CLINICAL CASE REPORT: FALCIPARUM MALARIA WITH HEMOPHAGOCYTIC SYNDROME

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Abstract. A 30-year-old Japanese woman with falciparum malaria was hospitalized because of fever and renal failure, and prolonged anemia was identified despite the eradication of malaria parasites through anti-malaria therapy. Bone marrow aspiration revealed the presence of macrophages with hemophagocytosis, and serum interleukin (IL)-18 and tumor necrosis factor (TNF)-α levels were high in the anemic phase. Hemophagocytosis was confirmed for at least 3 weeks, and prolonged hemophagocytic syndrome is thought to be one of the causes of prolonged anemia in patients with falciparum malaria.

INTRODUCTION

Hemophagocytic syndrome (HPS) is characterized by the proliferation of macrophages that exhibit phagocytosis of hematopoietic elements. It is well known that HPS is associated with viral infections, but few patients with malaria with HPS are ever reported.1-10 Recently, we treated a patient with falciparum malaria with HPS, but her HPS persisted despite effective anti-malaria chemotherapy, and serum levels of interleukin (IL)-18 and tumor necrosis factor (TNF)-α were high. We describe here a patient with falciparum malaria complicated with prolonged HPS.

CASE REPORT

A 30-year-old Japanese woman, who had been in Papua New Guinea from February 19 to 26, 2005, was referred to our hospital on March 17, 2005 because of 7 days of fever and renal failure. On admission, the patient was alert,1 blood pressure was 100/67 mm of Hg, pulse rate was 118/min, and body temperature was 37.9°C. She was well nourished but jaundiced. Her abnormal blood laboratory findings on admission were as follows: red blood cells (RBCs), 242 × 10^12/mm^3; hemoglobin (Hb), 7.2 g/dL; hematocrit (Ht), 20.5%; platelets (Plt), 2.2 × 10^11/mm^3; d-dimer, 16.76 mg/dL; C-reactive protein, 35 IU/L; alkaline phosphatase, 501 IU/L; reference range, 122–378 IU/L; and lactate dehydrogenase (LDH), 1,728 IU/L. A bone marrow aspiration on April 1, 2005 revealed the presence of macrophages with hemophagocytosis (Figure 1). Although intravenous methylprednisolone therapy and plasma exchange were performed, followed by prednisolone administered orally, the anemia persisted, and laboratory data on April 21 were as follows: RBC, 237 × 10^12/mm^3; Plt, 7.6 × 10^11/mm^3; LDH, 1,358 IU/L; and haptoglobin, < 4.0 mg/dL. On April 23, serum samples obtained on April 1, April 23, and May 30, 2005, were found in her blood smear (parasitemia, 25%). The serum hepatitis B virus (HBV) surface antigen, hepatitis C virus (HCV) antibody, hepatitis A virus (HAV) IgM antibody, and human immunodeficiency virus (HIV) antibody were all negative. She was diagnosed as having falciparum malaria complicated with renal failure. She received daily administrations of 420 mg of a quinine base intravenously on March 17 and 18, 200 mg of an artesunate suppository on March 17 and 18, and 750 mg of mefloquine orally on March 19, with blood smear examinations revealing no P. falciparum on March 22. Her renal function recovered slowly through continuous hemodiafiltration (CHDF) on March 18 and 19, hemodialysis (HD) on March 22, 24, 26, 29, and 31, and CHDF again from April 2 to 5. However, her hemolytic anemia progressed despite an RBC transfusion and the disappearance of malaria parasites through anti-malaria therapy, with laboratory findings on April 1 being as follows: RBC, 300 × 10^12/mm^3; Hb, 9.1 g/dL; Ht, 25.1%; T-Bil, 35.5 mg/dL; LDH, 1,358 IU/L. A bone marrow aspiration on April 1, 2005 revealed the presence of macrophages with hemophagocytosis (Figure 1). Although intravenous methylprednisolone therapy and plasma exchange were performed, followed by prednisolone administered orally, the anemia persisted, and laboratory data on April 21 were as follows: RBC, 237 × 10^12/mm^3; Hb, 7.6 g/dL; Ht, 24.0%; Plt, 3.3 × 10^11/mm^3; haptoglobin, < 4.0 mg/dL. The presence of macrophages with hemophagocytosis was found again in bone marrow aspirated on April 22; however, the number of these phagocytic macrophages was smaller than on April 1. Prednisolone was once again administered orally. Her laboratory findings on May 6 were as follows: RBC, 342 × 10^12/mm^3; Hb, 11.1 g/dL; Ht, 34.3%; Plt, 44.9 × 10^11/mm^3; T-Bil, 1.0 mg/dL; LDH, 186 IU/L. She was discharged from the hospital the same day.

Serum IgM antibodies against the herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV)-capsid antigen, and human parvo virus B-19 (HPVB-19) were negative on March 23 as measured by the EIA method. Cytomegalovirus (CMV)-DNA (normal: < 2 × 10^2 copies/mL) was not detected in serum obtained on April 2 and April 23 by polymerase chain reaction (PCR).

DISCUSSION

Our patient was free from active viral infections such as EBV, HSV, VZV, HPVB-19, CMV, HBV, HCV, and HIV.

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She was treated with HD, CHDF, and administrations with drugs containing anti-malarial agents (quinine, mefloquine, artesunate), anti-ulcers (famotidine, teprenone), protease inhibitors (gabexate mesilate, nafamostat mesilate), a diuretic (furosemide), a laxative (lactulose), prokinetic agents (metoclopramide, mosapride citrate), a cardiovascular agent (carperitide), an adrenergic agent (dopamine), an anticoagulant (heparin), a hematopoietic agent (epoetin α), a nonsteroidal anti-inflammatory agent (loxoprofen sodium), and antibiotics (cefmetazole, ampicillin sulbactam) between March 17 and April 1. To the best of our knowledge, no report that these medical treatments or drugs mentioned above induce HPS has been reported. Our patient was suffering from falciparum malaria, yet was a well-nourished healthy woman before traveling to Papua New Guinea. These facts lead us to believe that her HPS was associated with the falciparum malaria.

The mechanism of HPS in malaria patients is not known, but serum high levels of cytokines have been reported in patients with HPS with malaria. Enhanced phagocytosis and secretion of TNF-α, IFN-γ, and IL-1α by U 937 cells were observed when supernatants from EBV-infected T cells were co-cultured with a monocytic U 937 cell line for 24 hours and could be inhibited to a large extent by the addition of antibodies against TNF-α and almost completely inhibited by a combination of antibodies against TNF-α and IFN-γ. Erythrophagocytosis has been observed in bone marrow preparations from TNF-treated mice, and it has been reported that IL-18 may play an important role in the pathogenesis of HPS. The results of these studies and the fact that high levels of IL-18 and TNF-α were shown in the HPS phase and were reduced in the convalescent phase of anemia in our patient propose the idea that high levels of cytokines such as IL-18 and TNF-α may have induced the HPS. To the best of our knowledge, in malaria patients with HPS, HPS is resolved soon after successful treatment of the malaria, and prolonged HPS has not been reported in patients with falciparum malaria. Our patient underwent 2 days of intravenous quinine and 2 days of an artesunate suppository at the same time, followed by 1 day of mefloquine. It is believed that this treatment against malaria was effective and had no bearing on the cause of the prolonged HPS, because her blood smear examinations revealed no P. falciparum after the end of the anti-malarial therapy. Serum levels of IL-18 and TNF-α remained high for a long time after eradicating the malaria parasites in our patient, as shown in Table 1. Once the cytokine cascade is triggered, HPS may continue independently of the presence of malaria parasites.

The use of prednisolone or plasma exchange has been reported as being effective against HPS; however, it is not known whether these treatments were effective against HPS in our patient.

Malaria is one of many infections that can precipitate a secondary hemophagocytic syndrome, and it is possible to assume that the patient is in an HPS condition in falciparum malaria cases with continuing anemia after successful malaria therapy.

REFERENCE


