

CASE REPORT

Open Access

Blackwater fever in an uncomplicated *Plasmodium falciparum* patient treated with dihydroartemisinin-piperaquine

Chanthap Lon^{1*}, Michele Spring², Somethy Sok³, Soklyda Chann¹, Rathvichet Bun⁴, Mali Ittiverakul², Nillawan Buathong², Khengheng Thay⁴, Nareth Kong⁴, Yom You⁴, Worachet Kuntawunginn², Charlotte A Lanteri² and David L Saunders²

Abstract

The mechanism of massive intravascular haemolysis occurring during the treatment of malaria infection resulting in haemoglobinuria, commonly known as blackwater fever (BWF), remains unknown. BWF is most often seen in those with severe malaria treated with amino-alcohol drugs, including quinine, mefloquine and halofantrine. The potential for drugs containing artemisinins, chloroquine or piperaquine to cause oxidant haemolysis is believed to be much lower, particularly during treatment of uncomplicated malaria. Here is an unusual case of BWF, which developed on day 2 of treatment for uncomplicated *Plasmodium falciparum* infection with dihydroartemisinin-piperaquine (DHA-PIP) with documented evidence of concomitant seropositivity for Chikungunya infection.

Keywords: Malaria, *Plasmodium falciparum*, Cambodia, Blackwater fever, Dihydroartemisinin-piperaquine

Background

Haemoglobinuria is a feature of complicated malaria syndromes as defined by the World Health Organization (WHO) [1]. Blackwater fever (BWF) is due to massive haemolysis of red blood cells in the blood stream with subsequent haemoglobinuria, anaemia, often accompanied by renal failure. By published reports, BWF occurs most often in *Plasmodium falciparum* infections, but has also been documented in *Plasmodium vivax*, *Plasmodium malariae* and mixed infections [2-6]. Though the exact mechanisms involved remain unclear, several factors appear associated with BWF such as G6PD deficiency, severe malaria infection, treatment of malaria with amino-alcohol drugs, particularly quinine, and presence of other viral or bacterial infections [3,4,7].

Case presentation

A 43-year old male Cambodian farmer was screened and enrolled on 21 July 2013 to participate in a clinical trial evaluating the efficacy of a course of dihydroartemisinin-

piperaquine (360 mg/2880 mg) divided over three days for uncomplicated *P. falciparum* malaria with or without a single dose of primaquine 45 mg to prevent transmission of gametocytes (NCT 01849640). During the three days before enrollment, he reported experiencing mild fever, chills and fatigue, and self-treated with paracetamol and ampicillin. On the day of enrollment, he was found to have *P. falciparum* infection with 31,218 parasites per μ l on peripheral blood smear at an outside medical facility, and was referred to the study team. He denied having taken any anti-malarial or traditional herbal medications, but he did inform the study team that he has been consuming 1–2 cans per day of an energy drink containing taurine, caffeine, and B vitamins for the past year. He reported no chronic underlying illnesses. He had suffered four malaria episodes since 2010 which were variously treated with chloroquine, artesunate and mefloquine, but reported no prior history of adverse reactions to anti-malarials or history of BWF.

Initial vital signs included a heart rate of 70, blood pressure of 108/69 mmHg, and a tympanic temperature of 38.1°C. He was not ill-appearing and had no jaundice, icterus, conjunctival pallor or rash. The remainder of the physical examination was unremarkable, including a

* Correspondence: ChanthapL@afrims.org

¹Armed Forces Research Institute of Medical Sciences (USAMC-AFRIMS), Phnom Penh, Cambodia

Full list of author information is available at the end of the article

normal neurologic examination and no hepatosplenomegaly. Urine was light tea coloured. Initial laboratory assessment revealed mild anaemia (Hb, 10.3 g/dl and HCT, 30.3%), low serum calcium (6.7 mg/dl), and normal serum creatinine (0.92 mg/dL). His G6PD activity was normal (9.8 U/g Hb, normal range 4.6-13.5 U/g Hb), and serial 10-second surface EKG tracings were normal, with an average manual QTcF of 444 ms.

Twenty-eight hours following admission, after completing the first two doses of DHA-PIP, he was observed to have dark 'coca-cola' coloured urine. His fever was still present and new signs and symptoms developed including pallor, dizziness, fatigue, anorexia and semi-watery diarrhea with abdominal pain in the right lower quadrant. Acute renal injury with an increase in serum creatinine from 0.92 to 1.7 g/dL, along with a decline in haemoglobin to 8.1 g/dL (21% decrease from baseline), was observed. He was switched to intravenous artemether (160 mg on day 1, 80 mg per day on days 2-5) for severe malaria with blackwater fever. He continued to have an appropriate response to anti-malarial therapy, with a decline in peripheral parasitaemia to 286 parasites/ μ l within 48 hours, and was smear negative by day 5 (Table 1). Primaquine therapy was withheld.

On day 3, he continued to experience fatigue, anorexia and jaundice. Serum creatinine continued to rise to a maximum 3.79 g/dL on D9 although there were never any electrolyte abnormalities. Other laboratory abnormalities included maximum indirect hyperbilirubinaemia of 2.95 mg/dL, aspartate aminotransferase of 265 U/L, and alkaline phosphatase of 163 U/L peaking on days 2, 5 and 7 respectively. A single unit blood transfusion was given on day 4 for a continued low haemoglobin level (8.4 g/dL) with levels thereafter remaining stable at

approximately 8.0 g/dL (7.7-8.8 g/dL). Serology for co-infections was negative for IgM against leptospira, all four dengue serotypes, scrub typhus, HIV and *Salmonella typhi*, but positive for reactive IgM against chikungunya virus. Urine colour normalized on day 7, and serum creatinine returned to 1.8 mg/dL within 4 weeks, and there was normal to high urine output throughout the admission.

Discussion

There are not well-defined predictive risk factors for BWF, and the syndrome is often diagnosed only after malaria patients undergoing treatment are noted to have dark-coloured urine. The mechanisms of BWF remain unknown though it has been associated with low levels of *P. falciparum* parasitaemia, partial malaria immunity, G6PD deficiency, and treatment with amino-alcohol drugs [2-5,7]. In this case, the patient had no risk factors above for developing BWF and had been treated uneventfully for malaria on four prior occasions with various drugs including mefloquine over the past three years. A history of multiple malaria infections are associated with BWF, and this, along with a likely concomitant partial immunity, seems to have been his only risk factor [2,4,5,8]. The patient seemed to have a mild case of BWF as he had stable vital signs, few signs/symptoms, and electrolytes within normal limits suggesting preserved renal function despite acute injury. This is similar to a recent prospective case series in nearby Vietnam, which reported overall mild severity and better outcomes [1,2], but in contrast to previous reports of high mortality with a 26% case fatality rates in European patients [9-11] and 23% in African patients [12] with more severe malaria.

Table 1 Key laboratory values

| Parameters (normal values) | D1 | D2 | D3 | D5 | D7 | D9 | D10 | W2 | W3 | W4 | W5 |
|---|--------|-------|-------|-------|-------|-------|------|------|------|------|-----|
| WBC $10^3/\mu$ L (4.0-10.0) | 3.0 | 4.3 | 4.54 | 5.49 | 6.5 | 7.3 | - | 6.1 | - | 5.3 | 5.3 |
| Blood smear (parasites/ μ l) | 31,218 | 4,050 | 286 | Neg. | - | - | - | - | - | Neg | Neg |
| HB g/dL (13-18) | 10.3 | 8.1 | 8.4 | 7.9 | 8.8 | 8.5 | - | 7.7 | - | 8.3 | 8.2 |
| PLT $10^3/\mu$ L (140-450) | 71 | 68 | 70 | 113 | 215 | 283 | - | 347 | - | 264 | 193 |
| Cr. mg/dL (0.8-1.3) | 0.92 | 1.7 | 1.8 | 2.71 | 2.90 | 3.79 | 3.29 | 2.9 | 2.21 | 1.8 | - |
| BUN mg/dL (7-18) | 20.5 | 25.4 | 27.85 | 36.91 | 23.74 | 23.0 | 19.7 | 19.8 | 20.2 | 16.2 | - |
| AST IU/dL (15-37) | 43.6 | 261 | 249 | 265 | 111 | 58.0 | - | 36.7 | - | - | - |
| Tot. bil. mg/dL (0-1.0) | 0.818 | 2.95 | 2.2 | 2.1 | 0.809 | 0.595 | - | 0.5 | - | - | - |
| Dir. bil. mg/dL (0.0-0.5) | - | - | 0.2 | 0.3 | - | - | - | - | - | - | - |
| K + mEq/L (3.5-5.1) | 3.68 | 3.93 | 3.7 | 3.8 | 3.95 | 4.34 | 4.29 | 4.1 | 3.74 | 3.39 | - |
| Na + mEq/L (136-148) | | | 130 | 142 | | | | | | | |
| CHIKV (IgM) | | | pos. | | | | | | | | |

WBC; white blood cell ($10^3/\mu$ L). HB; haemoglobin (g/dL). PLT; platelet ($10^3/\mu$), Cr; serum creatinine (mg/dL). BUN; blood urea nitrogen (mg/dL). AST; aspartate amino transferase (IU/dL). Tot. bil.; serum total bilirubin (mg/dL). Dir.bil.; serum direct bilirubin (mg/dL). K+; serum potassium (mEq/L). Na+; serum sodium (mEq/L). CHIKV (IgM); Chikungunya virus (Immunoglobulin M). pos; positive.

This is the first report of a patient with uncomplicated malaria who developed BWF after administration of DHA-PIP. BWF is classically associated with the amino-alcohols quinine, mefloquine and halofantrine of which quinine is the most common culprit. Since chloroquine was introduced after World War II supplanting quinine as first-line treatment of uncomplicated malaria, there has been an observed decrease in BWF [1]. A recent report suggested that metabolism of quinine by the cytochrome P450 3A4 enzyme may be responsible for increasing oxidative stress within erythrocytes, making these cells more vulnerable to haemolysis in those with malaria and/or G6PD deficiency [13]. The role of artemisinin compounds in such potential oxidant acute haemolysis remains poorly understood [14]. Parenteral artesunate was associated with low, but comparable, rates of BWF compared to quinine in a large trial of paediatric patients with severe malaria (0.7% versus 1.2% respectively) [6]. Dihydroartemisinin-piperaquine (DHA-PIP) is a combination of a potent, rapid acting artemisinin derivative, combined with a long-acting 4-aminoquinoline (bis-quinoline), similar to chloroquine. Neither chloroquine, nor its more recently introduced analogue piperaquine, have been associated with blackwater fever [1,15]. There has been one published report of a patient who developed BWF three weeks after stopping prophylactic chloroquine and proguanil [3]. The dihydroartemisinin component contains a highly active endoperoxide bridge and like artesunate, may also be capable of inducing oxidant haemolysis, but has not yet been reported to be a cause of blackwater fever [14]. The patient reported consuming daily doses of taurine, which is involved in many crucial physiological processes [16]. However, its role is not clearly understood and the influence of high taurine doses is uncertain. There has so far been no evidence to implicate long-term ingestion of taurine as a risk factor for haemolysis, though synthetic taurine is obtained from isoethionic acid (2-hydroxyethanesulfonic acid), an oxidant haemolytic.

In this case, the patient did have serologic evidence of Chikungunya infection, but he lacked classic findings of Chikungunya including arthritis, arthralgia, petechiae or maculopapular rash. In a 2001 study by Bruneel *et al.* [5] five of eight BWF patients were found to be co-infected with viral infections including hepatitis C, B and Epstein-Barr virus. However, these co-infection have yet to be proven as significant factors influencing the haemolytic potential of BWF [17]. The strong temporal association here of administration of DHA-piperaquine and onset of haemolysis and haemoglobinuria suggests that clinicians treating uncomplicated malaria patients with DHA-piperaquine, and likely other combinations containing artemisinin derivatives, should be aware of the rare possibility for development of blackwater fever during or shortly after therapy.

Consent

Ethical approval and patient informed consent was obtained from the patient for the study and for publication of this case report.

Competing interests

The authors have declared that there are no financial or non-financial competing interests.

Authors' contributions

CL, MS, SS, RB, SC, CL1 and DS designed and wrote the article. CL, MS, CL1, DS, MI, NB conducted the study. SS, RB, SC and CL diagnosed and treated the patient and collected all the clinical and diagnostic laboratory data. KT, NK, YY, WK and laboratory team designed, performed and assessed the laboratory tests. All authors read and approved the final version.

Author details

¹Armed Forces Research Institute of Medical Sciences (USAMC-AFRIMS), Phnom Penh, Cambodia. ²Department of Immunology and Medicine, US Army Medical Corps, Armed Forces Research Institute of Medical Sciences (USAMC-AFRIMS), Bangkok, Thailand. ³Royal Cambodian Armed Forces, Phnom Penh, Cambodia. ⁴The National Center for Parasitology, Entomology and Malaria Control (CNM), Ministry of Health, Phnom Penh, Cambodia.

Received: 19 February 2014 Accepted: 6 March 2014

Published: 14 March 2014

References

1. World Health Organization, Division of Control of Tropical Diseases: **Severe and complicated malaria**. *Trans R Soc Trop Med Hyg* 1990, **84**(Suppl 2):1-65.
2. Tran TH, Day NP, Ly VC, Nguyen TH, Pham PL, Nguyen HP, Bethell DB, Dihn XS, Tran TH, White NJ: **Blackwater fever in southern Vietnam: a prospective descriptive study of 50 cases**. *Clin Infect Dis* 1996, **23**:1274-1281.
3. Van den Ende J, Coppens G, Verstraeten T, Van Haegenborgh T, Depraetere K, Van Gompel A, Van den Enden E, Clerinx J, Colebunders R, Peetermans WE, Schroyens W: **Recurrence of blackwater fever: triggering of relapses by different antimalarials**. *Trop Med Int Health* 1998, **3**:632-639.
4. Rogier C, Imbert P, Tall A, Sokhna C, Spiegel A, Trape J-F: **Epidemiological and clinical aspects of blackwater fever among African children suffering frequent malaria attacks**. *Trans R Soc Trop Med Hyg* 2003, **97**:193-197.
5. Bruneel F, Gachot B, Wolff M, Régnier B, Danis M, Vachon F, Corresponding Group: **Resurgence of blackwater fever in long-term European expatriates in Africa: report of 21 cases and review**. *Clin Infect Dis* 2001, **32**:1133-1140.
6. Dondorp AM, Fanello CI, Hendriksen ICE, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K, Kivaya E, Agbenyega T, Nguah SB, Evans J, Gesase S, Kahabuka C, Mtove G, Nadjm B, Deen J, Mwanga-Amumpaire J, Nansumba M, Karema C, Umulisa N, Uwimana A, Mokuolu OA, Adedoyin OT, Johnson WBR, Tshefu AK, Onyamboko MA, Sakulthaew T, *et al*: **Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial**. *Lancet* 2010, **376**:1647-1657.
7. Pasvol G: **The treatment of complicated and severe malaria**. *Br Med Bull* 2005, **75**:76:29-47.
8. Thomson JG, Robertson A: *Protozoology. A Manual for Medical Men*. London: Baillière, Tindall & Cox; 1929: xiii + 376 pp.
9. Salisbury Edward I: In *"Blackwater Fever" Malariology: A Comprehensive Survey of All Aspects of this Group of Diseases from a Global Standpoint by Sixty-five Contributors*, Volume 2. Edited by Boyd MF. Philadelphia; London: W.B. Saunders; 1949:1053-1070.
10. Kuczynski RR: *Demographic Survey of the British Colonial Empire*, Volume 1. West Africa: Geoffrey Cumberlege, Oxford University Press; 1948: xiii + 821 pp.
11. Wenyon CM: **The incidence and aetiology of malaria in Macedonia**. *J Roy Army Med Corps* 1921, **37**:83-108.
12. Bruce-Chwatt LJ, Bruce-Chwatt JM: *Health in Tropical Africa during the Colonial Period. Malaria and Yellow Fever*. Clarendon Press, Oxford; 1980.
13. Marcsisin SR, Jin X, Bettger T, McCulley N, Sousa JC, Shanks GD, Tekwani BL, Sahu R, Reichard GA, Sciotti RJ, Melendez V, Pybus BS: **CYP450**

phenotyping and metabolite identification of quinine by accurate mass UPLC-MS analysis: a possible metabolic link to blackwater fever. *Malar J* 2013, **12**:214.

14. O'Neill PM, Barton VE, Ward SA: **The molecular mechanism of action of artemisinin—the debate continues.** *Molecules* 2010, **15**:1705–1721.
15. Bruce-Chwatt LJ: **Quinine and the mystery of blackwater fever.** *Acta Leiden* 1987, **55**:181–196.
16. Xu Y-J, Arneja AS, Tappia PS, Dhalla NS: **The potential health benefits of taurine in cardiovascular disease.** *Exp Clin Cardiol* 2008, **13**:57–65.
17. Stephens JWW: *Blackwater Fever. A Historical Survey and Summary of Observations Made over a Century.* Liverpool; London: Hodder & Stoughton; 1937: xvi + 728 pp.

doi:10.1186/1475-2875-13-96

Cite this article as: Lon *et al.*: Blackwater fever in an uncomplicated *Plasmodium falciparum* patient treated with dihydroartemisinin-piperaquine. *Malaria Journal* 2014 **13**:96.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

