**Case Report**

# Confusions and dilemma around hepatic dysfunction associated falciparum malaria: A case report and brief review of the literature

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Malaria remains a big burden in East Indonesia. Severe malaria assaults children in endemic area and leads to enormous morbidities and mortalities. According to the World Health Organization's criteria, recognition of one or more of the following clinical features should raise the suspicion of severe malaria i.e, cerebral malaria (unrousable coma), severe anemia (hemoglobin <5 g/dl), renal failure (creatinine serum >3 mg/dl), pulmonary edema or adult respiratory distress syndrome (ARDS), hypoglycemia (glucose <40 mg/dl), circulatory collapse or shock, disseminated intravascular coagulation (DIC), repeated generalized convulsions, acidosis (pH <7.25), macroscopic hemoglobinuria, hyperparasitaemia (>5% of the erythrocytes infested by parasites), or jaundice (bilirubin >3 mg/dl).[1-3]

Jaundice in malaria due to hepatic dysfunction is a classical case, nevertheless, there are some confusions and dilemmas in managing it.[1] We report a case with jaundice due to hepatic dysfunction and hemolysis associated falciparum malaria that we treated in General Hospital of Fakfak, West Papua, and provide a brief literature review on the matter.

## The case

A 7-year old girl came to the emergency unit of general gospital in Fakfak, West Papua, on 29 May 2008 with four times vomiting, fatigue, and feeling cold. Physical examination revealed an alert girl with body weight of 15 kg. She looked malaise, with normal vital signs and no fever. Neither jaundice nor red conjunctiva was observed on her eyes examination. Abdominal examination was not conducted at that time. Since we can not obtain the result of malaria blood smear at that time, this patient was diagnosed as clinical malaria and the doctor who was in charged treated her with quinine HCl 150 mg in 150 cc 5% dextrose drip infusion and symptomatic therapy.

On the first day of admission, malaria blood smear showed (+4) of *Plasmodium falciparum*, hemoglobin level was 10.5 g/dl and white blood cell level was 16.500/$\mu$l.

On the fourth day of admission, the patient looked jaundice. Neither edema nor ascites was found. There was no history of ingesting hepatotoxic drugs or contact with viral hepatitis. There was no past history

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of jaundice. Abdominal examination revealed slight abdominal distention with hepatomegaly 4 cm under costal arc and mild splenomegaly; the peristaltic sound was normal. Laboratory findings showed AST 317 mg/dl, ALT 106 mg/dl, HbsAg (-), and total bilirubin of 4.87 mg/dl. The patient was then diagnosed as bilious malaria. The administration of intravenously quinine HCl was discontinued and changed to oral quinine sulfate 75 mg, three times a day.

On the fifth day of admission, the patient complained difficulty in defecation, and her stomach became more distended with decreased peristaltic sound afterwards. She also looked pale and her urine became tea color. Laboratory finding revealed hemoglobin level of 5 g/dl, and then we gave 150 cc packed red cell twice in two consecutive days with furosemide 1 mg/kg. She showed sign of paralytic ileus. Radiological finding of abdomen three positions confirmed this. We thought of conducting blood electrolyte examination for the possibility of hypokalemia as the cause of ileus but there was limitation in instrument. So, we blindly gave her 250 mg potassium supplementation. We also gave her cefotaxim gentamycin intravenously, and curcuma. After two days of fasting, abdominal distention decreased and soon she could manage to defecate again. We offered her to start gradually eating soft diet. Her jaundice appearance also gradually decreased.

After eight days of hospitalization, her AST decreased to 58.2 g/dl, ALT 27.1 g/dl, white blood cell 6400/$\mu$l, and total bilirubin 2.06 mg/dl, but there was still gametocyte of *Plasmodium falciparum* (+2) in her blood smear. Three days later, she was discharged.

## Discussion

Jaundice is one of the common severe manifestation of falciparum malaria.[1-11] Its incidence varies between 10% to 45% in different reports,[1] and it is seen more in adults than in children.[1,5,7,12] It may be present alone or with other complications[1] and may vary from mild to very severe. Mild jaundice in malaria is mostly due to hemolysis. However, moderate to severe jaundice could result from hepatic dysfunction.[12]

Presence of jaundice in falciparum malaria indicates a more severe illness with higher incidence of complications. Mortality also was higher in the group of patients with jaundice.[1] Jaundice, along with impaired consciousness, hypoglycemia, and respiratory distress are important predictors of death in African children from a high-endemicity.[4] Recovery from jaundice is usually faster than that of hepatitis, which usually takes a longer time to return to normal.[1]

The cause of jaundice in severe falciparum malaria is multifactorial: intravascular haemolysis of packed red blood cells (pRBCs), haemolysis of non-pRBCs (innocent bystanders), possibly microangiopathic haemolysis associated with DIC, hepatic dysfunction (bilious malaria), associated hemoglobinopathies (not uncommon in malaria-prone areas), drug-induced hemolysis (including quinine), G6PD deficiency, et cetera.[1] Therefore, we must consider these factors in the diagnostic approaches of jaundice in malarial patient. We have to keep in mind that more than one factor could concomitantly occur in one patient.

Jaundice developed in our patient due to hemolytic process and hepatic dysfunction (bilious malaria) that occurred simultaneously. Hemolytic process causes severe anemia and blackwater fever. Blackwater fever is hemoglobinuria due to massive intravascular hemolysis, characterized by tea color of urine.[1,2,5] Blackwater fever is not associated with renal dysfunction but can develop into acute renal failure in some profound case.[5] Blackwater fever also happens in G6PD deficiency patient who takes particular drugs. We do not have instrument to perform G6PD examination.[2,3,5]

Hepatic dysfunction in severe falciparum malaria had been investigated in some studies. A prospective study conducted on 216 children with complicated falciparum malaria showed hepatopathy in 33.3% cases with higher incidence in children aged above five years. Bilirubin and alanine aminotransferase moderately raised in most cases.[13]

Premaratna *et al*[14] report some cases of severe hepatic dysfunction associated with falciparum malaria in adult in India. Hyperbilirubinemia caused by hemolysis in malaria is predominantly unconjugated bilirubin. Low serum albumin levels, significant increase of amino transferases, and moderate prolongation of prothrombin time are all indication of hepatic dysfunction. The patients show markedly jaundiced and blood films confirm severe falciparum malaria. The excellent response to

quinine therapy made it very likely that the hepatic dysfunction was causally related to the malarial infection. Although the term "hepatitis" may not be appropriate as the aminotransferases were not elevated to levels seen in viral hepatitis, the evidence of liver cell dysfunction in the Indian patients and in these patients was strong.[14]

Devarbhavi *et al*[10] used the term of malarial hepatitis in their study to identify clinical and laboratory features of patients with malarial hepatitis simulating fulminant hepatic failure (MHsFHF) and distinguished it from viral fulminant hepatic failure (FHF) in adults. This study also found that hepatomegaly and splenomegaly were more frequent in patients with MHsFHF. The MHsFHF group had a significantly lower hemoglobin level, total leukocyte count, platelet count, and transaminases. Elevation of transaminases in MHsFHF was much lower than that in FHF. Although an increase of bilirubin levels was traditionally believed to be primarily due to hemolysis, our study and another recent study have shown that elevated bilirubin levels may be predominantly conjugated bilirubin. The pathogenesis of hepatitis or cholestasis in malaria is unclear. [10]

Moreover, patients with MHsFHF show no evidence of impaired hepatic synthetic function such as prolonged prothrombin time (PT). Prolonged PT is a prognostic marker of hepatocellular dysfunction. Prolonged PT and decreased liver span are the hallmarks in FHF, whereas hepatomegaly and normal PT are seen in MHsFHF. Therefore, the presence of normal PT in patients with MHsFHF suggests that the synthetic function of the liver is preserved, and the deranged liver tests may be secondary to the release of various cytokines such as tumor necrosis factor $\alpha$ and IL-10, as alluded previously.[10]

A retrospective and prospective analysis of hospitalized cases of malaria in children and adolescents over a five year period in a tertiary hospital was conducted by Bhave *et al*.[15] Cases were analyzed to correlate clinical features with types of malaria and four age groups: (0-1, 1-5, 6-12, 13-17 years). Smear negative cases (based on WHO Coding) were included as their clinical findings as well as laboratory findings suggestive of malaria which responded to anti-malarial drugs. Hepatic dysfunction, indicated by raised ALT, AST, and bilirubin, was prevalent in younger age group (<5 years) in both vivax and falciparum malaria compared to that in older children and adolescents. Hepato-splenomegaly was more common in less than 1 year age group followed by that in 1-5 years. However, splenomegaly alone was pronounced in two age groups (< 1 year and 13-17 years).[15]

Liver is the first organ to be affected in a case of *P. falciparum* malaria. In the patients of severe malaria, liver may be involved to different extents. Liver biopsy/necropsy usually shows Kupffer cell hyperplasia, mononuclear cell infiltration, and pigment deposits; while other studies found no structural change; there was only slight hepatocyte swelling. Centrizonal necrosis has also been reported.[1] The pathogenesis of this complication is poorly understood. Possible mechanisms may include congestion of the hepatic sinusoids caused by parasitized red cells or the effect of cytokines, such as TNF-$\alpha$, which are released in high concentrations in severe falciparum malaria, causing hepatic dysfunction.[13,16]

The jaundice appearance, elevated titer of transaminases as well as bilirubin, and hepatos-plenomegaly in our patient supported the diagnosis of hepatic dysfunction. To assure hepatic dysfunction in this patient we should perform additional liver function test such as prothrombin time, as well as albumin level. Hiperbilirubinemia in hepatic dysfunction was predominantly conjugated bilirubin. Unfortunately, in our hospital we can not measure conjugated bilirubin. There was clinically no evidence of bleeding manifestations or edema in our patient. In our hospital, viral hepatitis marker which we can conduct is only HbsAg examination, and the result was negative. There were no signs and symptoms of leptospirosis in this patient.

No specific management is needed to reduce hyperbilirubinemia. However, when associated with very high bilirubin levels (>28 mg/dl) in children, exchange transfusion is needed.[3,17] Firstly diagnosed as clinical malaria, this girl received 150 mg Quinine HCl diluted in 150 cc 5% dextrose drip infusion but considering that the girl could take it orally we switched the therapy into quinine sulfat 75 mg three times a day.

Mishra *et al*[12] stated that hepatic dysfunction leads to improper handling of drugs and antimalarials (as evidenced by hepatic blood flow measurement – indocyanine green (ICG) clearance). In patients

with severe malaria, ICG clearance is significantly lower than that in patients with uncomplicated malaria. It returns to normal during convalescence. Acute malaria also adversely affects the function of cytochrome P450 microsomal enzymes.[1]

Hence, this evidence has an effect on medication in patients suffers from hepatic dysfunction in severe malaria. Treatment with standard doses of quinine in patients with "malarial hepatitis" can result in quinine toxicity, but Premaratna *et al*[14] did not find this complication in their patients. In their case report, they did not mention whether they adjusted the dose of quinine used or not.[14] WHO guidelines of malaria treatment recommended dosage adjustment into one third in patients with hepatic dysfunction.[11] Mishra and Mohanty[3] suggested not to reduce the dose of quinine in the first 48 hours of therapy in presence of jaundice unless the alanine aminotransferase (or SGPT) is very high, the dose can be reduced to two-third after 48 hours. Harijanto[9] suggested to be careful in using some drugs like paracetamol and tetracyclin.[9] Considering these data, we reduced the dose of quinine sulfate half from its normal dose in our patient.

Related to hyperparacytemia, it is an interesting fact that this patient was not a Papuanese girl, and hyperparacytemia state brought out severe clinical manifestations to this girl. Papuanese children can tolerate surprisingly high densities of paracyte often without clinical manifestation. It might be due to immunity of malaria that has been accomplished in them.[2,5]

Anemia may be present in about 20% adults in a low endemic area. In an endemic zone, it may be the only presenting feature among the children below five years of age.[7] Anemia is caused by combination of multiple factors, which are hemolysis of pRBCs and even non-pRBCs; bone marrow depression, disseminated intravascular coagulation, or preexisting iron deficiency.[3,7] We should also perform reticulocyte count to assess possibility of bone marrow depression in our patient.

The presence of severe or rapidly progressing anemia in malaria needs prompt treatment, as it is associated with poor prognosis. Blood transfusion of packed cell is indicated when hemoglobin is below 5 g/dl; a rate of fall of > 2g in 24 hrs; hematocrit < 20, or in patients with features of cerebral anoxia. Volume overload must be avoided by giving only packed cells.

Furosemide 20 to 40 mg should be administered prior to blood transfusion when impending cardiac failure is suspected or already presents.[2,3] Severe anemia is a common manifestation in Fakfak. We gave transfusion of packed red cell for our patient with severe anemia.

Paralytic ileus that occurred the fifth day in our patient could be due to severe infection (hyperparacytemia) that cause septicemia.[18] Septicemia and severe malaria are associated and there is diagnostic overlap, particularly in children. The threshold for administering antibiotic treatment should be low in severe malaria.[2] Furthermore, considering the elevation of white blood cell, we gave broad spectrum antibiotic to this patient. We postponed oral feeding until ileus resolved clinically. Although we were sure whether that there is association between paralytic ileus and severe infection, blood electrolyte examination to asses potassium balance should had been conducted but as we stated above, we did not have the instrument.

On the last day of admission, transaminases titer had already fallen down as well as white blood cell and total bilirubin but there was still gametocytes of *P. falciparum* (+2) in her blood smear. Gametocytes in the malarial patient's blood do not cause any symptoms but they have a role in the transmission of disease. Primaquin is effective to combat gametocyte of *P. falciparum,* but quinine is not. Primaquin should had been started the first day of oral quinine being taken by the patient. However, the fact that primaquin is metabolized in the liver[5] and may give additional burden had prevented us to give her this drug. We do not have any literatures that suggest any other drug to destroy gametocytes in this case.

In conclusion, there are some confusions and dilemmas in managing hepatitis dysfunction in malaria. Bilious malaria, in some domestic literatures, is often used to term hepatic dysfunction in malaria.[6,9] However, they do not confirm the definition or diagnostic criteria of it. It elicits confusions in making decision what standard laboratory examination should be performed to ascertain diagnosis of bilious malaria. The question is whether transaminases is accurate enough for the assessment of liver fuction. Moreover, Harijanto[9] stated whether vitamin K can improve vitamin K dependent-coagulation factors disturbed in bilious malaria[9] but every patient

with such condition receive this therapy is still questionable. Note that not only hepatic dysfunction, disseminated intravascular coagulation could also contribute to the disturbance of coagulation factors in severe malaria.[3,5]

Further researches have to be established to evaluate more about hepatic dysfunction regarding its medication, such as the decision of whether and when we need to adjust antimalaria drugs (which we give as addition) or whether there are any drugs that we should avoid. By presenting this case we hope that there will be further apprehension about this issue in the future. Consequently, we will be more proficient and confident in taking care of such cases.

## Acknowledgments

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