

Management Malaria with Jaundice

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Abstract

Malaria is the most important parasitic disease in the world related to high morbidity and mortality. Jaundice is one of the common manifestation of severe malaria in adults and its incidence vary from 10-45% in different regions. Presence of jaundice in malaria indicates a more severe illness with higher incidence of complication. Jaundice plus evidence of other vital organ dysfunction vital as one of manifestation of severe malaria based on WHO guideline 2010. Jaundice in severe malaria caused by multi factorial and can result from haemolysis of parasitized and non-parasitized red blood cell, hepatic dysfunction and possibly an element of microangiopathic haemolysis associated with disseminated intravascular coagulation. Awareness of malaria biliosa is important to prevent complication and mortality. Death from severe malaria often occurs within hours of admission to hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible. Management of severe malaria comprises four main areas: clinical assessment of the patient, specific antimalarial treatment, adjunctive therapy and supportive care. Many trials are consistent and suggest that artesunate is the treatment of choice for adults with severe malaria. Management of malaria biliosa is not different from management the other severe malaria. Here we report one case of jaundice in falciparum malaria (malaria biliosa). There was problematic in management but the treatment malaria with jaundice with adequate dose of artesunate injection improved patient's health status and parasitological improvement.

Keywords: Malaria; Jaundice; Falciparum; Haemolysis

Background

Malaria is still a very important health problem in developing countries, especially in tropical areas with 300-500 million new cases and one million deaths per year [1]. Severe or cerebral malaria mortality in Indonesia ranges from 10.9 to 50.0%, depending on management procedures ranging from the speed of diagnosis and anti malaria treatment at health facilities. Clinical manifestations of severe malaria may vary from loss of consciousness to certain organ function impairment and metabolic disorders. Jaundice is common in malaria infections around 2.58% and can be caused by hemolysis or liver dysfunction, due to the reduced blood flow to the liver and will return to normal, probably caused by sequestration and sitoadheren that causes microvascular obstruction. This condition is often referred to as malaria hepatitis (biliosa) [2]. Here reported a case of falciparum malaria with problems in management where the right dose of artesunate injection with improvement clinical and parasitological occurs.

Case Report

A man, 39 years old came to the hospital with a referral from internal medicine specialist (internist) with a suspected diagnosis of typhoid fever, dengue fever and hepatitis. The patient complains of fever since the seven days, intermittent fever, sometimes with chills and sweats, there is a fever-free period. Fever accompanied by headache, nausea and vomiting. Yellow eye colors appear accompanied urine like tea water since 2 days. Patients do not have the same history of pain before, nor is there a history of systemic diseases such as high

blood pressure, diabetes, liver disease, heart, kidneys and lungs. In the family of the patient, no one suffered from the same disease. History of treatment only with medication for fever (paracetamol). Patients with a history of working in malaria-endemic areas (Sumbawa) and back home a week before illness. On physical examination (Table 1) found conscious awareness, blood pressure 140/90 mm Hg, pulse 114 beats / minute, regular, respiration 21 / min, axillary temperature 38, 8°C , 75 kg body weight. Conjunctiva not seems anemic but jaundice on sclera. No enlarged lymph nodes in the neck. Examination of the heart: heart sounds 1 and 2 regular without murmurs, in the lungs, vesicular breath sounds, no crackles or wheezing. On abdominal examination there is an enlargement of the liver three fingers below the costal arch with blunt edges, flat and pain suppression. Lien was not palpable. Examination of genitalia and extremities did not seem abnormality. The results of a complete blood count; WBC $9.77 \times 10^3/\mu\text{L}$, HGB 11.6 g/dL, HCT 35.1% and PLT $64 \times 10^3/\mu\text{L}$. Ig M and Ig G anti dengue negative. Examination of malaria with rapid test showed positive results for *Plasmodium falciparum* and *Plasmodium vivax* negative. Diagnosis of the patients with falciparum malaria, the treatment given were IVFD Ringer Lactate (RL) 20 drops / minute, paracetamol 1 gram by infusion every 8 hours, ACT (arthemycine combination therapy) in the form of a combination of artesunate 50 mg and amodiaquine 200 mg each 4 tablets per day for 3 days, primaquine 2 tablets 15 mg single dose, ceftriaxone 2 x 1 gram intra vena. After 3 days of administration of ACT, the fever had finish but jaundice still persistent. Furthermore, the blood replays malaria serology (RT) where the results remain positive on the *Plasmodium falciparum* and *Plasmodium vivax* negative. Liver function tests with results: total bilirubin 10.2 mg/dL, bilirubin direk 7.3 mg/dL, AST 79 U/L and ALT 83 U/L. Complete blood count: WBC $7.28 \times 10^3/\mu\text{L}$, HGB 10.0 g/dL, 29.9% HCT and PLT $115 \times 10^3/\mu\text{L}$. Based on these results, the management malaria by

administration of intravenous artesunate injection of 120 mg slowly every 12 hours on the first day followed by the same dose every 24 hours. Evaluation after three days of administration of intravenous artesunate, patients return fever reaches 38, 4°C and results of CBC: WBC $12.13 \times 10^3/\mu\text{L}$, HGB 9.7 g/dL, 31.0% HCT and PLT $32.9 \times 10^3/\mu\text{L}$, liver function: total bilirubin 6.51 mg/dL, bilirubin direk 2.15mg/dL, AST 90 U/L, ALT 93 U/L, urea 8.9 mg/dL, creatinine 1.3 mg/dL, while glucose 121 mg/dL, *Plasmodium falciparum* positive by RDT. Because it is still positive on the *Plasmodium falciparum*, artesunate dose increased to 180 mg every 24 hours, ceftriaxone replaced with cefepime 2 \times 1 gm and doxycycline 2 \times 100 mg. After administration of artesunate at a dose of 180 mg for two days, the fever go down and *Plasmodium falciparum* negative in serology and

microscopic. Artesunate injection was stopped, followed by the same dose of doxycycline for 7 days. Three days without fever, the patient was discharged with good clinical condition and laboratory findings: WBC $8.65 \times 10^3/\mu\text{L}$, HGB 11.4 g/dL, 34.1% HCT, PLT $447 \times 10^3/\mu\text{L}$, liver function: total bilirubin 5.08 mg/dL, bilirubin direk 1.48 mg/dL, AST 94 U/L, ALT 10² U/L. Blood culture results klebsiella pneu, sp pneumonia sensitive to amikacin, gentamicin, imipenem, meropenem, and chloramphenicol. On a visit polyclinic 11 days after discharge from the hospital, the patient looked healthy, had no complaints with the results of liver function are already close to normal values: total bilirubin 2.81 mg/dL, bilirubin direk 1.01 mg/dL, AST 61U/L and ALT 90 U/L, patients treated with hepatoprotective only.

Parameter(clinic/lab)	13/8 \times 10	15/8 \times 10	18/8 \times 10	24/8 \times 10	4/9 \times 10
Symptoms	Fever for 7 days, intermiten, jaundice (+)	Fever go down Jaundice (+)	Fever go up	Clinical improve No fever Jaundice go down	no fever no jaundice
Malaria lab	<i>Plasmodium falciparum</i> +(RDT)	<i>Plasmodium falciparum</i> +(RDT)	<i>Plasmodium falciparum</i> +(RDT)	<i>Plasmodium falciparum</i> RDT-micros neg	
WBC ($\times 10^3/\mu\text{L}$)	9,77	7,28	12,13	8,65	
HGB (mg/dL)	11,6	10,0	9,7	11,4	
HCT (%)	35,1	29,9	31	34,1	
PLT ($\times 10^3/\mu\text{L}$)	64	115	329	447	
bil. Total (mg/dL)		10,2	6,51	5,08	2,81
bil. Direk (mg/dL)		7,3	2,15	1,48	1,01
SGOT (U/L)		79	90	94	61
SGPT (U/L)		83	93	102	90
Treatment	ACT, primakuin 2 tab, ceftriaxon 2 \times 1 gm	artesunat intravena 120mg	Artesunat intravena 180 mg doxycycline 2 \times 100 mg cefepime2 \times 1 gr	artesunat stop doxycycline for 7 days	hepatoprotective

Table 1: Progress of clinical and laboratory.

Discussion

Diagnosis of malaria rapid and precise is needed in the management of malaria cases, mainly associated with infection *Plasmodium falciparum* causes severe malaria or complications. The history of travel to malaria endemic areas approximately 2 weeks before the appearance of clinical symptoms is very important in addition to the classic triad of symptoms of malaria, namely the period of cold (shivering) followed by periods of hot and sweaty period. Once clinically suspected of suffering from malaria, laboratory examination to find parasites should be promptly carried out. Various ways can be done from a conventional light microscope examination were stained with Giemsa (gold standard) until more modern examinations such as fluorescence microscopy, flow cytometric, automated blood analyzer, serology, molecular methods as well as with a variety of laser desorption mass spectrometry [3,4]. In addition to diagnosis, microscopic examination can be used to evaluate the results of treatment and this cannot be done with a rapid method (serological). Examination with RDT (rapid diagnostic test) is based on the detection of the malaria parasite antigens using methods immunochromatography in the form of the dipstick. This test is very useful in emergency rooms, amazing events and in remote areas that

are not available laboratory facilities as well as to survey [5]. In this case initially diagnosed with suspected typhoid fever, dengue fever and hepatitis. Once in the hospital and do history and physical examination more through diagnosis of malaria is confirmed by serological methods (RDT). Cases showing typical clinical symptoms of malaria such as high fever accompanied by chills and sweating intermittent and history coming from endemic areas (Sumbawa). For early diagnosis ideally using the gold standard examination by microscopic examination of thick and thin drops which can also assess the parasite density for the assessment of therapeutic response. In an emergency, it is justified serology but should be combined with microscopic examination

Jaundice is a common manifestation of severe malaria in adults with an incidence varying from 10-45%. In the past decade, cerebral malaria dominates the clinical manifestations of severe malaria, but recently a combination of hepatic dysfunction with kidney failure more is obtained [6]. Malaria with jaundice were found in Southeast Asia, including Indonesia. Thailand reported in approximately 30% of malaria cases treated in hospitals are malaria with jaundice. Studies in Vietnam reported 63% of cases of malaria in adults with acute renal failure also with jaundice and 20% without renal failure. Research in

North Sulawesi (Bethesda hospital and Gunung Maria Tomohon hospital) from 1991 to 2000 found 54.2% of 271 patients with severe malaria were treated malaria with jaundice (total bilirubin > 3 mg/dL) [1,7]. Definition of malaria with jaundice was *Plasmodium falciparum* asexual stage in the examination of peripheral blood with bilirubin levels above 3 mg/dL. Malaria with jaundice classified as severe malaria according to WHO criteria in 2010 when the vital organ dysfunction is accompanied others.³ Presence of jaundice in malaria sign of malaria more severe disease with higher incidence of complications and bad prognosis [8] In this case, falciparum malaria obtained (by serological methods/RDT) with total bilirubin levels were 10.2 mg/dL and direct bilirubin 7.3 mg/dL. Bilirubin levels decline along with the improvement of clinical conditions malaria until close to normal. Based on the above data, in case of jaundice is caused by malaria

The liver is the first organ exposed to *Plasmodium falciparum* malaria cases, after the initial phase (pre-erythrocytic) merozoites into the bloodstream and no exo-erythrocytic phase schizogony as well as vivax malaria. In liver biopsy seemed Kupffer cell hyperplasia, mononuclear cell infiltration and deposit pigment, some studies did not show changes in the structure of the liver or mild hepatocyte cell swelling. Acute malaria also interferes with the function of an enzyme microsomal cytochrome P 450. Liver function disorders also are common and sometimes encephalopathic on some cases [9]. The cause of jaundice in *Plasmodium falciparum* malaria is a multi-factor, among others:

1. Intravascular Hemolysis of red blood cells
2. The non-p Hemolysis of red blood cells (innocent bystanders)
3. Possible microangiopathic hemolysis associated with DIC (Disseminated Intravascular Coagulation)
4. Hepatic dysfunction
5. Hemoglobinopathy
6. Hemolysis due to drugs
7. G6PD deficiency

Hyperbilirubinemia occurs usually indirect type, often only mild jaundice with bilirubin below 5 mg/dL although sometimes bilirubin can reach more than 50 mg/dL. Usually elevated liver enzymes (3-8 fold) but SGPT levels never reached such levels of acute hepatitis. Routine liver biopsy on malaria with jaundice is not ethical and not helpful in the diagnosis and management. Recovery jaundice in malaria faster than with acute viral hepatitis needs more time [1,6]. Complications of falciparum malaria usually appear on the five days of fever [10]. Increased liver enzymes indicate hepatic dysfunction, severe hepatic dysfunction in malaria usually if there is concurrent infection with hepatitis virus infection or underlying disease are liver disorders [11]. Thrombocytopenia on malaria is caused by many factors such as coagulation disorders, splenomegaly, and bone marrow changes in antibody mediated platelet destruction, oxidative stress and there is said to be the role of platelets as co factors in precipitating of severe malaria [12]. Malaria causes jaundice in case of possible because of a combination of hemolysis and hepatic dysfunction due to indirect bilirubin level as a marker of hemolysis is quite high (2.9 mg/dL) in addition to the course of the disease there is a decrease in hemoglobin (11.6 g/dL to 9.7 g/dL) were then increased again in line with clinical improvement of malaria (HGB 11.4 g/dL), but unfortunately the evidence of hemolysis other evidence was not examined. The role of hepatic dysfunction seems to be smaller than hemolysis because of SGOT and SGPT increased only lightly. In the case of jaundice began to appear on day 5 of fever. Signs of multi-organ failure are not found

in other cases, renal function was within normal limits (urea 8.9 mg/dL, creatinine 1.3 mg/dL), except where thrombocytopenia. The presence of thrombocytopenia was suspected of a dengue infection, but the results of both dengue serology Ig M and Ig G negative. Thrombocytopenia in case possibly related to malaria because platelets also increased (from $64 \times 10^3/\mu\text{L}$ be $447 \times 10^3/\mu\text{L}$) in line with improved malaria

The management of malaria with jaundice in principle the same as the management of severe malaria (malaria with complications), namely the elimination of malaria as quickly as possible with parenteral administration of anti-malarial drugs, symptomatic and supportive therapy and treatment of complications. Selection of anti-malarial drugs in severe malaria is a derivative artemisinin (intravenous artesunate, artesunate suppositories, intra-muscular artemether, artemotil intramuscularly) as the first choice and cinchona (quinine or quinine antipirin HCl) as a second choice. Artesunate dose is 2.4 mg/kg intravenously at the time of hospital admission (0 hours) followed by the same dose 12 hours, 24 hours and then 2.4 mg/kg every 24 hours until the patient's condition improves replaced with artesunate oral 2 mg/kg until 7 days [3,7,13].

In the case initially given ACT (artemisinin combination therapy) is a combination of artesunate 50 mg and amodiaquine 200 mg for 3 days with primaquine 15 mg 2 tablets single dose, where the result is not satisfactory (*Plasmodium falciparum* remains positive and jaundice are stable). Replacement with artesunate intravenous (120 mg) was already a good choice, but unfortunately the dose given is inadequate. It should be given 2.4 mg/kg, so we need about 180 mg (patients with body weight 75 kg). After administering the proper dosage (180 mg) improvements in clinical and parasitological laboratory was found. Based on the theory of the early patients should have received intravenous artesunate or artemether intra muscular. The early recognize jaundice in malaria and appropriate treatment early member will give a better prognosis

Summary

Reported one case of malaria with jaundice. Early recognition is required against jaundice in malaria cases and provide appropriate therapy to severe malaria. Awareness of malaria biliosa is important to prevent complication and mortality

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