

Visceral leishmaniasis and pseudomonas septicemia associated with hemophagocytic syndrome and myelodysplasia in a Turkish child

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An 18-month-old boy presented with fever, hepatosplenomegaly, jaundice, pancytopenia, hyperferritinemia, hypertriglyceridemia and evidence of hemophagocytosis and trilineage myelodysplasia in the bone marrow aspiration. Appropriate treatment was begun but he died after 12 hours of hospitalization due to Gram-negative septicemia. Post-mortem examination of liver biopsy revealed diffuse hemaphagocytic lymphohistiocytosis and Leishmania-donovani bodies in macrophages.

Key words: hemophagocytic syndrome, visceral leishmaniasis, myelodysplasia.

Visceral leishmaniasis (VL) is a systemic disease caused by different forms of the intracellular protozoa, Leishmania. VL is endemic in tropical countries such as in the Middle East and the Mediterranean. The typical clinical and laboratory features are fever, hepatosplenomegaly, and pancytopenia. The clinical features of VL may mimic some hematologic disorders¹⁻³.

Hemophagocytic syndrome (HS) is a clinico-pathologic entity characterized by activation and proliferation of benign histiocytes showing phagocytosis of hematopoietic cells⁴. HS encompasses both primary and secondary hemophagocytic lymphohistiocytosis (HLH). Primary HLH is an autosomal recessive disorder, mainly affecting infants within the first months of life. Secondary HLH is commonly associated with viral, bacterial or parasitic infections, collagen diseases and malignancies⁵⁻¹⁰.

Some viral infections such as Parvovirus B19 cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have been reported to cause myelodysplasia in bone marrow and peripheral blood¹¹⁻¹⁴. VL associated with myelodysplasia has been reported in only one patient, but it was described as opportunistic infection in hematological malignancy¹⁵.

Here we report a Turkish child with visceral leishmaniasis who presented with HS and trilineage myelodysplasia mimicking myelodysplastic syndrome (MDS).

Case Report

An 18-month-old boy was referred from a regional hospital to our center with a three-week history of fever, abdominal distention, jaundice, bleeding gums, and edema of the dorsum of feet and tibia. The past medical and family histories were unremarkable.

On admission, his pulse was regular (148 beats/min); blood pressure 90/50 mmHg; body temperature 37°C; weight 11.5 kg (50th percentile); and height 80 cm (75th percentile). He was jaundiced with hepatomegaly (7 cm), and splenomegaly (8 cm). Lymph nodes were not enlarged.

Blood analysis revealed hemoglobin level of 55 g/L, white cell count of 3.3×10^9 (4% granulocytes, 72% lymphocytes including a few atypical forms, 6% monocytes, 14% stab, 4% meta), and platelet count of 43×10^9 /L. The peripheral blood smear revealed anisopoikilocytosis, nuclear abnormalities of neutrophils, pseudo-Pelger-Huët anomaly, and giant platelets (Fig. 1a). The following serum levels were measured: AST 1749 IU/L (normal 5-42 IU/L), ALT 572 IU/L (normal 5-40 IU/L), total bilirubin 11.8 mg/dl (normal 0.2-1.2 mg/dl), ESR 35 mm/h (normal <15 mm/h), C-reactive protein 164 mg/L (normal <5 mg/L), alkaline phosphatase 1270 IU/L (normal 145-420 IU/L), total protein 5.3 g/dl (normal 6.6-8.7 g/dl),

albumin 1.8 g/dl (normal 3.5-5.5 g/dl), GGT 185 U/L (normal 5-50 U/L), and lactate dehydrogenase 8965 U/L (normal 150-500 U/L). Serum vitamin B12 and folate, serum electrolyte levels and urine analysis were within normal limits. Triglycerides and ferritin were increased to 324 mg/dl (normal 0-200 mg/dl) and 1295 ng/ml (normal 15-250 ng/ml), respectively. Coagulation tests were abnormal with prolonged prothrombin time (PT) 37.5 s and activated thromboplastin time (aPTT) >150 s. The plasma fibrinogen level was 139 mg/dl (normal 200-400 mg/dl) and D-dimer was normal. The direct Coombs' test was negative.

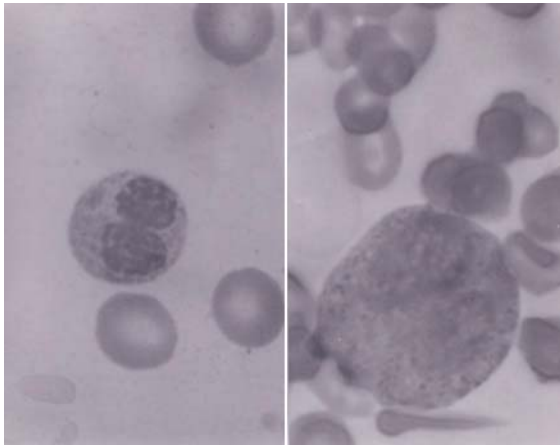


Fig. 1a. Patient's peripheral blood smear findings (10x100 Wright's stain).

Bone marrow aspiration revealed a hypocellular marrow, trilineage dysplasia and mature monohistiocytes with phagocytosis of red cells, leukocytes, platelets, and erythroblasts (Fig. 1b), but no signs of malignancy, leukemia, or other infiltrative process. Malaria was ruled out by a thick blood film. Massive hepatomegaly (diameter 11 cm) and splenomegaly (diameter 13 cm) were noted on abdominal sonography. Serological

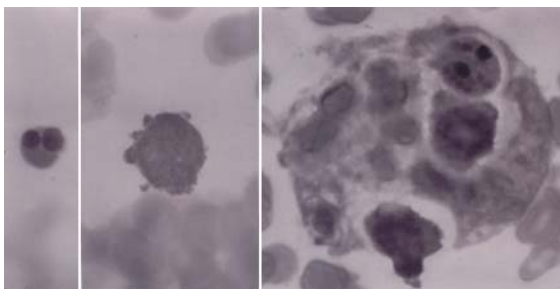


Fig. 1b. Patient's bone marrow aspiration smear findings (10x100 hematoxylin-eosin).

investigations for EBV, CMV, herpes simplex virus, Parvovirus, human immunodeficiency virus (HIV), and hepatitis A, B and C viruses were all negative. Serological studies for typhoid fever and brucellosis were normal.

On admission, treatment with cefotaxime and amikacin was started and packed red blood cell and fresh frozen plasma were given. Treatment was planned in accordance with the possible diagnosis of HS, but the patient died after 12 hours of hospitalization. Postmortem liver necropsy and splenic aspiration materials were obtained. They revealed myelodysplasia and *Leishmania-donovani* bodies within phagocytic cells (Figs. 2, 3). IFA (indirect fluorescent

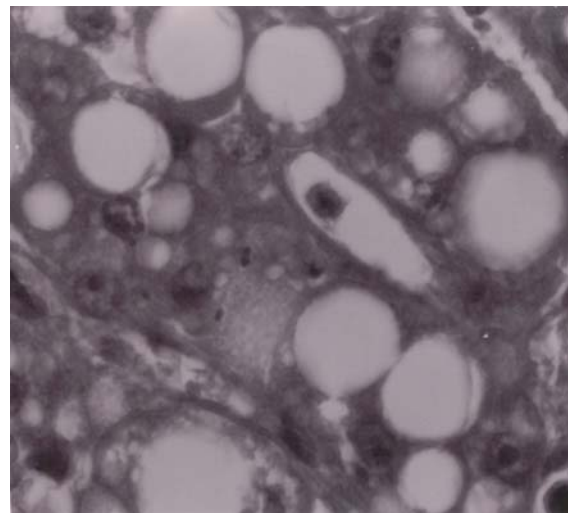


Fig. 2. Liver biopsy showing *Leishmania-donovani* bodies (10x100 hematoxylin-eosin).

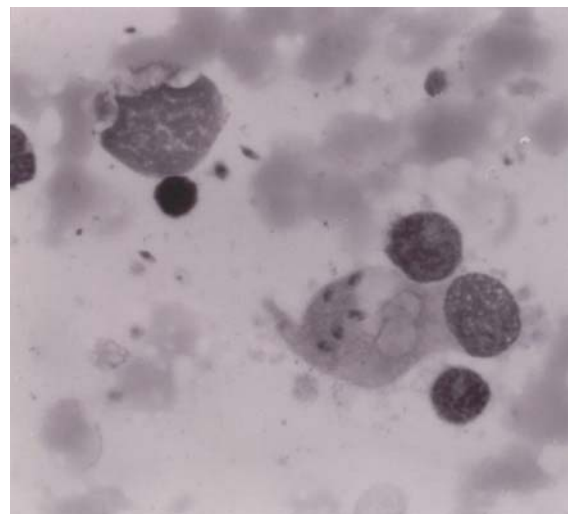


Fig. 3. Splenic aspiration showing *Leishmania-donovani* bodies in histiocytes (10x100 hematoxylin-eosin).

antibody) was 1/256 titer (normal <1/64). Blood and cerebrospinal fluid culture showed *Pseudomonas aeruginosa*.

Discussion

Hemophagocytic syndrome is an uncommon disease in childhood with a high mortality rate, and is characterized by proliferation of benign hemophagocytic histiocytes in the bone marrow, lymph nodes, spleen and liver. HS may be primary (familial or sporadic) or secondary. The diagnostic criteria of HS as defined by the FHL Study Group of the Histiocyte Society¹⁶ are high triglyceride levels, elevated liver enzymes, low plasma fibrinogen levels, coagulation abnormalities and hemophagocytosis. In addition to these, elevated lactate dehydrogenase (LDH) levels were found in all patients with primary HLH in Turkey⁸. HS has been seen with viral, bacterial, fungal and parasitic infections, collagen diseases, malignancies and genetic disorders⁹.

Our case presented with fever, jaundice, bleeding, hepatosplenomegaly, pancytopenia, elevated serum LDH, hypertriglyceridemia, hypofibrinogenemia, and the presence of numerous histiocytes with benign nuclei and hemophagocytosis of erythrocytes, platelets and leukocytes in the bone marrow. Fever, hepatosplenomegaly, and pancytopenia are also seen in HS and VL, but hypertriglyceridemia has not been reported in VL. The clotting time was abnormal and fibrinogen was reduced, which might develop due to ongoing disseminated intravascular coagulation and hepatic synthetic dysfunction, but contrary to expectation, D-Dimer level was normal in our patient. All the clinical and laboratory criteria for HS were present^{17,18}.

Hemophagocytic syndrome (HS) has been reported rarely in association with VL and *Pseudomonas* septicemia^{1,2,10,11}. The diagnosis should be confirmed by biopsy or aspiration of an involved site. In some cases of VL, *Leishmania* cannot be demonstrated in the bone marrow. We were also unable to see *Leishmania* bodies in the bone marrow in our patient. However, it was detected by liver biopsy, splenic aspiration material, and by using IFA technique.

In addition to hemophagocytosis, striking trilineage dysplasia of the hematopoietic cells was seen in examination of the bone marrow aspirate smears of the patient. Deficiencies of vitamin B₁₂ and folate; viral infections such as

Parvovirus B19, CMV, EBV, and HIV; and exposure to chemotherapeutic agents, ethanol, benzene or lead can induce some or all of the dysplastic abnormalities^{12-15,19}. We ruled these out as causes of dysplasia with history, physical examination and laboratory findings in the patient. Pati et al.¹⁶ reported three patients with hematological malignancy (one with acute lymphoblastic leukemia, one with chronic myeloid leukemia and one with myelodysplastic syndrome) complicated by VL. However, VL associated with myelodysplasia has not been reported previously.

The pathophysiology of HS may be related to production of high levels of cytokines from activated T lymphocytes and monocytes, including tumor necrosis factor (TNF)- α , interferon (IFN)- γ , soluble interleukin (IL)-2 receptor, IL-1 and IL-1 β ^{9,20}. Recently, over-secretion of IL-18 by monocytes in patients with HS has been described^{21,22}. IL-18 may enhance TNF- α , IFN- γ and Fas ligand expression. Serum level of soluble fas ligand can trigger apoptosis, which also appears to be increased in HS²³. Apoptosis is increased in myelodysplasia and impaired cycling of precursor of blood cells and cellular maturation. It is possible that the ineffective hematopoiesis found in MDS is due to increased apoptosis of bone marrow precursors^{24,25}. Mundle et al.²⁶ reported high levels of TNF- α and excessive apoptosis in the bone marrow of patients with MDS. TNF- α or other proapoptotic cytokines play a main role in the ineffective hematopoiesis of MDS²⁷.

In conclusion, various viral, bacterial, fungal, and parasitic infections such as *Leishmania* and *Pseudomonas aeruginosa* activate lymphocytes and monocytes, which produce many inflammatory cytokines. All of these influence the immune system and cause secondary myelodysplasia. Hyperproduction of cytokines may also play a role in the pathogenesis of HS. We believe that myelodysplastic findings and HS in this patient were associated with VL and *Pseudomonas* septicemia. VL is not rare in Turkey, but this patient is the first case of HS and secondary myelodysplasia associated with VL. When the typical *Leishmania* bodies are not seen in initial bone marrow aspiration, the diagnosis will be difficult. Thus, clinicians and pathologists must be aware of the association, especially in Mediterranean countries.

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