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Case Reporte

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Hemoglobinuria and acute kidney injury in severe malaria: Case reports from Borgou/Alibori Teaching Hospital, Benin

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Abstract. *The hemoglobinuric form of severe malaria can precipitate acute kidney injury (AKI) and potential multiorgan failure. This report discusses two cases of fatal AKI due to severe malaria, treated in 2024 at the Borgou-Alibori Departmental Teaching Hospital in Benin. It examines the pathophysiology, clinical symptoms, and treatments used, providing detailed insights into the progression of the disease and the therapeutic interventions attempted. Key takeaways highlight the importance of early, multidisciplinary care in improving outcomes, with hemodialysis playing a critical role in managing AKI caused by hemoglobinuria.*

Keywords: *acute kidney injury, hemoglobinuria, severe malaria, Benin.*

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Гемоглобінурія та гостре пошкодження нирок у пацієнтів з тяжкою малярією: клінічні випадки з університетської лікарні Боргу/Аліборі, Бенін

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Резюме. *Гемоглобінурічна форма важкої малярії може спровокувати гостре пошкодження нирок (ГПН) з можливою поліорганною недостатністю. У цій статті повідомляються два випадки летального ГПН, обумовлені важкою формою малярії у пацієнтів, які лікувались в університетській лікарні Боргу-Аліборі в Беніні у 2024 році. Стаття розглядає патофізіологію, клінічні симптоми та застосовані методи лікування, надаючи детальну інформацію про прогресування захворювання та спроби терапевтичного втручання. Ключові висновки підкреслюють важливість ранньої мультидисциплінарної допомоги для покращення результатів лікування та підкреслює вирішальну роль гемодіалізу в лікуванні ГПН, спричиненого гемоглобінурією.*

Ключові слова: *гостре пошкодження нирок, гемоглобінурія, малярія, Бенін.*

Introduction. The World Health Organization (WHO) has identified acute kidney injury (AKI) as a major criterion for assessing the severity of Plasmodium falciparum malaria [1]. The incidence of AKI in malaria cases varies: Esezobor [2] reported 11.4% in general pediatrics; Kunuanunua [3] found 42.8% in emergency departments; and Kaul [4] documented 2.5% in community settings.

AKI associated with severe malaria is primarily caused by acute tubular necrosis due to hemoglobinuria [2]. AKI refers to a sudden decline in kidney function, resulting in the accumulation of nitrogenous waste products [3]. Hemoglobinuria is most commonly seen in individuals who have experienced numerous infections with various Falciparum strains and several uncomplicated malaria episodes [4]. It results from massive intravascular hemolysis, overwhelming the haptoglobin and hemopexin systems that normally capture free hemoglobin [5]. Unfortunately, hemoglobinuria is often overlooked as a warning sign of severe malaria and potential renal damage, despite its strong association with AKI risk.

A WHO study on severe malaria in pediatric settings across ten African countries reported a 3.3% incidence of hemoglobinuria secondary to severe malaria [9]. Other studies have found similar rates: Verma et al. [10] in India reported 19.6%, Ajetunmobi et al. [11] in Ibadan, Nigeria, 19.1%, and Gbadoé et al. [12] in Togo, 17.2%.

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The clinical presentation of AKI secondary to hemoglobinuria is often atypical, which can delay timely management. Its progression may be insidious or fulminant, requiring specialized treatment. The prognosis for kidney function and patient survival often depends on rapid clinical control, a challenge in countries with limited economic resources.

This report presents two relevant clinical cases from our hospital in 2024, illustrating the clinical features, management, and outcomes of this potentially fatal complication, and offering insights for improved management. The macroscopic hemoglobinuria was identified by the characteristic dark "Coca-Cola" color of the urine, in the absence of any factors suggesting myoglobinuria or hematuria, aside from severe malaria.

Case reports. ***Observation 1.*** A 32-year-old male patient was referred for impaired kidney function, with a serum creatinine level of 142 mg/L, in the context of severe malaria. Symptoms began one week before admission, during which he experienced altered consciousness, convulsive seizures, and jaundice.

Upon admission, the clinical examination revealed the following: altered consciousness with a Glasgow Coma Scale score of 12, icteric bulbar mucous membranes, mucocutaneous pallor, and hyperthermia (40.1°C). The patient's oxygen saturation was 97% in ambient air, blood pressure was 130/78 mmHg, and he exhibited anuria, with a urine output of less than 100 mL in 24 hours (<0.3 mL/kg/24 h). Additionally, he presented with grade 1 hepatosplenomegaly. Urinalysis indicated hemoglobinuria (+++), a pH of 5, and a urine specific gravity of 1.025.

Further laboratory investigations showed:

- Biochemical results: Uremia at 2.56 g/L, creatinine at 227 mg/L, serum sodium at 134 mmol/L, potassium at 5.2 mmol/L, and chloride at 110 mmol/L.
- Complete blood count: Leukocyte count at 6.7 Giga/L, hemoglobin at 5.7 g/dL, mean corpuscular volume (MCV) at 83.4 fL, mean corpuscular hemoglobin concentration (MCHC) at 32.2 g/dL, and platelet count at 105 G/L.
- Liver function tests: Aspartate aminotransferase (AST) at 220 IU/L, alanine aminotransferase (ALT) at 160 IU/L, total bilirubin at 112 mg/L, direct bilirubin at 76 mg/L, and indirect bilirubin at 36 mg/L.
- Thick blood smear: Positive for Plasmodium falciparum, with a parasitic density of 9,550 parasitized red blood cells.
- Renal ultrasound: Revealed normal-sized kidneys with preserved cortico-medullary differentiation.

The diagnosis was established as severe malaria, presenting with neurological and hemoglobinuric manifestations, complicated by acute kidney injury.

The patient was admitted to the nephrology intensive care unit, where he received appropriate hydration and intravenous administration of an artemisinin derivative. Electrolyte intake was adjusted to 100 mL/kg/day. Due to the persistence of anuria and hyperkalemia (7.9 mmol/L), the patient underwent hemodialysis, receiving four sessions in total. He also received anticonvulsant treatment with diazepam and phenobarbital, along with two units of erythrocyte concentrates.

The patient's condition improved, marked by the onset of polyuria and resolution of clinical and biological abnormalities. He was discharged after a 12-day hospital stay.

Observation 2. A 26-year-old male patient was admitted following a referral from a peripheral health facility for acute kidney injury related to severe malaria and multiorgan failure, with a serum creatinine level of 346 mg/L. Symptoms had begun two weeks prior, characterized by intermittent diffuse myalgia and headaches, leading to self-medication without clinical improvement.

Upon admission, the clinical examination revealed an altered state of consciousness with a Glasgow Coma Scale score of 9, hyperthermia (38.7°C), mucocutaneous pallor, and icteric bulbar mucous membranes. His oxygen saturation was 92% in ambient air, and he presented with hypotension (blood pressure of 90/56 mmHg), mild lower limb edema, and anuria, with a urine output of approximately 80 mL in 24 hours (<0.3 mL/kg/24 h). Pulmonary examination showed dullness at both lung bases, crackling rales in both lung fields, and grade 2 hepatosplenomegaly. Urinalysis indicated hemoglobinuria (+++), a pH of 5, and a urine specific gravity of 1.030.

Laboratory findings included:

- Biochemistry: Uremia at 3.14 g/L, creatinine at 346 mg/L, serum sodium at 124 mmol/L, potassium at 6.5 mmol/L, and chloride at 112 mmol/L.
- Complete blood count: Hemoglobin level at 4.4 g/dL, mean corpuscular volume (MCV) at 78.2 fL, mean corpuscular hemoglobin concentration (MCHC) at 33.4 g/dL, leukocytes at 17.7 Giga/L, and platelets at 85 G/L.
- Liver function tests: Aspartate aminotransferase (AST) at 460 IU/L, alanine aminotransferase (ALT) at 380 IU/L, total bilirubin at 234 mg/L, direct bilirubin at 178 mg/L, and indirect bilirubin at 56 mg/L.
- Thick blood smear: Positive for Plasmodium falciparum, with a parasitic density of 20,550 parasitized red blood cells.
- Urinary sediment analysis: Revealed tubular cells, numerous bile pigment casts, and granular casts.
- Renal ultrasound: Showed normal-sized kidneys with good cortico-medullary differentiation and no dilation of the pyelocaliceal cavities.

The diagnosis was established as severe malaria in the hemoglobinuria form, complicated by visceral involvement affecting the renal, cerebral, cardiopulmonary, and hydro-electrolyte systems.

Therapeutically, the patient was admitted to the nephrology intensive care unit, where he received oxygen therapy at 5 L/min, intravenous administration of an artemisinin derivative, and antibiotic therapy with ceftriaxone and azithromycin. Additionally, injectable furosemide and calcium gluconate were administered, along with appropriate hydration two units of erythrocyte concentrates and one unit of platelet concentrates.

After 24 hours, with no clinical improvement in renal function and persistent hydro-electrolyte imbalances, the patient underwent hemodialysis, receiving three sessions. Unfortunately, the patient's condition deteriorated, and he passed away on the fourth day of hospitalization.

The clinical, paraclinical, therapeutic, and evolutionary characteristics are summarized in Tables 1, 2, and 3.

Table 1

Clinical characteristics of the patients with acute kidney injury secondary to severe malaria with hemoglobinuria

	Patient 1	Patient 2
Clinical data at admission		
Age (years)	32	26
Altered state of consciousness	Yes	Yes

Continuation of Table 1

	Patient 1	Patient 2
Glasgow score	12	09
Body temperature (°C)	40.1	38.7
Bulbar mucous membranes	Icteric	Icteric
Mucocutaneous pallor	Yes	Yes
Oxygen saturation in ambient air (%)	97	92
Blood pressure (mmHg)	130/78	90/56
Diuresis < 0.3ml/kg/24 h	Yes	Yes
Lower limb edema	Absent	Present
Pulmonary condensation syndrome	Absent	Here
Signs of heart failure	Absent	Present
Hepatosplenomegaly	Degree 1	Degree 2
Dipstick		
pH	5	5
Urinary density.	1.025	1,030
Hemoglobinuria	+++	+++

Table 2

Paraclinical characteristics of the patients with acute kidney injury secondary to severe malaria with hemoglobinuria

	Patient 1	Patient 2
Paraclinical data on admission		
Blood		
Uremia (g/l)	2.56	3.14
Serum creatinine (mg/L)	227	227
Complete blood count		
Hemoglobin level (g/dl)	5.7	4.4
VGM (fl)	83	78.2
CCMH (g/dl)	32.2	33.4
Leukocytes (Giga /L)	6.7	17.7
Platelets (g/l)	105	85
Tick drop	positive	positive
Plasmodium smear *falciparum*	Yes	Yes
Parasite density (parasitized red blood cells)		20550
Serum electrolytes		
Natremia (mmol /L)	134	124
Serum potassium (mmol /l)	5.2	6.5
Chloremia (mmol /l)	110	112
Transaminases (IU/L)		
ASAT	220	460
ALAT	160	380
Bilirubin (mg/L)		
Total	112	234
Direct	76	178
Indirect	36	56

Continuation of Table 2

		Patient 1	Patient 2
Urine	(Bullet)	Unrealized	
	Tubular cells	Not available	+++
	Cylinders	Not available	
	Granular	Not available	+++
	Bile pigments	Not available	+++
	Renal ultrasound		
	Change in kidney size	No	No
	Conservation of kidney structure	Yes	Yes

Table 3

Therapeutic and evolutionary characteristics of the patients with acute kidney injury secondary to severe malaria with hemoglobinuria

			Patient 1	Patient 2
Therapeutic and evolutionary data				
	Antimalarial			
		Artemisinin derivative	Yes	Yes
	Anticonvulsant			
		Diazepam	Yes	No
		Phenobarbital	Yes	No
	Antibiotics			
		Ceftriaxone	No	Yes
		Azithromycin	No	Yes
	Diuretic			
		Furosemide	No	Yes
	Hypokalemic			
		Calcium gluconate,	Yes	Yes
		Insulin	Yes	Yes
	Blood transfusion			
		RBC pellet	Yes	Yes
		Platelet concentrate	No	Yes
	Extrarenal purification			
		Hemodialysis	Yes	Yes
Therapeutic outcome				
	Length of stay (days)		12	04
	Healing / Death		Healing	Death

Discussion. This study highlights the significant kidney damage associated with hemoglobinuria in severe malaria, a condition often overlooked or mismanaged in clinical practice. Hemoglobinuria can lead to acute tubular necrosis (ATN), which is primarily caused by the obstruction of capillaries and post-capillary venules by parasitized red blood cells. This vascular obstruction occurs through two main mechanisms: cytoadherence and rosetting, both of which are particularly associated with Plasmodium falciparum infections [6, 7].

Hemoglobin itself is toxic to the renal tubules, contributing to ATN through mechanisms that, while not entirely understood, involve direct tubular toxicity and micro obstruction [8]. The clinical presentation of acute kidney injury (AKI) in this context can be variable and multifaceted, complicating diagnosis and treatment. In our cases, AKI manifested as oliguria and anuria a few days following the onset of febrile episodes [9-11].

Fluid and electrolyte imbalances are common in AKI associated with severe malaria, as observed in both of our patients who presented with hyponatremia and hyperkalemia. Such imbalances have been documented in the literature as frequent complications of severe malaria [10, 12]. The diagnosis of hemoglobinuria bilious fever was established based on the combination of fever, port-colored urine, jaundice, anemia, and oliguric AKI. This condition may arise from the dual sensitization of red blood cells to both Plasmodium falciparum and the aminoalcohols that induce hemolysis [13].

Delays in appropriate treatment often result from self-medication practices, wherein patients resort to anti-malarial drugs such as quinine, halofantrine, mefloquine, and artemether-lumefantrine without professional guidance. This can exacerbate the development of hemoglobinuria bilious fever and complicate malaria management [10, 14, 15]. As noted by Savadogo et al. [16], the emergence of chloroquine resistance has made quinine the drug of choice for severe malaria, leading to an increased incidence of hemoglobinuria.

In some instances, hemolytic uremic syndrome or thrombotic microangiopathy may occur, characterized by renal impairment, hemolytic anemia, and thrombocytopenia [13]. Additionally, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a recognized contributor to massive intravascular hemolysis and often overlaps geographically with malaria prevalence [17].

Multisystem failure can also be associated with sepsis. In severe sepsis cases, hemolysis may be triggered by the activation of endogenous phospholipase C and sphingomyelinase, resulting in the uncontrolled production of various mediators that damage platelets, erythrocytes, leukocytes, endothelial cells, and muscle cell membranes [18]. Hemolysis significantly elevates levels of transaminases, creatine phosphokinase, and lactate dehydrogenase due to the release of erythrocyte components into the plasma, thereby promoting acute tubular necrosis.

Timely and adequate treatment is crucial for improving outcomes in these patients. In our study, the majority received antimalarial therapy based on injectable artesunate or artemether, in line with current guidelines that prioritize injectable artesunate as the treatment of choice for severe malaria [19]. Early initiation of renal replacement therapy is also vital for improving prognosis [13].

Several factors contribute to poor patient outcomes, including late referrals at advanced disease stages and a lack of public awareness regarding the severity of symptoms associated with malaria [10]. To enhance patient care, more comprehensive investigations and resources are necessary, particularly for those from disadvantaged backgrounds who may face delays in accessing treatment.

Limitations. Our study's limitations include the unavailability of additional diagnostic tests in our hospitals, which could facilitate a more straightforward etiological diagnosis and help rule out other causes of hemoglobinuria in patients with severe malaria.

Conclusions. Hemoglobinuria should not be regarded as a benign indicator, particularly within the context of malaria. Its implication in the occurrence of necessitates heightened awareness and prompt intervention from both diagnostic and therapeutic perspectives.

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Data availability statement. The authors declare that the data pertaining to the writing of this article are available and can be accessed in the archives of the Haemodialysis Nephrology Department at the Departmental Teaching Hospital of Borgou, Benin.

Ethical and deontological considerations. This work was carried out in compliance with current ethical standards. The rules of anonymity and confidentiality were respected.

The authors' contributions.

Seraphin Ahoui: involved in patient management, wrote the first draft of the article, and conducted data analysis.

Nonvignon Eric Ayadji: involved in patient management and supervised the analysis of patient files.

Joseph Godonou: involved in patient management and conducted data analysis.

Sabrina Conchita Somakou: involved in patient management and analyzed patient files.

Aime Vinasse and Melikan Aubin: analyzed patient files and conducted data analysis.

Evariste Eteka and Nicanor Houeto: analyzed patient files.

Giovanna Zossoungbo: involved in patient management and supervised the analysis of patient files.

Jacques Vigan: involved in patient management and supervised the analysis of patient files, as well as conducting data analysis.

All co-authors contributed to the finalization of the article.

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