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Case Report

Hemophagocytic Lymphohistiocytosis Associated Visceral Leishmaniasis in a Child: Evolution Favorable Under the Specific Treatment of Visceral Leishmaniasis

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Abstract: Hemophagocytic lymphohistiocytosis (HLH) associated with visceral leishmaniasis (VL) in children is a rare clinicopathological entity, difficult to diagnose, fatal in the absence of treatment. It should be evoked in children with prolonged fever and splenomegaly. We report two cases of HLH caused by visceral leishmaniasis . In the first case, it was a 14-month old infant hospitalized for fever with pancytopenia. The diagnosis of HLH was made in front of a clinical and biological features, a corticotherapy was initiated. The search for an underlying infectious disease had shown the presence of leishmania bodies on the myelogram. The second case was a 15-month old infant hospitalized for fever associated with abdominal distension. The diagnosis of VL was made on the medullogram, during the hospitalization a macrophagic activation report was positive and treatment with meglumine antimoniate was introduced, the two infants had evolved well under treatment.

Keywords: Hemophagocytic lymphohistiocytosis (HLH); Visceral leishmaniasis (VL); infant; antimonials

INTRODUCTION

Hemophagocytic lymphohistiocytosis is a clinico-biological entity characterized by a large and unregulated production of pro-inflammatory cytokines with proliferation of lymphocytes and uncontrolled activation of medullary histio-macrophage cells [1], which are responsible for hemophagocytosis in the reticulo-endthelial system including bone marrow [2-5].There are two categories of HLH: primary HLH and secondary HLH, occurring in neoplastic, autoimmune or infectious conditions. These can be severe and life-threatening. We report two cases of HLH associated with visceral leishmaniasis (VL) in 14 and 15- month old infants who developed well under specific VL therapy.

CASE PRESENTATION

Case report 1

A 14-month old infant with no previous history had been hospitalized for fever, asthenia and weight loss associated with pancytopenia. Clinical examination of the patient revealed a fever at 39 ° C, anemic syndrome, splenomegaly at the umbilicus in a Persistent febrile context. Initial biological results showed pancytopenia with a positive biological data of macrophage activation: hemogram showed pancytopenia with 4.2 g / dL of hemoglobin, 2.2 giga / L of leukocytes and 8 giga / L of platelet counts. In addition, the triglyceride concentration was 3.29 g / l, fibrinogen was 1.69 g / l and the lactate dehydrogenase widely increased to 1143 IU / l. Ferritin was at 4787 ng / ml.

A diagnosis of hemophagocytic lymphohistiocytosis was made on clinical and biological criteria, corticosteroid therapy was initiated and an etiological investigation was undertaken to find out the cause.

The myelogram showed many leishmaniae bodies without images of hemophagocytosis.The serology of leishmaniasis was positive.

Serology for Epstein-Barr virus [EBV], Cytomegalovirus [CMV], hepatitis B and C, human immunodeficiency virus [HIV], toxoplasmosis, all of these examinations were negative.

The diagnosis of VL was confirmed by the National Institute of Hygiene. Treatment with meglumine antimonate had been started. Clinical and biological evolution had been favorable.

Case report 2

This 15-month-old infant had been hospitalized for a fever associated with an abdominal distension that had been evolving for 18 days.

The clinical examination of the patient was objectified, an anemic syndrome, splenomegaly without bleeding syndrome evolving in a persistent febrile context.

Hemogram showed : hemoglobin at 6 g / dL, leukocytes at 1.6 Giga / L, neutrophils at 0.42 Giga / L and platelets at 12 Giga / L, In addition protein at 56 g / l, Albumin at 23 g / l, normal renal assessment, speed of sedimentation at 21, HIV serology, CMV, hepatitis B and C not requested by parents.

The medullogram shows a medullary smear with marrow infiltrated by numerous bodies of leishmanias in extracellular amastigote with a discretely hypoplastic granular maturation. The diagnosis of VL was then retained.

The biological exam of macrophage activation was positive with a pancytopenia associated to an increase in triglycerides at 4.2 g / l, fibrinogen collapsed at 0.41 g / l, elevation of lactate dehydrogenases at 980 IU / L. hyperferritenemia at 717 ng / ml, transaminases elevated to 124 IU / l hyperbilirubinemia at 19 mg /.

The patient received meglumine antimoniate gradually and was kept under 80mg / kg / day for 21 days with good clinical improvement, disappearance of fever, progressive regression of splenomegaly and biological improvement.

DISCUSSION

These two clinical cases of HLH secondary to VL did not have the same clinical presentation. In the first case, the H LH was first diagnosed whereas in the second the LHH appeared during the course of the VL.

Hemophagocytic lymphohistiocytosis is a rare condition. The incidence is estimated at 51.7 cases per year [6] in Japan. In another Swedish study, the prevalence rate of familial HLH in children is 0.12 cases per 100,000 inhabitants / year [7, 8].

The main anomaly appears to be a cytotoxicity deficiency of CD8 and Natural Killer T lymphocytes (NK), with no limitation on their activation or cytokine production.

In a particular infection, a normal but ineffective activation of the CD8 / NK T lymphocyte system persists, allowing the causative agent to persist and the macrophages perpetuate the stimulation and proliferation of these same CD8 and NK T lymphocytes. Cytotoxic cells stimulate macrophage activation and the loop self-amplifies in an uncontrolled manner.

Various cytokines are involved (including interferon gamma (INF γ), TNF alpha, many interleukins (IL-2) and the macrophage colony stimulating factor (M-CSF) involved in the clinical and biological manifestations of HLH. [9-12]

Two forms of HLH are described, primary HLH that are the prerogative of children and especially infants (primary immunodeficiency, familial forms) or secondary HLH (infections, malignant diseases or autoimmune diseases) that occur in older children and adults in whom no notion Family or genetic abnormality are found. [4,12]

The most common infectious agents associated with H LH are herpes viruses (Herpes simplex, EBV, CMV Human Herpes Virus8), HIV, adenovirus, hepatitis A virus, parvovirus, enterovirus, influenza virus, mycobacteria,agents of VL, malaria and toxoplasmosis. [12]

The typical clinical picture associates fever, hepatosplenomegaly and cytopenia, biological signs are commonly present:

Hypertriglyceridaemia, hypofibrinogenemia, hyperferritinemia, hepatic cytolysis, more rarely, polyadenopathy, jaundice, cutaneous rash and edema are observed.

In a favorable clinico-biological context, myelogram would be done repeatedly for a confirmation value. It shows a rich marrow with medullary infiltration by histiocytes of benign aspects, an erythroblastosis and especially the endocytosis of the macrophages of the figurative elements of the blood: (Platelets, erythroblasts, lymphoid cells) hemophagocytosis [2-5,12, 13].

Two points are important to remember : The normality of the myelogram does not eliminate the diagnosis (hence the interest of repeating the sample) ,this is the case in our two observations. Therefore, the presence of haemophagocytosis images is neither sufficient nor pathognomonic of the diagnosis [14].

The authors developed a set of parameters to facilitate the diagnosis of HLH and the most recent of these guidelines was developed by Henter *et al.* [3] in its revised version of 2007 and adopted by the Histiocyte Society (Table 1).

Therapeutically, the treatment of HLH varies according to the etiology of the syndrome. The initial treatment of HLH is based on etoposide (VP16),

corticosteroid therapy [15] and ciclosporin. Some teams prefer the use of immunoglobulins. Allograft is indicated as a radical treatment of primary HLH.

Although there are not many publications, VL has been reported as a curable cause of LHH in the late 1980s. In both cases immunosuppressive therapy was not initiated because of the identification of the causative agent (VL) and the treatment with antimonials alone or with corticosteroids (observation 1) resulted in good evolution.

Table 1: Diagnostic criteria for hemophagocytic lymphohistiocytosis [|3]
(The diagnosis is made in the presence of criterion 1 or 2)

Criteria 1
Molecular diagnosis of hemophagocytic lymphohistiocytosis (primary LHH)
Criteria 2 (five out of eight criteria are required)
Fever> 7 days, with peaks> 38.5 ° C
Splenomegaly
Cytopenia on 2 or 3 lines (hemoglobin <9g / dl, neutrophils <1G / l platelet <100G / l) not explained by a poor or dysplastic marrow
Hypertriglyceredemia> 3 mmol / L and / or Hypofibrogenemia <1.5 g / l
Ferritin> 500µg / l
Natural killer activity decreased or absent CD 25 soluble> 2400 U / ml
Hemophagocytosis (medullary, splenic or lymph node).

CONCLUSION

HLH associated with visceral leishmaniasis (HLH-VL) has certain specificities. Similarity of the clinical and biological signs between Visceral leishmaniasis and induced HLH makes the diagnosis difficult. We must think of it in a clinical picture of prolonged fever with splenomegaly in children in endemic areas. The treatment of VL is easy and the course is often benign under specific treatment.

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