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Case Report

Case report: Acute Kidney Injury, Liver impairment, Severe Anemia in a child with Malaria and Hyperparasitaemia

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Abstract

Severe Malaria is a medical emergency mainly because of its rapid progression to complications and death if not promptly and adequately treated. In 2018 WHO put the incidence of *P. falciparum* Malaria in the African region to be around 99.7%.

We present a case where a boy who presented with high grade fever, prostration, and jaundice. On investigation he was found to have parasitemia of 35%, met multiple criteria for Severe Malaria namely: Hyper-parasitemia, Thrombocytopenia, Anemia and Metabolic acidosis. The child was treated with I.V. Artesunate and I.V. Antibiotics, developed AKI (Acute kidney injury) during the hospital stay necessitating multiple dialysis sessions before making a complete recovery. This is a rare case in several aspects as discussed below.

Introduction

P.falciparum Malaria is the most dangerous type of Malaria, it is often associated with high level of parasitemia in the blood. If untreated it is known to cause fatal complications. *P.falciparum* as suggested by many epidemiological studies happens to be the most prevalent of them all in Africa. Red blood cells that are infected with the parasite undergo hemolysis and sludging leading to microinfarctions in capillaries of the brain, liver, adrenal gland, intestinal tract, kidneys, lungs, and other organs.

Blackwater fever is a dreaded complication of malaria which was widely reported in the 1950s manifests as hemolytic anemia, hemoglobinuria, AKI, hypovolemia and has a mortality rate as high as 23 %. It is traditionally thought to be caused by antimalarial regimens mainly Primaquine and Quinine, Severe Malaria infection, erythrocyte enzymopathies particularly G6PD (glucose 6 phosphate dehydrogenase) deficiency and coinfection with viral and bacterial pathogens. However, this case is unique in the sense that despite using Artesunate as the only treatment, there was still presence of blackwater fever.

Case report

A 12-year-old boy from Bondo, a town in Western Kenya with no previous co-morbidities was brought into the emergency department with prostration. He had a 2-day history of episodic high-grade fever associated with chills and rigors, yellowness of eyes which began since the morning of admission and multiple episodes of vomiting. This was associated with right upper quadrant abdominal pain, the patient was born in Western Kenya a highly endemic Malaria zone, there was no recent history of travel. Past history was notable for a single episode of Malaria 7 years previous to this admission which was managed with oral Artesunate-Lumefantrine combination along with Paracetamol for the fever in an outpatient setting. Physical examination revealed pallor, deep scleral jaundice, dry mucous membranes, and capillary refill >2 seconds. Vital signs were as follows- BP (Blood Pressure):98/51mmHg, PR (Pulse Rate):133bpm, RR (Respiratory Rate):20 /min, Temp:36.9 °C, and SpO_2 of 97%. The patient appeared drowsy, with Glasgow coma scale of 13/15, neck was soft Brudzinski and Kerning signs were absent . There was notable tender hepatomegaly, no splenomegaly, no murmurs and the chest was clear on

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auscultation. The patient was resuscitated with intravenous fluids and shifted to the ICU. Table 1 shows the laboratory parameters on admission

Microscopic examination of blood smear revealed P. *falciparum* parasitemia of 35%, urine dipstick revealed presence of urine bilirubin , leukocytes, hemoglobin (confirmed with urine microscopy) and proteins. Arterial blood gas revealed state compensated Metabolic Acidosis which was measured at intervals to determine correction of Acidosis and Metabolic derangement. Blood culture was done as a percentage of patients have been shown to present with concurrent gram-negative Septicemia or Meningitis. Ultrasound of the abdomen revealed minimal ascites, edematous gall bladder wall and sludge in the gall bladder. CT scan of the head showed brain edema necessitating I.V. Mannitol therapy.

The patient was diagnosed with Severe Malaria and was managed with I.V. Artesunate, I.V. Meropenem (considering renal dosage adjustment) was initiated for an initial broad-spectrum prophylaxis, and I.V. fluids Dextrose in Normal Saline. Meropenem was added as a prophylaxis to prevent gram negative Septicemia commonly seen in Severe Malaria and due to elevated procalcitonin and CRP levels. At 12 hours of admission, oliguria was noted with generalized edema. Fluid input by this time was 2000ml against an output of 150ml. Renal consult was obtained, and a diagnosis of AKI stage 3 was made. A femoral dialysis catheter was inserted, and dialysis subsequently started. 24 hours after initiation of treatment the patient developed cola colored urine and worsening hemoglobin of 5.7g/dl, there was a slight improvement in Platelets to 24000/µL and a BUN (Blood Urea Nitrogen) of 25.72mmol/L. Indirect Coombs test turned out to be negative. The patient received continued management with Artesunate, transfusion of packed red blood cells on days 2 and 3 of admission and daily dialysis. Parasitemia cleared by 48 hours after initiation of I.V. Artesunate. On day 6 of admission patient was noted to develop a low-grade fever with a recorded temperature of 37.8 degree centigrade. A repeat blood smear showed a P. *falciparum* parasite load of 0.1%, management was switched to oral Artemether and Lumefantrine (Coartem) tablets. Metronidazole and Ceftazidime were added as prophylactic agents against gram negative Septicemia (blood cultures yielded no growth on day 2 and on subsequent days), WBC was 12.83 × 10^9/L. The patient developed femoral vein thrombophlebitis confirmed by Doppler ultrasound . Low molecular weight heparin (LMWH) considering renal dose adjustment was initiated and subsequently switched over to warfarin. Serum Creatinine had peaked to a maximum on 528.55 µmol/L on day 7 of admission but the BUN continued to decline and was 17.83 mmol/L. Dialysis was continued, liver and renal functions had normalized by day 10 with an input of 1250 ml against an output of 850 ml and the dialysis catheter was removed. Patient condition and laboratory parameters had improved by day 13 and the patient was discharged on oral Proguanil and Warfarin.

Table 1: Showing Lab parameters on admission.

Lab Parameter	Observed Value	Reference Range
Hemoglobin (Hb)	7.7gm/dl	11 - 13 gm/dL
Red bold cell count	2.99 million/mm^3	4.0 - 5.5 million/ mm^3
hematocrit	21.6%	41 - 50%
Red blood cell distribution width	18.7	12.2 - 16.1
Platelet (PLT)	17000/µL	150000 - 450000/µL
White blood cell count (WBC)	14.49 × 10^9/L	4.5 - 11.0 × 10^9/L
Differential Count: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	 55.3% 37.5% 6.3% 0.2% 0.7%	 25 - 60% 25 - 45% 1 - 6% 1 - 5% 0 - 2%
Procalcitonin	22.9 ng/ml	0 - 0.05 ng/ml
C Reactive Protein (CRP)	249.84 mg/L	0 - 5 mg/L
Prothrombin Time (PT)	15.20 seconds	11 - 13.5 seconds
International Normalization Ratio (INR)	1.31	0.8 - 1.1
Activated Partial Thromboplastin Time (APTT)	36.50 seconds	35 - 40 seconds
Total bilirubin	471.43 µmol/L	1.71 - 20.5 µmol/L
Direct Bilirubin	409.49 µmol/L	< 5.1 µmol/L
Indirect Bilirubin	37.64µmol/L	3.4 - 12 µmol/L
Aspartate Amino Transferase (AST)	117.72 U/L	5 - 40 U/L
Alanine Amino Transferase (ALT)	22.3 U/L	7-55 U/L
Serum Albumin	23.56 g/L	38 - 54 g/L
Blood Urea Nitrogen (BUN)	33.35mmol/L	2.5 - 7.1 mmol/L
Serum Creatinine	270 µmol/L	61.9 - 114.9 µmol/L
Serum Sodium (Na+)	127.34 mmol/L	136 - 145 mmol/L
Serum Potassium (K+)	4.96 mmol/L	3.4 - 4.7 mmol/L

One week follow up of the patient revealed a normal complete blood count, UECs (Urea, Electrolytes and Creatinine), INR (International Normalization Ratio) and a negative blood smear for Malaria. He had gained 2 kilograms since discharge from the hospital and was in fair general condition. Subsequent reviews were for INR monitoring and dose adjustment for Warfarin. Proguanil was continued for one-month post discharge. Due to the severity of presentation and nature of the disease process and possible publication potential, pictographic evidence was kept regarding the progress of the patient during the hospital stay. Figure 1 below shows the patients jaundice on the day of admission, Figure 2 shows improvement in the jaundice one week after admission and Figure 3 shows black debris in the urinary catheter tube suggesting hemolysis.

A verbal consent was taken from the patient for publication of this case report and accompanying images. However, due to the age of the patient a written informed consent was obtained from the patient's stepmother and legal guardian.

Discussion

Malaria is diagnosed by demonstrating the parasite in blood either using a QBC (Quantitative Buffy Coat) test or microscopy of the blood sample. Diagnosis of malaria in our case was made by direct demonstration of parasites in blood under microscopy both thick and thin smear were used as recommended by the Kenyan Ministry of Health.

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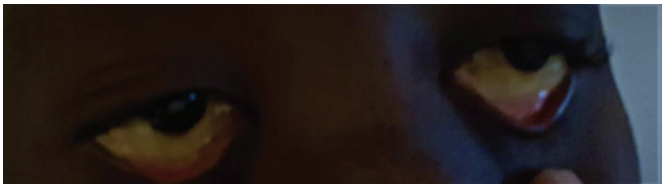

Figure 1: Deep scleral jaundice on the day of admission.

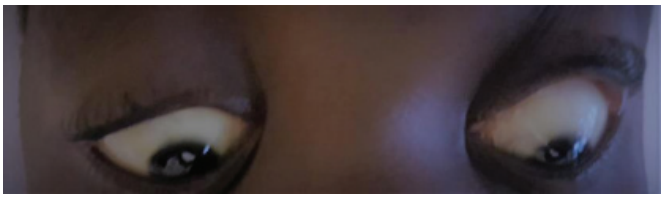

Figure 2: Improvement in jaundice on day 7 of admission.

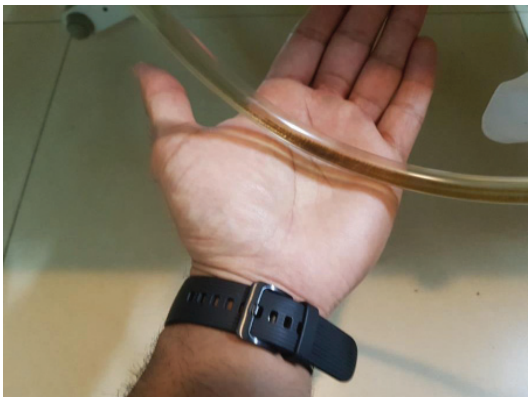

Figure 3: Black debris in the urinary catheter tube signifying hemolysis.

Due to the non-specific symptoms of malaria such as chills, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, and myalgia, it still tends to go undiagnosed in many parts of the world. Malaria remains a common public health issue especially in sub-Saharan Africa. laboratory investigations may show a picture of hemolytic anemia, elevated bilirubin, and thrombocytopenia. According to the CDC (Centers for Disease Control and Prevention) Severe Malaria occurs when infection is complicated by serious organ failures or abnormalities in the patient's blood or metabolism . Our Patient had the following criteria of Severe Malaria:

- Severe anemia due to hemolysis: Hb 5.7g/dl
- Hemoglobinuria due to hemolysis
- Abnormalities in blood coagulation: PT-15.2 seconds, INR-1.31, Platelets-17000/µL
- Low blood pressure caused by cardiovascular collapse: BP 98/51mmHg, PR:133bpm
- Acute kidney injury: serum creatinine of 528.55 µmol/L, BUN of 33.35 mmol/l
- Hyper-parasitemia: *P. falciparum* parasitemia 35%
- Metabolic acidosis.

The rarity of this case is in several aspects, firstly blackwater fever in itself is a rare occurrence in the modern-day era [1], with most cases being reported in sub-Saharan Africa [2], secondly a majority of the documented cases occur following administration of Quinine salts [3,4]. Although there are documented cases of blackwater fever occurring with Artemisinin combinations like Mefloquine-Artesunate combination and Artemether-Lumefantrine combination [4,5], there is only very few reported cases of blackwater fever following Artesunate monotherapy [6]. Thirdly AKI and jaundice although reported in adults are rare in children with Malaria [7,8].

Blackwater fever has been documented in 2 main groups of people it occurs in either non-immune immigrants or indigenous population in endemic areas [9], the latter being more likely in our case. However, there was clear history of only one previous episode of Malaria and other episodes may have been asymptomatic or the parasite load may have never cleared from the first attack. There have been documented cases of blackwater fever in children in endemic regions of Congo, but their blood parasite load was very low as compared to our case which had a high level [9]. A negative indirect coombs test ruled out other autoimmune causes of hemolytic anemia in our case. Although G6PD deficiency could lead to a similar picture in uncomplicated Malaria It is not ideal to test for G6PD deficiency during ongoing hemolysis or after blood transfusions, there was also no family history of G6PD deficiency.

The pathogenesis of AKI in Malaria is still not clearly understood. Blockage of renal microcirculation due to sequestration of infected erythrocytes, immune-mediated glomerular injury and volume depletion are some of the proposed hypotheses. The main histopathological finding in Malaria-associated AKI is ATN (Acute Tubular Necrosis) with reports of Interstitial Nephritis and Glomerulonephritis [10].

Contrary to popular belief of hemolysis and hepatocyte apoptosis causing Jaundice and hepatic injury, the primary pathology in the liver seems to be due to apoptosis of Kupffer cells and portal tract lymphocytes is a significant finding and is related to NF-κB activation [11]. The resulting effect is more of an Obstructive Jaundice evident in our case by an elevated direct bilirubin compared to indirect bilirubin and the abdominal ultrasound findings.

The mainstay of treatment of *P.falciparum* malaria remains Artemisinin, however Artemisinin mono therapy has been shown to have relapses due to the temporary arrest of the growth of ring-stage parasite after exposure and could have been the reason for the recurrence of parasitemia on day 6 of admission in our case. Despite the agent used to treat Malaria, blackwater fever must be considered for patients under antimalarial treatment who present with jaundice, abdominal pain, and AKI with hemoglobinuria. Rapid diagnosis, continued antimalarial treatment, blood transfusions and dialysis in an intensive care setup remain the mainstay of management for improving the patient prognosis.

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Conclusion

Blackwater fever although rare has traditionally been reported with the use of Quinine salts however must be considered in patients who present with jaundice, abdominal pain and acute renal insufficiency regardless of the treatment regimen. A prompt diagnosis and management are necessary to avoid the high mortality rate of between 25% and 50%. AKI must be rapidly corrected with supportive measures like dialysis to prevent high mortality. Blood transfusion remains a key factor in managing patients with acute hemolysis. Once adequately managed the recovery is usually prompt with jaundice resolving rapidly over 72-48 hours. It is important to draw blood cultures as there are normally concurrent gram-negative Septicemia and or Meningitis in many cases with Severe Malaria especially in the pediatric age group.

Authors' contributions

This work was carried out in collaboration among both authors. Author HG managed the child, wrote the first draft of the manuscript and managed the literature searches. Authors WO wrote the first draft of the manuscript and managed the literature searches. Both authors read and approved the final manuscript.

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