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Hemophagocytic syndrome secondary to *Plasmodium vivax* infection - A prospective study of 11 cases

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ABSTRACT

Background: Hemophagocytic syndrome is a reactive disorder of the mononuclear phagocytic system. The association of pancytopenia in severe malaria due to *Plasmodium vivax* with hemophagocytic syndrome is extremely rare and very few cases are reported in the world literature.

Aim: The study was undertaken to establish *P. vivax* infestation associated with hemophagocytosis in bone marrow as one of the causes of chronic pancytopenia/bicytopenia with fever and splenomegaly in endemic areas.

Materials and Methods: Prospective study of 110 patients of different age groups presenting with chronic fever with pancytopenia or bicytopenia from January 2015 to November 2017 was carried out. 49 patients showed the presence of *P. vivax* trophozoites in bone marrow. Among these 11 patients showed the presence of hemophagocytosis in bone marrow fulfilling 6 out of 8 criteria of diagnosing hemophagocytic lymphohistiocytosis according to 2004 criteria.

Results: The age of patients varied from 8 years to 54 years. 11 Cases showed the presence of *P. vivax* trophozoites with the presence of hemophagocytosis in bone marrow showing, hyperplastic marrow showing normoblastic and megaloblastic hyperplasia.

Conclusion: Hemophagocytic syndrome in malaria should be suspected in all cases of chronic fever with pancytopenia or bicytopenia, splenomegaly. Bone marrow aspiration is recommended to confirm the diagnosis of *P. vivax* as one of the causes of the secondary hemophagocytic syndrome in malaria-endemic areas.

Key words: Bone marrow aspiration, hemophagocytosis, malaria

INTRODUCTION

Hemophagocytic syndrome is a reactive disorder of the mononuclear phagocytic system, characterized by histiocytic proliferation with marked hemophagocytosis in the bone marrow. It is related to hematological diseases, autoimmune diseases, or infections such as virus, bacteria, fungi, and parasites. Malaria is one of the most common infectious diseases and a major public health problem. It affects >500 million people causing more than 1 million deaths each year worldwide.[1] The association of pancytopenia in severe malaria due to *Plasmodium vivax* with the hemophagocytic syndrome is extremely rare and very few cases are reported in the world literature.[2] According to the CDC reports, *Plasmodium falciparum* was listed one of the major causes of hantavirus pulmonary syndrome (HPS), but not *P. vivax*.[3] Hemophagocytic lymphohistiocytosis (HLH) secondary to infectious disease is an important entity especially in tropics where infectious diseases are rampant and still pose a major threat. A timely diagnosis and prompt treatment can improve the clinical outcome of this potentially fatal outcome.[4-6] The aim is to alert the clinicians that in persistent unresolved fever, a diagnosis of secondary HLH should be given due consideration. We present 11 cases in this series.

MATERIALS AND METHODS

Patients selection for the study was done on clinical parameters of chronic anemia and low-grade fever, splenomegaly, and bicytopenia/pancytopenia on peripheral blood examination. Bone marrow aspiration of such 110 patients was done over a period from January 2015 to November 2017. Age of these patients ranged from 8 years to 54 years. Bone marrow slides were stained with Giemsa stain. 49 Patients out of 110 patients showed the presence of *P. vivax* parasite in bone marrow aspiration. 11 Patients among these 49 patients showed the presence of hemophagocytosis in bone marrow aspiration.

RESULTS

Bone marrow aspiration was done in 110 patients over a period from January 2015 to November 2017, who presented with chronic anemia, low-grade fever, splenomegaly, and bicytopenia/pancytopenia. 49 Out of these 110 patients showed the presence of *P. vivax* parasite in bone marrow aspiration. Further 11 patients of these 49 patients showed the presence of hemophagocytosis in bone marrow aspiration. 9 patients of these 11 patients presented with pancytopenia and 2 patients presented with bicytopenia (anemia and thrombocytopenia). Bone marrow of these

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11 patients was hypercellular showing erythroid hyperplasia (late normoblastic and megaloblastic). Serum ferritin levels were raised in all these 11 patients; serum fibrinogen level, however, was within normal range, serum triglycerides was raised along with increased serum levels for serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase. In all 11 patients, 6 out of 8 criteria from HLH 2004 criteria were fulfilled.

Hemophagocytosis of lymphocytes, polymorphs, and platelets was seen in bone marrow aspiration [Figures 1 and 2].

DISCUSSION

Hemo lymphohistiocytosis is a hyperinflammatory condition which may be familial or secondary to autoimmune diseases or infection, malignancy or other triggers.[4,5] It is characterized by proliferation of monocytes or macrophages showing phagocytosis of hematopoietic cells. Malaria due to *P. vivax* is a very rare cause of pancytopenia associated with hemophagocytic syndrome. The probable pathogenesis of hemophagocytic syndrome in vivax malaria is due to inappropriate or excessive immunological response to T-cells. Excessive pro-inflammatory or defective anti-inflammatory responses cause cytokine storm leads to host tissue damage and organ dysfunction associated with the syndrome. There are activation and elaboration of cytokines such as interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor-alpha by T-helper cells which promote activation of macrophages resulting in phagocytosis of the blood cells. These cytokines cause sequestration, and rapid destruction of the formed blood cells suppresses the proliferation of progenitor cells which aggravate the pancytopenia. High levels of cytokines resolve soon after successful treatment of malaria.[6-8] HLH arising in a patient with the underlying genetic mutation is termed familial HLH, in an underlying rheumatologic disease like rheumatoid arthritis is termed as macrophage activation syndrome and in underlying infection, it is termed as reactive or secondary hemophagocytic syndrome (HPS) or secondary HLH Table 1. The reactive or infection associated HLH remains important and unfortunately underdiagnosed entity especially in the tropical areas; hence, it continues to be a potentially fatal disease.[9] Fever after a brief period of recovery from the first episode, coinciding with the cytopenias, unresponsiveness to broad-spectrum antibiotics, new onset of organomegaly or sudden increase in the size of organomegaly are some of the diagnostic clues for HLH. Even a single value of ferritin more than 10,000 in the absence of iron overload conditions, is a surrogate marker for HLH.[10] Tentative diagnosis of HLH is made based on 2004 HLH protocol. HPS secondary to infections is classified as a separate entity under the international classification of diseases by the World Health Organization[8] virus especially Epstein-Barr virus (EBV), dengue, herpes, cytomegalovirus (CMV), and HIV have been reported to have secondary HPS.[10-15] Secondary, HPS due to bacterial infections such as tuberculosis,[16] salmonella, leptospirosis, malaria, toxoplasmosis, Leishmania, and Rickettsia are also reported.[17,18] There are various case reports and case series of reactive HLH secondary to infectious causes especially in the tropical countries, but still, it remains as an under diagnosed

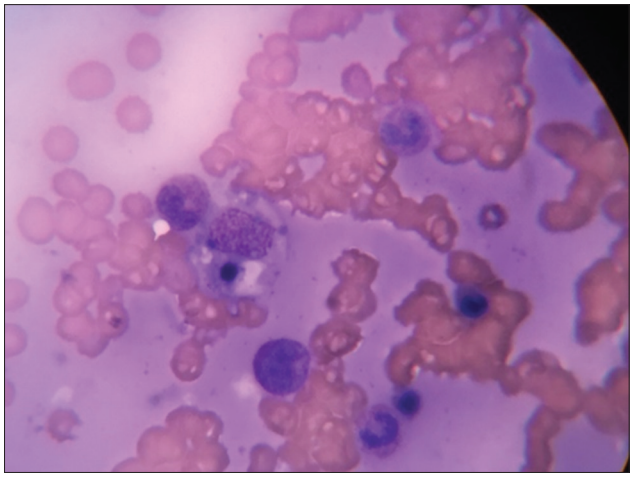

Figure 1: Bone marrow, Giemsa stain, ×40 hemophagocytosis of lymphocyte

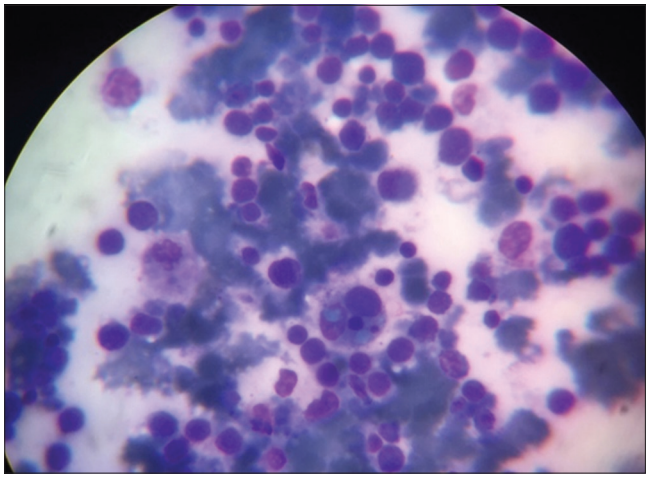

Figure 2: Bone marrow, Giemsa stain, ×40 hemophagocytosis

Table 1: Diagnostic criteria for HLH. According to the HLH 2004 protocol

A diagnosis of HLH can be made if either criteria 1 or 2 is met:
Molecular diagnosis consistent with HLH
Clinical and laboratory criteria (at least 5/8 criteria should be fulfilled)
Fever
Splenomegaly
Cytopenia > 2–3 cell lines in peripheral blood (hemoglobin < 9 g/100 ml, platelets < 100 × 10/L, neutrophils < 1.0 × 10/L)
Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides > 3.0 mmol/L, fibrinogen < 1.5 g/L)
Hemophagocytosis in bone marrow, spleen, CSF, or lymph nodes. No sign of malignancy
Decreased or absent NK-cell activity (according to local laboratory reference)
Ferritin > 500 ug/L
sCD25 (soluble IL-2 receptor) > 2400 U/ml
Supportive evidence includes:
Cerebral symptoms with moderate pleocytosis and/or
Elevated protein
Elevated transaminases
Elevated bilirubin
Elevated LDH

HLH: Hemophagocytic lymphohistiocytosis, CSF: Cerebrospinal fluid, NK: Natural killer, IL: Interleukin, LDH: Lactate dehydrogenase

and under reported entity.[5,11] The treatment of secondary HLH includes aggressive treatment of underlying condition along with immunosuppressive therapy. Clinicians worldwide use the standard HLH 2004 protocol.[18] Most of the infection associated HLH reported to a course of corticosteroids. Rajagopala and Singh in their review of hemophagocytosis trigger as a cause in 51% of the adult patients.[11] *Leishmania* was seen in 40.6%, *Rickettsia* in 18.8%, malaria in 15.6%, enteric fever in 9.4%, and viral agents in 30% of cases. In children 56% patients were secondary to the virus, 26% secondary to dengue virus, 17.3% secondary to EBV, and 8.7% each to CMV and parvovirus B19. In India, HLH associated with dengue fever and malaria with high parasitic index has been documented.[19] Both falciparum and vivax have been reported to cause HPS, although malarial infection has been rarely reported to cause secondary HPS.[6,20,21] Ohno *et al*. had described one of the first cases of hemophagocytosis secondary to malaria (falciparum) which resolved with antimalarials.[6] Park *et al*. reported four cases of HLH secondary to vivax malaria all of which resolved with antimalarials.[22] Studies in the pediatric population show degree of parasitemia is associated with severity of the disease.[19] According to the data till date only 20 patients in 18 studies have been reported having HPS secondary to malaria.[23] In the present series, 11 cases of HLH were diagnosed secondary to *P. vivax* infection. In our cases, the presence of hemophagocytosis and *P. vivax* parasite in bone marrow aspiration were in accordance with the current criteria for HPS. Total clinical and hematological recovery after antimalarial treatment rules out the possibility of familial HPS. Hemophagocytosis was observed in the bone marrow of patients with malaria showed erythrophagocytosis, phagocytosis of neutrophils and platelets. Malaria-induced HPS usually responds to antimalarial alone, but rarely steroids have been used. Most of the cases reported in literature have responded completely with antimalarials. Very rarely parasites are not found in peripheral blood smears from patients with malaria, even in severe infections, and are diagnosed based on bone marrow study alone.[24,25] 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.[25]

CONCLUSION

Hemophagocytic syndrome in malaria should be suspected in all the cases of severe and or complicated malaria, especially when anemia does not improve even after antimalarial therapy. A diagnostic bone marrow aspiration is recommended in such cases to confirm the diagnosis. *P. vivax* should be listed as one of the causes of secondary hemophagocytic syndrome especially in children from malaria-endemic areas. Regular follow-up should be done after antimalarial therapy as prolonged anemia is one of the serious complications.

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