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A Rare Case of Severe Malaria with Multiple Complications

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Abstract: ***Malaria represents a medical emergency because it may rapidly progress to complications and death without prompt and appropriate treatment. Severe malaria is almost exclusively caused by Plasmodium falciparum. The incidence of imported malaria is increasing and the case fatality rate remains high despite progress in intensive care and antimalarial treatment. Clinical deterioration usually appears 3-7 days after onset of fever. Complications involve the nervous, respiratory, renal, and or hematopoietic systems. Intravenous artemisinin is the most widely used drugs in the initial treatment of severe falciparum malaria. As soon as the patient is clinically stable and able to swallow, oral treatment should be given. The intravascular volume should be maintained at the lowest level sufficient for adequate systemic perfusion to prevent development of acute respiratory distress syndrome. Renal replacement therapy should be initiated early. Exchange blood transfusion has been suggested for the treatment of patients with severe malaria and high parasitemia. For early diagnosis, it is paramount to consider malaria in every febrile patient with a history of travel in an area endemic for malaria.***

Keywords: Plasmodium falciparum, severe malaria, treatment

1. Introduction

Malaria is a parasitic infectious disease caused by *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* that attacks erythrocytes and characterized by the discovery of the shape asexual in the blood. It transmitted by the bites of infected female Anopheles mosquitoes.1Among the species, *P. falciparum* causes severe clinical courses and is classically associated with significant morbidities and case fatality. The World Health Organization (WHO) defines a case of severe malaria as clinical or laboratory evidence of vital organ dysfunction, which include impaired consciousness, acidosis, hypoglycemia, severe malarial anemia, renal impairment, jaundice, pulmonary edema, significant bleeding, shock, and hyperparasitemia (>10%).2Malaria is still an endemic disease in Indonesia, despite years of government efforts to cure and prevent malaria. WHO has a goal to reduce malaria case incidence globally at least 90.0% in 2030 compared with 2015. Papua is one of the high endemic areas in Indonesia, making Papua one of the target areas for malaria elimination programs.3Treatment of severe malaria consists of 3 important components, i. e. specific treatment (anti malaria), supportive treatment (general care and symptomatic treatment), and complications treatment. Prognosis of severe malaria depends on speed and accuracy diagnosis and treatment.4In this paper, I sought to report a rare case of multiple complicated with severe falciparum malaria.

2. Case Report

On January 15, 2018 a previously healthy 30 - year - old male, who came from Java 20 days ago presented with fever, vomiting, nausea and dizziness for 5 days. Two days ago the patient went to public health center and received chloroquine. He also complained the passage of black urine and decreased urine volume for 1 day (less than 200cc/ 24 hours). He did not take medications for malaria prophylaxis before the travel. He had a history of mosquito bites but denied fever during his stay in Papua. He visited to the emergency room of DOK 2 Hospital under the impression of septic shock. His laboratory findings revealed thrombocytopenia and disseminated intravascular coagulation. The initial vital signs were as follows: blood pressure 80/48 mm Hg; pulse rate 135 beats per minute; respiratory rate 20 breaths per minute; and axillary temperature 39.0℃. The patient was alert but acutely ill looking. Hissclerae were icteric. The liver was palpable at two fingerbreadths and spleen was palpable at one fingerbreadth. Blood test results: white blood cell 13.8×10^3/µL; hemoglobin 9.5 g/dL; hematocrit 34.1%; platelet 60×10^3/µL; sodium 131 mmol/L; potassium 3.6 mmol/L; chloride 99 mmol/L; blood urea nitrogen 180 mg/dL; creatinine 7.5 mg/dL; aspartate aminotransferase 67 IU/L; alanine aminotransferase 140 IU/L; albumin 2, 86 g/dL; total bilirubin 14.7 mg/dL, direct bilirunin 10, 7 mg/dL, blood sugar 100 mg/dL and prothrombin time international normalized ratio (INR) 1.48 INR. Stained peripheral blood smears showed that 5% of the red blood cells were infected with *P. falciparum*. Chest x - ray was normal.

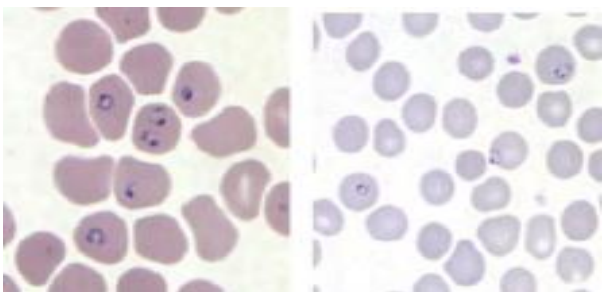

Figure 1: Different morphological characteristics of Plasmodium falciparum were observed in case patients (thin film; Wright - Giemsa stain, x1.000)

The clinical diagnosis was severe malaria, with complication anemia, black water fever, malaria related acute kidney

injury (MAKI), hepatic dysfunction and jaundice. The patient was admitted to the intensive care unit for close monitoring, and management. As long as patient care is still complaining sometimes appears fever, no bleeding the gastrointestinal tract, but passage of the urine is still black. Routine blood obtained Hb levels (7.6 g/dL), and kidney function decreases (203 mg/dL urea and 9.89 creatinine mg/dL), while the total bilirubin level started to improve. Because the patient had low urine production (200cc/ 24 hours) and creatinine urea levels which continues to increase patient dohemodialysis. Patient also receive therapy specifically for malaria, was Artesunate 2.4 mg/kg body weight (i. v) at hour0 and 12, 24 o'clock Artesunate1.2 mg/ kg body weight /day (day 1). On day 2 to 7 the patient receive Artesunate with 1.2 mg/ kg body weight/day. Other therapies that given was intravenous vancomycin and meropenem was administered intravenously to cover possibly combined bacterial infection, intravenous inotropic drugs were infused continuously, omeprazole injection 40 mg/12 hours, sistentol tablet if fever, curcuma 3x1 tablet and 3 bags packed red cell for transfusion.

After 5 days, stained blood smears showed 1% of the red blood cells were infected with malarial parasite. Clinical condition has improved; therefore, the patient was transferred to the general ward. Patient can drink well, therapy continued with primaquine oral therapy tablets 75 mg single dose and dihydroartemisinin - piperaquine (DHP) 1x3 tabs for 3 days. On the 7th day, blood smears showed no parasitized red blood cells for the first time. On the 8th day, inotropic was tapered off. On the 9th day, even though the patient's blood smears were negative for 3 consecutive days. After several hemodialysis the kidney function has improved also with enzyme testing transaminases and routine blood was batter. On the 12th day, urine color has returned to yellow. On the 15th day, the patient was discharged with no sequela.

3. Discussion

I had been reported a rare case about multiple complication of severe falciparum malaria in a Javanese people, who traveled to Papua. Malaria which is caused by a Protozoan from genus Plasmodium is a global health problem with an estimated incidence of about 216 million worldwide causing 445, 000 deaths in 2016.1, [5] Four species of genus Plasmodium including falciparum, vivax, malaria, and ovale cause malaria when sporozoites enter the circulation and subsequently the liver after being bitten by a mosquito which is infected.2 All species have similar clinical symptoms such as fever, chills, sweating, headache, nausea, and general weakness.4, [5]In Indonesia, clinicians should consider malaria as one of the differential diagnosis if the patient has travel history provides the most important clue. Definitive diagnosis is obtained by microscopic demonstration of malaria parasites on stained blood smears. If initial blood smears are negative but the patient is still suspected of having malaria, the smear should be repeated every 12 to 24 hours for 72 hours.6The most common laboratory abnormalities are thrombocytopenia, hyperbilirubinemia, and anemia.7 Rapid malaria tests are now available and target histidine - rich protein 2 of Plasmodium falciparum or lactate dehydrogenase that is species specific. Their sensitivity is high but specificity is low; therefore microscopy is commonly done to supplement the rapid tests. The choice of antimalarial drug is based on the species, potential drug resistance, and the severity of disease. Therefore, clinicians should always check an up - to - dated information about malaria endemicity and drug resistance.[1, 8]

In this case, the patient visited Papua20 days ago. Papua is estimated to be a high risk area of malaria for Indonesia by Centers for Disease Control and Prevention, and the incidence of malaria in Indonesia was several hundred thousand infections and approximately 2, 000 deaths each year in Indonesia. Progress toward malaria elimination has been made in the western part of the country but is stagnant in Papua Province, which accounts for 74% of reported cases annually.9 There are three components for treatment of severe malaria, consists of: specific treatment with antimalarial, supportive treatment and complications treatment. The current recommendation states that patients with severe malaria require intensive care and immediate initiation of treatment of intravenous artesunate. Intravenous (IV) artesunate (ART) is the first line drug to treat severe malaria. Artesunate is a hemisuccinate ester of dihydroartemisinin (DHA), known as the most potent compound of the class of artemisinin derivatives. Artesunate is also included in drug combination (artemisinin - based combined therapies: ACTs) to be used orally for non - severe malaria treatment.[3, 6, 8]

In this case, the patient had many complication, there was: anemia. Malaria anaemia (MA) is a multifactorial disease for which the complex etiological basis is only partially defined. Severe MA is one of the main clinical presentations of severe malaria caused by *P. falciparum*. The aetiology of severe MA in malaria endemic areas may include a number of discrete as well as overlapping features, such as lysisof infected and uninfected RBCs, splenic sequestration of RBCs, dyserythropoiesis and bone marrow suppression, infectious diseases, and chronic transmission of malaria.9While haematological insults resulting in moderate and severe anemia and thrombocytopenia were also important factors associated with AKI both at 48 hours and day 7. Both anemia and thrombocytopenia are standalone complications of severe malaria and as such highlight the coexistent severity at presentation of such patients. Anemia contributes to circulatory insufficiency and hypoxic state that has the potential to worsen the renal impairment in MAKI. Severe thrombocytopenia may predispose to systemic bleeding leading to hypotension or shock or renal hemorrhage that will worsen the AKI. Improvement in platelet counts upon institution of appropriate treatment is frequently used a clinical parameter to gauge treatment response to the systemic symptoms of malaria by clinicians. The high presence of thrombocytopenia may be considered as a marker of disease severity as indicated by Maina et al. and not parasite burden as no association was observed between platelet counts and parasite density. Albeit studies in Nigeria revealed children with low platelet counts were likely to have anaemia, findings from this study reveal no significant association between platelet counts and Hb or parasite density.[5, 6, 10]

Another complication was black water fever. Blackwater fever is a phenomenon demonstrated as acute intravascular hemolysis with hemoglobinuria, and a dramatic fall in hemoglobin value with scant or absent parasitemia. It usually occurs in patient living in malaria endemic area for long period, and is associated with irregular taking of amino - alcohol drugs (e. g., quinine, halofantrine, or mefloquine) for prophylaxis and treatment purpose. Blackwater fever is a rare but one of potential complication s following antimalarial treatment. The pathogenesis of blackwater fever remains unclear; however, hypotheses had been postulated previously. Historically, the dramatic decrease in incidence of blackwater fever was evident when quinine was superseded by chloroquine in 1950 and the reemergence was shown after the reintroduction of quinine because of the development of resistance to chloroquine in *P. falciparum*. This historical context strongly suggests that quinine plays a major role in the development of blackwater fever. In a French study to investigate the potential causative agent of black water fever, quinine was the possible potential trigger in 29.5% of cases, halofantrine in 26.5% of cases, and mefloquine in 17.5% of cases. The median time interval from the last administration of these drugs to the onset of black water fever was 24 hours (range, 5 to 120 hours). In the patient presented in this report, there are clinical evidences to suspect the blackwater fever: a recent stay in a malaria endemic area, chloroquine, recurrent fever, abrupt hemolysis, and hemoglobinuria in the absence of parasitemia.5, [11] There is no evidence of other infections or cause of hemolysis in laboratory examination. Chloroquine is potential causative agents of black water fever in this case on the previous report.

Acute kidney injury (AKI) is one of the most dreaded complications of falciparum malaria. Resistance to drugs and increased virulence increases the chances of this and other complications of malaria. Several hypotheses for pathogenesis of malaria associated kidney injury are proposed including mechanical obstruction by infected red blood cells and exaggerated immune response but exact mechanism is not known.1[1, 12] In malaria endemic countries, up to 40% of patients with severe P. falciparum malaria can have acute kidney injury and mortality can be as high as 75% if renal replacement is delayed. This kidney injury can be part of multiorgan dysfunction or can be the only organ injured and has better prognosis when renal injury is not accompanied with other organ failure. One study in Ethiopia of patients with severe malaria showed a third of them had some degree of acute kidney injury while another showed 21% of consecutively acute kidney injured patients had Plasmodium falciparum infection. Anemia, thrombocytopenia, and proteinuria also frequently accompany AKI in such patients.1[2, 13]Mortality of malaria associated kidney injury is reported to be as high as 39.7%. The mechanisms of nephroinflammation in MAKI are different compared to pathologic mechanisms of systemic inflammation in AKI due to bacterial sepsis where determination of acute phase proteins may hold more value.1[3]Among the common clinical dilemmas in MAKI is when to institute dialysis. In this case, our approach was to dialyse patients based on clinical indications rather than just basing the decision on the patient's creatinine. So while changes in the patient's creatinine were used to diagnose AKI, creatinine alone was not used as criteria for starting dialysis.[11]

Hepatic dysfunction and jaundice are common features of severe malaria. Histopathological changes in the liver range from hepatocyte necrosis, granulomatous lesions, Kupffer cell hyperplasia, malarial pigmentation, cholestasis, monocyte infiltrations to malarial nodules. These complications can contribute significantly to liver failure and other systemic complications. The underlying pathogenesis of liver damage is largely unknown. Liver function test (LFT) abnormalities were graded using an adaptation of the World Health Organization (WHO) Adverse Event Grading System 2003: mild LFT elevations (>1·0 ≤ 2·5× upper limit of normal (ULN)), moderate (>2·5 ≤ 5·0xULN), and severe (>5·0XULN) elevations. Abnormal bilirubin levels were not included in the incidence or grading of LFT abnormalities, since the bilirubin increases found in the imported malaria cases most likely reflect haemolysis and could possibly bias the elevated liver enzyme prevalence in imported malaria.[14]

This case gives us lesson to note such infection in non immune people with recent travel history and to be aware of possible complications during the course of treatment. *Plasmodium falciparum* causes severe clinical courses and is classically associated with significant morbidities and case fatality.1[3]Blackwater fever, anemia, acute kidney injury, hepatic dysfunction and jaundiceare some of the complications that arise in severe malaria. Rapid and comprehensive management of the patient will give a good outcome, as this patient recovers within 15 days of treatment.

4. Conclusion

Malaria should be included in the differential diagnosis of every febrile illness in a person with a history of travel to a malaria - endemic area. Delays in recognition and appropriate treatment of malaria increase morbidity and mortality. The major complications of severe malaria in this case was includeanemia, black water fever, malaria related acute kidney injury (MAKI), hepatic dysfunction and jaundice. Any of these complications can develop rapidly and progress to death within hours or days. Light microscopy of blood smears is the standard method for diagnosing malaria, although new and promising nonmicroscopic diagnostic methods are under development. All patients with severe malaria should receive parenteral treatment immediately. Currently, intravenous artemisinin derivatives in general are recommended for treatment of *P. falciparum* infections.

5. Declarations

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