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Fatal hemophagocytic lymphohistiocytosis, probably secondary to leishmaniasis, in an immunocompetent adult, with no response to any treatment

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a rare syndrome, attributed to genetic and acquired factors and is associated with overactivation of macrophages. There are better chances of treatment, when HLH is triggered by an infection. Herein, we describe a rare case which raises questions about this statement. A 53 year's old, immunocompetent man, presented with relapsing fever for four months. The patient underwent a full workup with no diagnostic findings, apart from detectable IgG antibodies in the plasma and PCR positive for Leishmania in bone marrow aspirates. The patient received liposomal amphotericin B with no fever remission. Patient's blood tests revealed thrombocytopenia, anemia, high ferritin levels and hypertriglyceridemia. Image analysis revealed splenomegaly. Diagnostic criteria of hemophagocytic syndrome were fulfilled. Genetic testing was negative. The patient received two additional cycles of liposomal amphotericin B, with no response. Finally, he received etoposide, cyclosporine and dexamethasone, according to 2004 HLH protocol. After a long hospitalization the patient passed away.

Keywords: Hemophagocytic lymphohistiocytosis; Macrophages.

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare disease, characterized by the activation and proliferation of T-lymphocytes and macrophages, as well as the overproduction of inflammatory cytokines. This syndrome could be characterized as idiopathic, due to genetic factors (familial HLH or Familial Erythrophagocytic Lymphohistiocytosis- FEL) or it could be acquired due to infections, rheumatological diseases, or other rare conditions [1,2]. Zoonoses are a special part of infections that can mimic various situations. Visceral Leismaniasis (VL) has reported to be associated with HLH in some cases, but especially in children or immunocompromised patients. The diagnosis of HLH is based on the HLH diagnosis criteria 2004 (revised on 2007) published by Histiocyte Society [1,3] (Table 1). HLH is more common in children or immunocompromised adults and it can be treated by treating the triggering factor (such as the infection) or by chemotherapy. However, herein we describe a rare case of a fatal HLH, possibly due to leismaniasis at an immunocompetent adult, with no response to any treatment.

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Table 1: HLH diagnostic criteria 2004 according to Henter [1,3].

HLH Diagnostic Criteria 2004
• specific gene deficiency (or at least 5 of the following): • Low or absent natural killer cell function • prolonged fever • cytopenia in at least two lines • enlarged spleen • hypertriglyceridemia and/or hypofibrinogenemia • Increased serum ferritin level (usually more than 500microg/L) • Tissue demonstration of hemophagocytosis • Elevated levels of CD25.

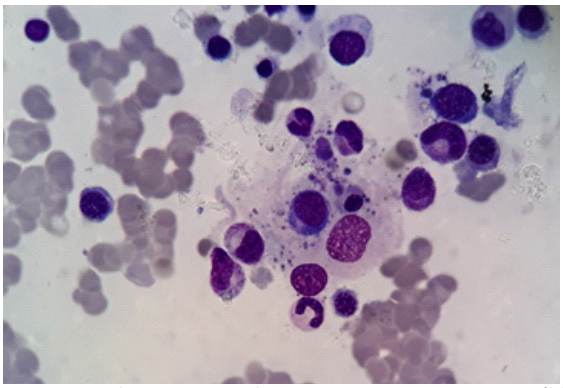

Figure 1: Hemophagocytosisin bone marrow aspirate smear (black arrow).

Case presentation

A 53 year's old man with a medical record of stroke and smoking, presented to emergency department due to fever for ten days, with no response to doxycycline. The medical history started four months ago, when he was hospitalized for persistent fever. At that time, after a long workup, he was treated with doxycycline, staying afebrile. After two months he presented fever again that was again treated with doxycycline. However, this time after a full dose of doxycycline there was no response. The patient was hospitalized once again and he underwent a full clinical and laboratory examination in the context of Fever of Unknown Origin (FUO). The patient was hospitalized and underwent a full clinical and laboratory testing in the context of Fever of Unknown Origin (FUO). However, there were no important findings except from mild splenomegaly as detected by computed tomography of the abdomen, and positive IgG antibodies against Leismania and a positive PCR in the blood and bone marrow. Though, no amastigotes were detected in the first bone marrow aspiration. Computed tomography of the chest, blood and bone marrow cultures for basic pathogens and B Koch revealed no findings. Laboratory tests for malaria, Human Immunodeficiency Virus (HIV), Hepatitis viruses, Epstein Barr Virus (EBV), Cytomegalovirus (CMV), Brucella, Ricketsia, Coxiella, electrophoresis and immunoprecipitation of the peripheral blood, were all negative. Transthorasic and transesophageal ultrasound of the heart showed no evidence of endocarditis. There were no findings following gastroscopy, colonoscopy, bone scan and fundoscopy, as well. According to the findings above, the patient received liposomal amphotericin B, with the possible diagnosis of VL. The patient presented no response to such treatment and continued to be febrile, with anemia and thrombocytopenia. A second bone marrow aspiration was performed with the suspicion of HLH syndrome, considering the VL as the main triggering factor. The patient received a second round of liposomal amphotericin B, with doses of an immunocompromised patient (4 mg/kg at day one to five, day seventeen, day twenty four, day thirty one and thirty eight). The second bone marrow aspiration presented some hemophagocytic indications: Histiocytes with hemophagocytosis (Figure 1).

The patient underwent a new clinical and laboratory examination aiming to exclude any any other possible triggering factors of HLH. However, nothing was detected. The HLH diagnosis criteria 2004 were fulfilled as the patient suffered from thrombocytopenia (platelets: 22000/mm^3), anemia (Hb: 8.5%, Hct: 25.6%), hyperferritenemia (ferritin: 4180 ng/ml), mild splenomegaly, hypertiglyceridemia (triglycerides: 810 mg/dl), prolonged fever and indications of hemophagocytosis by the bone marrow aspiration. The patient received three cycles of liposomal amphotericin B in total; the last cycle was administered in combination of dexamethasone in the context of HLH due to VL. However, the patient presented no response. The patient underwent genetic testing for HLH genes, which was negative. After no remission of the symptoms, but worsening of the patient's clinical status, the treatment according to HLH 2004 protocol was used. The patient received cyclosporine, etoposide and dexamethasone with no response. After a long hospitalization, several complications and nosocomial infections, the patient succumbed.

Conclusion

HLH is a rare and potentially fatal disease; however, there are good chances of treatment when a specific trigger can be found. Secondary HLH is usually connected with infection of EBV, CMV, HIV and VL [4-6]. At the most of the published case reports the patients who suffered from HLH had a good response to the treatment when the trigger was the VL. The use of chemotherapy is needed at some really rare cases [7-9]. However, in the present case, although there were clinical and laboratory signs of VL, the treatment was not effective. Liposomal amphotericin B is the indicated therapy according to the guidelines and according to the data of drug resistance presented in Greece [9]. However, the patient suffered a stable worsening HLH, with no response to any treatment, even when HLH 2004 protocol was used. To our knowledge this case is a first report in the literature with such an outcome, especially in Greece. Questions could be raised about the possible treatment of VL or the changes in resistance to anti-leismanial drugs, whereas attention should be paid on the early diagnosis of HLH.

Declarations

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Conflict of interest: The authors would like to declare no conflict of interest.

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