Introduction

Kala-azar is a generalized protozoan infection of the reticuloendothelial system caused by the genus Leishmania. The disease is endemic in the Middle East, East Africa and Southern Europe. Kala-azar is characterized by fever, hepatosplenomegaly, lymphadenopathy and various hematological abnormalities. The most common hematologic manifestation of kala-azar is anemia however the patient may develop leukopenia, thrombocytopenia, pancytopenia, and coagulation abnormalities. Rarely, hemophagocytic syndrome (HPS) – a disorder caused by activation and proliferation of T-cells and macrophages with subsequent cytokine production, leading to fever of unknown origin, hypertriglyceridemia may develop. The disease may be primary and familial or secondary to various etiologies that include viral, bacterial, fungal and parasitic infections as well as malignancies. It may occur in the setting of some immunodeficiency syndromes (Chediak-Higashi, Griscelli and X-linked lymphoproliferative syndrome) and as a complication of autoimmune disorders, particularly rheumatoid arthritis. Clinical presentations of HPS mimic visceral leishmaniasis. In addition, visceral leishmaniasis may be complicated by hemophagocytosis, thus differentiating between the primary and secondary forms of HPS is an important task. Infection-associated HPS resolves with treatment of the underlying infection whereas in the primary form, cytotoxic drugs are the mainstay of therapy. In this study we described the bone marrow findings of visceral leishmaniasis complicated by HPS.

Materials and Methods

Bone marrow aspirates and peripheral blood samples from 18 (11 females and 7 males) documented cases of kala-azar complicated by HPS were reviewed in order to determine clues for the diagnosis of leishmaniasis-associated HPS. Patients ages ranged from 9 months to 10 years (mean: 4.5 years).

Results

The bone marrow smears were hypercellular with erythroid hyperplasia. Megaloblastic changes, foamy macrophages, activated macrophages with cytoplasmic vacuoles and elongated cytoplasmic process, intra- and extracellular amastigotes, cytoplasmic fragments (blue bodies), plasma cells with inclusions and hemophagocytic cells were seen. Leishman bodies (amastigotes) were also found in some hemophagocytic cells.

Conclusion: Kala-azar should be considered as an etiology of HPS, particularly in endemic areas.

Keywords: Bone marrow aspiration findings, hemophagocytic syndrome, kala-azar
Diagnosis of visceral Leishmaniasis is based on the presence of amastigotes (Leishman bodies) in bone marrow or tissue sections, serologic assays, cultivation of the organism and PCR. Demonstration of Leishman bodies remains the gold standard in the diagnosis of kala-azar.

The most common hematological abnormality in our patients was anemia followed by thrombocytopenia and pancytopenia. The development of anemia in kala-azar may be due to malnutrition, sequestration, an immune mechanism, hemolysis, bone marrow depression and hemophagocytosis. Thrombocytopenia and leukopenia may occur as a consequence of hypersplenism and hemophagocytosis.

Some authors previously described bone marrow smear findings of visceral Leishmaniasis such as intra- and extracytoplasmic amastigotes, plasma cells, free cytoplasmic bodies, hemophagocytic cells and myelodysplasia. In keeping with their results we found intra- and extracellular amastigotes, megaloblastic changes, plasma cells, free cytoplasmic bodies, and hemophagocytic cells in bone marrow aspirates of our patients. We also observed the
presence of foamy macrophages, activated macrophages with cytoplasmic vacuoles and elongated cytoplasmic processes in addition to Leishman bodies in the hemophagocytic cells.

HPS is a life-threatening condition characterized by uncontrolled activation of the immune system secondary to various inherited and acquired disorders.\textsuperscript{5,6}

It was first thought that the viruses were the main etiology of infection-associated HPS, however, numerous other agents such as gram-negative bacteria, tuberculosis, leishmaniasis, and fungi have been reported to cause HPS.\textsuperscript{16} Epstein-Barr virus is the most common virus in inducing HPS. This virus is proposed to be a triggering agent in both the familial and malignancy-associated forms of HPS.\textsuperscript{6,8,9,17,18}

HPS is characterized by an increased inflammatory response due to hypersecretion of pro-inflammatory cytokines that lead to cytopenia, coagulopathy and high serum triglyceride levels.\textsuperscript{5,9,10,19} Despite the pro-inflammatory state, there is impaired function of cytotoxic T lymphocytes and natural killer cells. In infection-associated HPS, high levels of cytokines and interference by infective agents may be the cause for cytotoxic T cell dysfunction.\textsuperscript{6,8}

The cardinal signs of HPS of fever, hepatosplenomegaly and cytopenia may occur in response to various infections such as visceral Leishmaniasis but increasing severity of these signs should raise the possibility of a more serious problem such as HPS.\textsuperscript{6}

**Conclusion**

The presentation of HPS and visceral Leishmaniasis are very similar. Therefore in the presence of hemophagocytic cells, plasma cells, free cytoplasmic bodies, and activated macrophages an extensive search for Leishmania amastigotes should be performed, particularly in endemic areas. Performing serological tests and PCR on bone marrow or peripheral blood specimens will increase the sensitivity of diagnosing Leishmaniasis-associated HPS.

**References**