



Case report

Post-artemisinin delayed hemolysis after oral therapy for *P. falciparum* infection



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ABSTRACT

A documented side-effect of artemisinin therapy is post-artemisinin delayed hemolysis (PADH), primarily occurring after parenteral treatment for severe *P. falciparum* infections. PADH has been infrequently reported after oral therapy and is rarely severe enough to require hospitalization and blood transfusions. A 24 year old man was diagnosed with *P. falciparum*, prompting initiation of oral artemether-lumefantrine (AL). Further work-up demonstrated that he met WHO criteria for severe malaria infection on the basis of high parasitemia and his regimen was switched to intravenous quinidine and oral doxycycline. He was transitioned back to AL after 4 days and was discharged on hospital day six. Five days later, he was readmitted for hemolytic anemia. His peripheral blood was absent of malaria parasites and he was diagnosed with PADH, ultimately requiring multiple blood transfusions. Severe hemolytic anemia requiring blood transfusions after oral artemisinin therapy is rare and may be associated with higher parasite loads. This case demonstrates the importance of close reassessment and consideration of PADH in patients treated with oral therapies, particularly in the setting of severe malarial infections.

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Introduction

P. falciparum is a major cause of morbidity and mortality throughout the world, responsible for over 400,000 deaths annually with the vast majority of cases occurring in Africa [1]. The current recommended therapy for *P. falciparum* infection per the 2015 World Health Organization (WHO) and 2019 Center for Disease Control (CDC) guidelines is oral artemisinin derivatives for uncomplicated infections and a combination of oral and parenteral for severe infections [2,3]. The primary parenteral therapy employed for severe malaria infections is artesunate, which has shown success globally but is a relatively new medication with controlled access in the United States [2,3]. Intravenous quinidine was frequently used in the United States to treat severe malaria cases until its discontinuation in April 2019. IV artesunate replaced IV quinidine under strict regulation and distribution by the CDC (pending FDA approval).

A serious reported side-effect of artemisinin based therapies is post-artemisinin delayed hemolysis (PADH) [4–8]. PADH is classically of clinical significance after parenteral artesunate

therapy for severe malaria cases, with reports of the hemolysis onset ranging 7–30 days after therapy initiation [4–7]. Reports indicate as high as 22 % of patients with severe malaria experience PADH after parenteral artesunate therapy and a significant portion require blood transfusions [8]. One study correlates parasite burden with the degree of hemolysis, suggesting the direct effects of artesunate on infected erythrocytes induces delayed hemolysis [8]. The same study theorized “pitting” and associated damage occurs in the infected cells after artesunate-induced death and expulsion of the malaria parasite, precipitating early destruction of the previously infected erythrocytes over the following weeks [8].

Here we present a case of PADH after oral artemisinin therapy (artemether-lumefantrine (AL)) in the setting of severe *P. falciparum* infection.

Case report

A 24-year-old previously healthy man presented to the Emergency Department for diarrhea, emesis, intermittent fevers, and anorexia of four days duration. He was noted to be febrile to 103.1 °F with labs demonstrating severe thrombocytopenia and indirect hyperbilirubinemia. The patient had traveled to Chad, Nigeria, and Kenya within the previous month and he had not taken any malaria chemoprophylaxis. A rapid malaria test returned

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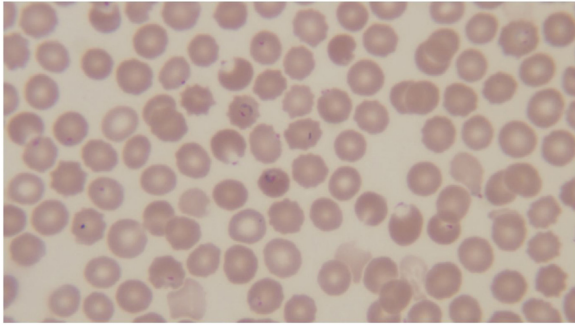


Image 1. Thin Smear demonstrating multiple trophozoites consistent with *P. falciparum* infection, credit to Benjamin Cook, MD, CPT, Department of Pathology, Madigan Army Medical Center.

positive for *P. falciparum*. The patient was admitted to the hospital and initiated on a course of oral AL for active *P. falciparum* infection overnight (approximately 1–2 doses given overnight).

Upon further evaluation, the peripheral blood smear demonstrated 12 % parasitemia (Image 1). This met criteria per the WHO and CDC for severe malarial infection and the patient was transferred to the intensive care unit for treatment with intravenous quinidine plus oral doxycycline. Malaria smears were monitored daily and on hospital day four, parasitemia decreased below 0.1 %. He was transitioned back to oral AL for a three day course and was discharged on hospital day six. At discharge his labs demonstrated an improving anemia (hemoglobin 11.4 g/dL) and normal total bilirubin (1.0 mg/dL).

Five days after discharge, he again presented to the Emergency Department for fever and was scheduled with an appointment the following day in the Infectious Disease clinic. At that appointment, he was directly readmitted to the hospital for recurrent fevers, nausea, and emesis. Repeat labs were notable for worsened indirect hyperbilirubinemia (total bilirubin 2.3 mg/dL), low haptoglobin (<10 mg/dL), elevated LDH (1759U/L), and anemia (hemoglobin 10.2 g/dL). Repeat peripheral blood smears were absent of parasites. He was noted to have normal G6PD levels obtained during his hospitalization. He was diagnosed with PADH and while admitted, his blood counts were monitored daily with persistent decline in hemoglobin/hematocrit. He ultimately required transfusions totaling four units of packed red blood cells during his second hospitalization (transfusion threshold Hgb <7 g/dL or Hct<21 g/dL). The patient continued supportive treatment and recovered fully prior to discharge with improving blood counts. Prior to discharge, further serology noted a positive direct antiglobulin test (DAT) and negative cold agglutinins.

Discussion

The above case demonstrates the development of PADH requiring blood product transfusions after treatment of severe *P. falciparum* infection with oral artemisinin derivatives, specifically AL. This is a rare finding with AL, in contrast to the far more substantial body of literature describing PADH after the use of artesunate (IV artemisinin) in the treatment of severe malarial infections.

Previous literature on oral artemisinin therapy does indicate that the oral agent can lead to 40 % of treated patients meeting the criteria for PADH (hemoglobin below normal values), though the effect is typically minimal with a median hemoglobin decrease of 1.35 g/dL without significant clinical symptoms [9]. There have been few reported cases of PADH leading to hospitalization after oral artemisinin therapy, with only 2 patients requiring blood transfusions [10–12]. Both patients who required blood

transfusions were being treated for severe malaria (parasite loads >5% per CDC criteria) and, as in our case, one had received a course of parenteral quinine with oral doxycycline prior to oral artemisinin therapy [10,12].

Quinidine induced hemolytic anemia and quinidine induced systemic lupus erythematosus (SLE) with hemolytic anemia were both considered but deemed unlikely considering the patient's normal G6PD levels (although obtained during a hemolytic state), lack of other clinical manifestations consistent with SLE, hemolysis onset after drug cessation, and brief medication exposure.

Determining the risk of developing PADH after AL therapy for severe malaria is confounded by the fact that patients with severe infections often receive parenteral artesunate therapy prior to transitioning to oral therapy. While parenteral artesunate has been clearly linked to PADH, this case highlights the importance of considering the diagnosis when a patient receives AL even without preceding intravenous artesunate. Close reassessment of patients' blood counts after treatment for severe malaria with AL should be considered, especially when there is an initial high parasite burden.

Our patient was treated successfully with supportive care and blood transfusions as needed, in keeping with the current standard treatment regimen for PADH. Recent research and case reports propose a possible role for corticosteroids in PADH patients as researchers observed attenuated hemolysis when corticosteroids were implemented after disease recognition [13,14]. These findings suggest an autoimmune component to PADH. A recent retrospective review of malaria cases in a single hospital found high rates of positive direct antiglobulin test (DAT) among patients hospitalized with PADH [13]. The authors suggested that drug-dependent hemolytic anemia may be playing a role in the disease process [13]. Further highlighting the potential benefit of corticosteroids in the treatment of PADH, a recent case report describes a patient hospitalized for severe PADH-related anemia who was found to have a positive DAT [14]. The patient was able to avoid blood transfusion and rapidly recover hemoglobin/hematocrit levels after corticosteroid (1 mg/kg daily) administration [14]. Further evaluations are warranted to more fully articulate the role of corticosteroids in PADH and to determine whether their use might reduce transfusion requirements in these patients.

Conclusion

Artemisinin based regimens are frequently utilized in the treatment of *P. falciparum* infections. PADH is a well-documented complication of artemisinin therapy, with a majority of the literature describing cases involving treatment with intravenous artesunate. This case describes PADH after treatment of severe *P. falciparum* infection with a regimen including artemether-lumefantrine without parenteral artesunate therapy. The case highlights the importance of post-treatment monitoring of patients' blood counts and consideration of PADH even in the setting of oral artemisinin use. Further research is warranted to elucidate whether there is a role for corticosteroid therapy in the management of PADH as a means of potentially reducing blood transfusion burdens.

CRedit authorship contribution statement

Christian C. Conlon: Conceptualization, Writing - original draft, Writing - review & editing. **Anna Stein:** Conceptualization, Writing - review & editing. **Rhonda E. Colombo:** Writing - review & editing. **Christina Schofield:** Supervision, Writing - review & editing.

Declaration of Competing Interest

We have no competing interests to declare. Approval was not required for this project and patient consent was obtained. No funding was procured or utilized for this case. The views expressed are those of the author(s) and do not reflect the official policy or position of the US Army Medical Department, Department of the Army, Department of Defense or the U.S. Government.

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