 cm below the costal margin, and a closed Traube's space. Other system examinations were regular. It was noted that he had received two erythrocyte transfusions. Laboratory tests showed white blood cell count (WBC)= 2180/mm$^3$, neutrophil count= 710/mm$^3$, hemoglobin (Hb)= 10.8 g/dL, platelets= 79,000/mm$^3$, C-reactive protein (CRP)= 42 mg/L, aspartate aminotransferase (AST)= 37 IU/L, alanine aminotransferase (ALT)= 38 IU/L, lactate dehydrogenase (LDH)= 315 U/L, blood urea= 19 mg/dL, and creatinine= 0.5 mg/dL. No *Plasmodium* was detected in thin smear and thick drop preparations. Brucella tube agglutination test was negative. Viral-bacterial respiratory polymerase chain reaction

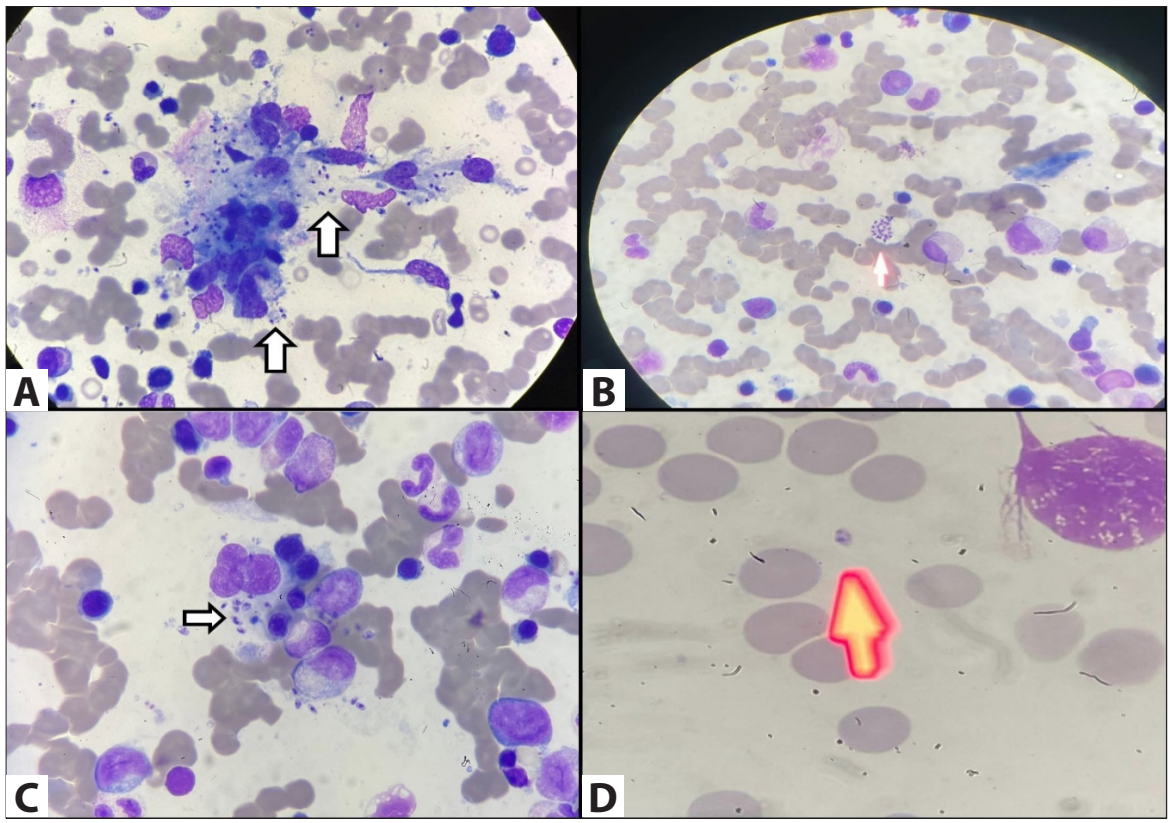


**Figure 1.** Amastigotes of Leishmania observed in the indicated areas of the bone marrow smear. **(A)** Bone marrow aspiration sample of Case 1 showing cellular bone marrow; in the marked areas, *Leishmania* amastigotes are observed both freely and within histiocytes. **(B)** Case 2 demonstrating abundant amastigotes within histiocytes, rarely within eosinophils, and freely in the extracellular space. **(C)** Bone marrow sample of Case 3 showing amastigotes consistent with *Leishmania* together with a hemophagocytic histiocyte in the indicated area. **(D)** Bone marrow aspiration material of Case 4 showing an amastigote in association with a histiocyte.

(PCR) panel and other diagnostic tests were negative. No growth was observed in urine and blood cultures. Abdominal ultrasonography showed a liver size of 155 mm and a spleen size of 185 x 73 mm. Bone marrow examination revealed no signs of malignancy, and structures resembling *Leishmania* amastigotes were observed (Figure 1A). *Leishmania* spp. PCR was positive, and the *Leishmania* dipstick test was negative. The patient was diagnosed with VL and received liposomal amphotericin B (3 mg/kg/day) on days 1-5 and days 14 and 21, totaling seven doses. Treatment began on day three of hospitalization, with WBC and neutrophil counts normalizing by day 14 of therapy. Platelet counts returned to normal by the third week. The liver was within normal limits at the one-month follow-up, but the spleen remained at the upper limits at the six-month follow-up.

**Case 2**

A six-year-old male patient with no known medical issues was referred from Southeastern Anatolia due to a high fever persisting for about two weeks. The fever rose with chills 2-3 times daily, and the patient experienced night sweats. Physical examination revealed pallor and hepatosplenomegaly. WBC was= 5680/mm$^3$, neutrophil count= 1240/mm$^3$, lymphocyte count= 3300/mm$^3$, Hb= 7.0 g/dL, platelets= 96.000/mm$^3$, sedimentation rate= 76 mm/h, CRP= 91 mg/L, AST= 114 U/L, ALT= 66 U/L, LDH= 335 U/L, and ferritin= 501 µg/L. Viral serological tests were negative, and no growth was observed in urine and blood cultures. Bone marrow examination showed no malignancy. Numerous amastigotes were detected within histiocytes and eosinophils (Figure 1B). *Leishmania* dipstick test and *Leishmania* ELISA IgM and IgG were positive. The patient was diagnosed with VL and received seven doses of liposomal amphotericin B. Neutrophil and platelet counts normalized by the first week of therapy.

**Case 3**

A three-year-old male patient from a local healthcare facility in Southeastern Anatolia presented with fever, abdominal distension, and respiratory distress. The patient had intermittent fever, abdominal pain, and abdominal distension for approximately three weeks. He did not describe any accompanying symptoms. The patient was hospitalized in an external center with these complaints, and ampicillin and cefotaxime treatment was started. After the follow-up, the fever continued, splenomegaly and increased free fluid in all quadrants of the abdomen were observed and the general condition deteriorated, and therefore the treatment was changed to piperacillin-tazobactam and amikacin. No etiological factor could be determined. The patient was diagnosed with HLH due to findings of thrombocytopenia, elevated liver enzymes, coagulation abnormalities, and hypoalbuminemia. Intravenous immunoglobulin and corticosteroid treatments were initiated. However, there was no clinical improvement and the patient's condition deteriorated, so they were referred to our hospital. The patient appeared pale, tachycardic, and tachypneic with poor general health on physical examination. There was a 2 x 2 cm ecchymosis in the umbilical region, hepatomegaly of approximately 5 cm below the costal margin, and splenomegaly of 3 cm. The patient was admitted to the pediatric intensive care unit. Laboratory results were as follows: WBC= 1610/mm$^3$, neutrophils= 290/mm$^3$, lymphocytes= 590/mm$^3$, Hb= 5.0 g/dL, platelets= 5000/mm$^3$, BUN= 50 mg/dL, creatinine= 0.36 mg/dL, AST= 182 U/L, ALT= 28 U/L, total bilirubin= 1.7 mg/dL, direct bilirubin= 1.1 mg/dL, triglycerides= 303 mg/dL, LDH= 513 U/L, ferritin= 27682 µg/L, NT-Pro BNP= 18361 ng/L, troponin I= 19 ng/L, PT= 18.3 seconds, APTT >120 seconds, international normalized ratio (INR)= 1.6. Supportive treatment with platelets, red blood cells, and fresh frozen plasma was provided. Blood and urine cultures showed no growth, and *Plasmodium* was not detected in thick and thin blood smears. *Brucella* tube agglutination and slide agglutination tests were negative. The respiratory viral-bacterial PCR panel and other viral serology tests were also negative. *Leishmania* spp. PCR returned positive at a low titer, and the bone marrow smear revealed numerous histiocytes with hemophagocytosis and *Leishmania* amastigotes, confirming VL (Figure 1C). Liposomal amphotericin B treatment was initiated, but the patient passed away on the third day of hospitalization.

**Case 4**

A 17-year-old male, previously diagnosed with aplastic anemia and right kidney agenesis in Syria, was admitted with complaints of fever reaching 40 ºC for the past 10 days, abdominal pain, and chills over the past three months. On physical examination, there was tenderness in the lower right quadrant of the abdomen, hepatomegaly 3 cm below the costal margin, and splenomegaly 1 cm below the costal margin. Other system examinations were normal. Laboratory findings were as follows: WBC= 1230/mm$^3$, neutrophils= 410/mm$^3$, lymphocytes= 410/mm$^3$, Hb= 9.4 g/L, platelets= 50000/mm$^3$, CRP= 86 mg/L, AST= 60 U/L, ALT= 57 U/L, LDH= 317 U/L, ferritin= 523 µg/L, and other biochemical parameters were normal. Abdominal ultrasonography showed the liver at the upper limit of normal (145 mm) and the spleen size of 145 mm. Blood, bone marrow, and urine cultures were negative. Bone marrow smear showed a few *Leishmania* amastigotes (Figure 1D). Blood, stool, and respiratory viral/bacterial PCR panels were negative; the *Plasmodium* dipstick test, *Brucella* tube agglutination, slide agglutination, and interferon-gamma release assay were also negative. The patient was diagnosed with VL and treated with liposomal amphotericin B. By the end of the first week, WBC, neutrophil, and platelet counts returned to normal, and lymphocyte count normalized by the end of treatment. At discharge, hepatosplenomegaly

persisted. The family was informed that the initial aplastic anemia diagnosis given in their country was incorrect.

## Discussion

*Leishmania* infection can present in three forms: Cutaneous, mucocutaneous, and visceral. VL has the highest mortality rate, especially in Southeast Asia, where the visceral form is endemic. While the cutaneous and mucocutaneous forms are more common in the Mediterranean region, VL cases have also been reported (1). It may be asymptomatic or may lead to different clinical conditions that may lead to mortality. Initial symptoms usually include fever, weight loss, and splenomegaly (5). The reticuloendothelial system is most frequently affected. The parasite proliferates in the reticuloendothelial system, leading to bone marrow suppression, hemolysis, splenic sequestration, and liver dysfunction. This situation may cause patients to receive different diagnoses, such as aplastic anemia, as in our fourth case. The clinic is mostly similar to hematological malignancies as in our cases. Diagnosis may be delayed due to lack of specific findings.

HLH is a life-threatening syndrome caused by excessive activation of the macrophage-monocyte-histiocyte system or failure to down-regulate cytokine-secreting immune cells. Secondary HLH due to VL is a rare complication in the literature that presents diagnostic and therapeutic challenges. The clinical picture of VL overlaps with HLH. Early diagnosis and prompt treatment are essential in children to reduce severe complications, such as secondary HLH and the need for blood transfusions (6). Diagnosis requires clinical suspicion and pathogen isolation, commonly from bone marrow aspiration material, using histopathological, molecular methods or culture. In the review published by Scalzone et al., it was noted that six of the 50 cases of HLH secondary to Leishmaniasis reported died due to late diagnosis and hemorrhagic-infectious complications, which is similar to our patient. In some cases reported in the publication, diagnosis was delayed due to negative bone marrow and *Leishmania* antibodies in early stages (7). Therefore, repeating the tests in endemic areas and in patients with clinical suspicion may help prevent mortality.

In addition to bone marrow, samples from other affected tissues can be used for diagnosis (8). While paramomycin, miltefosine, and sodium stibogluconate can be used in treatment, liposomal amphotericin B is the most effective agent (9). The commonly used regimen involves administering liposomal amphotericin B intravenously on days 1 and 5 and on days 14 and 21 to reach a total dose of 20-21 mg/kg. In the United States, liposomal amphotericin B is used for seven days (10,11). All our patients were treated with liposomal amphotericin B. In line with the literature, fever subsided within one to two weeks, weight gain was achieved within a month, and spleen size decreased in three patients (12). However, one patient, initially treated at a local hospital for HLH without success, was diagnosed with VL and subsequently developed VL-associated HLH. Liposomal amphotericin B treatment was started, but the patient passed away. Another patient, previously diagnosed with aplastic anemia in their country, was diagnosed with VL, and hematological parameters were normalized after treatment.

## Conclusion

Due to the geographical location of our country, VL should be considered in patients presenting with fever, hepatosplenomegaly, and cytopenia or pancytopenia. Delays in diagnosis and treatment may lead to mortality. Since the disease can present with various clinical manifestations, it is essential to thoroughly evaluate the patient's history and to include Leishmaniasis in the differential diagnosis.

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**Peer-review:** Externally peer-reviewed.

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