

Blackwater fever: Re-visiting this nearly forgotten complication of malaria

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Keywords (MeSH): Blackwater fever; Plasmodium falciparum; Hemoglobinuria; Quinine; Artemether; Lumefantrine;

INTRODUCTION

Blackwater fever (BWF) is an intravascular hemolysis, hemoglobinuria and renal failure occurring in repeated Plasmodium falciparum malaria with irregular quinine exposure. We present a case from Rwanda whose presentation meets criteria for Blackwater fever as a complication of malaria occurring while being treated with a fixed combination of Artemether-Lumefantrine.

Malaria is a health burden in Africa and remains a threat and a major public health concern in Rwanda. Clinical manifestations vary widely and can be life threatening. It is a deadly disease if left untreated and is associated with many complications. Blackwater fever (BWF) is one of the unfrequently reported complications of severe malaria which is characterized by rapid intravascular hemolysis leading to hemoglobinuria and eventually acute kidney injury. This complication was classically reported in European expatriates who have been living in endemic areas of Plasmodium falciparum and had been intermittently taking quinine [1].

We report the case of a patient seen at the emergency room at the Centre Hospitalier Universitaire de Kigali (University Teaching Hospital of Kigali, CHUK) with clinical and laboratory features fitting the classical definition of BWF. The literature is reviewed to raise awareness of clinicians caring for such patients in order to allow for prompt recognition and timely management of this lethal disease.

CASE REPORT

A 17-year-old female student with a one-week history of smear-positive malaria was transferred from a district hospital following clinical deterioration marked by abdominal pain and dark urine. Two weeks prior to referral, she presented with progressive generalized body swelling, dark and decreased urine, fevers and was found with a positive blood smear for malaria parasites. She was treated in an outpatient clinic for 3 days with the oral anti-malarial agent artemether- Lumefantrine. One day after the completion of this regimen, she experienced progressive abdominal pain associated with dark urine, described as "Coca-Cola" by the patient. After another week, she revisited the health center and was transferred to the District Hospital where her blood smear remained positive for malaria parasites. She was treated with intravenous artesunate as per national protocol, transfused with two units of packed red blood cells, then referred to our hospital for further management.

Upon arrival at our hospital, she appeared severely ill. Initial vital signs included BP 96/64 mm Hg, pulse rate of 118, respiratory rate 24, Oxygen saturation 92% on room air. Exam was notable for severe conjunctival pallor, jaundice, and anasarca. A Foley catheter was draining dark urine [Figure 1].

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Acknowledgment: The authors would like to acknowledge the care provided by the nursing staff at the Centre Hospitalier Universitaire de Kigali.

Review: This manuscript was peer-reviewed by three reviewers in a double-blind review process;

Received: 14th December 2017; **Initial decision given:** 9th January 2018; **Revised manuscript received:** 19th January 2018; **Accepted:** 4th July 2018

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The urine analysis was negative for red blood cells and her initial hemoglobin was 8.9 g/dL. Her general condition quickly deteriorated with a rapid decline in renal function, hyperkalemia, and fluid overload refractory to medications. Hemodialysis was initiated and she ultimately underwent seven sessions of intermittent hemodialysis. On hospital day 4, her hemoglobin was found to be 5.5 grams per deciliter and she received two units of packed red blood cells. She was treated as inpatient in medical ward over a period of 3 weeks and recovered fully. All laboratory parameters normalized by the time of discharge. Her full blood count and blood chemistry results are shown in table 1 below.



Figure 1: picture of the urinary bag with dark urine

Table 1. Evolution of laboratory values over the course of patient's admission and treatment

Time	Hemoglobin	Potassium	Creatinine	Urea
Day 1	8.9g/dL	4.1mmol/L	240 μ mol/L	204mg/dL
Day 4	5.5g/dL	4.19mmol/L	188 μ mol/L	178mg/dL
Day 10	9g/dL	5.4mmol/L	139 μ mol/L	150mg/dL
Day 13	11g/dL	4.7mmol/L	88 μ mol/L	25mg/dL

DISCUSSION

Blackwater fever (BWF), also known as malarial hemoglobinuria or "*fièvre bilieuse hémoglobinurique*" in the French literature, has been classically reported in European expatriates as a combination of severe intravascular hemolysis, anemia, jaundice, hemoglobinuria, and renal failure associated with plasmodium falciparum infection. Parasitemia can be scanty or even absent, which is thought to be due to extensive hemolysis. This is a "hyperhemolytic" process which was postulated to be driven by immune-mediated destruction of erythrocytes that are altered by quinine or the parasite, or both [2][3].

This complication has been described since Hippocrates time, then in West Africa in 1819 by Tidlie as severe febrile illness characterized by passage of dark urine. Other reports came from tropical regions and J. Farrel Easmon named this condition blackwater fever in 1884 [4]. BWF virtually disappeared after 1950, when chloroquine superseded quinine as it was found to cause less oxidant hemolysis [5]. If we look at the clinical presentation of our patient, she fits into the classical definition of Blackwater fever apart from the choice of medication used to treat malaria [6][7]

Our observation resurrects the need to re-visit the definition of BWF, especially because similar observations were made in Ugandan children with malaria who were treated with artesunate [8]. The pathophysiology of BWF is unknown both for classical BWF and the blackwater fever associated with arthemisin derivatives as may well be the culprit in our case.

During the course of our patient's illness the blood smear was read negative at our hospital which is not surprising in view of the hyper-hemolytic process found in blackwater fever. However, the preceding smears that were positive for malaria parasites constitute strong evidence for the causative pathogen that is Plasmodium falciparum; this is the malaria species found to be more prevalent and associated with severe disease in our region.

Based on this case, and similar reports from Africa [1][8][9], we are questioning the validity of the classic definition for Blackwater fever as tied to quinine exposure as well as the controversy regarding the target population. We would suggest its review and possible amendment in order to allow for a timely suspicion, prompt diagnosis and timely treatment of this disease entity that is associated with a high morbidity and mortality if left untreated.

The patient's failure to respond to the Artemether-Lumefantrine started when the malaria smear was initially positive and remaining positive after 3 days brings up the question of the optimal dosage of this fixed combination therapy Artemether-Lumefantrine in the adult population. However, artesunate appears to have been used with success in patients with Blackwater fever who had taken quinine as their initial drug of choice [10]. We suspect an under-dosage of Artemether-Lumefantrine in adults as two patients with different weight can get the same dosage based on weight range in contrast to artesunate which is an exact weight dosage.

We strongly think that this "sub dosage" might be associated with the disease recurrence and suboptimal treatment of malaria in patients who are taking Artemether-Lumefantrine alone as per current national protocol, and until proven otherwise we highly recommend to the clinicians to always order malaria smears for control parasitemia at the mid & end of treatment course, in order to ensure the therapy has been effective in eliminating the malaria parasites. Another recommendation is to encourage physicians practicing in malaria endemic areas to remain vigilant for this fearful complication anytime they notice severe hemolysis in patients they are treating for plasmodium falciparum infection. This topic deserves further investigation.

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