Black Water Fever Complicated by Acute Kidney Injury: A Case Report

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Black water fever, also called malarial haemoglobinuria occurs exclusively with Plasmodium falciparum infection and is characterized by intravascular haemolysis with severe anaemia and intermittent passage of black coloured urine. It frequently leads to acute kidney injury (AKI) with increased morbidity and mortality. Although Sri Lanka has achieved remarkable success in eliminating malaria since 2016, still Sri Lanka gets malarial cases via overseas visitors from African countries and India. Here we report a case of black water fever complicated by AKI with a brief account of its pathophysiology.

Keywords: Black water fever, hemoglobinuria, acute kidney injury

Introduction

Malaria is protozoal parasitic disease caused by the plasmodium species. Among five plasmodium species, plasmodium falciparum is the deadliest malaria parasite in the world and the most prevalent parasite in the African region. Black water fever is a rare severe form of malarial infection solely associated with plasmodium falciparum and is characterized by triad of severe intravascular haemolysis, severe anaemia and intermittent passage of black colored urine. It frequently leads to significant multi organ dysfunction including acute kidney injury. The pathogenesis of acute kidney injury is not clearly explained, but proposed mechanisms of Acute Tubular Necrosis (ATN) in malaria include immune and inflammatory response to parasites, impaired renal perfusion and production of excessive amount of reactive oxygen species.

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Case history

A 50-year-old previously healthy gentleman from South Sudan was admitted to the high dependency unit (HDU) with a history of fever with chills and rigors for four days and black-colored urine for one day. On admission to HDU, his temperature was 39.8^{0}C, severely dehydrated and icteric. His pulse rate was 128/min and low in volume. His capillary refilling was more than 2 seconds and the peripheries were cold. His blood pressure was 90/60 mmHg. Respiratory rate was 28/min and oxygen saturation were 93% on room air and 96% with 2 liters of oxygen. There was tender hepatomegaly. Following catheterization 50 ml of black colored cloudy urine was removed which was for the last 06 hours (figure 1).

Laboratory results are as follows (Table 1): A peripheral blood smear examination revealed a significant number (1-10 parasites per single thick film field) of plasmodium falciparum parasites (figure 2). Urinalysis revealed the presence of a significant amount (+++) of proteins. His serum creatinine was 3.2 mg/dl and electrolytes were within normal range. Full blood count showed

hemoglobin 9.8 g/dl, white cell counts of 3100/mm^3 with 68% neutrophils and platelet of 55000/mm^3. Hepatic profile derangement was present with an AST level of 428 IU/l, ALT of 60 IU/l, total bilirubin of 3 mg/dl and albumin of 3.4 g/dl. C-reactive protein was 48 mg/dl. Lactate dehydrogenase was 1610 IU/l. His serology tests for hepatitis A, B, C and dengue NS1 antigen were negative. His ABG showed, pH 7.25, pCO_2 27 mmHg, pO_2 100 mmHg, BE – 9 mmol/l, HCO_3 15.7 mmol/l.

Intravenous Ringer's lactate boluses were given as his IVC was collapsing ultrasonically. Patient was resuscitated with 4000 ml within 4 hours followed up by 150 ml /hr. He remained anuric even though he was hemodynamically stable. After an IV 10mg of frusemide, patient started producing urine of 50ml and 100ml in 1st and 2nd hour respectively. IV frusemide infusion of 5mg/hour started and titrated to maintain urine output more than 100ml/hour. As urine output improved, frusemide infusion gradually tailed off and was discontinued on 4th day. His serum creatinine gradually increased, reaching a peak of 5.2 mg/dl on day 08 of the illness and started to decline thereafter. His peripheral blood smear was completely cleared of parasites by day 09.

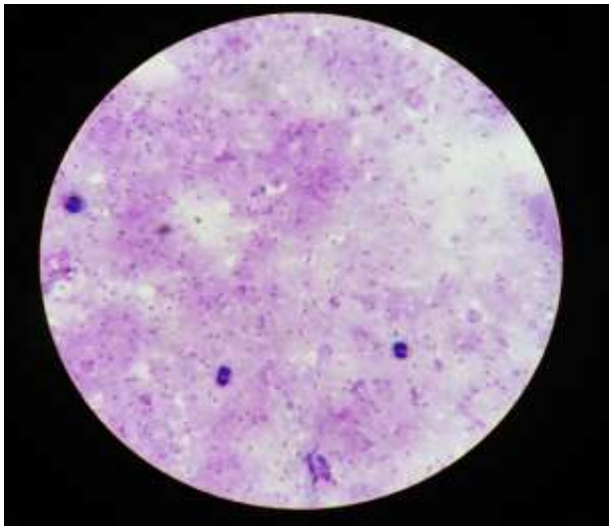
He was managed with IV artesunate followed by oral artemether and oral primaquine for 14 days. In addition, he was given all other supportive care throughout his hospital stay. He was referred to a nephrologist as his creatinine remained high.

***Table 1**: Laboratory results*

	Day 5 of illness	Day 6 of illness	Day 7 of illness	Day 8 of illness	Day 9 of illness
Blood Urea(mg/dl)	76	76	78	81	82
S. Creatinine(mg/dl)	3.2	4	4.6	5.2	4.9
S. Sodium(mmol/l)	134	138	139	138	138
S. Pottasium(mmol/l)	3.8	3.9	3.9	3.7	3.7
WBC (/ mm^3)	3100	4000	4700	5000	5000
Neutrophils (%)	68	70	70	73	66
Lymphocytes (%)	27	28	27	24	30
Eosinophils (%)	02	01	01	02	02
Haemoglobin (g/dl)	9.8	9.5	10.2	10.4	10.2
Platelets (/mm^3)	55000	70000	94000	1190000	129000
Total bilirubin (mg/dl)	3.0	3.2	3.3	2.9	2.9
Indirect (mg/dl)	2.3	2.3	2.5	2.0	2.0
Direct (mg/dl)	0.7	0.9	0.8	0.9	0.9
ALT (IU/l)	60	64	68	72	85
AST (IU/l)	428	390	398	411	402
LDH (IU/l)	1610	1524	984		
CRP (mg/l)	48	48	32	24	18
Parasites in blood film	+++	+++	++	++	Not seen

Image 1*: Urine samples from the patients on admission (left), 4 days later (right)*

Image 2: *large number of ring stages in a blood film*



Discussion

Acute kidney injury in falciparum malaria is multifactorial. Exaggerated immune response is known to be a detrimental factor in the pathogenesis of acute kidney injury in severe malaria.[1] Both infected and non-infected red blood cells release host and parasite related molecules called damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) respectively.[2] Once released, these molecules induce the secretion of proinflammatory cytokines (IL-1, IL-6, TNF) and activation of endothelium. Thus, activated endothelium facilitates sequestration of falciparum infected red blood cells and infiltration of leukocytes into the renal parenchyma contributing to inflammatory reaction. Activation of alternative compliment pathway by contents released from red blood cells further aggravate tubular injury.[3,4]

Reduction of local blood flow to the kidney is considered to be a major contributing factor in malarial acute kidney injury. Reduced fluid intake, increased loss by pyrexial sweating and vomiting contribute to renal hypoperfusion.[5] Moreover, generalized vasodilation and fluid leakage through endothelium in severe disease further contribute to renal hypoperfusion. Hypovolaemia induced activation of angiotensin 2 -angiotensin receptor complex stimulates inflammatory mediator release from endothelium which also contributes to renal damage.[5]

Obstruction in renal microvasculature results in renal hypoperfusion. In severe malaria, non-infected and infected red blood cells form red cell clumps called “rosettes” within the blood vessels and obstruct blood flow, leading to tissue hypoxia and endothelial dysfunction.[3] These aid extensive sequestration of parasites into the renal parenchyma and consequently elicit strong local inflammatory reaction leading to exacerbation of renal injury.[3] Released free haeme activates neutrophils to release neutrophil extracellular traps (NETs) which are web like structures of chromatin and antimicrobial peptides. NETs promote thrombi formation and propagation within the vasculature leading to obstruction to blood flow.

There are different sources of oxidative stress seen during blood stage of malaria. They are either from direct results of infection of red blood cells, like haeme, or from indirect results of host response to parasite, which comprise phagocytic oxidative burst in macrophage and upregulation of oxidative enzymes, like xanthine oxidase, in host. Excessive amount of reactive oxygen species promotes

inflammation in severe malaria through release of pro inflammatory cytokines from activated macrophages.[3] Kidneys are most vulnerable to become damaged by these overwhelming reactive oxygen species, as those molecules are cleared through kidneys when the scavenging system is saturated.[3]

Management of Malarial AKI

Mainstay of management of AKI includes antimalarial drug therapy, volume replacement, maintain adequate renal perfusion pressure and renal replacement therapy.

Maintenance of adequate renal blood flow and perfusion pressure prevent further deterioration of renal function. Fluid adequacy should be assed carefully while administering fluid, as excessive amount may lead to deleterious effects like pulmonary oedema and cerebral oedema. Vasopressors need to be added, if perfusion pressure is not adequate.

Oliguric renal failure is a poor prognostic sign. Frusemide is often used to improve urine output in this patient category. Although this may produce some urine output, there is no evidence that frusemide improves renal functions and mortality.[6] However, use of loop diuretics is associated with shorter duration of haemodialysis.[7] Moreover, frusemide is useful in volume overloaded patients in the absence of haemofiltration facilities especially in low resource setting. Early dialysis is indicated to counteract hypercatabolic state. Either peritoneal or haemodialysis have been successfully used, while continuous haemodialysis showed significant lower mortality compared to peritoneal dialysis (15% Vs 47%).[8] The rate of resolution of renal functions with haemodialysis is twice faster than that with peritoneal dialysis.

In this case, ultrasound guided meticulous fluid therapy and treatment with frusemide in correct time prevented him going into oliguric renal failure, although it did not apparently improve his renal functions.

Conclusion

Acute kidney injury is commonly seen in plasmodium falciparum infection. The precise mechanism of AKI is not known. However, several hypotheses including Immune and inflammatory response to the parasite, Hypovolaemia and hypovolaemia-related inflammation, obstruction of renal blood flow and Oxidative stress have been proposed. The mainstay of management of malarial AKI includes antimalarial drug therapy, volume replacement, maintenance of adequate renal perfusion pressure and renal replacement therapy, if indicated.

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