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Hemophagocytic syndrome in *Plasmodium vivax* malaria

Sriram Pothapregada & Banupriya Kamalakannan

Department of Paediatrics, Indira Gandhi Medical College and Research Institute, Puducherry, India

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Malaria is one of the most common infectious diseases and a major public health problem. It afflicts >500 million people causing more than one million deaths each year worldwide[1]. The association of pancytopenia in severe malaria due to *Plasmodium vivax* in children with hemophagocytic syndrome is extremely rare and very few cases are reported in the world literature[2].

Case report

An 8-yr old girl child from a malaria endemic area was admitted in our hospital with high grade fever associated with chills and rigor of one week duration. There were multiple episodes of generalized tonic clonic seizures, altered sensorium and oliguria for a period of two days. She was born of non-consanguineous marriage with normal birth history, normal development and was fully immunized. There was no associated history of measles, febrile seizures, allergy, anaphylaxis or contact with tuberculosis.

On examination, the child was febrile with altered sensorium with glasgow coma scale (GCS) of 7. There was tachycardia with poor peripheral pulses and blood pressure was 60/40 mmHg. There was severe pallor with splenomegaly. The fundus examination was normal. The child was provisionally diagnosed as a case of severe malaria and was treated with artemisinin combination therapy and ceftriaxone. Artesunate 2.4 mg/kg IV followed by 1.2 mg/kg/day after 12 h on Day 1, followed by 1.2 mg/kg for a period of 5-days and with single dose of sulphadoxine 25 mg/kg and pyrimethamine 1.25 mg/kg on Day 1 were given. The child was given intravenous fluids to correct hypotension and blood transfusion to correct anaemia.

Investigations revealed haemoglobin of 4.2 g%, total leukocyte count of 1400 mm^3, differential count showed $N_{21}L_{70}E_7M_2$, platelet count 11,000 mm^3 and the peripheral smear showed normocytic normochromic anemia with trophozoite and gametocyte forms of *P. vivax*. The slide for malarial parasite was repeated every day till complete parasite clearance was achieved. The rapid diagnostic test (OptiMal test) was positive for *P. vivax* and negative for *P. falciparum*. Bone marrow examination showed erythroid hyperplasia and macrophages with hemophagocytosis and with gametocyte form of *P. vivax*. Serum ferritin was 316 µg/l (normal 15–140 µg/l), serum fibrinogen level was 0.9 g/l (normal >1.5 g/l), serum triglyceride was 284 mg/dl (normal 35–114 mg/dl) and glucose-6-phosphate dehydrogenase (G6PD) activity was normal. Urinalysis, renal function test, liver function test and metabolic profile were normal. The chest X-ray, CSF study and CT brain tests were normal.

The repeat blood counts after receiving antimalarial therapy showed haemoglobin of 6.4 g/dl, total leukocyte count 3500 mm^3, differential count of $N_{40}L_{48}E_4M_8$, platelet count 50,000 mm^3 and malarial parasite was absent in the peripheral smear. The blood counts done after one week showed haemoglobin of 8.6 g/dl, total leukocyte count 7100/mm^3, differential count $N_{48}L_{44}E_3M_5$, platelet count was 1,80,000/mm^3 and smear showed microcytic hypochromic anaemia. The child improved gradually and was discharged when clinical improvement and parasitological clearance were achieved. The child was advised to complete the course of primaquine to ensure eradication of *P. vivax* infection. The hematological parameters reached normal values within three months of receiving antimalarial therapy and the repeat bone marrow examination after three months was found to be normal.

DISCUSSION

Severe malaria is associated with high morbidity and mortality[3]. Pancytopenia due to *P. vivax* malaria is extremely unusual and is seen only in 0.9% of cases and is mainly reported with *P. falciparum*[4]. Pancytopenia in acute severe malaria is commonly a result of bone marrow suppression, microangiopathic haemolytic anaemia and rarely as a result of inappropriate macrophage activation associated with hemophagocytosis[5].

Hemophagocytic syndrome is characterised by pancytopenia, hyperferritenemia, hypertriglyceridemia and hypofibrinogenemia. The usual causes of primary hemophagocytic syndrome are genetic, malignant and autoimmune diseases. The causes of secondary

hemophagocytosis are attributed to different infections including viral (epstein barr virus, cytomegalovirus and varicella), bacterial (gram-negative organisms, pneumococcus and *Mycoplasma pneumoniae*), fungal (*Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*) and parasitic (*Babesia microti, Plasmodium falciparum*, *Strongyloides stercoralis, Leishmania brazilensis*) and medications[6].

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 of T-cells. There is activation and elaboration of cytokines like IL-1, IL-2, IL-6 and TNF-α 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. It also depresses the proliferation of progenitor cells which aggravate the pancytopenia. The high levels of cytokines have been reported to resolve soon after successful treatment of malaria. However, there are few cases once the cytokine cascade is triggered. Hemophagoctyosis may continue independent of the presence of the malarial parasite. Prolonged hemophagocytosis is one of the complications of hemophagocytic syndrome in malaria and results in prolonged anaemia and has been reported in falciparum malaria but not yet reported in vivax malaria in children. Other complications reported are hyperbilirubinemia, with acute renal failure, encephalopathy, seizures and coagulation abnormalities. Hemophagocytic syndrome with complications is mainly reported in falciparum malaria[7–9].

Park *et al*[10] described vivax malaria complicated by pancytopenia with hemophagocytic syndrome in immunocompetent servicemen. Yamakawa *et al*[11] described vivax malaria with pancytopenia secondary to bone marrow hypoplasia in a 39-yr old male who travelled to Southeast Asia and pancytopenia improved with sulphadoxine and pyrimethamine. Aouba *et al*[12] described a case of hemophagocytic syndrome associated with *P. vivax* infection in 41-yr old woman who improved with chloroquine. Albaker[13] reported a case of pancytopenia secondary to hemophagocytic syndrome due to *P. vivax* in a 37-yr old Nepali woman in Saudi Arabia. Thapa *et al*[14] reported a case of pancytopenia complicating cerebral malaria due to *P. vivax* in a 7-yr old girl child.

In the present case, there were features of severe malaria in the form of fever, altered sensorium, and hypotension with pancytopenia, hyperferritenemia, hypertriglyceridemia and hypofibrinogenemia due to hemophagocytic syndrome which was confirmed by bone marrow examination. There were complications in the form of encephalopathy, seizures and severe anaemia. The child improved with antimalarial therapy and did not require prednisolone or plasma exchange. However, there was delayed recovery of hematological values and the anaemia persisted up to three months after receiving antimalarial therapy. The bone marrow examination after three months did not show hemophagocytosis.

Hemophagocytic syndrome in malaria should be suspected in all the cases of severe and/or complicated malaria and especially where the anaemia does not improve even after receiving antimalarial therapy. We recommend a diagnostic bone marrow aspiration in such cases to confirm the diagnosis. It is our belief that *P. vivax* should be listed as one of the causes of secondary hemophagocytic syndrome especially in children from malaria endemic areas. A regular follow up of such cases should be done even after successful antimalarial therapy as prolonged anaemia is one of the serious complications in such cases.

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Correspondence to: Dr Sriram Pothapregada, Associate Professor, Paediatrics, Plot No. 7 & 8, Ground Floor, Logu Nagar, Periyar Street, Gorimedu, P.O. Dhanvantri Nagar, Puducherry–605 006, India.
E-mail: psriram_ped@yahoo.co.in

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