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Plasmodium falciparum-Induced Autoimmune Hemolytic Anemia in a Pregnant Patient with Sickle Cell Disease

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 29-year-old
Final Diagnosis: *Plasmodium falciparum*-induced autoimmune hemolytic anemia
Symptoms: Anemia • tachycardia
Clinical Procedure: —
Specialty: Hematology • Infectious Diseases

Objective: Unusual clinical course

Background: Sickle cell disease (SCD) is an autosomal recessive hereditary condition characterized by chronic hemolytic anemia and painful vaso-occlusive episodes. Homozygous sickle cell patients are at increased risk of morbidity and mortality from malaria. Autoimmune hemolytic anemia (AIHA) secondary to, or in the setting of, malarial infection is rare. In our case, the concurrence of *Plasmodium falciparum* malarial parasitemia and AIHA led to severe hemolytic anemia with an extensive packed red blood cell transfusion requirement. The patient's underlying SCD also contributed to the severity of the anemia and persistence of the malarial infection.

Case Report: We report the case of a 29-year-old woman in the second trimester of pregnancy, with a history of SCD, who presented with severe anemia beyond her typical baseline in the setting of *P. falciparum* malaria. Hemolysis markers, including lactate dehydrogenase and bilirubin, were elevated. Direct Coombs testing was positive for IgG and C3 antibodies. Treatment with antimalarial agents and steroids led to clinical improvement and eventual clearance of the parasitemia.

Conclusions: Our patient's clinical course was most compatible with *P. falciparum* malaria-induced AIHA. Although she received a short course of steroids, it was treatment and clearance of the parasitemia that led to resolution of the hemolysis and a return to baseline hemoglobin levels. While the exact mechanism of AIHA in malaria is not well characterized, several unique mechanisms have been proposed and should be considered in cases of *P. falciparum* malaria manifesting with particularly severe hemolytic anemia.

Keywords: Anemia, Hemolytic, Autoimmune • Anemia, Sickle Cell • Malaria

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938854

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Background

Sickle cell disease (SCD) is an autosomal recessive hereditary condition characterized by chronic hemolytic anemia and painful vaso-occlusive episodes [1]. SCD is most common in sub-Saharan Africa, although it affects approximately 100,000 Americans [2,3]. *Plasmodium falciparum* malaria can present with a broad spectrum of clinical conditions including severe anemia and cerebral malaria. More than 20 polymorphisms, including sickle cell trait, have been selected in human populations as they offer protection against fatal *P. falciparum* infections [4]. We present the case of a 29-year-old woman in the second trimester of pregnancy, with a history of SCD, who presented with severe anemia beyond her typical baseline in the setting of *P. falciparum* malaria. Hemolysis markers including lactate dehydrogenase and bilirubin were raised. Direct Coombs testing was positive for IgG and C3 antibodies. The concurrence of *P. falciparum* malarial parasitemia and autoimmune hemolytic anemia (AIHA) on a background of SCD led to severe hemolytic anemia with an extensive packed red blood cell transfusion requirement. Treatment with antimalarial agents and steroids led to clinical improvement and eventual clearance of the parasitemia.

Case Report

A 29-year-old woman in the second trimester of pregnancy, with a history of SCD (HbSS genotype), presented with severe anemia. Three months prior to presentation she had traveled to Mali and Senegal, where she was diagnosed with *P. falciparum* malaria and started on an unknown antimalarial. However, according to her own report, she was not fully compliant with her prescribed course of treatment. The patient did not report any sickle cell vaso-occlusive episodes after she was diagnosed with *P. falciparum* malaria.

During an outpatient visit at our institution to follow up on her pregnancy, she was found to have severe anemia beyond her typical baseline. She was therefore referred for inpatient admission.

Upon presentation, she was tachycardic, though well-appearing and in no distress. She was anemic to a hemoglobin (Hgb) level of 4.6 g/dL (from her typical baseline of 8-9 g/dL). Reticulocyte percentage was 21.8% (from her typical baseline of 7-8%). Lactate dehydrogenase (LDH) was 734 U/L (from her typical baseline of approximately 300 U/L). Total bilirubin was 4.6 mg/dL (from her typical baseline of 1.5 mg/dL). Haptoglobin was undetectable. Direct Coombs testing was positive for IgG and C3. A peripheral blood smear demonstrated *P. falciparum* in 1% of her red blood cells (**Figure 1**) and blood parasite culture was positive for *P. falciparum*. She was transfused with 4 units of packed red blood cells (PRBCs) and admitted for management of malarial parasitemia and concurrent AIHA.

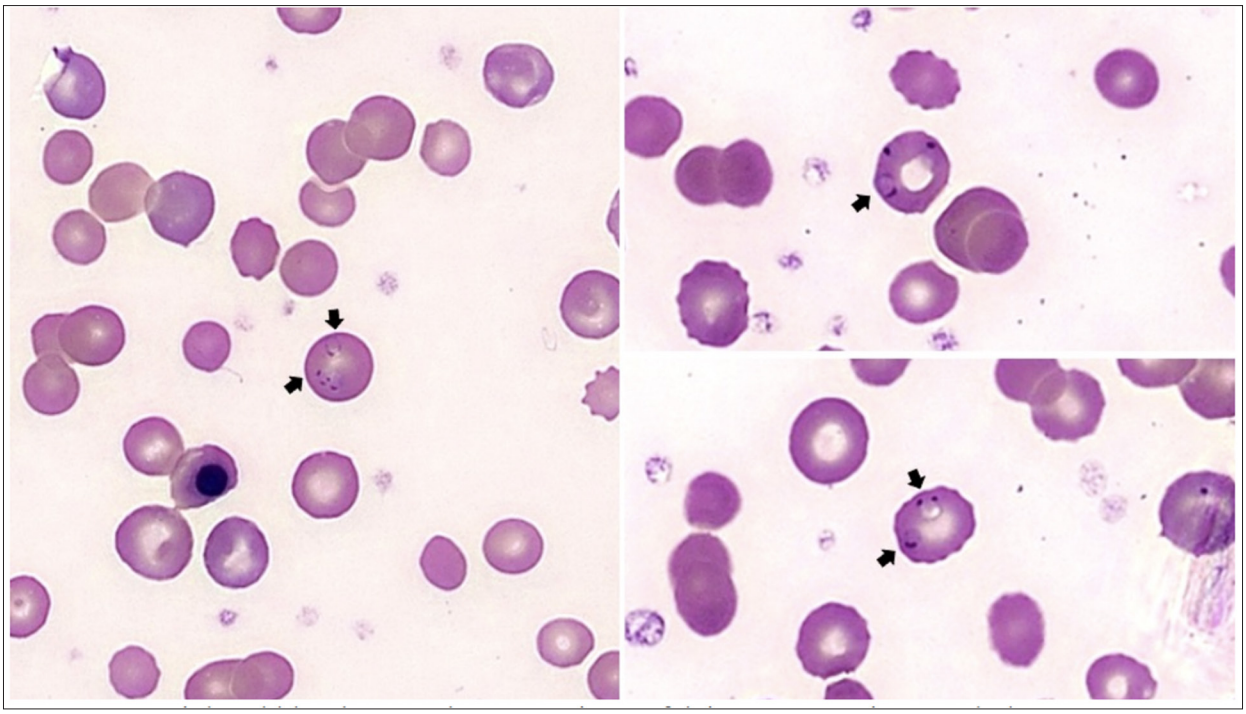

Figure 1. Peripheral blood smear demonstrating *Plasmodium falciparum* parasite morphology. Peripheral blood smear on presentation demonstrated *P. falciparum* in 1% of red blood cells (arrows).

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For treatment of malaria, she was started on intravenous artesunate 2.4 mg/kg every 12 hours. Following 3 doses of intravenous artesunate, 2 consecutive blood parasite cultures and 2 peripheral smears were negative for *P. falciparum*. She was then transitioned to quinine 648 mg every 8 hours for 24 hours (3 doses total), and clindamycin 450 mg every 8 hours for 7 days. For the management of concurrent AIHA, she was started on intravenous methylprednisolone 500 mg daily for 2 days and thereafter transitioned to prednisone 1 mg/kg/day (equivalent to prednisone 60 mg daily) which she received for 2 days while hospitalized. Laboratory markers of hemolysis (LDH and bilirubin) down-trended and hemoglobin stabilized with no further transfusion requirement. She was thereafter discharged on prednisone 60 mg daily for 7 days (she was also completing her course of clindamycin at the time of discharge). She was scheduled for followup 1 week after discharge.

One week following discharge, repeat thick and thin smears sent in the outpatient setting demonstrated recurrent *P. falciparum* parasitemia (to <1%). She was readmitted for refractory malaria and started on artemether/lumefantrine 80-480 mg for 6 doses (every 8 hours for the first 2 doses, followed by every 12 hours for the following 4 doses). She thereafter again cleared her parasitemia. During this second hospitalization, her hemoglobin and hemolysis markers remained stable at or near her baseline levels. Prednisone was discontinued with no evidence of recurrent AIHA. Prior to discharge, she had 2 blood parasite cultures and 2 peripheral smears that were negative for *P. falciparum*. Parasitemia and AIHA did not reoccur during followup after this second hospital discharge.

Discussion

The geographic distribution of SCD mirrors that of malaria [5,6]. This corresponding epidemiological distribution is not coincidental, as there is evidence that heterozygotes for the sickle cell gene (HbAS genotype), also known as sickle cell trait, are protected against mortality from malaria. Sickle cell trait confers a high degree of resistance to complicated and severe malarial infections [7-10]. The invasion and development stages of *P. falciparum* are reduced secondary to the unique physical and biochemical properties of the red blood cells (RBCs) in patients with sickle cell trait [11,12]. Furthermore, RBCs in patients with sickle cell trait that are parasitized by *P. falciparum* have a high propensity to sickle and undergo deformation due to low oxygen tension caused by the parasite. These infected cells become vulnerable to phagocytosis and undergo destruction by the spleen [11,13].

In contrast, patients who are homozygous for the sickle cell gene (HbSS genotype) experience increased susceptibility to severe and complicated infections and are at increased risk of morbidity and mortality from malaria [14-16]. *P. falciparum*-induced destruction of parasitized RBCs precipitates a severe exacerbation of the pre-existing chronic hemolytic anemia in these patients [17,18]. Malarial infection can also trigger painful vaso-occlusive episodes in sickle cell patients and is a leading cause of hospitalizations in endemic regions [14,19]. Furthermore, patients with SCD often have impaired splenic function, frequently to the extent of functional asplenia due to vaso-occlusive disease-related autosplenectomy, rendering them incapable of clearing the parasitized erythrocytes [20].

There are 5 cases in the literature describing an association between SCD and AIHA [21]. However, AIHA related to SCD is not the likely cause of our patient's severe anemia at presentation. Anemia is frequently associated with malaria secondary to destruction of RBCs by the *Plasmodium* parasites, splenic sequestration of RBCs, production of inflammatory cytokines, dyserythropoiesis related to infection, and bone marrow suppression [22]. AIHA secondary to, or in the setting of, malarial infection is rare. While 9 cases in the literature describe an association between malaria and AIHA [23-29], there is only 1 case of *P. falciparum* malaria mimicking AIHA in pregnancy that resolved following treatment with antimalarial agents alone [29]. Lastly, the risk of delayed hemolytic anemia after antimalarial treatment, specifically intravenous artesunate, is well documented but we do not believe that this was the likely cause for our patient's presentation since it did not reoccur with treatment at our institution [30-37].

In our case, the concurrence of *P. falciparum* malarial parasitemia and AIHA led to severe hemolytic anemia with an extensive PRBC transfusion requirement. The patient's underlying SCD also contributed to the severity of the anemia and persistence of the malarial infection. Although she received a short course of steroids, it was treatment and clearance of the parasitemia that led to resolution of the hemolysis and a return to baseline hemoglobin levels.

Conclusions

While it is difficult to definitively establish that this patient's AIHA resulted from her malarial infection, this relationship appears likely since treatment of the malaria led to resolution of the AIHA. Several unique mechanisms for AIHA in patients with malaria have been proposed. For example, alterations in the levels of antibody- and complement-binding in the setting of *Plasmodium* infection may play a role, as may reduction in the threshold for splenic sequestration of RBCs [38-40]. Although the exact mechanism of AIHA in malaria is not well characterized, it should be considered in cases of *P. falciparum* malaria manifesting with particularly severe hemolytic anemia.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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