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REVIEW

The Hematological Manifestations and Aspects of Visceral Leishmaniasis

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Leishmaniasis is caused by infection with the flagellate protozoan parasites of the genus Leishmania including over 20 *Leishmania* species. Over 90 sandfly species are known to transmit *Leishmania* parasites. There are 3 main forms of the disease, with Visceralleishmaniasis being the form of hematological interest.

Visceral leishmaniasis (VL), also known as kala-azar (black fever in Hindi) is a disease primarily caused by *Leishmaniadonovani* and *L. infantum* (synonym *L. chagasi*) that is transmitted by phlebotomine. Rarely, visceral disease has been reported in patients infected with leishmanial species usually associated with cutaneous disease, in particular, *L. mexicana* and *L. tropica*. VL is fatal if left untreated in over 95% of cases. It is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia. Most cases occur in Brazil, East Africa and in India. An estimated 50 000 to 90 000 new cases of VL occur worldwide annually, with only between 25 to 45% reported to WHO. It remains one of the top parasitic diseases with outbreak and mortality potential.[1,2]

The cycle of life of leishmanial includes: the injection of promastigotes into the skin of a vertebrae host when boten by a sandfly and transformed into amastigotes after having been phagocytized by macrophages or other types of mononuclear cells, where they divide and then rupture the host cell. Afterwards they enter either macrophages of the reticuloendothelial organs or skin, leading to hyperplasia of th mononuclear phagocytic system, thus producing hematological changes.[3]

Usually patients complain of pyrexia (although some patients have no fever or intermittent, periodic fever), weight loss,abdominal discomfort and fullness that may be localized to the left upper quadrant. The spleen is usually large, firm and tender, but in some patients palpation is quite painful, howeverhepatomegaly is usually less marked than splenomegaly. The size of the spleen is related to the duration of the infection. Lymphadenopathy may be observed in East African VL but is rare outside this region except for HIV positive patients and children.[2]

Since parasites replicate in the reticuloendothelial system, very high parasite loads accumulate in the spleen, liver, and bone marrow. Severe anemia can occur due to bone marrow suppression, hemolysis, and splenic sequestration. Advanced kala-azar is associated with marked cachexia, hypoalbuminemia, and edema. Late in the course of disease, hepatic dysfunction, jaundice, and ascites can occur. Thrombocytopenia and hepatic dysfunction contribute to hemorrhagic complications. Coagulation disorders in the form of prolonged PT and APTT have been reported, with one third of the patients develops disseminated intravascular coagulation.[4]Patients may have spontaneous bleeding from the gingiva, nasal mucosa, or other sites. Rarely, chronic

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diarrhea and malabsorption can occur as a result of parasitic invasion of the intestine.

Among other, VL may mimic manyhaematologicalconditions or malignancies, therefore these patients present quite often to the haematologist at first. Differential diagnosis of VL and splenic lymphoma can be troubling resulting in splenectomy as well as differentiating atypical myelodysplastic syndrome due to the occurring cytopenias and dyserythropoiesis can give the hematologist a hard time. Often enough, type III cryoglobulins, a small band of monoclonal paraprotein or diclonalgammopathy can be observed.[5]

Hemophagocyticlymphohistiocytosis (HLH) is a systemic disorder of excess immune activation that can be triggered by certain infections; it is an uncommon complication of VL. VL related HLH is often under-recognized because of overlapping clinical features and negative marrow evaluation at onset, leading to high mortality rates.

Timely diagnosis is important; while 60 to 70 percent of patients with HLH secondary to VL respond to antileishmanial treatment alone, a delay in diagnosis of HLH may increase the need for adjunctive therapy.[6,7]

In VL the bone marrow is usually hypercellular or normocellural, even though it can be fibrotic resulting in a dry tap or even hypoplastic in advanced or chronic stages. Other findings can be erythroid hyperplasia and dyserythropoiesis as well as megaloblastic change due to folic acid deficiency, reduced myeloid to erythroid ratio, left shifted granulopoiesis, reactive plasmacytosis, increased macrophages and histiocytes, haemophagocytosis, Mott cells or Russel bodies. A mild increase in eaosinophil precursors may be also be observed. Amastigotes either intracellular or extracellular may be demonstrated in 54-86% of bone marrow aspirates.[8] Hematological improvement is noted within a week and complete hematological response occurs in 4–6 weeks of treatment with the bone marrow returning to normal appearance almost nine months after cure. The haemoglobin response may be delayed due to anaemia of chronic disorder. Relapses are rare and increased risk of being diagnosed with hematolymphoid malignancies on long term follow up is not noted.[9]

Both innate and acquired immune responses contribute to resolving or pathogenesis of leishmaniasis. Innate immune cells including neutrophils, natural killer (NK) cells, macrophages, and dendritic cells (DCs) move towards the infection site inducing the immune responses against Leishmania infection. During leishmaniasis, neutrophils are infiltrated rapidly at the infection site and contribute with host protection or disease progression, depending on parasite species. Neutrophils recruit DCs to the site of infection via a chemokine ligand 3-dependent pathway (CCL3) that leads to expression of apoptotic markers on neutrophils as well as decreasing differentiation of T helper type 1 (Th1) responses and cross-presentation for CD8+ T cell activation resulting in increasing parasite survival in DCs and promoting aggravated disease.[10]

However it is also very clear that the T-cell mediated immunity and the cytokines secreted from different immune cells play a crucial role in promoting the disease outcome. Th1 cells associate with host resistance against leishmaniasis via releasing pro-inflammatory cytokines such as IL-2 or interferon γ (IFN-γ), while Th2 cells mediate susceptibility to the disease by creating anti-inflammatory cytokines such as IL-4, 5 and 10. It is revealed that IFN-γ affects macrophages to increase nitric oxide (NO) synthase (iNOS)2 enzyme and NO sacrifices the intracellular amastigotes. While Th2 immune response restricts Th1 action via IL-10 and IL-4 production, it causes depletion of macrophage, leading to intracellular parasite growth and disease progression. For survival, the Leishmania parasite needs the host system to suppress the immune system or promote pro-parasitic host reactions.[11]

Leishmaniasis remains a neglected tropical disease, with a need for additional clinical trials with better design and

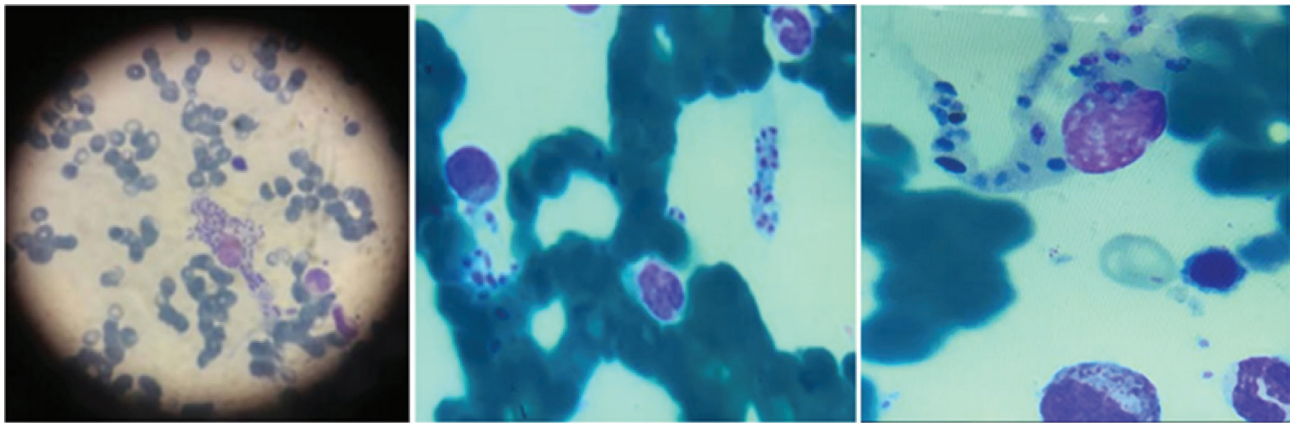

FIGURE 1. Peripheral blood smear and bone marrow aspirate demonstrating Leishmania amastigotes.

reported endpoints to lead evidence-based treatment recommendations – especially in leishmaniasis in the immunocompromised host.

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