

Case Report

Acute pancytopenia secondary to hemophagocytic syndrome due to *plasmodium vivax* malaria with chloroquine treatment failure: case report

Rajnish Kumar^{1*}, Avantika Sharma²

¹Department of Medicine, ²Department of Gynaecology, Lifeaid Medical centre, Gurgaon, Haryana, India

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*Correspondence:

Dr. Rajnish Kumar,

E-mail: drsahukumar@gmail.com

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ABSTRACT

Pancytopenia as a manifested complication of *plasmodium vivax* malaria is extremely rare and mainly reported with *plasmodium falciparum*. We report a 29-year old Indian pregnant female who lives in rural area of Haryana (northern India) and presented with a two-week long history of intermittent fever, chills and rigor. She was found to have splenomegaly, pancytopenia, hyperferritinemia with positive peripheral blood smear for *plasmodium vivax*. not responding to oral chloroquine. The patient had a full recovery from pancytopenia with artesunate therapy.

Keywords: Artesunate therapy, Chloroquine, Hemophagocytosis, Malaria, Pancytopenia, *Plasmodium vivax* resistance

INTRODUCTION

Malaria disease has number of complications including life threatening ones, out of which in most cases *falciparum* species is responsible. *Plasmodium vivax* malaria is rarely associated with severe complications like falciparum malaria. One of such complication is pancytopenia, which can occur in vivax infection secondary to microangiopathic hemolytic anemia. Another mechanism of pancytopenia in vivax infection is hemophagocytic syndrome, but this is extremely rare, and few cases are reported in the world literature.

We report a rare case of *plasmodium vivax* malaria with pancytopenia, secondary to hemophagocytic syndrome. We think that physicians in india and developing world should be aware of such a presentation since there are a lot of people from endemic regions were missed out for proper workup and adequate management.

CASE REPORT

A 29-year old female patient from rural Haryana (northern india), presented at the Emergency Department in Sept 2017 with fatigue, headache, intermittent fever, chills and rigor for last two weeks duration, she was also 16week pregnant at the time of presentation. She gave a history of several febrile episodes in the past two weeks that were presumed to be malaria/typhoid and treated respectively, although no documentation was available. Upon presentation, she was febrile with a temperature of 103°F. She was very pale, dehydrated had a palpable spleen, 4 cm below left costal margin. The rest of the physical examination was unremarkable. Her initial blood tests were remarkable for pancytopenia with WBC of $3.8 \times 10^9/l$, platelet of $78 \times 10^9/l$ and hemoglobin of 7.6g/dl. She had a normal reticulocyte count of 1.8% and an indirect bilirubin of 0.4mg/dl. Her ferritin level was more 638ng/dl. Her initial peripheral blood smear showed ring

forms, developing trophozoites and mature schizonts of *plasmodium vivax*. She had negative serological evidence of CMV, Parvovirus B19 and hepatitis. All her septic blood and urine work up were unremarkable. She was started on oral chloroquine therapy, but her condition didn't improve much her blood picture deteriorated further on day 2 of chloroquine so she was shifted to i/v artesunate therapy. This time she showed significant response and improved rapidly with complete resolution of her pancytopenia and *plasmodium vivax* (Table 1) on day 5 of i/v artesunate therapy. Bone marrow aspiration was not considered since she demonstrated quick response of pancytopenia following i/v artesunate therapy on the 2nd day of treatment her i/v artesunate therapy completed. Her pancytopenia recovered completely by the completion of i/v artesunate therapy. She was discharged on chloroquine 500mg weekly till delivery as primaquine is contraindicated in pregnancy for vivax eradication and planned for primaquine eradication therapy after delivery for 14 days to assure complete eradication of the vivax infection. Though there was high suspicion of CQ in effectivity but given in view of no other choice left for prevention of vivax recurrence. In the meantime, patient evaluated twice for fetal well-being and fetal development found to perfectly normal.

Table 1: Laboratory results before and after treatment.

Parameters	Before artesunate therapy	After complete artesunate therapy
HB	7.6	10.2
TLC	2700	6700
Plt. count	65000	234000
Serum ferritin	638	356
Serum fibrinogen	74	180
Serum triglycerides	332	140

DISCUSSION

Vivax malaria is vector born disease caused by protozoa *Plasmodium vivax* vect one of this parasitic infection is anopheles mosquitoes. It usually results in minimal complications with intermittent fever, chills and rigors following mosquito bites. Its life cycle is characterized by a hepatic phase which keeps the vivax infection in a dormant stage resulting in recurrence and relapse after treatment.¹

We report a rare case of *plasmodium vivax* with pancytopenia secondary to hemophagocytic syndrome. Our patient had a fever, splenomegaly, pancytopenia, hyperferritinemia and hypofibrinogenemia which are consistent with hemophagocytic syndrome based on the recent revised criteria 2014 (Table 2). Any 5 out of 8 criteria is sufficient to label it as haemophagocytic syndrome. These criteria did not mandate bone marrow aspiration for diagnosis.

Table 2: Diagnostic criteria for hemophagocytic syndrome¹ matched in case study.

Criteria	Case presentation
Fever	Yes
Splenomegaly	Yes
Cytopenia (affecting >1 of 3 lineage)	Yes
Hyper ferritinemia	Yes
Hypertriglyceridemia/ hypofibrinogenemia	Yes
Soluble cd25/il-2 receptor >2400u/ml	Not done
Low or no Lk-cell activity	Not done
Hemophagocytosis in bone marrow, spleen or lymphnodes	Not done

Hemophagocytic syndrome (HPS) starts because of inappropriate or excessive immunologic responses of T cells. In HPS, high levels of IFN-gamma, soluble IL-2 receptor, TNF- α , IL-1, and IL-6 have been demonstrated, suggesting that elaboration of activating cytokines by T-helper cells promotes activation of macrophages in this disease. These cytokines depress the proliferation of progenitor cells, which aggravate the pancytopenia as a result of phagocytosis of the blood cells.

This has been attributed secondary to different infections including Viral (e.g. EBV, CMV, *Varicella*) Bacterial (e.g. Gram-negative rods, *Pneumococcus*, *Mycoplasma pneumonia*) Fungal (e.g. *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*) and Parasitic (e.g. *Babesia microti*, *Plasmodium falciparum*, *Strongyloides stercoralis*).²⁻⁴ Mohapatra et al from India reported that pancytopenia is a rare manifestation of *plasmodium vivax*, it occurs in only in 0.9 % confirmed cases of *plasmodium vivax*.⁵

In best of our knowledge very few cases of HPS secondary to *plasmodium vivax* is reported in the literature. We have found only five such reported cases of isolated *plasmodium vivax* with pancytopenia with no other associated medical conditions.⁵⁻⁸

In this case we confirmed the case on basis of peripheral demonstration of causative organism along with clinical and hematological findings suggestive of hemophagocytic syndrome. Chloroquine was started immediately, but patient haematological parameter further deteriorated hence patient put on i/v artesunate therapy resulting in quick recovery from the pancytopenia, thus eliminating the need for diagnostic bone marrow aspiration. In view of high incidence of *plasmodium vivax* infection in developing world more research work is needed in same field. Hence isolated *plasmodium vivax* should be listed as one of the causes of hemophagocytic syndrome. Diagnostic bone marrow aspiration should be delayed in patients with known *plasmodium vivax* and pancytopenia, since these patients respond quickly to antimalarials. Repeated peripheral

blood smears and antigen test are very essential to reduce false negative results and subsequent misdiagnosis in this type of presentation.

We were fortunate to manage CQ resistant *vivax* induced HPS without any fetal/maternal remenant complication

Malaria especially resistant ones should be considered in the differential diagnosis of fever and pancytopenia in at least endemic areas.

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