Case Report

Artesunate-related fever and delayed hemolysis in a returning traveler

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**ABSTRACT**

Malaria is a serious and sometimes fatal disease caused by an intraerythrocytic parasite, and is commonly seen in developing countries. Approximately 1500 cases of malaria are diagnosed in the United States each year, mostly in travelers and immigrants returning from endemic areas [1]. There are many different regimens used to treat malaria, some of which are not approved in the USA. The side effects of these medications may not be familiar to physicians in the USA. We report a case of a returning traveler from Nigeria presenting with fever and hemolytic anemia caused by a delayed response to artesunate given 3 weeks earlier while in Nigeria. To our knowledge, there are few cases reported in the United States of hemolytic anemia secondary to artesunate therapy [2].

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**Introduction**

Malaria is a serious and sometimes fatal disease caused by a parasite, which is commonly seen in developing countries. Parenteral artesunate is the first line treatment for severe malaria worldwide, however it is not yet licensed in the United States [3]. Therefore, side effects may not be familiar to physicians in the USA. We report a case of a returning traveler with fever and delayed hemolytic anemia from artesunate given while in Nigeria.

**Case description**

A 68 year old African American woman presented with a three day history of fever to 102 °F, periods of intermittent confusion, fatigue, anorexia, and myalgia. The patient was treated with artesunate for malaria in Nigeria 3 weeks prior to admission. The symptoms completely resolved 2 weeks after completing treatment with artesunate. She returned to the USA 1 week before presentation.

On physical examination, the patient appeared ill. The temperature was 101.6 °F, with a pulse of 106 beats/min, blood pressure of 125/80 and oxygen saturation of 99% on room air. The sclerae were pale and icteric. Cardiopulmonary examination was normal and there was no hepatosplenomegaly, skin rash or petechiae. Laboratory examination revealed a leukocyte count of 21,000/μL with 70% neutrophils, 23% lymphocytes, 4% monocytes and 3% eosinophils, a hemoglobin of 8.4 g/dL which dropped to 7.0 on the fifth day of hospitalization, and a platelet count of 306,000. The serum in the chemistry tube was grossly hemolyzed, with a potassium of 15 mEq/L and normal renal function. Hemolysis was noted on repeat specimens.

On the first hospital day, the temperature was 102 °F, and the patient was lethargic and confused. A CT scan of the head did not reveal any intracranial pathology. Wright–Giemsa stain from multiple blood samples did not reveal intraerythrocytic parasites. However, the peripheral smear was remarkable for rouleaux formation and erythrocytes with atypical diamond-shaped central blanched pitting [Fig. 1]. Further laboratory testing on hospital day 2 revealed an indirect bilirubin of 3.2 mg/dL, total bilirubin 4.4 mg/dL, LDH 965 IU/dL and haptoglobin 326 mg/dL (normal 43–212). The anemia and hemolytic picture worsened over the next few days, before improving [Table 1].

On hospital day 3, the patient was treated with hydroxychloroquine, despite having several peripheral smears negative for parasites. It was later discontinued because the patient developed a diffuse puritic rash thought to be a hypersensitivity reaction. On hospital day 5, the patient was treated with doxycycline. All antimalarial drugs were discontinued by hospital day 7. The patient’s hospital course was complicated by development of a small pulmonary embolus. The patient was discharged to home on hospital day 11 with oral anticoagulation for the pulmonary embolus.

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It is estimated that 584,000 malaria-related deaths occur in Africa. With an estimated 207 million clinical cases of malaria each year and more than 600,000 malaria-related deaths, the burden of disease remains unacceptably high [4].

Artesunate is a derivative of the “qing hao”, or sweet wormwood plant, which has been used worldwide for more than 20 years for the treatment of malaria. It inhibits parasite metabolism and enhances the clearance of infected erythrocytes. It is used as first line therapy for severe malaria in sub Saharan Africa and Southeast Asia, but is not yet licensed in the United States. Although other agents are FDA-approved for the treatment of uncomplicated malaria, intravenous quinidine gluconate is currently the only non-oral drug that is FDA approved and available to treat severe malaria in the United States. In 2007, intravenous artesunate was only approved as an investigational new drug (IND) protocol by the FDA in the United States [5]. There have been 19 reported cases of delayed hemolytic anemia after treatment of severe malaria with artesunate during 2010–2012. Worldwide, there have been 37 reported cases of hemolysis associated with the use of artemisinin derivatives in the treatment of severe malaria [2]. To our knowledge, there have been only two similar cases of delayed hemolysis due to artesunate therapy described in the United States [6].

Two distinct patterns of hemolysis after artesunate therapy have been described: a delayed onset or a persistent pattern of hemolysis [7]. Persistent hemolysis is defined as continuing hemolysis starting around day 7 of artesunate treatment and persisting beyond day 14. Delayed hemolysis typically occurs 2–3 weeks after completion of artesunate therapy, as in our patient. A delayed hemolytic pattern is defined by a decrease in hemoglobin associated with a low haptoglobin or increase in LDH occurring at least 7 days following artesunate treatment [7]. These latter findings were demonstrated in our patient, and after reviewing the clinical presentation and peripheral smear, it was determined that fever and delayed hemolysis were more likely to have been secondary to recent artesunate therapy in Nigeria.

The cause of hemolysis from artesunate remains unclear. One proposed mechanism is a splenic process called pitting, a process where artesunate exposed parasites are expelled from infected erythrocytes in the spleen. The erythrocytes then reseal (instead of lysing) and reenter circulation as pitted erythrocytes where they have a shortened lifespan. The delayed clearance of these pitted erythrocytes by the spleen may explain the features of post artesunate delayed hemolysis [9]. The degree of initial parasitemia increases the risk of this entity. A recent French study analyzed the hematologic parameters of 123 travelers treated with artesunate for severe malaria. Among 60 nontransfused patients observed for more than 8 days, 13 (22%) had delayed hemolysis [8].

The onset of hemolysis in the second or third week after treatment means that it is most likely to occur after a patient has been discharged from the hospital. Therefore, active screening for this side effect is important.

Physicians should be aware of this delayed side effect in order to prevent unnecessary further treatment of presumed malaria. There is no specific treatment or antidote. CDC has amended the artesunate IND protocol and now recommends that persons treated for severe malaria with artesunate be followed for 4 weeks after treatment and evaluated for hemolytic anemia [2]. Still, in many parts of the world where malaria is endemic, artemisinin-based drugs are considered miracle drugs for resistant malaria. A multidisciplinary team approach is important for early diagnosis and appropriate management of this clinical presentation.

**Conclusion**

In returning travelers from countries in which malaria is endemic, physicians in the U.S.A. should be aware of delayed hemolysis after artesunate therapy. Parenteral artesunate is only released by the CDC when parenteral quinidine is contraindicated, not tolerated or not available. Hemolysis probably results from delayed clearance of once infected erythrocytes which continue to circulate after artesunate has killed the parasites.

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**Table 1**

| Hospital day | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  |
|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| WBC (K/UL)   | 12.2| 14.0| 21.1| 21.7| 25.2| 23.9| 23.9| 21.8| 21.1| 18.9| 17.4|
| Hgb (gm/dL)  | 10.1| 9.5 | 8.1 | 8.2 | 7.7 | 7.7 | 7.2 | 7.3 | 7.6 | 7.2 | 7.7 |
| Hct (%)      | 31.0| 28.8| 24.5| 24.2| 22.8| 23.8| 21.1| 21.7| 22.7| 21.5| 22.8|
| PLT (K/ul)   | 306 | 308 | 289 | 345 | 423 | 463 | 504 | 525 | 561 | 522 | 545 |
| Tot bili (mg/dL)| 3.0 | 4.4 | 0.8 |     |     |     |     |     |     |     |     |
| Ind bili (mg/dL)| 2.2 | 3.2 | 0.5 |     |     |     |     |     |     |     |     |

WBC: white blood cell count; Hgb: hemoglobin; Hct: hematocrit; PLT: platelet count; Tot bili: total bilirubin; Ind bili: indirect bilirubin.
References

[1] Centers for Disease Control and Prevention (CDC): Division of Parasitic Diseases and Malaria. website www.cdc.gov/malaria/about/facts.html. Last updated March 4th, 2015. Accessed on March 16th, 2015.

[2] CDC. Published reports of delayed hemolytic anemia after treatment with artesunate for severe malaria worldwide, 2010–2012. MMWR 2014;63:753–5. 8/29/2014.

[3] Dondorp A, Nosten F, Stepniewska K, Day N, White N, South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–25.

[4] World Health Organization. Malaria report. Geneva: WHO; 2013.

[5] CDC. Notice to readers: new medication for severe malaria available under and investigational new drug protocol. MMWR 2007;56:769–70.

[6] Lee J, Krajden S, Graham C, Boggild AK, Pokenski K, Keystone JS, et al. Severe delayed hemolysis associated with regulated parenteral antimalarial drug. Emerg Infect Dis. 2015;21(1):164–6.

[7] Rehman K, Lötsc F, Kremsner PG, Ramharter M. Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence. Int J Infect Dis. 2014;29:268–73.

[8] Jauréguiberri S, Ndour PA, Roussel C, Ader F, Safeukui I, Nguyen M, et al. Postartesunate delayed hemolysis is a predictable event related to the lifesaving effect of artemisinins. Blood. 2014;124(2):167–75.

[9] Angus BJ, Chotivanich K, Udomsangpetk R, White NJ. In vivo removal of malaria parasites from red blood cells without their destruction in acute falciparum malaria. Blood 1997;90(5):2037–40.