Plasmodium falciparum-induced severe malaria with acute kidney injury and jaundice: a case report

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Abstract. *P. falciparum*-induced severe malaria with life-threatening complications like acute kidney injury (AKI), jaundice, cerebral malaria, severe anemia, acidosis, and acute respiratory distress syndrome (ARDS). A 31-year-old soldier man who works in Aceh Singkil, Indonesia which is an endemic malaria area presented with a paroxysm of fever, shaking chills and sweats over four days, headache, arthralgia, abdominal pain, pale, jaundice, and oliguria. Urinalysis showed hemoglobinuria. Blood examination showed hemolytic anemia, thrombocytopenia, and hyperbilirubinemia. Falciparum malaria was then confirmed by peripheral blood smear, antimalarial medications were initiated, and hemodialysis was performed for eight times. The patient’s condition and laboratory results were quickly normalized. We report a case of *P. falciparum*-induced severe malaria with AKI and jaundice. The present case suggests that *P. falciparum* may induce severe malaria with life-threatening complications, early diagnosis and treatment is important to improve the quality of life of patients. Physicians must be alert for correct diagnosis and proper management of imported tropical malaria when patients have travel history in endemic areas.

1. Introduction
Malaria is a major public health problem in tropical countries. Malaria is caused by infection of red blood cells by protozoan parasites of the genus *Plasmodium* inoculated into the human host by a feeding female *Anopheles* mosquito. The five human *Plasmodium* species transmitted from person to person are *P. falciparum*, *P. vivax*, *P. ovale* (two species) and *P. malariae*. Error! Reference source not found. Patients with *P. falciparum* infection are prone to develop severe malaria in 30% of cases Error! Reference source not found., which resulted in case fatality rate of 20%. Error! Reference source not found. In Southeast Asia, acute kidney injury (AKI) is one of the most common complications in adults with falciparum malaria. Error! Reference source not found. Error! Reference source not found. The incidence of AKI in patients with severe malaria varies widely ranging from 15% to 48% Error! Reference source not found. Error! Reference source not found. Error! Reference source not found. Error! Reference source not found. which resulted in a high fatality rate of over 70% in untreated patients. Error! Reference source not found. The availability of renal replacement therapy (RRT) and appropriate antimalarial chemotherapy has been shown to reduce case fatality rate as well as enhance the recovery of renal function. Error! Reference source not found. AKI associated with jaundice had high mortality in comparison with non-jaundiced AKI patients. Error! Reference source not found.
Jaundice is one of the common manifestations of severe malaria. Incidence varies from 10-45% in different reports and more common in adults than in children. Over a decade ago cerebral malaria was the predominant manifestation of severe malaria, whereas today the combination of hepatic dysfunction and renal failure is more common. Presence of jaundice in malaria indicates more severe illness with a higher risk of complications. Mortality rate was also a higher in this group of patients.

In Indonesia based on Household Health Survey 2001, there are 15 million cases of malaria with 38,000 deaths annually. Expected 35% of Indonesians live in areas at risk of contracting malaria. From 293 districts/cities, 167 of which are endemic areas, Aceh Singkil is one of them.

Severe malaria usually manifests with one or more of following: cerebral malaria, metabolic acidosis, severe anemia, hypoglycemia, AKI or acute pulmonary edema. If left untreated, severe malaria is fatal in the majority of cases.

We present a case of a 31-year-old soldier man with P. falciparum-induced severe malaria with AKI and jaundice, the combination of the antimalarial drugs and RRT were helpful to bring glomerular filtration rate (GFR) to within almost 50% of the normal value.

2. Case
A previously healthy 31-year-old soldier man presented to our hospital on October 19, 2015, with a paroxysm of fever, shaking chills and sweats over four days, headache, arthralgia, abdominal pain, pale, jaundice and oliguria. The patient noted that a fever and severe headache began approximately 13 days after his return from Aceh Singkil, Indonesia on October 3-15, 2015. He did not take antimalarial prophylaxis in Aceh Singkil, no consumption of special food, and no history of medication.

Vital signs were as follows: consciousness of *compos mentis*, a temperature of 38.1°C, heart rate of 96 beats/minute, blood pressure of 140/90 mmHg and respiration rate of 22 breaths/minute. The patient appeared acutely ill with icteric sclera (Figure 1A). His abdomen was soft, distended and tenderness without hepatosplenomegaly. The neurological examination was reported headache. Laboratory results were as follows: complete blood count revealed hemoglobin of 9.6 g/dL, a white blood cell (WBC) count of 13,400/mm$^3$ with segmented neutrophils (72%), and a platelet count of 61,000/mm$^3$. Urinalysis showed macroscopic hemoglobinuria (Figure 1B), leukocyturia (WBC 8-10/high power field), and protein (+) in the urine. Hepatorenal impairment was present with an aspartate aminotransferase level of 159 IU/L, alanine aminotransferase level of 61 IU/L, total bilirubin of 15.8 mg/dL, direct bilirubin of 11.71 mg/dL, blood urea nitrogen (BUN) of 57 mg/dL, and creatinine of 4.43 mg/dL. A peripheral blood smear examination was positive for P. falciparum ring-form trophozoites. Tests for hepatitis markers (type B) was negative.

Figure 1A. The patient appeared acutely ill with icteric sclera.

Figure 1B. Urinalysis showed macroscopic hemoglobinuria.
Patients received artemether 3.2 mg/kg intramuscularly on day 0, followed by 1.6 mg/kg daily then continue until oral therapy is possible (5 days), after artemether is completed then followed by oral therapy, a single dose of primaquine was administered, then followed by dihydroartemisinin-piperaquine (DHP) three tablets single daily dose for threedays.

After three days his fever persisted, and his headache had worsened. Oliguria and symptoms of the AKI were increased. Laboratory examination revealed increased BUN of 95mg/dL, creatinine of 9.89mg/dL, and a decreased GFR of 11 mL/min/1.73 m². The indicated treatment was hemodialysis. Intermittent hemodialysis was performed for eight times. Once hemodialysis was started, kidney function slowly improved (Figure 2). On day 24, after eight hemodialysis sessions, the GFR returned to the normal range.

![Figure 2](image)

**Figure 2.** Clinical progression of urine output/24 hours and glomerular filtration rate in the reported patient.

The patient's evaluation was performed daily until no parasites were found in the peripheral blood smear for three consecutive days then repeated on days 4, 7, 14, 21 and 28 after treatment. Peripheral blood smears showed *P. falciparum* parasitemia >5% (250,000/µL) on the day of admission (Figure 3A) and after three days (Figure 3B) were reported to be negative for malaria. The GFR normalized within four days of initiating the antimalarial drug. He was discharged on day 24, and the laboratory results were in normal range as follows: Total bilirubin of 0.49mg/dL, direct bilirubin of 0.29mg/dL, the BUN of 17mg/dL and creatinine of 0.85 mg/dL. A complete blood count on day 24 revealed a hemoglobin of 13.1g/dL and a platelet count of 346,000/mm³. Vital signs were stable, the patient did not report any symptoms, and the amount of urine is sufficient. He was discharged with no medication and followed for one year in our outpatient clinic with no subsequent health problems.
3. Discussion
Malaria is caused by infection of red blood cells by protozoan parasites of the genus *Plasmodium* inoculated into the human host by a feeding female *Anopheles* mosquito. The five human *Plasmodium* species transmitted from person to person are *P. falciparum*, *P. vivax*, *P. ovale* (two species) and *P. malariae*. All cases of suspected malaria should have a parasitological diagnosis, the two methods used routinely are light microscopy and immunochromatographic rapid diagnostic test (RDT) to confirm the diagnosis. Severe malaria usually manifests with one or more of the following: AKI, jaundice, cerebral malaria, severe anemia, acidosis, and ARDS. If left untreated, severe malaria is fatal in the majority of cases. AKI and jaundice are the important manifestations of severe falciparum malaria. WHO has defined AKI in malaria as plasma or serum creatinine >3 mg/dL or blood urea >20 mmol/L and jaundice as plasma or serum bilirubin >3 mg/dL with a parasite count >100,000/µL. In our case, a parasitological test confirmed the diagnosis and manifestation of severe malaria were present like AKI and jaundice.

Cholestasis jaundice and bile acid as well have been shown to be involved in the pathogenesis of AKI in malaria. Endotoxin released in jaundice increases the vascular response to catecholamines, increases plasma renin activity further increasing renal ischemia and compromising renal function. Hyperuricosuria due to jaundice could further compromise renal function in states of low urine flow and acidic urine.

Prompt and accurate diagnosis of malaria is needed for implementation of appropriate treatment to reduce associated morbidity and mortality. The management of malaria-induced AKI includes appropriate antimalarials, fluid electrolyte management, supportive therapy, avoidance of nephrotoxic drugs, and RRT at the earliest.

4. Conclusion
In conclusion, we report a case of *P. falciparum*-induced severe malaria with AKI and jaundice. Antimalarial drugs were immediately initiated due to diagnosis. The combination of antimalarial drugs and renal replacement therapy were helpful to bring the GFR to almost 50% of the normal value and clinical improvement of jaundice.
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