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(CASE REPORT)

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Malaria acute kidney injury: Case report from Tumbi regional referral hospital in Pwani, Tanzania

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Abstract

Malaria is a most significant parasitic disease worldwide. The overall burden of malaria infection in Tanzania has been decreasing over the past 10 years. On the other hand, there is an observation of an increase in severe forms of malaria, notably malaria-associated kidney injury, across hospitals in Tanzania. We are reporting two cases of severe malaria-associated acute kidney injury admitted at Tumbi Regional Referral Hospital in Eastern Tanzania. The patients were young adults who live in an area with a moderately high malaria transmission rate in the country. Patients recovered well after various inpatient interventions. The cases highlight not only an increasing number of severe malaria cases associated with acute kidney injury but also the challenges of managing malaria in a low-income endemic setting and the potential treatment failure of artemisinin-based compounds. The cases underscore the importance of early presentation to health facilities, early detection of severe malaria patients, and timely interventions, including hemodialysis, which are crucial in improving the prognosis of severe malaria patients.

Keywords: Acute kidney injury; Malaria; Hemodialysis; Artemisinin

1. Introduction

Malaria remains a significant cause of morbidity and mortality in sub-Saharan Africa. The disease is caused by an infection with a parasite of the genus Plasmodium (1). The clinical features are mainly non-specific and include general body malaise, vomiting, fever, chills, loss of appetite, headache, convulsions, impaired consciousness, jaundice, pallor, bleeding tendency, and changes in behaviour. (2).

Acute kidney injury is one of the most dreaded complications of malaria. It is defined as a sudden deterioration in kidney function, evidenced by a reduction in urine output to less than 0.5 ml per kilogram per hour for more than 6 consecutive hours, an increase in serum creatinine by more than 26.5 mmol/L in 48 hours, or an increase in baseline creatinine by fifty percent above the baseline value in seven days (3). In malaria infection, acute kidney injury is hypothesized to occur due to several pathophysiological mechanisms, including mechanical blockade of renal microvasculature caused by sequestration and agglutination of parasitized red blood cells, hypovolemia related to malaria infection, and toxic effects of parasite pigments and free heme molecules on the glomeruli (4).

Tanzania is among the top ten countries with the highest number of malaria cases worldwide, accounting for 3.1% of cases globally (5). Overall, the malaria burden in the country has been decreasing, with reports indicating a decrease from 18.1% in 2008 to 7% in 2017. The burden of malaria varies in different geographical locations within the country, in the eastern part of the country it ranges from 5 to 30%, which is classified as a moderate malaria risk strata (1). It is estimated that around 2% to 39% of individuals suffering from severe malaria end up being admitted with acute kidney injury in Tanzania (6).

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2. Case Presentation

The first case involved a 33-year-old male who experienced a sudden onset of high-grade fever, non-projectile vomiting containing mainly recently consumed food material, and general malaise. He was initially diagnosed with uncomplicated malaria at a nearby primary health facility and commenced on oral artemisinin-based combination therapy following Tanzanian national guidelines. The following day, he exhibited confusion and reduced urine output, prompting his referral to our facility.

Upon admission to our facility, he was fully conscious but extremely weak, pale, and febrile, with a temperature of 38.5°C, and no edema in the lower limbs. Blood pressure was 100/60 mmHg, pulse rate was 90 beats per minute, respiratory rate was 16 breaths per minute, and oxygen saturation was 97% on room air.

Initial investigations at our facility revealed a positive rapid test for malaria, with a blood slide showing 720 malaria parasites per microliter of blood. Other investigations revealed severe microcytic hypochromic anemia with hemoglobin of 7 g/dL (reference range 13-18 g/dL), severe thrombocytopenia of 41 x 10^3 cells per microliter (reference range 150-450 x 10^3/µL), elevated serum creatinine of 209 µmol/L (reference range 61.9 to 114.9 µmol/L), and blood urea nitrogen level of 19.2 mmol/L (reference range 2.1 to 8.5 mmol/L). Serum sodium, potassium, and chloride levels were within normal ranges.

He was started on intravenous artesunate 170 mg at 0, 12, and 24 hours, followed by doses every 24 hours for 3 days. Additionally, he received intravenous fluid (0.9% sodium chloride) at a rate of 140 mL per hour in the first 6 hours. Despite these interventions, his urine output did not increase, and he began experiencing desaturation. His oxygen saturation dropped to 85% on room air, and he developed tachypnea and bilateral coarse crackles. Even after receiving a high dose of furosemide and oxygen therapy via a non-rebreather face mask, his oxygen saturation levels continued to fluctuate. Subsequently, he was placed on continuous positive airway pressure (CPAP). His serum creatinine level surged to 789 µmol. At this stage, he commenced intermittent hemodialysis sessions lasting 4 hours each, three times a week. Pulmonary edema resolved shortly after initiating dialysis, and a follow-up blood smear after 48 hours revealed no malaria parasites. He regained normal urine output after seven hemodialysis sessions. He was transferred to the general medical ward and discharged after one week.

After three months of follow-up at the clinic, he was discharged with normal renal function, but he still had mild anemia with a hemoglobin level of 11.5 g/dL. His last serum creatinine and blood urea nitrogen levels were 60µmol/L and 5mmol/L, respectively.

The second case involved a 25-year-old male who was a self-referral to our facility. He had a five-day history of fever, reduced appetite, passing loose stools, and black-colored urine. The day before admission, he developed confusion and was brought to our facility.

Upon arrival at our facility, he was confused with a Glasgow Coma Scale score of 14. He was dehydrated and afebrile, with a temperature of 36.9°C. His blood pressure was 110/69 mmHg, and his pulse and respiratory rate were 90 beats per minute and 14 breaths per minute, respectively. Upon admission, he was oliguric, with urine resembling Coca-Cola.

Initial investigations revealed a positive rapid malaria test with 3880 malaria parasites per µL of blood, moderate microcytic hypochromic anemia of 8.8g/dL, and thrombocytopenia of 90 x 10^3 cells per microliter of blood. His serum creatinine at the time of admission was 195 µmol/L; however, baseline serum creatinine and urea levels were not known. Serum sodium, potassium, and chloride levels were within normal ranges. The patient was also tested for HIV, Hepatitis B, and Hepatitis C, and all results were negative. Protein, glucose, and red blood cells were not detected in the urinalysis.

He was initiated on intravenous 0.9% normal saline over the first 6 hours of ICU admission at a rate of 150ml/hour and later maintained at 100ml/hour while monitoring blood pressure, urine output, and level of consciousness. Additionally, he was started on intravenous Artesunate 140mg at 0, 12, 24 hours, and then every 24 hours for 3 days. His urine output increased to more than 3ml/kg/hr in the first 24 hours, and his serum creatinine dropped to 150 µmol/L on the second day. By the second day, he was oriented to time, place, and people. He was transferred from the ICU after 5 days to the general medical ward and later discharged through the medical clinic.

Two months later, he attended a follow-up clinic and had a normal renal profile; he did not show up for the next clinic visit (3 months since discharge).

3. Discussion

The two reported cases highlight the clinical observation of an increasing number of patients with malaria-associated acute kidney injury and the challenges that healthcare workers in limited resource settings face daily in managing these patients. For so long, cerebral malaria has been the predominant presentation of the most severe forms of malaria in many malaria-endemic regions (4) However, studies conducted in Vietnam and Thailand have reported a changing pattern of predominance from cerebral malaria to malaria-associated acute kidney injury and jaundice over the past three decades (7). With the increasing numbers of acute kidney injuries related to malaria in our region, could this be an indication of a changing pattern in Eastern Africa? The puzzle remains unanswered.

Above reported cases represent a minority of severe forms of malaria patients. The burden of malaria-related complications is still very high. Studies conducted in Dar es Salaam reported a prevalence of acute kidney injury among malaria patients ranging from 8% to 26%. Moreover, nearly a quarter of malaria patients have severe anemia, and a significant proportion have cerebral malaria, pulmonary edema, respiratory distress, and hypoglycaemia (8,9).

Low baseline hemoglobin levels, thrombocytopenia, and male gender are among the factors associated with acute kidney injury in several studies conducted in different regions (6,9). The two cases presented reflect these findings, as both patients were male and had anaemia and thrombocytopenia. Early recognition of these risk factors among patients with malaria is crucial for identifying individuals at risk of developing more severe complications.

Early interventions have been shown to improve the overall outcomes of malaria patients. Efforts on health education about malaria need to be emphasized to the community to highlight the benefits of early presentation to hospital facilities. One of the two cases presented late to the health facility, five days after the onset of symptoms. Therefore, members of the community as well as clinicians need to emphasize on early presentation to health facilities as it is crucial in addressing the impact of malaria.

Hyperparasitaemia, defined as having 200,000 malaria parasites per microliter of blood (1) has been proposed as a significant risk factor in patients who develop acute kidney injury. This is theorized to be due to more intense immunological interactions between the host and the parasite (4,10). In spite of this, the association between malaria parasite burden and the development of acute kidney injury is not a direct one. For example, in the cases we have reported none had hyperparasitaemia, though they ended up with acute kidney injury. This may partly be explained by the fact that in some individuals, a low peripheral parasite count may not reflect the actual parasite burden as some parasitized erythrocytes are sequestrated in the microvasculature, especially the asexual forms of the parasite(7), Whether malaria patients have a true low parasite count or an apparent low parasite count due to sequestration cannot be precisely concluded in a routine clinical setting. Therefore, clinicians need to be aware that close follow-up is warranted for any level of parasitaemia, regardless of the peripheral parasite count.

Fluid management remains a challenge in severe malaria patients. Studies support more restricted fluid therapy in hypovolemic patients with severe malaria without shock, unlike patients with hypovolemia-related bacterial sepsis (11). The difference is attributed to underlying pathophysiological mechanisms. Severe malaria is characterized by cytoadherence of infected erythrocytes to microvasculature, whereas bacterial sepsis is characterized by a predominant release of pro-inflammatory cytokines. Attaining optimal fluid therapy in adults with severe malaria is challenging, as noted by the World Health Organization in the 2023 malaria guideline: "there is a very thin dividing line between over-hydration, which may lead to pulmonary oedema, and under-hydration, which contributes to shock, worsening acidosis, and renal impairment" (p. 191)(12). One of the reported cases developed signs of acute pulmonary oedema despite receiving restrictive fluid therapy, which required mechanical ventilation, albeit non-invasive one. Close monitoring of respiratory rate is essential as it is among the earliest signs of impending pulmonary oedema in patients with severe malaria (7).

The availability of dialysis services in regional hospitals in Tanzania is a significant milestone in patient management. However, patients still face a dilemma regarding the high cost of care, as the cost of this service is very high. Due to the endemic nature of malaria in our region, the number of patients in need of dialysis services may increase. We believe that expediting the introduction of universal health insurance is necessary to address these financial challenges.

Resistance to artemisinin therapy, used to treat malaria, has already been documented in some parts of Southeast Asia and West Africa (13) Given the observed increase in the prevalence of severe malaria cases, we suggest routine phenotypic and genotypic surveillance at all referral levels of care to detect antimalarial drug resistance early and implement appropriate measures. Equally important is the need to address factors associated with drug resistance, such as patient adherence to antimalarial drugs and the removal of all artemisinin monotherapies from our drug outlets.

Triple artemisinin-based combination therapy (TACT) has been proposed as a strategy to mitigate the development of resistance. Several partner drugs have been suggested, and doxycycline is one of them. Doxycycline, a tetracycline antibiotic, is a slow-acting schizonticidal drug that is currently utilized for malaria prophylaxis in non-immune adults. (1) We recommend addition of doxycycline in the management of malaria as malaria parasite resistance to doxycycline has rarely been documented (14,15), Additionally, its use may confer additional benefits as an adjunctive therapy in the management of severe malaria, which has been shown to be effective in some reports (15).

Naturally acquired immunity has been proven to be effective in preventing severe forms of malaria. This immunity develops after repeated exposure to malaria infection. There has been a decline in the incidence of malaria cases in Tanzania, as indicated by local surveillance data from supplementary malaria strategic plan reports, (1). Consequently this naturally acquired immunity may be waning, a trend that could lead to an increase in the number of severe malaria in malaria-endemic areas, this may be one of the explanations behind increasing number of severe malaria cases in our setup (16).

4. Conclusion

Malaria associated kidney injuries are on the rise and challenges related to patients' management are multifactorial, ranging from medical challenges such as fluid therapy and access to advanced interventional measures like hemodialysis and mechanical ventilation, to socio-economic challenges such as the cost of care. With the rising number of malaria-related complications, more efforts should be directed towards malaria prevention using existing and novel techniques to mitigate the devastating consequences of malaria.

Compliance with ethical standards

Acknowledgment

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Disclosure of conflict of interest

The authors declare that there are no competing interests in this work. No funding was provided by any financial or academic institution for this case report. No conflict of interest to be disclosed.

Statement of informed consent

The ethical clearance for our study was sought and a written informed consent was obtained from the two patients for case reporting and anonymous publication. Confidentiality was guaranteed.

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