Case Report/Relato de Caso

Hemophagocytic lymphohistiocytosis associated with H1N1 virus infection and visceral leishmaniasis in a 4.5-month-old infant

Linfohistiocitose hemofagocítica associada pela infecção do vírus H1N1 e leishmaniose visceral em um bebê de 4,5 meses de vida

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ABSTRACT

We present a case of a 4.5-month-old boy from Turkey with hemophagocytic lymphohistiocytosis (HLH) associated with *H1N1* virus and *Leishmania* spp. coinfection. Because visceral leishmaniasis can mimic hematologic disorders like HLH, it is important to rule out this clinical condition before starting immunosuppressive therapy. In our case, treatment with liposomal amphotericin B resulted in a dramatic resolution of clinical and laboratory abnormalities.

Keywords: H1N1 virus. Visceral leishmaniasis. Hemophagocytic lymphohistiocytosis.

RESUMO

É relatado um caso de um menino de 4,5 meses de idade, da Turquia, com linfohistiocitose hemofagocítica (HLH) associado à coinfecção com o vírus H1N1 e leishmaniose visceral. Como a leishmaniose visceral pode imitar doenças hematológicas como HLH, é importante afastar essa condição clínica antes de iniciar a terapia imunossupressora. No caso relatado, o tratamento com anfotericina B lipossomal resultou em uma resolução dramática das anomalias clínicas e laboratoriais.

Palavras-chaves: Vírus H1N1. Leishmaniose visceral. Linfohistiocitose hemofagocítica.

INTRODUCTION

Visceral leishmaniasis is a generalized infection of the reticuloendothelial system resulting in a chronic progressive disease that often is fatal without treatment. It may mimic or lead to several types of hematological disorders. Here, we present a case of a 4.5-month-old boy from Turkey with H1N1 virus and *Leishmania* coinfection with associated hemophagocytic lymphohistiocytosis (HLH) who was treated successfully with liposomal amphotericin B.

CASE REPORT

A 4.5-month-old boy was admitted to the hospital because of fever for 25 days. He was hospitalized for further research and treatment especially because of concurrent H1N1 *influenza* epidemics. On admission, he was conscious and had a heart rate of 140/min, breath rate of 40/min, and body temperature of 39.4°C. He had a body weight of 7,450g (50p) and a height of 65cm (50p). He had hepatomegaly below costal arch and massive splenomegaly without any other pathological finding in his examination. The perinatal history of the baby was unremarkable. Birth weight was 2,850g, and he was still being breastfed by the time of admission. His growth and development was compatible with his chronological age. There was no consanguinity between parents.

Laboratory tests revealed 8-10 times elevated transaminases and pancytopenia. Total leukocyte count of 3,320/mm^3, neutrophil count of 740/mm^3, hemoglobin level of 9.8g/dl, and platelets of 146,000/mm^3 (less normal value for the method used: 150,000/mm^3) were consistent with pancytopenia. He also had an aspartate aminotransferase (AST) of 1,162mg/dl, alanine aminotransferase (ALT) of 396mg/dl, total protein of 8.8g/dl, albumin of 2.2g/dl, and C reactive protein level of 4.5mg/dl (normal values were eliminated). Splenomegaly and enlarged kidneys were demonstrated in abdominal ultrasonography.

Blood and urine cultures were negative**.** *Epstein Barr Virus* (EBV) immunoglobulin M (IgM) and immunoglobulin G (IgG), cytomegalovirus IgM and IgG, antihuman immunodeficiency virus (antiHIV*), parvovirus B19* IgM and IgG, hepatitis A virus (HAV) IgM, hepatitis B surface antigen (HBsAg), antibodies to hepatitis B core antigen (antiHBc) IgM, and antihepatitis C virus (antiHCV) also were negative. Antibodies to hepatitis B surface antigen (antiHBs) and HAV IgG were positive. There was no serological evidence of *Brucella* spp. with rapid diagnostic tests. Nasal smear test in cell culture showed positive result for H1N1 virus. There was no other proven cause of infection except presence of H1N1, and oseltamivir treatment was started. However, unresponsiveness to that therapy revealed requirement for further investigations. Presence of hepatosplenomegaly and pancytopenia accompanied with prolonged fever led us to consider HLH. The other diagnostic criteria of HLH were sought, and elevated levels of ferritin (3,440ng/ml) and triglyceride (290mg/dl) and a mild decrease in levels of fibrinogen (155mg/dl) were demonstrated. Bone marrow examination diagnosed normocellular bone marrow with diffuse hemophagocytosis with no evidence of any endemic *Leishmania* spp., which was suspected because of massive organomegaly and pancytopenia. The primary diagnosis was familial HLH triggered by H1N1 infection because of his young age. However, perforin/syntaxin mutations were found to be negative, and also, there was no clinical or laboratory response to oseltamivir and IV immunoglobulin (IVIG), which was administered for 2 days (1g/kg/d). Immunosuppressive therapy for HLH was

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planned but before the start of treatment; serological testing to exclude leishmaniasis was preferred even if there no parasite could be found in the bone marrow exam. The aim was to prevent any possible harm of immunosuppressive therapeutics against visceral leishmaniasis. The indirect fluorescent antibody test (IFAT) revealed a positive titer of 1/640 and was diagnosed as secondary type of HLH associated with visceral leishmaniasis. Parenteral liposomal amphotericin B therapy was administered at the dose of 3mg/kg/d for 10 days. All the clinical findings including fever were regressed, and he was completely recovered. After discharge, he is in follow up for one year, and still, there is no clinical relapse or increase in serological test titers.

DISCUSSION

Visceral leishmaniasis can cause mortality in early childhood if complicated with HLH especially if it is not treated. As is known, the disease is caused by at least three subspecies of *Leishmania donovani* complex. The onset is generally insidious with intermittent low-grade fever, sweating, weakness, weight loss, and progressive enlargement of the liver and spleen[1]. Fever can be continuous, intermittent, or remittent, often reaching 40ºC. In some patients, the rapid disease course can cause death within few weeks. It may mimic or lead to several types of hematological disorders including pancytopenia, hemolysis, megaloblastic findings, and fibrinolysis and rarely causes autoimmune hemolytic anemia and cold agglutinin syndrome[2]. There are many cases presented with HLH during *Leishmania* spp. infection[3-5] and also a case report of a 9-month-old girl with HLH-associated *Epstein Barr Virus* and *Leishmania donovani* coinfection from Cyprus[6].

Our case was diagnosed as HLH according to the clinical findings, bone marrow examination, and serology results. It is very important to predict the primary form of HLH in patients with high-grade fever and hepatosplenomegaly in young age groups. However, the presence of an infection does not exclude the primary form because the primary form also can be triggered by an infection. However, in our case, the perforin/syntaxin gene mutation was negative, and there was no similar medical history in his family. Therefore, the patient was evaluated as the secondary form. The underlying disease was firstly described as possible *influenza* infection because of concurrent H1N1 epidemia. However, unresponsiveness to oseltamivir therapy and presence of hemaphagocytosis revealed a requirement for further investigations for leishmaniasis even if there was no evidence in bone marrow examination. High titers in serological test for *Leishmania* spp. have promoted the diagnosis. In our case, the critical time to make a decision for chemotherapy for HLH was the time before leishmaniasis was diagnosed serologically because visceral leishmaniasis can be fatal under immunosuppresive therapy if it is not treated with appropriate antibiotherapy. Although there are some cases reported as EBV- or HIV-related HLH in the literature and immunosuppressive therapy can be efficient in those patients[7-9].

Substantially, visceral leishmaniasis can be treated with amphotericin B or rarely with miltefosine or pentamidine[10]. In a case report study, the outcomes of sodium stibogluconate and amphotericin B therapies were compared, and amphotericin B was found to be successful in all reported cases but antimonials only in 65.4% of the reported cases[2]. The superiority of liposomal amphotericin B is attributed to the preferential reticuloendothelial uptake of this drug with lesser toxicity and better efficacy. Immunoglobuline IV is a potentially beneficial therapy for the underlying disease, HLH, or coexistent sepsis and provides time for evaluation in an ill patient. Our patient was treated successfully with a 10-day course of amphotericin B, and no recurrence or relapse occurred.

Visceral leishmaniasis can manifest with atypical presentations as in this case, which can lead to a diagnostic dilemma. Prompt recognition of the underlying infection and starting appropriate treatment can be lifesaving.

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