Case report

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VISCERAL LEISHMANIASIS ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Visceral leishmaniasis (VL) is caused by the dissemination of the protozoan parasite Leishmania donovani throughout the reticuloendothelial system. This systemic disease may mimic or lead to several types of hematological disorders including hemophagocytic lymphohistiocytosis (HLH). Infection associated hemophagocytic syndrome caused by Leishmania is very rare and difficult to diagnose. Herein, we describe an infant with HLH associated with VL. The severity of HLH secondary to visceral leishmaniasis ranges from pure biological forms that resolve with antimicrobial therapy to life-threatening emergencies that require specific treatment. Our patient was treated with meglumine antimoniate. The outcome of the disease was favorable with a follow-up of 12 months.

Key words: Leishmaniasis ▪ Hemophagocytic lymphohistiocytosis

Introduction

The leishmaniases are parasitic diseases caused by different species of protozoa of the genera Leishmania. Visceral leishmaniasis (VL) is the most severe clinical form of disease which usually has a fatal outcome without appropriate treatment. The disease is endemic in over 60 countries on five continents. It is estimated that 500 000 cases occur every year in five countries: India, Bangladesh, Nepal, Sudan and Brazil (1). In the Mediterranean region, VL is also endemic and affects mostly children. VL is still rare in Europe, although its incidence has increased significantly. The increased incidence is due to a greater number of new cases among HIV-infected individuals and better reporting (2). New endemic areas have been detected in France, Italy, northern

Croatia, Switzerland and Germany (3). Since this is still a rare disease in our country, diagnostic and therapeutic delays are common.

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially lethal disease. It occurs as a result of multisystem inflammation due to uncontrolled activation of normal T lymphocytes and macrophages. Classification of HLH is given in Table 1 (4).

On the basis of the diagnostic and therapeutic protocol HLH-2004, diagnosis of HLH is as shown in Table 2 (5).

Secondary HLH is usually triggered by an infection. VL associated HLH may be misdiagnosed even in endemic areas due to the overlapping clinical features of these two conditions (6).

Table 1 Classification of hemophagocytic lymphohistiocytosis

Primary HLH
Familial HLH (Farquhar's disease)
Known gene defects (perforin, MUNC 13-4, syntaxin 11)
Unknown gene defects
Immunodeficiency syndromes
Chediak-Higashi syndrome
Griscelli syndrome
X-linked lymphoproliferative syndrome
Acquired HLH
Exogenous agents (microorganisms, toxins)
Infection-associated hemophagocytic syndrome (IAHS)
Endogenous agents (tissue damage, metabolic products)
Rheumatic diseases
Macrophage activation syndrome (MAS)
Malignancies

Table 2 Diagnostic criteria for hemophagocytic lymphohistiocytosis

1. Familial HLH – known gene defect OR
2. Clinical and laboratory criteria (5 out of 8 necessary for diagnosis)
1. Fever
2. Splenomegaly
3. Bi - or pancytopenia
Hemoglobin <90 g/l
Platelets $<100x10^9$/l
Segmented neutrophils $<1x10^9$/l
4. Hypertriglyceridemia and/or hypofibrinogenemia
Fasting serum triglycerides >3 mmol/l
Fibrinogen <1.5 g/l
5. Ferritin >500 μg/l
6. sIL-2R(CD25) >2400 U/ml
7. Low or absent NK cell activity
8. Hemophagocytosis in bone marrow, lymph nodes or CSF

sIL-2R= Soluble interleukin-2 receptor; CSF = Cerebrospinal fluid; The diagnosis is supported additionally by central nervous system (CNS) symptoms, CSF pleocytosis and/or hyperproteinorrachia, elevated transaminases, bilirubin or LDH.

We present the case of an infant from a non-endemic area in southern Serbia with HLH associated with VL.

Case report

An eleven month old male infant was evaluated for fever of four weeks duration, pancytopenia and splenomegaly. The fever was intermittent, reaching a peak of 39 °C, two to three times a day. Physical examination at onset of illness was normal. On the third day of fever complete blood count was performed showing normal cell count and differential count, and moderate normocytic anemia. Urinalysis was normal. The fever persisted after seven days of empiric cefprozil. Re-examination showed splenomegaly (2 cm below the left costal margin) and he was referred to this hospital. There was no family history of hematological diseases and his parents had a non-consanguineous marriage.

On admission, the child was anxious, febrile, pale, with normal vital signs, well-developed and nourished according to age. The liver was palpable 2 cm below the right costal margin and the spleen 4 cm below the left costal margin. The rest of the physical examination was unremarkable. The results of laboratory analysis are presented in Table 3.

Table 3 Summary of clinical investigations

Investigation	Value	Normal value*
Hemoglobin	65	105-140 g/l
Leukocyte count	3.0	6.0-17.5 x 10^9/l
Platelet count	58	150-400 x 10^9/l
Serology		
• HIV (ELISA)	Negative	-
• Hepatitis A (IgM), B (HBsAg) and C (IgM) (ELISA)	Negative	-
• CMV IgM and IgG (ELISA)	Negative	-
• EBV IgM and IgG (ELISA)	Negative	-
• Parvo B19 IgM and IgG (ELISA)	Negative	-
Mantoux skin test	Negative	-
Cultures		
• Blood	Sterile	-
• Urine	Sterile	-
CRP	23	<3 mg/l
Serum ferritin	560	6-80 μg/l
Serum triglyceride	4.2	0.8-2.0 mmol/l
Serum bilirubin (total)	17	<21 μmol/l
Serum albumin	45	39-50 g/l
Alanine transaminase	182	5-45 U/l
Aspartate aminotransferase	84	15-55 U/l
Alkaline phosphatase	152	145-420 U/l
Lactate dehydrogenase	630	170-580 U/l
Fibrinogen	1.1	2-4 g/l
Prothrombin time	19s	10.6-11.4s
Activated partial thromboplastin time	45s	24-36s
D-dimer	760	64-494 μg/l
Solubile IL-2 receptor	23.35	0.5-1.5 ng/ml
Spinal tap		
• Cells	0	0-3 lymphocytes/μl
• Protein content	40	40-45 mg/dl

* Normal value according to the age of our patient.

Chest X ray was normal. Abdominal ultrasound showed a normal liver and enlarged spleen (97 mm), without focal lesions. Examination of peripheral blood smear showed moderate anisopoikilocytosis. The bone marrow aspirate stained by May-Gruenwald-Giemsa technique revealed normal cell morphology of all blood cell precursors, as well as adequate counts and appropriate level of maturity. However, there were a few histiocytes exhibiting hemophagocytosis with a few intracellular and extracellular amastigotes (Figure 1). Serological testing for Leishmania, namely the Rapid Dipstick rK39 test (strip-test; DiaSys Europe Ltd., Wokingham, UK), was positive.

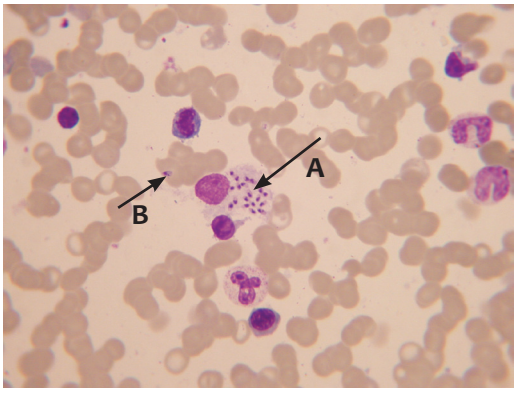

Figure 1 *Hemophagocytosis in bone marrow and intracellular (A) and extracellular amastigotes (B)*

Treatment was started with meglumine antimoniate, 20 mg/kg per day, intramuscularly. Fever resolved on the second day of treatment followed by gradual normalization of laboratory parameters. There were no adverse events during the treatment. Treatment was continued in the outpatient setting for a total of 4 weeks. He remains asymptomatic at one year of follow-up with no disease recurrence.

Discussion

Secondary HLH caused by VL is rare in countries where leishmaniasis is a sporadic disease. Serbia is not considered endemic for leishmaniasis; however southern parts of the country used to be endemic previously. The last reported cases in this region were in 1968-69. Most of our patients with VL have a history of travel to an endemic area, mostly to Montenegro (7, 8). Our patient did not report travel to any endemic area. Additionally, the age of onset suggested primary, familial HLH. However, the diagnosis of VL associated HLH was made, sparing the patient from highly toxic immunosuppressive and cytotoxic treatment used in primary HLH. Our patient is probably a case of zoonotic infection, but the animal reservoir is unclear. Notwithstanding the absence of traveling history to an endemic area, it is recommended to exclude leishmaniasis in all children with prolonged fever of unknown origin. Repeated bone marrow aspiration, liver biopsy, blood cultures and serological analysis can contribute to the diagnosis. Initial bone marrow examination may often yield negative results. In the case of repeated negative bone marrow findings, liver biopsy may lead to diagnosis of VL. The existence of bleeding disorders and thrombocytopenia may be a contraindication to percutaneous liver biopsy. Serological tests are of satisfactory sensitivity and specificity (9), but the bone marrow finding is the gold standard for diagnosis. Antiprotozoal treatment is the therapy of choice in secondary HLH caused by VL in most cases. Pentavalent antimony salts and amphotericin B are most frequently used in the treatment of VL in children. Meglumine antimoniate treatment in our patient led to complete recovery. Resistance of Leishmania infantum to pentavalent antimony salts is increasingly becoming a significant problem (10). In such cases, use of amphotericin B and its liposomal formulations is recommended due to lower toxicity and shorter duration of treatment (11). Additionally, amphotericin B lipid formulation is superior

to antimony salts in secondary 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 (12). Use of intravenous immunoglobulins (IVIG) in VL associated HLH has been reported to have variable benefits and is probably related to the delay in initiation of therapy. Hyperferritinemia implies ongoing macrophage activation, and additional therapy with IVIG, guided by clinical judgment, is warranted (13). There are some anecdotal reports about successful use of etoposide (14). However, the use of steroids and etoposide in IAHS may be problematic, especially in areas where tuberculosis, malaria or VL might trigger HLH (15).

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