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Case Report

Managing Acute Kidney Injury in Severe *Falciparum* Malaria: Insights from a Challenging Case

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Abstract

Malaria continues to pose a significant public health challenge, particularly in certain regions of Indonesia, where it remains endemic. *Plasmodium falciparum* is responsible for the most severe form of the disease, often leading to life-threatening complications such as acute kidney injury (AKI). Here, we report the case of a 22-year-old male from Sikka Regency, East Nusa Tenggara, Indonesia, with a seven-day history of intermittent fever following recent travel to malaria-endemic areas. On physical examination, he appeared somnolent and exhibited icteric sclera, hepatomegaly, and dark yellow urine. Laboratory findings were notable for impaired kidney function (serum creatinine 3.52 mg/dL (311 µmol/L)), elevated transaminases, hyperbilirubinemia, thrombocytopenia, and a *P. falciparum* parasitemia level of 9.7%. Imaging studies revealed pulmonary edema, enlarged kidneys, ascites, pleural effusion, and hepatomegaly. The patient was diagnosed with severe falciparum malaria, complicated by AKI, pulmonary edema, and jaundice. He was then treated with intravenous artesunate for six days, followed by a three-day course of oral dihydroartemisinin/piperaquine and a single dose of primaquine. Additionally, he underwent two sessions of timely hemodialysis. His clinical condition and kidney function gradually improved thereafter, and he was discharged without sequelae. This case highlights that early diagnosis and appropriate treatment can lead to full recovery from AKI caused by severe *P. falciparum* malaria.

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Introduction

Malaria remains a major global health challenge, affecting 249 million people worldwide, with an estimated 698,000 deaths in 2022 (1). As one of nine malaria-endemic countries in Southeast Asia, Indonesia reported 443,530 confirmed cases in 2022, with the majority occurring in Papua and East Nusa Tenggara provinces. Sikka Regency, located in East Nusa Tenggara, is classified as a moderately endemic area, with an annual parasite incidence of 1–5 per 1,000 population (2). Malaria is an infectious disease caused by protozoan parasites of the *Plasmodium* genus (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*), transmitted in regions where the disease is endemic by female *Anopheles* mosquitoes (3).

Among *Plasmodium* species, *P. falciparum* infection is associated with an increased risk of developing severe malaria, with acute kidney injury (AKI) being one of the most dreaded complications. As AKI significantly contributes to the high morbidity and mortality in patients with severe *falciparum* malaria (SFM), early recognition and effective management are paramount (4). However, managing malarial AKI remains challenging due to the lack of specific guidelines to support clinical decision-making.

Herein, we report a case of complete resolution of AKI in SFM achieved through timely and multifaceted interventions.

Case Report

A previously healthy 22-year-old male presented to the local Emergency Department with a seven-day history of intermittent fever. In addition to the fever, he reported chills, sweats, fatigue, headache, nausea, anorexia, and abdominal pain. Over the past three days, he had developed diarrhea and noticed tea-colored urine. The patient resides in Sikka Regency, East Nusa Tenggara, Indonesia, and had traveled to Waiblama and Talibura Districts, areas within the regency known for high malaria incidence, two weeks before symptom onset.

Written informed consent was obtained. Ethical approval was not required per institutional guidelines.

On admission, the patient was somnolent. His vital signs were as follows: temperature 39.6°C (103.3°F), pulse rate 102 beats/minute, blood pressure 120/70 mmHg, respiratory rate 20 breaths/minute, and oxygen saturation 96% on room air. Physical examination was significant for icteric sclera, hepatomegaly, upper abdominal tenderness, and dark yellow urine. Laboratory studies were notable for impaired kidney function (serum creatinine (SCr) 3.52 mg/dL (311 µmol/L)), elevated transaminases (aspartate aminotransferase 109 U/L, alanine aminotransferase 101 U/L), hyperbilirubinemia (total bilirubin 11.3 mg/dL, direct bilirubin 4.03 mg/dL), and thrombocytopenia (23×10^3/µL). He tested negative for HBsAg, anti-HCV, and anti-HAV IgM. Peripheral blood smears revealed *P. falciparum* with a parasitemia level of 9.7% (437,000 parasites/µL) (Fig. 1A).

Baseline and follow-up laboratory findings during hospitalization are shown in Table 1. Chest X-ray showed evidence of pulmonary edema. Abdominal ultrasound demonstrated mildly enlarged kidneys (suggestive of bilateral acute nephritis), ascites, minimal pleural effusion, and hepatomegaly.

The patient was diagnosed with SFM, complicated by AKI, pulmonary edema, and jaundice. Given the presence of hyperparasitemia and multiple organ dysfunction, intravenous (IV) artesunate was promptly initiated at a dosage of 168 mg (2.4 mg/kg). Artesunate was administered at 0, 12, and 24 hours on the first day, followed by once every 24 hours until oral therapy could be tolerated. Supportive and symptomatic treatments, including IV flu-

ids with close monitoring of fluid balance, nasogastric tube feeding, as well as antipyretics, analgesics, diuretics, and hepatoprotective agents, were also provided.

On the third day post-admission, he had a seizure with subsequent deterioration in consciousness. Laboratory results revealed a marked increase in ureum and SCr levels. Based on these findings, the patient was suspected to have uremic encephalopathy. He then underwent emergent hemodialysis (HD), which resulted in a gradual improvement in consciousness over the following days. By the sixth day of hospitalization, a follow-up blood smear was negative for malaria parasites (Fig. 1D).

As the patient was able to tolerate oral therapy, IV artesunate was switched to oral dihydroartemisinin/piperaquine (DHA/PPQ, 160 mg/1,280 mg) and primaquine (PQ, 15 mg). Although the patient's clinical condition improved, his kidney function continued to decline after the initial HD, with SCr peaking at 12.4 mg/dL (1,096 µmol/L), necessitating a second HD session. Subsequently, SCr levels showed a downward trend, returning to normal by day 20.

During the hospital stay, the patient received six days (eight doses) of IV artesunate, underwent two HD sessions, and completed a full course of oral antimalarial therapy (a three-day regimen of DHA/PPQ with a single dose of PQ). His condition improved significantly without sequelae, and he was discharged with follow-up care at the outpatient clinic.

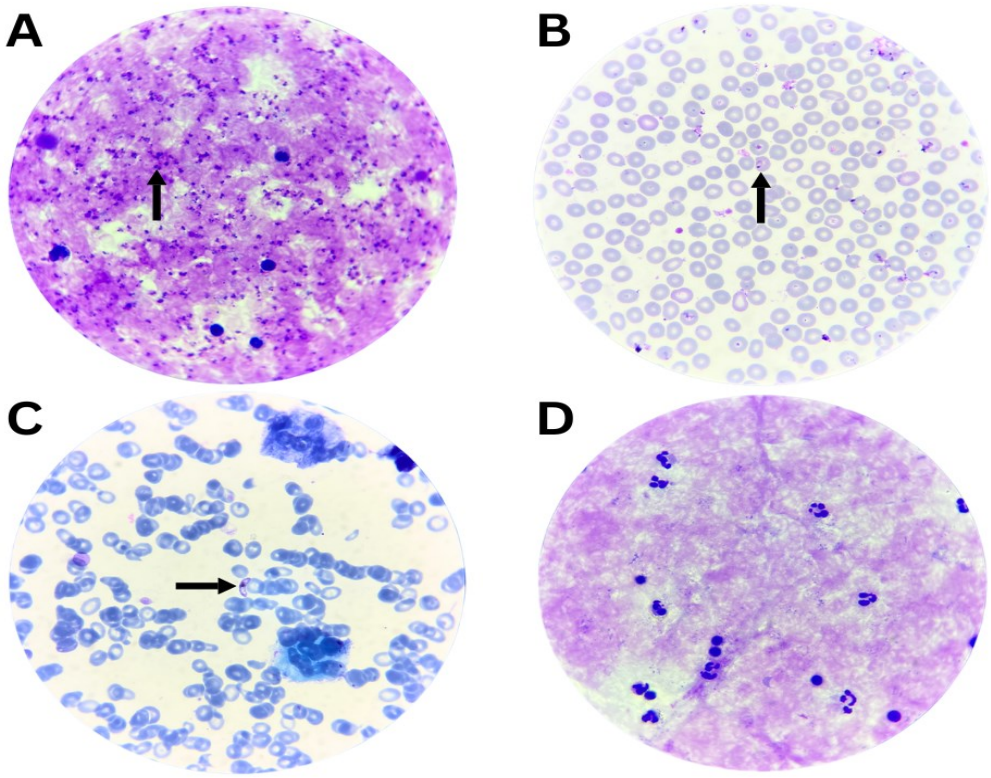

Fig. 1: Giemsa-stained thick and thin blood smears. (**A**) Asexual stages of *Plasmodium falciparum* in a thick smear (Day 1). (**B**) A *P. falciparum* ring-form trophozoite in a thin smear; note that the infected erythrocyte remains normal in size. (**C**) A *P. falciparum* gametocyte (crescent- or sausage-shaped) in a thin smear. (**D**) No asexual stages or gametocytes were found in a thick smear (Day 6)

Table 1: Patient's laboratory findings and treatment timeline during hospitalization

Parameter (reference)	Day of hospitalization												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**	**12**	**16**	**20**
Hemoglobin (13.5–17.5 g/dL)	13.2	10.3	–	8.5	8.3	–	8.1	8.9	7.4	–	8.2	–	8.9
Hematocrit (41–53%)	36	30	–	22	24	–	24	24	20	–	25	–	25
Leukocyte (4.5–11 × 10^3/µL)	9.65	17.2	–	11.2	10.7	–	11.6	10.6	7.02	–	6	–	4.63
Thrombocyte (150–450 × 10^3/µL)	23	54	–	81	87	–	140	141	190	–	288	–	183
Total bilirubin (0.2–1 mg/dL)	11.3	–	–	–	–	–	1.6	–	–	–	–	–	–
Direct bilirubin (0.1–0.2 mg/dL)	4.03	–	–	–	–	–	1.04	–	–	–	–	–	–
AST (10–40 U/L)	109	–	–	–	–	–	–	–	–	–	–	–	–
ALT (10–40 U/L)	101	–	–	–	–	–	–	–	–	–	–	–	19
Ureum (17.1–42.8 mg/dL)	–	197	258	215	233	248	256	259	153	–	–	60	–
Creatinine (0.7–1.3 mg/dL)	3.52	4.26	8.67	8.34	9.25	11.3	12.1	12.4	7.85	–	4.4	2.54	0.95
BUN (7–21 mg/dL)	–	92	–	–	109	–	–	–	71	–	–	–	–
Malaria blood smear (Neg.)	Pos.	Pos.	Pos.	Pos.	Pos.	Neg.	Neg.	Neg.	Neg.	Neg.	–	–	–
Treatment	Dose or session												
Intravenous artesunate	1, 2, 3	4	5	6	7	8							
Dihydroartemisinin/piperaquine							1	2	3				
Primaquine							1						
Hemodialysis			1					2					

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; BUN, Blood urea nitrogen; Neg., Negative; Pos., Positive

Discussion

The development of AKI in SFM is an independent predictor of mortality in adult patients, with a case fatality rate reaching up to 75% in the absence of renal replacement therapy (RRT) (5). The case of a 22-year-old male with SFM complicated by AKI highlights the life-threatening nature of malaria and underscores the need for timely, multifaceted interventions to manage the disease and its complications effectively.

While the exact pathogenesis of malarial AKI remains unclear, several mechanisms have been proposed, including hemodynamic (mechanical), immunologic, and metabolic pathways. Hemodynamic derangements arise from the cytoadhesion and sequestration of parasitized erythrocytes in the renal microvasculature, leading to renal hypoperfusion, hypoxia, and ischemic injury. Immune-mediated glomerular injury occurs when surface antigens on parasites and host erythrocytes induce the production of monocyte-derived cytokines, such as *TNF-a*, IFN-γ, and interleukins, which contributes further to renal immune complex deposition and subsequent inflammation. Moreover, cell-free hemoglobin released from

lysed erythrocytes generates reactive oxygen species, promoting oxidative stress and tubular damage (6). Additionally, the presence of hyperbilirubinemia can lead to AKI through direct bilirubin toxicity and intratubular obstruction via bile cast formation. Renal impairment may also result from hepatorenal syndrome (7). The cumulative effect of the aforementioned mechanisms is acute tubular necrosis, which manifests as AKI.

The clinical manifestations of malaria are non-specific and can resemble those of many other febrile infections. Therefore, any patient presenting with fever or a history of fever, particularly if they have lived in or recently traveled to malaria-endemic areas, should undergo parasitological testing (blood smear microscopy or rapid diagnostic test) to confirm the diagnosis. SFM, as defined by the WHO, is characterized by the presence of *P. falciparum* asexual parasites, accompanied by clinical or laboratory evidence of vital organ dysfunction, such as AKI, defined as SCr > 3 mg/dL (265 µmol/L) or blood urea > 20 mmol/L (3). In this case, the diagnosis of SFM was confirmed by microscopic examination of blood smears, with severe features manifesting as AKI, pulmonary edema, and jaundice. Additionally, the patient's hyperparasitemia (parasite density > 4% or > 200,000/µL) heightens the risk of mortality and treatment failure, necessitating prompt and aggressive management to improve outcomes (8).

The two key pillars of malaria-induced AKI treatment are appropriate antimalarial therapy and supportive care, which includes fluid management, avoidance of nephrotoxic drugs, and, if indicated, RRT. Parenteral artesunate, considered superior to quinine, is now the treatment of choice for SFM in adults. The mechanism by which artesunate substantially reduces mortality compared with quinine is its rapid parasiticidal activity on young ring-stage parasites, preventing their maturation and sequestration (9). According to the WHO guidelines, parenteral artesunate is administered at a dose of 2.4 mg/kg at 0 (on admission), 12, and 24 hours, and then once daily until the patient can tolerate oral medication, with a maximum treatment duration of seven days. A course of injectable artesunate should always be followed by a three-day course of oral artemisinin-based combination therapy (ACT), such as DHA/PPQ, to complete the treatment (10). To further reduce *P. falciparum* transmission at the community level, it is strongly recommended that a single dose of PQ (as a gametocytocide) be added to an ACT regimen (11). After receiving six days (eight doses) of IV artesunate, our patient was able to tolerate oral therapy and was subsequently switched to a three-day course of DHA/PPQ with a single dose of PQ.

Despite the availability of effective antimalarial drugs, mortality remains high among patients with malarial AKI, highlighting the importance of supportive treatment in improving outcomes (4). Fluid management should be tailored to the individual needs and reassessed frequently. Maintaining optimal fluid balance is essential, as SFM patients with AKI are not necessarily hypovolemic and are very vulnerable to fluid overload (12). Timely intervention with RRT, preferably HD, is an integral component of malarial AKI management, as it reduces mortality from 75% to 26% (5,13). However, the precise indications for initiating RRT in malaria-related AKI have yet to be well defined. For all causes of AKI, RRT is urgently indicated when overt uremic manifestations, severe electrolyte or acid-base disturbances, or diuretic-resistant fluid overload are present (14). The additional thresholds in the WHO malaria guidelines are based on findings that anuria and a rapidly rising SCr (> 2.5–3 mg/dL/day or 220–265 µmol/L) are sensitive indicators for the initiation of RRT (15). On the third day of hospitalization, our patient exhibited a marked increase in ureum and SCr levels, along with significant uremic manifestations, necessitating emergent HD. Despite clinical improvement, his kidney function further deteriorated after the first HD session. He subsequently underwent a second HD,

after which his SCr decreased gradually to within the normal range.

Conclusion

This case highlights the importance of prompt diagnosis and comprehensive management of SFM complicated by AKI to improve outcomes and reduce mortality. Timely administration of IV artesunate, followed by a full course of oral ACT, along with supportive management such as cautious fluid therapy and RRT, was essential for the patient's recovery.

Conflicts of Interest

There are no conflicts of interest.

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