Rare Case of Direct Hyperbilirubinemia Due To Malarial Hepatopathy in Severe Falciparum Malaria

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ABSTRACT

Jaundice commonly occurs in severe malaria, seen in approximately 2.5% patients with falciparum malaria infection. Jaundice in malaria can be caused by intravascular hemolysis, disseminated intravascular coagulation (DIC) or malaria-related liver disorders. Malarial hepatopathy is a term that is often used to describe hepatocytic dysfunction in severe malaria, although inflammation does not occur in the liver parenchyma. Malarial hepatopathy also characterized by a rise in serum bilirubin along with the rise in serum glutamate pyruvate transaminase levels. This two condition are similar but must be distinguished because of different treatment required.

Keyword: *malarial hepatopathy, jaundice, severe malaria, falciparum malaria*

ABSTRAK

Ikterus sering terjadi pada malaria berat, dan angkanya sekitar 2,5% pada pasien infeksi malaria falciparum. Ikterus pada malaria bisa disebabkan karena proses hemolisis intravaskuler, koagulasi intravaskuler diseminata (disseminated intravascular coagulation/DIC) atau gangguan hati terkait malaria. Malarial hepatopathy merupakan istilah yang digunakan untuk menggambarkan disfungsi hepatosit akibat malaria berat, walaupun inflamasinya tidak terjadi pada parenkim hati. Malarial hepatopathy juga ditandai dengan penigkatan serum bilirubin seiring dengan peningkatan kadar serum glutamat piruvat transaminase (SGPT). Kondisi ini tampak serupa namun harus dibedakan sebab diperlukan perawatan yang berbeda.

Kata kunci: *malarial hepatopathy, ikterus, malaria berat, malaria falciparum*

INTRODUCTION

Malaria is an infection caused by *Plasmodium* parasite transmitted between humans by female *Anopheles* mosquito bites. There are 5 species of *Plasmodium*, with *P. falciparum* and *P. vivax* most commonly found in severe malaria cases.[1] Global incidents of the disease between 2010 and 2015 reached 21%, with the mortality rate at 29%.[2]

Malaria symptoms appeared 10–15 days after the infected *Anopheles* mosquito bite occurred. The incubation period for each species is different. The symptoms appear to be varied. It ranges from mild symptoms such as fever, muscle and joints pain, up to severe symptoms such as jaundice, anemia, shock, organ disfunction, and event death.[2] Malaria-induced jaundice shows hepatic dysfunction, though 10–45%

of the incident are not accompanied by the rise of liver enzymes. Hemolytic and hepatic dysfunction are the most common causes.[3] Jaundice caused by malaria are commonly diagnosed as malarial hepatopathy, even though the causes are multifactorial. Malarial hepatopathy are more correctly used on malaria jaundice caused by hepatocellular damage, where the incident are significantly lower that jaundice caused by hemolysis.[4]

Hematology abnormalities are commonly found on malaria patient, anemia and thrombocytopenia are the most common. Thrombocytopenia with platelets level under 150.000/mm^3 happens to 24–94% patients of acute malaria, and there are no differences between those who suffers from *P. falciparum* and *P. vivax*. Despite not being a criteria for severe malaria, thrombocytopenia is related to a higher morbidity and mortality rate.[5] This case reporting an acute malaria patient caused by *Plasmodium falciparum* with jaundice and thrombocytopenia.

CASE REPORT

A 37-year-old male was admitted to the hospital with complaints of right upper abdominal pain, fever, and yellowish eyes. He suffered daily bouts of fever with fluctuating temperature; shivering and then followed by high fever around 2–3 hours. After that, the fever went down alongside cold sweat in the whole body. Fever occurred noon and reduces during afternoon. Yellowish eyes occurred in the past 1 week, followed by tea colored urine, and putty colored feces. He also had nausea and vomiting every time he eats, though there were no indication of black vomit or stool. No calf pain, nosebleed, or bleeding gum. The patient lived and worked at Mimika, Papua for 4 years and had just recently moved to Madura since last month. The patient had had a similar disease roughly 3 years ago, of which he was prescribed blue pill tablets that must be consumed 3 times a day for 3 days. A lot of the patient's roommates also suffered from fever and consumed the same medicine.

On examination, he was somnolence, glasgow coma scale (GCS) 13, blood pressure 110/80, pulse 120 bpm, regular and weak pulse, respiratory rate 24 respirations/minute, axillary temperature 41°C. The physical examination found scleral joundice and subconjuntival anemia, hepatosplenomegaly and tenderness on right upper quadrant abdomen. No sign of conjunctival suffusion. The laboratory findings included anemia with Hb 7.9 g/dL, lukocytosis (36,780/mm^3), and thrombocytopenia (77,000/uL). Elevated alanine aminotransferase (184 u/L), aspartate transaminase (154 u/L), elevated levels of direct bilirubin (4.9 mg/dL), total bilirubin (5.8 mg/dL), hypoalbuminemia, and prolonged hemostasis were also found in the laboratory test. Lactic acidosis with normal renal function test and electrolyte serum. Urinalysis showed hemoglobinuria and bilirubinuria. The patient had no history of liver disease. Due to the presence of fever, jaundice and previous living in malaria endemic areas, the patient was now suspected cause of malaria fever and then malaria rapid diagnostic test and microscopically was performed and the results shows malaria ICT rapid test: *Plasmodium* (+), *Plasmodium falciparum* (+), a blood smear revealed *P. falciparum*, in ring stages schizonts, and gametocytes; index parasitemia 4.6% parasite/pL. He was diagnosed with severe falciparum malaria with suspected malarial hepatopathy, hepatocelluler jaundice caused by malarial hepatopathy and thrombocytopenia. The differential diagnosis was a hemolytic anemia associated with malaria. The patients was transferred to high care unit (HCU) with nasogastric tube (NGT) alimentation, albumin correction and Artesunate therapy with 2.4 mg/kg was given immediately then at 12, 24 hourly then daily. The patient also treated with ceftriaxone 1 gr 2 times/day, paracetamol 500 mg 3 times/day, and vitamin K 3 mg/day IM.

After three days treated in HCU, the patients showed several improvements. He was finally able to eat, bilirubin levels was decreased and parasitic index also decreased and artesunate injection was discontinued and then followed by parenteral antimalaria treatment for 3 days, dihydroartemisinin-piperaquine 2–6 mg/kg/day for three days and single dose primaquine of 0.25 mg/kg was administered. After five days in HCU, the patients showed very encouraging progress. Blood smear showed no parasite found. Oral antimalaria was discontinued after three days. The patient was discharged after nine days.

DISCUSSION

Suspected cases of malaria can be considered as medical emergency because it is potentially life threatening. Clinical manifestation of malaria are varied from mild to severe. Classic symptoms include high fever, with a period of shivering and diaphoresis. Severe malaria manifestation such as impaired consciousness, acidosis, hypoglycemia, severe malarial anemia, renal impairment, jaundice, pulmonary edema, significant bleeding, shock, and

hyperparasitemia.[1,2] *P. falciparum* frequently caused microvascular obstruction because of the adhesion of infected erythrocytes to vascular endothelial cells (sequestration). Tissue hypoxia due to this process caused ischemia. Organs frequently involved are the brain, kidneys, lungs and gastrointestinal tract. In addition, auto agglutination/rosette can also occur due to adhesions. Other complications such as hypoglycemia and lactic acidosis are common in falciparum malaria.[3,6] In this patient, we found almost all the severe malaria presentation, such as impaired consciousness, respiratory distress, prostration, jaundice, anemia, hyperparasitemia, and acidosis.

Malaria diagnose are definite if there are malaria detected in the blood. WHO recommend microscopic examination and rapid diagnostic test (RDT) to all suspected malaria patients before the treatment begins.[1,7] Thin and thick blood smear to find, determine its species, morphology, and the density of *Plasmodium* parasite. On some condition, RDT can be used as an adequate diagnostic tool.[7] In this patient, microscopic examination and RDT revealed *Plasmodium falciparum* malaria in ring stages, schizonts, and gametocytes with index parasitemia 4.6%.

Plasmodium life cycle has 2 hospices, mosquito and human. Asexual cycle occurs inside the human body (schizogony*)* and the sexual cycle occurs inside the mosquito (sporogony) that produce sporozoite. The sporozoite of female *Anopheles* mosquito enters the human blood stream through bites and in a span of 1–2 hours will infest hepatocyte cells as the target cell, and started the exo-erythrocytic stadium that lasts for 32 weeks. Inside the hepatocyte cell, parasite grow to be schizont and continue to grow to be merozoite, depends on the species. Hepatocyte cells that contain parasite (schizont) will rupture and exudes merozoite to the blood stream, some will phagocytize and some will infest on erythrocyte cells. Erythrocytic cycle start when merozoite enters erythrocyte cells. Parasite starting to form trophozoite which will divide into merozoite. With the completion of division, the infected erythrocyte (schizont) will rupture releasing merozoites, bilirubin pigment and debris will enters plasma. Parasite will infect other erythrocyte and repeating the schizogony cycle. After entering 2–3 blood schizogony cycle, some will form gametocytes the sexual form (male and female) which will go through sexual phase inside the mosquito's body, if a female *Anopheles* mosquito suck blood that contains gametocytes. Ruptured erythrocyte during merozoite release will cause clinical symptoms on the patient. In severe cases, severe hemolysis can lead to anemia and jaundice, exacerbated also by the process of infected erythrocyte phagocytizes in the spleen. Severe anemia could happen on *P. falciparum*.[6,8]

Jaundice commonly occurs on severe malaria infection. Definition of malaria jaundice namely if the present of asexual stage *P. falciparum* accompanied by bilirubin levels ≥ 3 mg/dL. Malaria with jaundice according to WHO criteria in 2010 included in severe malaria if accompanied by a parasite count > 100,000/mL which is equivalent to a parasitemia index of > 2%. Jaundice in malaria can be caused by intravascular hemolysis, DIC or malaria-related liver disorders.[1,4] Erythrocyte hemolysis has a significant contribution to increase bilirubin in severe malaria *P. falciparum*, which invades erythrocytes in large numbers, will be destroyed in the spleen which will result in hemolysis anemia and enlargement of the spleen. This process is also characterized by an increase in indirect bilirubin levels without a significant increase in liver enzymes.[9]

Altough indirect hyperbilirubinemia is more common in malaria, we reported a case with hepatocellular jaundice or the-so-called malaria hepatopathy with incidence of approximately 4.47% case in Asia.[10] Harris et al found that patients with jaundice had direct hyperbilirubinemia and elevated liver enzymes suggesting hepatocellular damage.[11] Malarial hepatopathy is a term that is often used to describe hepatocytic dysfunction in severe malaria, although inflammation does not occur in the liver parenchyma. It is characterized by an increase in serum bilirubin along with an increase in serum glutamate pyruvate transaminase (SGPT) more than 3 times the normal threshold value. This occurred after previously confirmed that there was no exposure to hepatotoxic drugs and serologically there was no viral hepatitis infection.[4,10] Malarial hepatopathy was associated with a higher incidence of cerebral malaria, shock, acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI). Malarial hepatopathy had significant association with duration of hospitalization, parasite clearance time, fever clearance time and jaundice clearance time.[10] It is an epiphenomenon in severe malaria and indicative of severe disease.

Hepatosplenomegaly on malaria is associated with the liver as the first target of *Plasmodium* and spleen as the filter of the infected erythrocytes. Apart from the liver, the spleen is an organ that is directly affected by malaria infection. Spleen has the ability to selectively filter then destroy erythrocytes containing *Plasmodium*, and modulate the immune response.[12] Our patient

experienced hepatosplenomegaly with elevated transaminase serum and direct hyperbilirubinemia, hypoalbuminemia, and prolonged hemostatis as result as liver dysfunction.

Thrombocytopenia, although not included in the criteria for severe malaria, is a frequent complication of *P. falciparum* and *P. vivax*. Patel et al wrote that the platelet incidence < 150,000/mm^3 occurred in 24–94% of patients with acute malaria, and there was no difference between the 2 species.[13] Thrombocytopenia in malaria is caused by many factors such as impaired coagulation, splenomegaly and changes in the bone marrow microenvironment related to platelet destruction by autoantibodies, oxidative stress, and other unexplained factors.[9,13] The incidence of heavy bleeding in malaria is very rare, usually only gum bleeding, epistaxis and petechiae; because primary hemostasis is still normal. This is evidenced by the frequent finding of megakaryocytes in peripheral blood smears and thrombopoietin levels which actually increase in acute malaria infection.[13] Recently, there are no standard guidelines for the management of malaria patients with thrombocytopenia. Platelet transfusion for prophylaxis is indicated only if the platelet count is < 10,000/mm^3 or there is evidence of impaired production in the bone marrow, as well as maintaining platelet levels between 50,000–100,000/mm^3 in patients undergoing surgery. In cases of malaria with bleeding manifestations and suspected disseminated intravascular coagulation (DIC), platelet transfusion is an indication. Corticosteroid administration is not recommended because thrombocytopenia will improve on its own along with the clinical improvement of malaria.[9,13]

The artemisinin derivate, artesunate, is established as the treatment of choice for severe malaria. IV artesunate showed a 35% reduction in death rates in adults in Asia when compared with quinine. In contrast to quinine, artesunate action on early circulating ring-stages reduces the risk of sequestration of red blood cell infected with mature forms of *P. falciparum* and related clinical manifestations of severe malaria. Artesunate, available in vial of 60 mg dry powder of artesunic acid with 0.6 mL of 5% sodium bicarbonate as solvent. Its use is by mixing dry artesunic powder with its solvent and adding 3–5 cc of 5% dextrose solution. This solution is given at a dose of 2.4 mg/kgBW intravenously 3 times at 0, 12, 24 hours then every 24 hours until the patient can take medication. If the patient can take medication, replace it with a dihydroartemisinin-papraquinin (DHP) regimen or other ACT for 3 days + primaquine tablets for 1 day. No need to adjust the dose if organ failure persists.[14]

CONCLUSION

Severe falciparum malaria can be life-threatening unless it is early diagnosed. Joundice is a common feature of its, altough indirect hyperbilirubinemia is more common in malaria as a results of anemia hemolysis, direct hyperbilirubinemia can occur due to liver dysfunction, so called malarial hepatopathy. The Artesunate regiment treatment given will give the best results because of its great efficacy.

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