Case Report

Hemophagocytic Lymphohistiocytosis Associated with Visceral Leishmaniasis

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Summary

Visceral leishmaniasis (VL), is a systemic disease caused by the dissemination of protozoan parasite *Leishmania* throughout the reticuloendothelial system. It may mimic or lead to several types of hematological disorders including hemophagocytosis. Infection associated hemophagocytic syndrome implicating *Leishmania* is very rare and often difficult to diagnose. Here, we describe a child with hemophagocytic lymphohistiocytosis (HLH) associated with VL.

Key words: *Leishmania*, hemophagocytosis, children

Introduction

Visceral leishmaniasis (VL) is a strongly immunosuppresive, generalized infection of the reticuloendothelial system resulting in a chronic progressive disease that is often fatal [1]. Typical disease manifests with intermittent fever, paleness, massive hepatosplenomegaly, pancytopenia and progressive deterioration of the host. Rare manifestations of VL are hemophagocytic syndrome, acute hepatitis, cholecystitis and Guillain–Barre syndrome [2, 3]. VL revealed by hemophagocytosis can cause considerable diagnostic difficulty because of the similarities between these two disorders involving the mononuclear phagocyte system. Patients reported in the literature have been limited even from countries where leishmaniasis is endemic [4] We report a child who had concomitant VL and HLH.

Case report

A 2-year-old boy presented with a 1 month history of high fever, fatigue, poor feeding, weight loss, pallor and abdominal distension. On physical examination, he was febrile (39.6°C) and pale. There was severe weight loss and failure to thrive. He had hepatomegaly (4 cm below the right costal margin) and splenomegaly (8 cm below the left costal margin). Neither lymphadenopathy nor bleeding signs were observed. Hematological investigation revealed hemoglobin 5.1 g/dl, white blood cell count 3300/mm^3 (16% neutrophils, 76% lymphocytes and 8% monocytes), platelet count 55 000/mm^3. Erythrocyte sedimentation rate was 55 mm/h, C reactive protein was 9.52 mg/dl and ferritin was 6364 ng/ml. Fibrinogen level was normal. Serum triglycerides were increased to 266 mg/dl with normal cholesterol, and the serum lactate dehydrogenase level was elevated at 2762 U/l. Serological markers for Epstein–Barr virus, cytomegalovirus, parvovirus B19, toxoplasmosis, hepatitis A and B viruses, HIV, salmonella and brucella agglutinins were all negative and blood cultures could not demonstrate any infectious agent.

On bone marrow aspiration hemophagocytosis and *Leishmania* amastigotes were observed (Fig. 1A and B). The patient was diagnosed with HLH associated with VL. Liposomal amphotericin B 3 mg/kg/day was administered on 1–5, 14 and 21 days. Treatment was well tolerated, no side effects were observed. Symptoms and clinical findings improved gradually. Fever was controlled on the third day of treatment. After 5 days of treatment laboratory testing revealed hemoglobin 8 g/dl, white blood cell count 4500/mm^3, platelet count 144 000/mm^3. One week later, the hepatosplenomegaly gradually regressed. On discharge, physical examination was normal, with no enlargement of spleen. No relapse was seen in a 6 months follow-up period.

Discussion

HLH comprises two different conditions that may be difficult to distinguish from one another: a primary and a secondary form. The primary autosomal

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doi:10.1093/tropej/fmm024

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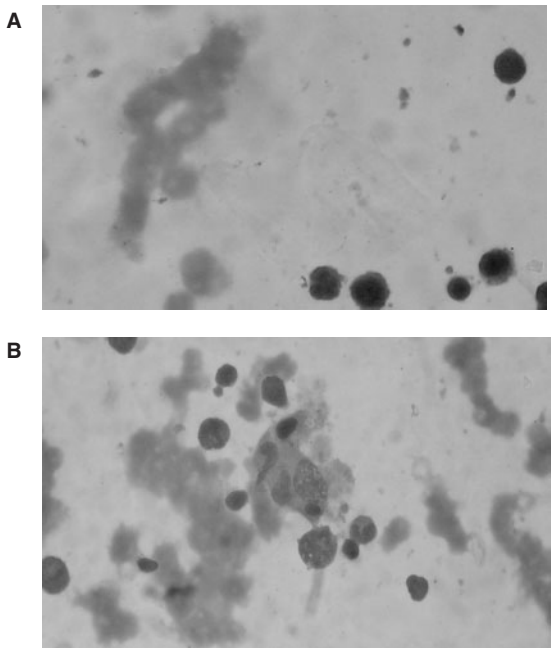


FIG. 1. (A) *Leishmania* amastigotes. (B) Hemaphagocytosis.

recessive form, familial hemophagocytic lymphohistiocytosis (FHL) of the infants and reactive hemophagocytic syndrome (RHS) are encountered at any age. RHS may occur in association with a wide variety of infections due to strong immunological activation of the immune system. Infection-associated forms of HLH may subside spontaneously but may also be associated with increased mortality [5]. Infection associated HS accounts for nearly 50% of all cases of HLH.

Patients with fever, hepatosplenomegaly and pancytopenia suggesting lymphoproliferative disorders are usually admitted to hemathology departments. When a diagnosis of hemophagocytic syndrome is made identification of an ethiological cause may not be easy. Because the patients may be over treated with cytotoxic drugs as a primary HLH a high index of suspicion is required for early recognition of associated infections as the cause of hemophagocytosis [2].

Our patient had pancytopenia, hepatosplenomegaly, fever, elevated ferritin and triglyceride levels and bone marrow hemophagocytosis in keeping with diagnostic criteria of HLH reported by Hunter *et al.* [5]. Identification of *Leishmania* amastigotes as a cause of HLH in the initial bone marrow prevented unnecessary further investigations. In a recently reported French series of HLH associated with VL the parasite was not detected in 22% of cases [6]. Hemophagocytosis in VL is usually mild, however; *Leishmania* amastigotes are rarely detected on an initial bone marrow smear in cases with severe hemophagocytosis. Presence of severe hemophagocytosis in bone marrow smears can correlate with marked cytopenias [7]. For our patient although the degree of pancytopenia is a indirect sign of severity of hemophagocytosis, amastigotes and hemophagocytic cells could be seen together on initial bone marrow smear. Thus specific treatment could be given without any delay. Diagnostic delay may cause severe complications and moreover death may occur in patients without specific treatment [8].

Primary treatment of RHS should include therapy for the underlying or triggering disorder. Management of VL has improved considerably since it was discovered that amphotericin B is effective against *Leishmania* spp. According to the literature this agent seems most suitable for VL associated HLH, because lipid-associated amphotericin B is taken up by macrophages and targets the drug to the site of infection, leading to very high concentrations in the liver and spleen [9]. We chose liposomal amphotericin B for our patient based on the successful treatment outcomes reported in other patients [2]. Like the previously reported cases, clinical and laboratory response was observed within the first week. Although antimony drugs are suggested for developing countries these drugs are not available in our country.

Infection by *Leishmania* is a public health problem in most countries bordering Mediterranean basin. Most of the patients reported in the literature presenting as hemophagocytic syndrome are from Mediterranean countries [3, 8, 10]. Out of 22 known species, the majority of causes in these countries are due to *L. infantum*. VL is endemic in western, southern, northern and central provinces of our country where the climate is relatively warm. The East Anatolia region of Turkey has a cold climate and has not been known to be an endemic region for VL. However, it has recently been reported that the region Kağızman from the eastern part of the country, where our patient comes from, is a new endemic area. Kağızman is a warm pocket in an otherwise cold region. Our case reinforces the fact that the meticulous search for amastigotes of *Leishmania* should be made in patients presenting with HLH especially those coming from endemic areas.

In conclusion, when confronted with a patient with bicytopenia or pancytopenia in the setting of fever or documented HLH, the possibility of associated VL should be considered for the etiology. Awareness of this association and early diagnosis of VL may prevent prolonged hospitalization and potentially harmful investigations and treatments.

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