CASE REPORT

Hemophagocytic syndrome associated with *Plasmodium falciparum* infection

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ABSTRACT

Hemophagocytic syndrome (HPS) has been associated with infections, hematological malignancies and autoimmune conditions. Malaria is rarely reported to cause HPS. We report a case of an 11-month-old infant with fever, hepatosplenomegaly, pancytopenia, high serum ferritin, hypertriglyceridemia, and bone marrow hemophagocytosis, consistent with hemophagocytic syndrome. Gametocytes of plasmodium falciparum were identified on bone marrow aspiration. Rapid recovery was observed after treatment with antimalarials.

KEY WORDS: Hemophagocytic syndrome, *Plasmodium falciparum*, pancytopenia

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INTRODUCTION

Hemophagocytic syndrome (HPS) is a disorder of the mononuclear phagocytic system, characterized by histiocytic proliferation, with marked hemophagocytosis in the bone marrow. HPS has been related to hematological diseases, autoimmune diseases, or infections such as virus, bacteria, fungi, and parasites. *Plasmodium falciparum* and vivax are rarely reported as causes of HPS. We report the case of an 11-month-old infant, who presented with fever and hepatosplenomegaly, and was found to have pancytopenia, high serum ferritin, hypertriglyceridemia, and bone marrow hemophagocytosis consistent with a hemophagocytic syndrome. The gametocytes of *Plasmodium falciparum* were identified on bone marrow aspiration.

CASE REPORT

The 11-month-old child presented to our emergency clinic with a 20-day history of high fever and abdominal distention. There were no previous hospital admissions and his treatment history was non-contributory. He appeared lethargic with a temperature of 38.8°C. Physical examination revealed pallor and hepatosplenomegaly; there was no significant lymphadenopathy or skin rash. Initial laboratory data showed anemia (hemoglobin 5.6 g/dL), thrombocytopenia (platelets 75×10^9/L), leucocyte count of 10.19×10^9/L (P34%, L59%, M5%), deranged liver enzymes (Aspartate aminotransferase-146IU/L, alanine aminotransferase-130IU/L), negative Widal test (1:80 titers) and negative peripheral smear for malarial parasite done thrice. Peripheral smear showed hypochromic microcytic picture. His blood and urine cultures were sterile. As the fever spikes persisted, repeat blood examination was performed after three days, which showed pancytopenia, with the leucocyte count of 3.5×10^9/L (P30%, L59%, E2%, M6%), a hemoglobin of 5.6 g/ dL, and a platelet count of 90×10^9/mm^3. The direct Coombs' test, reticulocyte count, and coagulation profile were normal. HIV serology, hepatitis B surface antigen, and antibodies against hepatitis C virus were negative. In view of hypochromic microcytic anemia, serum ferritin was carried out, which was found to be increased to 2193 μg/L. Hence, the investigation for HPS was conducted. Serum triglycerides were elevated to 3.2 mmol/L and fibrinogen plasma level was low (0.75 g/L). Bone marrow aspiration revealed normal cellularity with mature monohistiocytes containing phagocytosed erythrocytes (Figure 1). Numerous gametocytes of *Plasmodium falciparum* were identified on the bone marrow smear examination (Figure 2). After administration of intravenous artesunate, he became afebrile and abnormalities on laboratory data improved gradually. He was discharged after a full recovery of all abnormal laboratory data. Due to cost and non-availability, local perforin mutation and soluble interleukin were not performed. He was followed up regularly in the Outpatient Clinic and was found to be well for the following six months.

DISCUSSION

Hemophagocytic syndrome is a clinicopathological entity, characterized by the proliferation of monocytes or macrophages showing phagocytosis of hematopoietic cells. It has been associated with infections, hematological malignancies, and autoimmune conditions.[1]

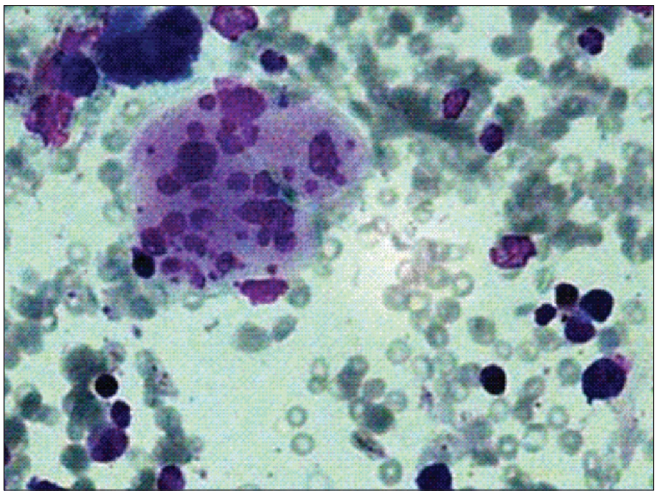

Figure 1: Hemophagocyte in bone marrow smear; (Leishman, ×100)

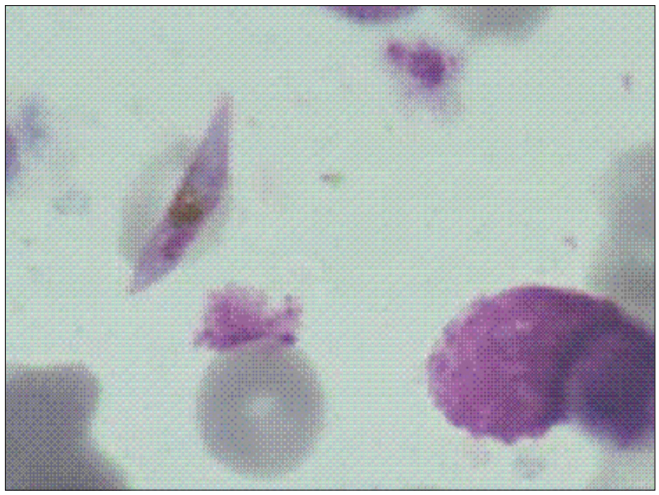

Figure 2: Gametocyte of *Plasmodium falciparum* in bone marrow smear; (Leishman, ×100)

Although most cases have been associated with *Epstein-Barr virus*, cases of HPS due to *cytomegalovirus*, *Herpes simplex*, *Varicella zoster*, *Adenovirus*, *Parainfluenza virus*, *Dengue virus*, and *Hepatitis B virus* have also been reported. In addition, infections with *Mycobacterium tuberculosis*, *Staphylococcus aureus*, Streptococcus species, *Salmonella typhi*, *Escherichia coli*, Hemophilus species, *Brucella melitensis*, Acinetobacter species, *Rickettsia tsutsugamushi*, *Histoplasma capsulatum*, *Candida albicans*, *Cryptococcus neoformans*, and *Leishmania donovani* have also been associated with histiocytic reaction.

Malarial infection has been rarely reported to cause secondary HPS. Both falciparum and vivax have been reported to cause HPS; however, vivax has been rare.[2-4] In our case, pancytopenia, liver dysfunction, hyperferritinemia, hypertriglyceridemia, and the presence of hemophagocytosis in bone marrow aspiration were in accordance with the current criteria for HPS. Our patient had the etiological role of *Plasmodium falciparum* causing HPS, which was suggested by the presence of *P. falciparum* gametocytes in the bone marrow aspiration,with total clinical and hematological recovery after antimalarial treatment, which almost rules out the possibilities of familial HPS triggered by infections.

Erythrophagocytosis were usually observed in the bone marrow of patients with malaria, but in one reported case of *Plasmodium falciparum* infection, 80% of the monocytes showed platelet phagocytosis.[5] In our patient bone marrow aspiration showed monohistiocytes containing both erythrocytes and platelets.

Experimental studies have demonstrated that several soluble exoantigens of *P. falciparum* induce an inappropriate macrophage activation and a Th1-stimulated hypercytokinemia with excessive production of the tumor necrosis factor α (TNF-α), interferon γ (INF-γ), and the macrophage colony stimulating factor (M-CSF).[6] Once the cytokine cascade has been triggered, it induces free oxygen radical release. Hypercytokinemia and high-serum levels of sIL-2R, IL-6, INF-γ, and TNF have been suggested to reflect a poor prognosis, although these parameters do not show a significant difference between infection-associated HPS, malignancy-associated HPS, and malignant histocytosis.[7] We have not been able to do serum cytokines, especially of the Th1, type in our patient due to financial reasons.

Malaria-induced HPS usually responds to antimalarial alone, but rarely steroids have been used.[8] Most of the cases reported in literature have responded completely with antimalarials. Very rarely can parasites not be found in peripheral blood smears from patients with malaria, even in severe infections, and are diagnosed based on bone marrow study alone.[9,10] This may be explained by pretreatment with antimalarial drugs in inadequate doses, causing partial clearance of the parasite, low levels of parasitemia not detected by conventional microscopy or by sequestration of the parasitized cells, in deep vascular beds.[10]

Hemophagocytic syndrome may play a crucial role in the pathogenesis of pancytopenia observed during malarial infestation. HPS could be implicated as a life-threatening complication due to infection by the plasmodium species. We report this for the physicians in developing countries where there is a high prevalence of malaria, to be aware of its association with HPS.

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