

## Case Report

# Autoimmune Hemolysis in Malaria: A Report of Three Cases

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### Abstract

We have recently treated three patients with malaria who developed post malaria immune mediated hemolysis. These cases, seen with in a span of three month period (September 09 to November 09) form the basis of this report. Out of three patients, two were treated with steroids and both responded favorably.

## Introduction

Malaria continues to be an important disease in humans. Its clinical manifestations are due to (a) invasion and destruction of RBCs by the parasite and (b) host reaction to the malarial parasite infection. Anemia, the most common complication, is due to accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony, and ineffective erythropoiesis. However the extent of hemolysis in malaria is much greater than encountered in other parasite induced hemolytic states. An associated or added immune mediated hemolysis has been postulated. We describe here three cases that developed post malaria immune mediated hemolysis.

### Case 1

A 15 year old girl was admitted at our hospital with the history of high grade intermittent fevers for 4 days. Her peripheral smear was positive for both *P. vivax* and *P. falciparum* malarial parasites. On admission her Hb was 9.1g/dl; the platelet count was 24,000/mm<sup>3</sup>. She was treated with intravenous artesunate 120 mg/day for 5 days. The fever responded but recurred on the 4<sup>th</sup> day. A repeat peripheral smear for malarial parasites and the rapid malaria antigen test were negative. Ceftriaxone 1gm IV bd and doxycycline 100mg/bd PO were added to the treatment but the fever persisted. On the 9<sup>th</sup> day, the Hb dropped to 4.8g/dl; the reticulocyte count was 1.88%, LDH was 481U/L (N = 4-240), plasma Hb was 273 mg/L (N=1-40) and Coombs' test was negative. She was given 2 units of packed RBC's; Hb improved to 6.3 g/dl. The fever continued. Hb again dropped to 3.5g/dl on the 13<sup>th</sup> day. In view of continued fever and two episodes suggestive of hemolysis, she was treated with prednisolone 1mg/kg/day and further investigated. APLA IgG and IgM tests were strongly positive, ANA was negative, G-6PD value was normal and cold agglutinins were elevated at 1:1280. Her fever improved and Hb rose to 6gm/dl. On follow up after 4 weeks she was better; Hb was 8.2g/dl. Prednisolone was tapered over 6 weeks and stopped.

### Case 2

A 7 year old girl developed high grade, intermittent fever with chills in the first week of September 09. Peripheral smear showed both *P. vivax* and *P. falciparum* malarial parasite (MP). She was admitted to another facility. On admission her Hb was 11.1g/dl, platelet count was 50,000/mm<sup>3</sup> and bilirubin was 5.2 mg/dl (direct 4.0mg/dl, indirect 1.2 mg/dl). She was treated with intravenous artesunate 2.4mg/kg/day for 5 days followed by mefloquine 15mg/kg. She also received injectable ceftriaxone 1g IV OD and quinine 10mg/kg tid PO for 4 days. The fever improved on the 3<sup>rd</sup> day of treatment. A repeat peripheral smear was negative. Fever recurred on 7<sup>th</sup> day of admission and the Hb dropped to 5.1gm/dl. She received 2 units of PRBCs and transferred to our hospital. On admission at our Hospital she was febrile (temp 102F), pale; Hb was 9.0g/dl, bilirubin was 1.7mg/dl and peripheral smear was negative for MP. Rapid malaria antigen test was negative. Urine examination showed reddish colour with urobilinogen +++, 12 WBCs and 15 RBC/hpf. Fever continued, and Hb dropped to 4.9g/dl on the 13<sup>th</sup> day of her illness. She received 1 unit of PRBC under steroid cover. Other investigations showed reticulocyte count 7.18%, plasma Hb 270mg/dl(N=1-40), LDH 670U/L, ANA 1:100 +++ speckled pattern, P-ANCA 1+, cold agglutinins 1:16 positive, APLA IgG and IgM 16 and 14 U/ml (N< 10 U/ml), G-6PD was normal. She became afebrile on 20<sup>th</sup> day of her illness and started passing clear colored urine. She was discharged on the 12<sup>th</sup> day of admission. On follow up after 4 weeks she was better, off treatment and the Hb was 10.1gm/dl.

### Case 3

A 15 year old female suffered from fever with chills in the second week of November' 09 and was admitted in another facility. Her peripheral smear was positive for *P. falciparum*, Hb was 11.1g/dl and the platelet count was 1.60lacs/mm<sup>3</sup>. Her platelets dropped to 25000/mm<sup>3</sup> in 4 days and she developed icterus and was transferred to Hinduja Hospital on the 4<sup>th</sup> day. On admission, her Hb was 8.7g/dl, platelet count was 3000/mm<sup>3</sup>, S. bilirubin 21.8mg/dl (direct 15.2 mg/dl, indirect 6.6 mg/dl), albumin 1.6 gm/dl. She was started on IV artesunate 120mg/day, ceftriaxone 2g/day and was treated with platelet transfusions (6 RDPs). The platelet count improved gradually, S. bilirubin decreased to 6 mg/dl within a week, but the fever continued and Hb dropped gradually to 4.5 mg/dl by the 11<sup>th</sup> day. Repeated peripheral smears were negative for MP, rapid malaria test was negative, G6 PD was normal, reticulocyte count was 0.28%, LDH 458 (N=135-214), Haptoglobin 5.83 g/dl (13-163), plasma Hb 442

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Received: 15.07.2010; Accepted: 17.09.2011

mg/l (N=1-40), Coombs' test and ANA were negative, APLA IgG, IgM were mild positive. The cold agglutinins titres were 1:16. She was started on prednisolone 0.5 mg/kg body weight. The fever improved and Hb stabilised. She was discharged on 15<sup>th</sup> day of admission with no fever and Hb 7.3 g/dl. On follow up after 2 months her Hb was 12.1 g/dl and prednisolone had been tapered down to 5 mg/day, it was discontinued.

## Discussion

Anemia is frequently associated with malaria; its rate of occurrence depends on age of the patient and endemicity. Anemia is caused by a variety of pathophysiological mechanisms which include hemolysis, reduced red cell deformation of parasitized and non-parasitized erythrocytes, increased splenic clearance, variable degree of bone marrow dyserythropoiesis and cytokine dysregulation (significant increase in IFN gamma, IL-6, TNF-alpha, IL-1, MIF, HIF-1 and decrease in IL-10 and IL-12 levels).<sup>5</sup> In areas where malarial infection is endemic, co-morbidities like other parasitic infections, iron, folate and Vitamin B12 deficiency, deficiency of other nutrients and effects of anti-malarial drugs both through immune and non-immune mechanisms are important considerations.<sup>5</sup> However extent of hemolysis in malaria is much greater than that seen in other parasite induced hemolysis and combined mechanism with immune mediated hemolysis has been suggested.<sup>1</sup>

All the three patients being reported had sudden and significant drop in Hb levels between 7<sup>th</sup> to 14<sup>th</sup> day of illness necessitating PRBC transfusion. Peripheral smears were negative for MP and rapid malaria test was negative at the time of drop in Hb. All had high plasma Hb levels with raised LDH levels. But the reticulocyte count was increased in only one patient, and direct Coombs' test was positive in only one patient. The hemolytic episodes cannot be explained by malarial parasitemia alone and would fit in with autoimmune hemolysis. Moreover two patients had persistent high fever after clearance of parasitemia and both fever and anemia responded to corticosteroid treatment.

A proportion of patients suffering from malaria develop immune hemolysis.<sup>2</sup> The reasons for immune hemolysis are multifactorial e.g. antibodies directed to parasite antigens sticking to red cells, immune complex deposition leading to bystander hemolysis due to parasite antigen or drug antibody complex, or due to oxidative damage and aggregation of red cell anion channel protein, subsequent coating of this denatured protein by naturally occurring autoantibody followed by their removal by reticuloendothelial system<sup>3</sup>. In addition, increased levels of cytokines including TNF-alpha can activate macrophages which, in a hyperactive stage, may reduce their threshold for amount of antibody coating needed for phagocytosis. Also, anticomplementary defense of red cell membrane, which protects rbc's from inadvertent complement mediated lysis, is reduced in malarial infection due to loss of complement regulatory proteins CD-55 and CD-59. This coupled with increased levels of immune complexes in malarial infection makes rbc's susceptible to complement mediated lysis.<sup>4</sup>

Besides anti-erythrocyte Ab, other autoantibodies have also been observed during the course of malaria. Important among these are ANA, APLA and occasionally ANCA. Anti phospholipid antibodies were strongly positive in two and weakly positive in one patient. Benign antiphospholipid antibodies are known to develop in malaria, but whether these contribute to hemolysis is not known. Cryoglobulin titers were high in all the three patients, with very high titers in one patient. High cryoglobulin titres have been reported in patients with malaria, especially with falciparum malaria, however their role in hemolysis in malaria is not known.

There have been two single case reports of association of malaria and autoimmune hemolysis, one was from Korea and other from Canada.<sup>6,2</sup> In India, prevalence of malaria is very high, but there have been no similar cases reported from India. It could be due to rarity of this phenomenon or due to underreporting. The autoimmune hemolysis seems to be short lived or self limiting as two of our patients responded very well to steroids which were stopped gradually in 6 weeks. After discontinuing steroids patients did not have drop in Hb and remained asymptomatic. The purpose of this communication is to emphasize that autoimmune hemolysis should be thought of if a patient with malaria develops post treatment hemolysis or persistent anemia.

## Acknowledgments

We are grateful to **Prof. V.R. Joshi**, MD, Consultant Rheumatologist and Director, Research, for his critical review of manuscript and **Dr. Nagaraj S**, DNB(Paed), PG Registrar, Department of Rheumatology, PD Hinduja National Hospital and MRC, for help in the preparation of manuscript.

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