Cold Agglutinins associated with Plasmodium falciparum malaria: A case report

Deepak Nayak M.[1], Sushma V. Belurkar[2], Chethan Manohar[3], U. Shashikiran[4]

[1]Assistant Professor; Department of Pathology, Kasturba Medical College-Manipal, Manipal University.
[2] Associate Professor; Department of Pathology, Kasturba Medical College- Manipal, Manipal University.
[3] Professor; Department of Pathology, Kasturba Medical College- Manipal, Manipal University.
[4]Professor; Department of Internal Medicine, Melaka Manipal Medical College-Manipal Campus, Manipal University.

Abstract- The combination of anemia in malarial infestations ranges from nutritional deficiency to marrow suppression. An immune hemolytic anemia in Plasmodium falciparum malaria is also a part of this wide-ranging spectrum. But the co-existence of cold agglutinins in a Plasmodium falciparum malaria has only sporadically been reported in literature. We present a case of a patient with falciparum malaria who developed severe anemia and jaundice at the time of presentation. The Coombs' test and cold agglutinin test were negative. This case underlines a rare association of cold agglutinins in Plasmodium falciparum malaria.

Index Terms- Plasmodium falciparum; cold agglutinins; hemolytic anemia; jaundice.

I. INTRODUCTION

Malaria continues to be a premier disease in India; with an increasing prevalence and geographical diversity. *Plasmodium falciparum* malaria in particular has been associated with a multitude of complications. Moreover, the varied presentations of the disease and its diversity in terms of hematological manifestations have been well endowed in literature. Anemia, by far, is the most important manifestation. The aetiology of anemia seen in falciparum malaria is multifactorial. This anemia ranges from nutritional deficiency to hemolytic anemia due to an accelerated red blood cell removal by the spleen. Also, an ineffective erythropoiesis is also incriminated in few cases. Drug-induced hemolytic anemia is the other dimension to this aspect. However, an immune-mediated hemolysis in malaria has gathered the attention of researchers in recent years. As literature keeps expanding with varied immune-mediated complications, the role of cold agglutinins is seldom mentioned. We report a case of *Plasmodium falciparum* malaria where clinical and laboratory evidence of hemolysis due to cold agglutinins were evidenced.

II. CASE REPORT

A 27-year old male patient with a two-day history of high grade, intermittent fever with chills and rigors presented to the medicine outpatient department of our hospital. Clinical examination showed pallor and icterus. A mild to moderately enlarged spleen was palpated on general examination. The laboratory investigations revealed anemia (hemoglobin: 7.3g/dl) and thrombocytopenia (platelet count: 23,000/mm^3). Both the peripheral smear and quantitative buffy coat (QBC) test showed abundant gametocytes and ring forms of *Plasmodium falciparum* malarial parasite (figure 1). But the autoanalyzer had given a suspect flag for 'H &H' check fail. The RBC count and hematocrit were disproportionately low for the degree of anemia (1.34×10^6 / cu.mm and 15.2% respectively). Additionally, the peripheral smear showed clumping of erythrocytes with occasional spherocytes and mild polychromasia; suggesting a hemolytic anemia due to cold agglutinins (figure 1). The sample was warmed to 37 degree Celsius for 30 minutes and run on the analyzer. The cell counts improved marginally. As such, a Coombs' test and cold agglutinin test were advised along with a follow up count for thrombocytopenia.

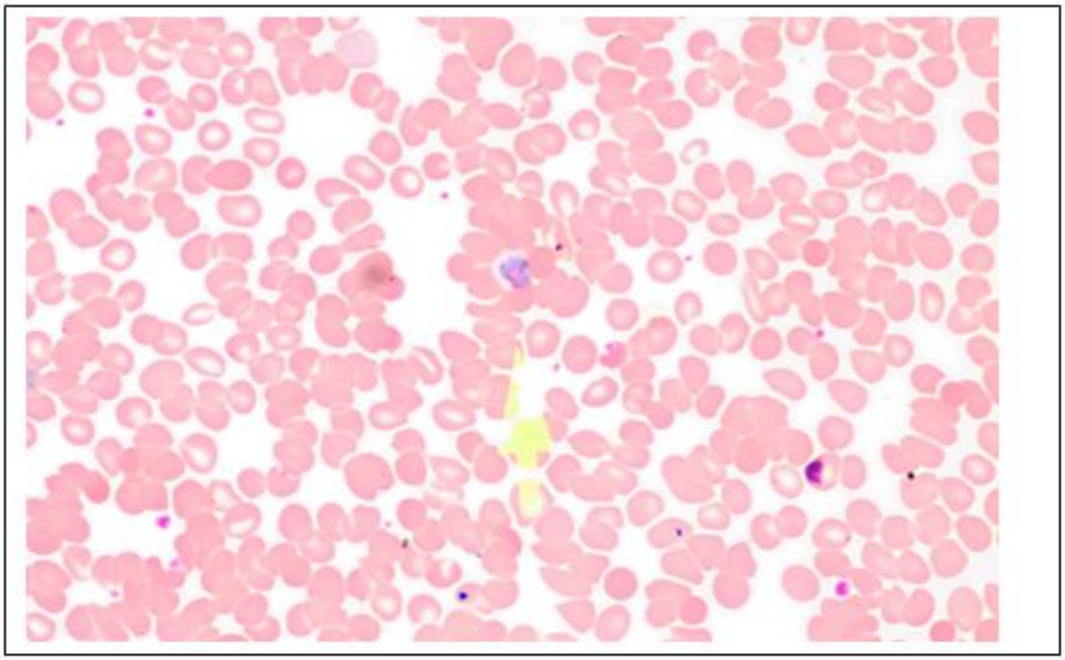

Figure 1: Peripheral blood smear showing erythrocyte clumping and trophozoites and ring forms of *Plasmodium falciparum* (arrow) (Leishman; x200)

The direct Coombs' test (DAT) was negative. The biochemical tests showed a raised serum bilirubin; with an appreciably high fraction of unconjugated bilirubin (2.1mg/dl); confirming the pre-hepatic hemolytic anemia. Other investigations showed a reticulocyte count of 5.6%; which was not significantly high for the degree of anemia. No hemoglobin was detected in the urine examination. The cold agglutinin test performed on the same sample showed a negligibly positive titre of 1:128. Thus, based on the clinical parameters and laboratory evidence, a diagnosis of cold agglutinin disease associated with *Plasmodium falciparum* malaria was rendered.

The patient was placed on anti-malarial therapy and improved clinically within four days. Laboratory investigations-wise, the counts appreciated in these days as well. The peripheral smear on day four of admission did not show clumping of erythrocytes.

III. Discussion

Anemia in malaria is not an uncommon association. The prevalence of anemia depends on many variables such as age and nutritional status of the patient and endemicity. Besides these, the other causes of anemia includes an accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony (due to reduced red cell deformation of parasitized and non-parasitized erythrocytes) and ineffective erythropoiesis.[1] The recent advancements have showed that a variety of cytokine dysregulations are indeed vital participants in inducing and accelerating the pathogenesis of hemolysis in malaria. They include a significant increase in interferon (IFN) gamma, interleukin (IL)-6, tumour necrosis factor (TNF)-alpha, IL-1, hypoxia inducing factor (HIF)-1 and decrease in IL-10 and IL-12 levels.[1,2] Compounding this problem is the anecdotal evidence that hemolysis in malaria is much greater than that seen in other parasite- induced diseases. Thus, an underlying immune-mediated pathology has been suggested.[3]

Hemolytic anaemias are manifested due to an excessive destruction of red blood cells. Cold agglutinin disease of the secondary type is associated with infections far more than neoplastic processes; with malaria being one of the uncommon aetiologies.[4] Immune hemolytic anemias caused by cold-active antibodies are associated with IgM antibodies, directed at the 'I' or 'i' antigens on the surface of RBCs.[5] A vast majority of these antibodies rarely cause symptomatic anemia with the level of hemoglobin infrequently dropping below 7gm/dl.[6] In this case, the clumping of erythrocytes on the peripheral smear and RBC indices on the autoanalyzer hinted towards the role of an IgM antibody. Additionally, the degree of hemolysis was not severe. Although the patient's condition improved with treatment, the pertinent question is whether the transient hemolysis which was observed at presentation significant?

A raised titre of IgM antibodies in in malaria is practically unheard of. If one considers the prototype example of *Mycoplasma pneumoniae* infection and development of secondary cold agglutinin disease, some hypothesis can be speculated.[7,8] The generation of IgM antibodies in this particular falciparum malaria case may be due to the changes (sialylation) of I or i antigens on erythrocyte membrane surface of the parasitized erythrocytes. This minor modification in the antigen could have incited a transient IgM response. Other possibility is

that of a by-stander effect. The fact that the RBC clumping disappeared in the next three days can also be attributed to the clearance of the parasitized RBCs; thus reducing the antigenicity.

IV. Conclusion

Anemia in falciparum malaria has been assigned to a number of aetiologies. Immune hemolytic anemia is probably the least mentioned one. Still rarer is the combination of cold agglutinins and malaria. The definitive answer as to whether this hemolytic reaction is transient or clinically significant can only be answered by more research in the future

References

[1] Ghosh K, Ghosh K. Pathogenesis of anemia in malaria: A concise review. Parasit Res 2007; 101:1463-1469.

[2] Sharma V, Samant R, Hegde A, Bhaja K. Autoimmune hemolysis in malaria: A report of three cases. JAPI 2012; 60:129-130.

[3] Dhaliwal G, Cornett PA, Tierney LM jr. Hemolytic anemia. Am Fam Physician 1979; 69:2599-2606.

[4] Friedberg RC, Johari VP. Autoimmune hemolytic anemia. In: Wintrobe's Clinical Hematology. Twelfth ed. Vol 1. Greer JO, Foerster J, Rodgers GM. et al (editors). Lippincott, Williams & Wilkins, Philadelphia 2009:956-977.

[5] Petz LD, Garratty G. Acquired immune hemolytic anemias. New York: Churchill Livingstone 1980.

[6] Evans RS, Bingham M, Turner NE, *et al*. Autoimmune hemolytic disease: observations of serological reactions and disease activity. Ann NY Acad Sci 1965; 124: 422.

[7] Loomes LM, Uemure K-I, Childs RA, *et al*. Erythrocyte receptors for *Mycoplasma pneumoniae* are sialylated oligosaccharides of Ii antigen type. Nature 1984; 307: 560-563.

[8] Costea N, Yakulis V, Heller P. Inhibition of cold agglutinins (anti-I) by *M. pneumoniae* antigens. Proc Soc Exp Bio Med 1972; 139: 476-479.

Authors

First Author – Dr. Deepak Nayak M., Assistant Professor, Department of Pathology, Kasturba Medical College-Manipal, Manipal University
Second Author – Dr.Sushma V. Belurkar, Associate Professor, Department of Pathology, Kasturba Medical College-Manipal, Manipal University
Third Author – Dr. Chethan Manohar, Professor, Department of Pathology, Kasturba Medical College-Manipal, Manipal University
Fourth Author – Dr. U. Shashikiran, Professor, Department of Internal Medicine, Melaka Manipal Medical College-Manipal Campus, Manipal University

Correspondence Author – Dr. Deepak Nayak M. , Assistant Professor, Department of Pathology, Kasturba Medical College-Manipal, Manipal University, Manipal 576104. Karnataka , India
E-mail: drdeepak.manipal@gmail.com
Contact no: 0820-2922201