Hematol Oncol Stem Cell Ther (2016) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc

CASE REPORT

Severe *Plasmodium vivax* cerebral malaria complicated by hemophagocytic lymphohistiocytosis treated with artesunate and doxycycline

Sawsan Amireh, Hamid Shaaban *, Gunwant Guron

Internal Medicine Department and Department of Hematology and Oncology, Saint Michael's Medical Center, Newark, NJ, USA

Received 19 March 2016; accepted 29 June 2016

KEYWORDS
Plasmodium vivax;
Malaria;
Hemophagocytic lymphohistiocytosis;
Artesunate;
Doxycycline

Abstract
Malaria-related hemophagocytic lymphohistiocytosis is a rare, potentially fatal, hyperinflammatory disease entity which can be challenging to diagnose and treat. It is usually associated with *Plasmodium falciparum* infection. It is less frequently associated with *Plasmodium vivax*. Here we report an unusual case of a 23-year-old healthy Nigerian man who presented with fever, microangiopathic hemolytic anemia, acute renal failure, and confusion, and was diagnosed as having cerebral malaria-related hemophagocytic lymphohistiocytosis caused by *P. vivax* infection. He was successfully treated with intravenous artesunate and doxycycline with dramatic clinical improvement.

Introduction

Malaria continues to remain a major health burden worldwide. According to the World Malaria Report 2015, the estimated number of malaria cases was 214 million and the number of deaths was 438,000 in 2015 alone [1]. The World Health Organization defines cerebral malaria as a clinical syndrome caused by *Plasmodium falciparum* infection manifesting as coma (defined with Glasgow Coma Scale of less than 11 in adults and Blantyre Coma Scale of less than 3 in children) persisting for more than 30 minutes after termination of seizure and no other cause of explanation for the coma [2]. Another rare complication of malaria is

* Corresponding author at: Department of Hematology and Oncology, Saint Michael's Medical Center, New York Medical College, 111 Central Avenue, Newark, NJ 07102, USA.
E-mail address: hamidshaaban@gmail.com (H. Shaaban).

http://dx.doi.org/10.1016/j.hemonc.2016.06.001
1658-3876/

hemophagocytic lymphohistiocytosis (HLH), which is a syndrome characterized by multisystem inflammation that results from prolonged and excessive activation of the antigen presenting cells (macrophages and histocytes) and CD8+ T cells that leads to phagocytosis of hematopoietic cells [3]. HLH compromises two different conditions: (1) the primary (familial) form that is usually seen during infancy or childhood; and (2) the secondary HLH which results from an excessive immune reaction to infections, autoimmune disorders, or malignancy.

Case report

A 23-year-old healthy Nigerian man was brought to the emergency department with symptoms of relapsing fever, confusion, and lethargy ongoing for 5 days. Past medical history and family history were unremarkable. He had not taken any medications. On physical examination, the patient was stuporous with a Glasgow Coma Scale of 10; he did not have neck stiffness or focal neurological signs. He had splenomegaly and scleral icterus. His vital signs were as follows: blood pressure of 119/70 mmHg, heart rate of 119 bpm, temperature of 39.2 °C, and a respiratory rate of 24 breaths per minute.

Laboratory workup revealed a platelet count of 19,000 cells/mL, hemoglobin of 7.9 g/dL, total white cell count of 5,600 cells/mL, and reticulocyte count of 10.0%. Biochemical tests were as follows: total bilirubin of 15.5 mg/dL, direct bilirubin of 13.5 mg/dL, alkaline phosphatase of 206 IU/L, aspartate transaminase of 123 IU/L, alanine transaminase of 96 IU/L, lactic acid dehydrogenase of 2,023 IU/L, lactate of 4.2 mmol/L, blood urea nitrogen of 28 mg/d:, creatinine of 1.13 mg/dL, and normal electrolytes. Other investigation results were as follows: D-dimer of 6,369 mg/L, haptoglobin of <8 mg/dL, fibrinogen of 508 mg/dL, ferritin of 4,622 mg/L, fasting triglycerides level of 322 mg/dL, and soluble interleukin-2 receptor (i.e., soluble CD25) of 3,677 U/mL (reference range, 223–710 U/mL). Prothrombin time and activated partial thrombin time were in normal range, Direct antiglobulin test was negative, and two sets of blood cultures and urine cultures were all negative. Serology test for hepatitis A, B, and C viruses, cytomegalovirus, Epstein–Barr virus, and human immune deficiency virus were also negative. Abdominal computed tomography scan showed hepatosplenomegaly, and computed tomography scan of the head along with the chest X-ray were normal. Lumbar puncture was not performed due to the patient's low platelet count. Thick and thin blood smears showed ring forms and trophozoites of *Plasmodium vivax*. Polymerase chain reaction of the blood confirmed the patient had *P. vivax* infection.

Given the patient's clinical presentation, the findings on the blood smear, and the fact that he met six out of eight hemophagocytic lymphohistiocytosis diagnostic criteria (Table 1), the diagnosis of cerebral malaria due to *P. vivax*, complicated by HLH was established.

Treatment with intravenous quinidine and doxycycline was initiated. After 24 hours of initiating treatment, the patient's mental status improved drastically and returned to baseline. Quinidine was discontinued because of QTC prolongation and the patient was started on atovaqoune–proguanil. On the 3rd day of hospitalization, the patient's mental status deteriorated again and he developed acute renal failure with a creatinine level of 5.22 mg/dL and a blood urea nitrogen level of 80 mg/dL. Given the glomerular filtration rate of 17 mL/min and the relapse of the patient's mental status, atovaqoune–proguanil was discontinued and the US Center of Disease Control and Prevention was contacted to obtain artesunate that was delivered and initiated on the same day. Over the course of the following 2 days, the patient completed his artesunate course and his mental status returned to normal again. However, his kidney function continued to worsen, which prompted the initiation of hemodialysis. Three daily consecutive blood smears that were done after completing treatment with artesunate

Table 1 Clinicopathological characteristics and data of our patient with malaria-related hemophagocytic lymphohistiocytosis (HLH) diagnosed as per the HLH 2004 criteria.

HLH 2004 diagnostic criteria	Patient's clinical & lab criteria
Fever ⩾38.5 °C	Fever 39.2 °C
Splenomegaly	Present
Peripheral blood cytopenia, with at least 2 of the following: hemoglobin <9 g/dL (for infants <4 wk, hemoglobin <10 g/dL); platelets <100,000/μL; absolute neutrophil count <1000/μL	Platelet count 19,000 cells/mL, hemoglobin of 7.9 g/dL
Hypertriglyceridemia (fasting triglycerides >265 mg/dL) &/or hypofibrinogenemia (fibrinogen <150 mg/dL)	Triglyceride level 322 mg/dL
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	N/A
Low or absent NK cell activity	N/A
Ferritin >500 ng/mL	Ferritin 4,622 mg/L
Elevated soluble CD25 (soluble IL-2 receptor α)	Soluble CD25 level 3,677 U/mL (reference range, 223–710 U/mL)

Note: IL-2 = interleukin-2; N/A = not applicable; wk = weeks.

Please cite this article in press as: Amireh S et al., Severe ***Plasmodium vivax*** cerebral malaria ..., *Hematol Oncol Stem Cell Ther* (2016), http://dx.doi.org/10.1016/j.hemonc.2016.06.001