

Acute Kidney Injury and Jaundice in a Patient With Concurrent Severe Malaria and Acute Exacerbation of Hepatitis B

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Abstract

Patients chronically infected with hepatitis B virus (HBV) may travel to areas with high endemicity of malaria. The overlap between malaria and HBV infection can be clinically severe and present a diagnostic challenge as both diseases manifest similar symptoms. This case describes a fatal case of a 43-year-old man with chronic HBV infected with *Plasmodium falciparum* malaria that presents as acute kidney injury (AKI) and jaundice following a trip to malaria-endemic region. Despite administering antimalarial and 6 courses of renal replacement therapy, the patient's clinical condition did not improve, leading to septic shock, multi-organ dysfunction, and eventually, death. AKI and jaundice are commonly seen in severe *P. falciparum* malaria, as well as acute exacerbation of chronic HBV. This case emphasizes the importance to consider malarial screening when evaluating sick returning travelers, even in those with underlying chronic HBV. Given the severity of coinfection, prompt identification of this overlap can avert the rapid deterioration of severe malaria by early administration of intravenous artesunate and renal replacement therapy.

Keywords

severe malaria, hepatitis B, acute kidney injury, jaundice, *Plasmodium falciparum*

Introduction

Malaria remains a major health concern in the Eastern part of the Indonesian archipelago, with an annual parasite incidence (API) >10% and parasite prevalence reaching 75%, considerably outnumbered the overall number nationwide (both <1%).¹ Severe malaria is described as a case with systemic complications, where cerebral malaria and severe anemia are common presentations in children, while adult patients frequently present with multiorgan dysfunction.² Severe malaria is almost always associated with *Plasmodium falciparum* and intravenous artesunate has been the management of choice for many years.³

Meanwhile, hepatitis B virus (HBV) also present as an endemic infection in Eastern Indonesia due to low socioeconomic profile and uneven vaccination coverage.⁴ Forty percent of asymptomatic chronic HBV patients may develop acute exacerbation of chronic HBV (CHB-AE),⁵ causing derangement of liver functions resulting in jaundice and eventually acute kidney injury (AKI) from hepatorenal syndrome.⁶ Similarly, AKI and jaundice are common complications in severe malaria, creating a diagnostic challenge due to overlapping clinical manifestations.⁷

Concurrent HBV/malaria coinfection has been reported previously in African and South America populations,⁸ contributing to the high mortality for people living in co-endemic

regions. Nonetheless, such association noted in Southeast Asia is still limited. Here we describe a fatal case of a 43-year-old man from Jakarta who acquired a concurrent severe malaria and acute HBV exacerbation.

Case Report/Case Presentation

A 43-year-old man from Jakarta presented with jaundice, preceded by nausea, vomiting, and abdominal pain for 7 days. The patient initially developed a flu-like syndrome for several days (fever and chills, headache, myalgia, and arthralgia). Over several days, he experienced passing tea-colored urine with decreased urine output. His medical story included asymptomatic chronic HBV infection for 11 years and never consumed anti-viral medication. The patient was treated as acute exacerbation of chronic HBV in another

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Table 1. Summary of Laboratory Examinations and the Trend During Hospitalization.

Measure	Reference	Day of hospitalization						
		1	2 ^a	3	4	5	6	7
Ureum (mg/dL)	20-50	327	396	280	112	88	174	256
Creatinine (mg/dL)	0.5-1.5	13.2	12.1	11.0	3.5	2.9	3.29	5.01
eGFR (mL/min/1.73m ²)		4.01	4.5	5.1	20.2	25.3	22.2	13.1
Total bilirubin (mg/dL)	<1.5	42.9	37.2	36.8	33.1	30.06	45.9	39.7
Indirect bilirubin (mg/dL)	<1.1	34.6	27.9					28.0
Direct bilirubin (mg/dL)	<0.3	8.3	9.3					10.8
ALT (U/L)	<35	149	91	86	71	72		124
AST (U/L)	<40	109	62	43	36	37		34
Albumin (g/dL)	3.5-5.0	2.6	2.9	2.8	2.4	2.3	2.9	2.6
PT (s)	9.3-11.6	11.7	17.6	21.6	13.5	11.9	14.6	14.0
APTT (s)	23.4-31.5		66.3	64.7	45.5	45.4	40.8	50.6
Hemoglobin (g/dL)	13-18	9.8	7.6	9.2	8.7	9.1	10	8.1
WBC count (10 ³ /uL)	4.8-10.8	12.0	19.9	18.1	17.7	15.9	13.6	12.7
Platelets (10 ³ /uL)	150-400	128	462	523	470	293	252	202
Sodium (mmol/L)	135-147	134	140	138	134	135	135	133
Potassium (mmol/L)	3.5-5.0	4.1	3.6	3.5	3.8	3.4	3.8	5.4
Chloride (mmol/L)	95-105	98	100	100	100	98	98	97
Urine bilirubin	Negative	Positive						
pH	7.37-7.45		7.09	7.33	7.38	7.48		
Bicarbonate (mmol/L)	22-29		3.0	19.8	25.1	22.5		
Malaria rapid test	Negative		Positive					

Abbreviations: eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, partial thromboplastin time; APTT, activated partial thromboplastin time; WBC, white blood cell.

^aSevere malaria diagnosed on day 2 of hospitalization, intravenous artesunate + oral primaquine were started and continuous renal replacement therapy (CRRT) was initiated immediately.

hospital for 2 days, but his symptoms were not resolved and was transferred to our hospital. He does not drink alcohol. Clinical examination on admission showed the patient was alert with profound jaundice. He had abdominal upper quadrant tenderness but no hepatosplenomegaly or ascites. Neurological examination was normal.

Baseline laboratory assessments and changes during hospitalization are shown in Table 1. Initial laboratory tests were notable for acute kidney injury (creatinine 13.18 mg/dL, ureum 327 mg/dL, eGFR 4.06 mL/min/1.73m²), elevated total bilirubin (36.06 mg/dL), indirect bilirubin (29.06 mg/dL), and liver transaminases, accompanied with anemia, thrombocytopenia, and hypoalbuminemia. Urinalysis revealed positive bilirubin and urobilinogen in urine, but no hemoglobin was detected. Polymerase chain reaction test was negative for Covid-19. HBV serological profile showed positive HBsAg, IgM anti-HBc, and anti-HBe, but negative HBeAg. HBV-DNA quantification could not be performed. He tested negative for hepatitis C, hepatitis D, and human immunodeficiency virus (HIV). Abdominal ultrasound showed normal liver size and parenchyma without signs of splenomegaly and ascites. Hepatic elastography revealed severe liver fibrosis (F3-F4) with median liver stiffness at 14.9 kPa.

The clinical scenario was initially interpreted as an acute exacerbation of chronic HBV. Treatment included telbivudine, cefoperazone, furosemide, ursodeoxycholic acid, and supportive management. On the second day of hospitalization, he developed altered consciousness with metabolic acidosis (pH 7.087, HCO₃⁻ 3.0 mmol/L) and oliguria (<200 mL/24 hours). Ammonia level was not measured. Further questioning to his wife revealed that his symptoms occurred 4 days after returning from a 1-year trip in Serui, Papua. At this time, rapid diagnostic test for malaria was ordered which showed positivity. Peripheral blood smear showed intraerythrocytic *P. falciparum* (63 parasites per 500 erythrocytes) with a high degree of parasitemia (12.6%) (Figure 1).

Diagnosis of severe malaria was made, and intravenous antimalarial artesunate with oral primaquine were administered. He was transferred to the intensive care unit, intubated, and started on continuous renal replacement therapy (CRRT) with continuous venovenous hemodiafiltration (CVVHDF) method, and after 4 sessions we observed an initial downward trend in ureum, creatinine, bilirubin, and liver enzymes level, accompanied with improvement in eGFR. However, over the following days his renal function continued to progressively decline, and the liver injury deteriorated. Eventually, he developed pulmonary edema, septic shock,

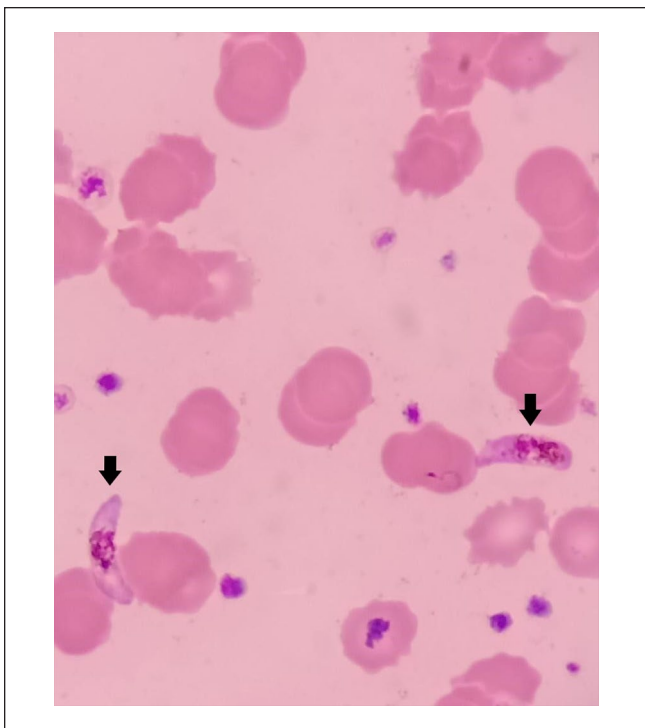


Figure 1. The gametocytes of *Plasmodium falciparum* seen in a peripheral blood smear (arrows).

multiorgan dysfunction and died on the seventh day of hospitalization despite cardiopulmonary resuscitation.

Discussion and Conclusion

The majority of malarial cases (86%) are concentrated in Eastern Indonesia, with the following provinces had a high cumulative incidence (API 5.0–49.0): Papua (31.93), West Papua (31.29), East Nusa Tenggara (7.04), and Maluku (5.81). In contrast, Sumatra, Kalimantan, and Sulawesi have shown low-to-medium endemicity, whereas malaria has been completely eliminated in Java and Bali.⁹ Due to lack of exposure to infection, non-native Papuans abruptly exposed to endemic malaria are at greater risk of developing severe symptoms due to low acquired immunity.¹⁰ Non-immune adults trigger innate or cross-reactive acquired immune responses that induce an aberrant production of pro-inflammatory cytokines resulting in severe form of malaria, as seen in our patient that had no previous malarial immunity.^{10,11}

Severe multi-organ complications can occur in *P. falciparum* malaria.⁷ Severe manifestations in this case include renal failure, jaundice, anemia, acidosis, and shock. The mortality rate of malaria-associated AKI reached up to 51%, and worst prognosis was associated with delayed referral, severe jaundice, oliguria, and multi-organ involvement.¹² The pathogenesis of AKI is believed to be caused by infected red blood cell (RBC) sequestration in the renal vasculature leading to hypoperfusion and tissue hypoxia, combined with

immune complex deposition in renal tubules. Malaria-induced AKI manifests pathologically as acute tubular necrosis. Diagnosis of AKI is suspected when urine output falls to <400 mL/24 hours and should be confirmed when serum creatinine level reaches 3 mg/dL or higher.¹² Jaundice is another common manifestation of severe malaria. Jaundice associated with malaria is often biphasic in nature, with elevation of both conjugated and nonconjugated bilirubin contributed by cholestasis and hemolysis of RBC, respectively. This RBC hemolysis also leads to peripheral blood pooling leading to renal hypoperfusion and AKI. Enzyme elevation in malarial hepatopathy might be mild.¹³

The highly variable presentation of severe malaria associated with *P. falciparum* may mimic that of many other diseases creating a diagnosis confusion. This case was initially suspected as some morbidity affecting the liver, due to the presentation of jaundice and acute kidney injury in a patient with underlying history of chronic HBV, collectively supported the diagnosis of hepatorenal syndrome often seen in CHB-AE. In severe malaria, serum concentrations of urea, creatinine, bilirubin, and liver and muscle enzymes may be elevated, although the levels of liver enzymes are much lower than in acute viral hepatitis.⁷

Chronic HBV is recognized as a risk factor for severe malaria.¹⁴ Although reactivation commonly seen in patients with altered immune function, it is commonly seen in concurrent infections with other pathogens, especially in endemic areas.¹⁵ Overlapping HBV/malaria coinfection cases have been reported previously.^{16,17} Both pathogens share an intrahepatic life cycle developmental stage, which may increase mortality and morbidity.¹¹ Nonetheless, whether HBV exerts an effect on the clinical presentation of malaria remains debatable. Andrade et al¹⁶ found that *Plasmodium*-infected individuals with HBV induce pro-inflammatory Type 1 immune response, essential for plasmodium clearance, leading to lower parasitemia and a less severe form of malarial disease. Similarly, Dabo et al¹⁸ showed an increased level of interferon gamma released during an HBV infection may reduce malaria parasite load and its severity. Meanwhile, other study demonstrated that HBV-DNA load was not associated with parasitemia level in asymptomatic HBV/malaria coinfection.¹⁹ Also, Scotto and Fazio²⁰ reported that the presence of malaria did not affect the severity of liver disease between HBV mono- and co-infected patients.

In contrast, it is believed that hepatocyte damage in HBV exacerbation leads to diminished clearance of the malarial parasite during intrahepatic stage, hence increasing the disease severity.¹¹ Increased cytokine release induced by *P. falciparum* may exacerbate apoptosis of HBV-infected hepatocytes which influence the course of HBV infection.¹⁷ This was supported by Kolawole et al,²¹ who reported that liver functions were found to be significantly affected in patients co-infected with HBV and malaria compared to mono-infected HBV patients. Barcus et al¹⁴ also showed that HBV

presence significantly increase the risk of cerebral malaria. Therefore, in this patient, whether malaria induces CHB-AE or vice versa remains unclear. The interaction between these pathogens requires further investigation.

Interestingly, this patient did not develop any manifestations of malaria while living in Papua for 1 year, prompting the need to consider other differential diagnoses such as leptospirosis or dengue, diseases commonly found in tropical countries causing acute febrile illness.²² Furthermore, blackwater fever (BWF), a condition that describes severe intravascular hemolysis associated with the use of antimalarial quinine or G6PD deficiency, is also important to differentiate with severe malaria. In BWF, massive release of hemoglobin into urine also resulted in jaundice and AKI due to direct tubular injury, while macroscopic hemoglobinuria is exceedingly rare to find in severe malaria.^{7,12} Although the patient presented with the classic “tea-colored urine” in BWF, he had no history of taking antimalarial prophylaxis before the trip to endemic malaria, and a trace of hemoglobin was not found in urinalysis; thus, a diagnosis of BWF was not considered.

Clinicians in Indonesia and other tropical countries should be aware of malaria and HBV coinfection. Molecular and serologic diagnostic tests for both illnesses should be ordered promptly to properly diagnose and manage patients with acute febrile illnesses complicated with AKI and jaundice. Even if parasitological confirmation of malaria is not readily available, intravenous artesunate should be started promptly based on the clinical presentation. Supportive therapies, fluid restrictions, and renal replacement therapy should be considered early when supportive therapy is insufficient.^{7,12}

Hemofiltration does not interfere with antimalarial drugs, and prompt dialysis administration has been associated with a 25% mortality reduction and 30% improvement in renal function among malarial patients with AKI.²³ This case did not receive intravenous artesunate until the 10th day after onset (second day of hospitalization), which was delayed due to missed diagnosis in the prior admission. The patient eventually received CRRT with CVVHDF mode. However, despite an initial renal function improvement after 4 sessions, his clinical condition deteriorated afterward. In conclusion, symptoms overlap between severe malaria and fulminant hepatic failure created a diagnosis challenge; thus, clinicians need to recognize that these 2 infections co-exist and influence each other’s clinical course.

Author’s Note

This case poster was previously presented in abstract form at the 4th Asia Pacific AKI CRRT Virtual Meeting, Bangkok, Thailand (December 12-15, 2020).

Declaration of Conflicting Interests

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Ethics Approval

The present case report was approved by Gatot Soebroto Central Army’s committee on human research.

Informed Consent

Verbal informed consent was obtained from the patient’s wife for their anonymized information to be published in this article.

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References

- Hanandita W, Tampubolon G. Geography and social distribution of malaria in Indonesian Papua: a cross-sectional study. *Int J Health Geogr*. 2016;15(1):13.
- Dondorp AM, Lee SJ, Faiz MA, et al. The relationship between age and the manifestations of and mortality associated with severe malaria. *Clin Infect Dis*. 2008;47(2):151-157.
- Brejt JA, Golightly LM. Severe malaria: update on pathophysiology and treatment. *Curr Opin Infect Dis*. 2019;32(5):413-418.
- Muljono DH. Epidemiology of hepatitis B and C in Republic of Indonesia. *Euroasian J Hepatogastroenterol*. 2017;7(1):55-59.
- Kumar M, Jain S, Sharma BC, Sarin SK. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. *Dig Dis Sci*. 2006;51(3):594-599.
- Chancharoenthana W, Leelahavanichkul A. Acute kidney injury spectrum in patients with chronic liver disease: where do we stand? *World J Gastroenterol*. 2019;25(28):3684-3703.
- World Health Organization. *Management of Severe Malaria: A Practical Handbook*. 3rd ed. World Health Organization; 2012. <https://apps.who.int/iris/handle/10665/79317>. Accessed August 19, 2021.
- Kotepui KU, Kotepui M. Prevalence of and risk factors for Plasmodium spp. co-infection with hepatitis B virus: a systematic review and meta-analysis. *Malar J*. 2020;19(1):1-17.
- Ministry of Health of the Republic of Indonesia. *InfoDATIN Malaria*. Jakarta, Indonesia: Ministry of Health of the Republic of Indonesia; 2016. [In Indonesian]
- Baird JK, Basri H, Weina P, et al. Adult Javanese migrants to Indonesian Papua at high risk of severe disease caused by malaria. *Epidemiol Infect*. 2003;131(1):791-797.
- Scotto G, Fazio V, Lo Muzio L. Co-infection HBV and malaria: a striking association. *Infez Med*. 2019;27(1):3-10.
- Brown DD, Solomon S, Lerner D, Del Rio M. Malaria and acute kidney injury. *Pediatr Nephrol*. 2020;35(4):603-608.
- Anand AC, Puri P. Jaundice in malaria. *J Gastroenterol Hepatol*. 2005;20(9):1322-1332.
- Barcus MJ, Hien TT, White NJ, et al. Short report: hepatitis B infection and severe Plasmodium falciparum malaria in Vietnamese adults. *Am J Trop Med Hyg*. 2002;66(2):140-142.

15. Puri P. Acute exacerbation of chronic hepatitis B: the dilemma of differentiation from acute viral hepatitis B. *J Clin Exp Hepatol*. 2013;3(4):301-312.
16. Andrade BB, Santos CJN, Camargo LM, et al. Hepatitis b infection is associated with asymptomatic malaria in the Brazilian Amazon. *PLoS ONE*. 2011;6(5):e19841.
17. Anabire NG, Aryee PA, Abdul-Karim A, Quaye O, Awandare GA, Helegbe GK. Impact of malaria and hepatitis B co-infection on clinical and cytokine profiles among pregnant women. *PLoS ONE*. 2019;14(4):e0215550.
18. Dabo N, Sharif A, Muhammed Y, Sarkinfada F. Malaria and Hepatitis B co-infection in patients with febrile illnesses attending general outpatient unit of the Murtala Muhammed Specialist Hospital, Kano, Northwest Nigeria. *Bayero J Pure Appl Sci*. 2015;8(1):89.
19. Freimanis GL, Owusu-Ofori S, Allain JP. Hepatitis B virus infection does not significantly influence Plasmodium parasite density in asymptomatic infections in Ghanaian transfusion recipients. *PLoS ONE*. 2012;7(11):e49967.
20. Scotto G, Fazio V. Hepatitis B and asymptomatic malaria coinfection in Sub-Saharan African immigrants: epidemiological and clinical features of HBV infection. *Rev Soc Bras Med Trop*. 2018;51(5):578-583.
21. Kolawole OM, Kana SN. Hepatitis B virus and malaria co-infection causing significant changes in hematological and liver function indices in a cohort of subjects in Ilorin, Nigeria. *Int J Infect*. 2018;5(3):e81528.
22. Sachu A, Madhavan A, Vasudevan A, Vasudevapanicker J. Prevalence of dengue and leptospirosis co-infection in a tertiary care hospital in South India. *Iran J Microbiol*. 2018;10(4):227-232.
23. Wang C, Lv LS, Huang H, et al. Initiation time of renal replacement therapy on patients with acute kidney injury: a systematic review and meta-analysis of 8179 participants. *Nephrology (Carlton)*. 2017;22(1):7-18.