Brief Report

Refractory Pancytopenia and Megaloblastic Anemia due to Falciparum Malaria

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Summary

Anemia is a common complication in malarial infection. Direct destruction and ineffective erythropoiesis does not adequately explain the cause of anemia in malaria. We present a case with refractory megaloblastic anemia with asymptomatic falciparum malaria. We hypothesize that promoter variants in the inducible nitric oxide synthase gene might be the cause of severe refractory megaloblastic anemia and pancytopenia in our patient. Malaria should always be kept in mind as a cause of anemia especially in endemic areas even if the child is asymptomatic or there is no demonstrable parasite on routine smear examination.

Key words: megaloblastic anemia, pancytopenia, malaria, nitric oxide.

Introduction

Anemia is a well-known complication of Plasmodium falciparum malaria [1]. Various pathophysiological mechanisms underlie the onset of anemia in this infection. In malaria endemic areas, co-morbidities like other parasitic infestations, iron, folic acid, vitamin B₁₂ deficiency and deficiency of other nutrients also play a role. A lack of acquired immunity to P. falciparum malaria in young children appears to underlie the high rates of morbidity and mortality from malaria in endemic regions [2]. We present a child who had severe pancytopenia with refractory megaloblastic anemia due to asymptomatic falciparum malaria.

Case report

A 7-year-old boy presented with complaints of gradually increasing pallor and petechial spots all over the body. He had no history of fever, joint pains, recurrent diarrhea or sore throat. He had not received any blood transfusions previously. There was no history of similar complaints in the family. His dietary intake was adequate. On examination, he had pallor and few petechial spots over trunk and limbs. There was no icterus, lymphadenopathy, hepatosplenomegaly or edema. Systemic examination was normal.

His blood counts had shown a hemoglobin (Hb) of 3.5 g dl\(^{-1}\), total leukocyte count (TLC) of 1800 \(\mu\)l\(^{-1}\) and platelet count of 20 000 \(\mu\)l\(^{-1}\). The mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration were 120 fl, 25 pg per cell and 30 g dl\(^{-1}\), respectively. His corrected reticulocyte count was 0.8%. Peripheral smear revealed anisopoikilocytosis, macroovalocytes with decreased TLC and reduced platelets. The liver and kidney function tests were normal. The blood and urine cultures were repeatedly sterile. Peripheral smear for malaria and rapid malaria antigen test were negative. Bone marrow aspirate smears were suggestive of megaloblastic anemia.

The child was given packed red cell and platelet transfusion and was started on with folic acid and vitamin B₁₂ supplementation. However, after 2 weeks of follow-up, there was no improvement in cell counts and he was readmitted with severe anemia for which he required a repeat blood transfusion. A repeat bone marrow aspirate and biopsy was done to rule out aplastic anemia. Bone marrow aspirate smears confirmed the earlier finding of megaloblastic anemia. Cytogenetic studies for constitutional hypoplastic anemias were planned at this point. However, report of the bone marrow biopsy showed that the marrow was filled with P. falciparum. Repeat blood cultures were sterile. But in view of neutropenia, the child was started on antibiotics. The history was reviewed. There was no history of fever or past history of treatment for malaria. He was started on artesunate combination therapy. His Hb, platelet and leukocyte counts improved (Hb: 7.8 g dl\(^{-1}\); TLC: 4800 \(\mu\)l\(^{-1}\) and platelet
count: 78 000 µl⁻¹). On the third day of therapy, he had a sudden deterioration of clinical state and developed cardiovascular collapse. In spite of upgrading antibiotics and aggressive management, the child could not be revived. The cause of the same could not be ascertained.

**Discussion**

Invasion of host erythrocytes by plasmodium parasite and release of merozoites during schizogony results in intravascular hemolysis. However, this is not sufficient to explain severe anemia seen in cases of malaria [3]. Hematological data from experimental human *P. falciparum* infections [4] as well as analysis of clinical data from endemic areas [5] have suggested that up to 12 uninfected RBCs are lost for every infected RBC.

Many other mechanisms have been given by various authors for explaining the cause of anemia. Anemia due to erythrocyte destruction may be due to macrophage activation in the spleen [6]. Other mechanisms implicated are immune-mediated hemolysis [7] or oxidative stress to erythrocytes [8].

In addition, malaria is associated with dyserythropoiesis due to cytokines and other factors [9–11]. The prime candidates for the host factors mediating dyserythropoiesis have been growth factors and cytokines. The concentrations of tumor necrosis factor-α (TNF-α) and interferon (IFN)-γ have been correlated with the severity of the disease and high levels of TNF-α have been shown to suppress erythropoiesis [12]. These cytokines may also contribute to reduced production of erythropoietin and to increased erythrophagocytosis. To the contrary, high levels of the T helper type 2 produced cytokine interleukin-10 (IL-10) might prevent the development of severe malarial anemia. Low levels of IL-10 have been described in African children with severe malarial anemia [13].

*In vitro* studies show that TNF-α and IFN-γ induced suppression of human hematopoiesis is in part mediated by nitric oxide NO [14]. NO is an inhibitor of erythropoiesis [15]. Cytokine-induced NO is known to decrease human erythropoiesis, and NO is likely an important mediator of the anemia of chronic disease in humans [16].

Although the low levels of Hb were attributed to the overproduction of NO, it is mainly seen in asymptomatic children rather than in children with severe anemia [17]. In addition, NO can inhibit the enzyme methionine synthase thereby functional vitamin B₁₂ deficiency state may occur which can lead to megaloblastic anemia [18].

Development of severe pancytopenia in a patient with megaloblastic anemia implies bone marrow failure. We present a case with refractory megaloblastic anemia with asymptomatic *falciparum* malaria. Though, NO levels could not be done in our patient, we hypothesize that promoter variants in the inducible nitric oxide synthase gene might be the cause of severe refractory megaloblastic anemia and pancytopenia in the patient. The cause of sudden death in the case could not be determined. Probably, some interaction with NO and the response to antimalarial drugs be causative.

We conclude that malaria should always be kept in mind as a cause of anemia especially in endemic areas even if the child is asymptomatic or there is no demonstrable parasite on routine smear examination. The interaction with the antimalarial drugs needs further exploration.

**References**


