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Severe falciparum malaria with acute kidney injury: a case report

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Abstract. Malaria is still a health problem in the world, particularly in Indonesia with high morbidity and mortality rate. Since infections with P. falciparum generally result in serious disease, their identification is important. We reported a case of kidney injury associated with malaria in a 36-year-old Australian who resided recently in Sumba Barat, Nusa Tenggara Timur, Indonesia who had been treated as malaria without knowing the species of plasmodium with oral dihydroartemisinine-piperaquine and primaquine. Clinical manifestation included jaundiced, thrombocytopenia, elevated creatinine and urea. The rapid diagnostic test for malaria and microscopic examination of blood smears were positive for P. falciparum. On the basis of this, the patient was diagnosed as having acute kidney injury as a complication of severe malaria. The patient was treated for malaria with intravenous artesunate for 3 days, then followed by oral treatment of dihydroartemisinine-piperaquine. He also had six rounds of dialysis after which he partially recovered renal function. This outcome is not always the rule. Prognosis depends much on early diagnosis and appropriate supportive treatment.

1. Introduction

Malaria is still a major health problem in the world and it occurs in 107 countries. It is estimated that 500 millions of people are infected by malaria with mortality rate over 1,000,000 cases each year. In Indonesia, 424 of 576 municipalities/cities (73.6%) are endemic area; therefore, almost forty-five percent of Indonesia citizen are having risk for malaria infection. Malaria cases are concentrated in the outer islands such as Papua, Maluku, Nusa Tenggara, Sulawesi, Kalimantan and Sumatera. Indonesia was home to over 230 million people in 2010. These islands also harbour 20 known anopheline vectors of malaria transmitting all four of the species of Plasmodium that routinely infect humans. By a narrow margin over Plasmodium vivax, P. falciparum is the most common cause of human malaria in Indonesia with an estimated 12 million (6–21 million) clinical cases of P. falciparum cases each year [1]. Diagnosis malaria is made by direct demonstration of parasites in blood[4]. According to the program by Ministry of Health, Republic of Indonesia, diagnosis should be made based on the gold standard blood microscopic test (thin and thick) [2].

All cases of falciparum malaria are potentially severe and life threatening, especially when managed inappropriately. A major reason for progression from mild through complicated to severe disease is missed or delayed diagnosis. Once diagnosed, the priority for treatment of complicated and severe disease is the parenteral administration of adequate, safe doses of an appropriate antimalarial, in the setting of the highest possible level of clinical care (i.e. usually an intensive care unit). Supportive management of complications such as coma, convulsions, metabolic acidosis, hypoglycaemia, fluid and

electrolyte disturbances, renal failure, secondary infections, bleeding disorders and anaemia is also important [3].

We reported one case of severe falciparum malaria presented with acute kidney injury who had been treated previously with oral dihydroartemisinin-piperaquine plus primaquin. Unrecognized or delayed diagnosis of severe falciparum malaria can lead to severe complications.

2. Case report

A-36-year-old Australian man, who had been in Sumba Barat, Nusa Tenggara Timur for several months, flew from Sumba to Bali and came in to our hospital on December 8, 2017 with history of fever for 3-4 days 7 days prior to consultation when he was in Sumba with additional symptoms of extreme fatigue, less urination, and yellowish colour of eyes and skin. He denied any severe headache, chest pain, shortness of breath, respiratory symptoms, diarrhea, joint aching, muscle aching, or abdominal pain. He was in Sumba for working. He did some watersports during his staying in Sumba. He didn't take any malaria prophylaxis. He was assessed in medical fascility in Sumba, had blood test from the fingertip and was told malaria with unknown species of plasmodium. He was then treated with DHP (dihydroartemisinin-piperaquine) plus primaquine. Because of persistent weakness and exhaustion, he then flew to Bali, did blood test in other laboratorium. The result were negative for Dengue, negative for malaria, and complete blood count showed low platelet count.

On admission, the patient was alert, blood pressure was 100/60mmHg, pulse rate was 62/min, respiratory rate was 16/min, he was afebrile with body temperature was 36,9C, and oxygen saturation was 97% on room air. On presentation he looked unwell with signs of moderate to severe dehydration and jaundiced. Physical examination reveals normal lung and heart condition, abdominal examination reveals no organomegaly palpable nor tenderness on palpation, no joint swelling, no skin rash, no significant gastrocnemius tenderness. His last urination was 12 hours before admission. His blood laboratory findings on admission were as follow: red blood cells (RBCs) 4.14x106 (reference range 4,5-6,2x106/uL), hemoglobin (Hb) 12,4g/dL (reference range 13.0-18.0 g/dL), hematocrit (Ht) 32.9% (reference range 40.0-54.0%), white blood cells (WBC) 10.56x103/uL (reference range 4.0-10.0/uL), platelets (Plt) 75x103/uL (reference range 150-400x103/uL), albumin 3.4g/dL (reference range 3.5-5.2g/dL), SGPT 152U/L (reference range <41U/L), SGOT 129U/L (reference range 129U/L), random glucose 95mg/dL (reference range 65-140mg/dL), blood ureum 296,04mg/Dl (reference range 16.6-48,5mg/dL), blood creatinine 11.91mg/dL (reference range 0.7-1.2 mg/dL), sodium 130mmol/L (reference range 136-145mmol/L), potassium 4.3mmol/L (reference range 3.1-5.1mmol/L), chloride 95mmol/L (reference range 98-107mmol/L), prothrombin time 10.5 second (reference range 9.9-11.6 seconds) with INR 0.92, APTT 26.9 second (reference range 26.4-37.6 second), bilirubin total 0.97 mg/dL (reference range <1.3mg/dL), direct bilirubin 0.83mg/dL (reference range <0.3mg/dL), indirect bilirubin 0.14mg/dL (reference range 0.0-0.7mg/dL). Blood gas analysis showed metabolic acidosis with pH 7.345, bicarbonat ($HCO3^-$)16.4mmol/L, pCO2 26.4mmHg, pO2 109mmHg.

We still strongly suspected our patient having malaria with other differrential diagnosis including typhoid fever, leptospirosis, hepatitis. Blood workup for those were ordered and the result were as follow: Salmonella typhi IgM was negative, IgG and IgM anti Dengue were negative, the serum hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) antibody, and human immunideficiency virus (HIV) were all negative. We repeated the test for malaria and rapid test came back positive for Plasmodium falciparum. Blood smear examination found Plasmodium falciparum ring form +1 (1-10 malaria parasite/100power-field). IgM anti Leptospira was negative. Initial urinalysis founds proteinuria (+3) with nitrite and leucocyte esterase, bilirubinuria, eyrthrocyte sediment 2-3/HPF . Chest X ray showed mild cardiomegaly and lungs were within normal limit. Abdominal ultrasound found hepatosplenomegaly, fatty liver, sludge gallbladder with cholelithiasis (tiny stone 2.8mm), bilateral acute parenchymal kidney diseases, other organ were all normal. He was diagnosed as having severe falciparum malaria complicated with acute kidney injury. Patient was then managed with artesunate 2.4mg/kgBW on December 9, 2017 on admission (0h) and then repeated at 12h-24h and then every 24 hours with blood smear examinations revealing no P. falciparum on December 11, 2017 (day 3). He

was then prescribed for dihydroartemisinine-piperaquine (DHP) 4 tablets once daily for 3 days without additional primaquine when he felt better and able to tolerate oral intake on day 4. His renal function recovered slowly through serial hemodyalisis on December 9, 10, 11, 13, 15, 16. As suspicion of rapid progressive glomerulonephritis, we also gave him methylprednisolone 500mg every 24 hours intravenously for 3 days then tapped down to 125mg every 12 hours for 3 days, then 62,5 mg every 12 hours, for 3 days then switch to oral prednison 20mg, twice daily until discharge time and the tappering was continued on follow up time. During admission no fever noted. His urine production is getting better from 0.3ml/kgBW/hour on admission to 0.9ml/kgBW/hour during hospitalisation.

Last blood test evaluation during admission showed improvement in liver function with SGOT 29U/L, SGPT 67U/L, total bilirubin normal 0.35mg/dL, direct bilirubin normal 0.16, indirect bilirubin 0.19mg/dL,improvement in kidney functon with blood ureum 127.53mg/dL, blood creatinine 4.14mg/dL. The platelet count improved to 266x103/uL, however the hemoglobin level was low 8.9g/dL, reticulocyte count 0.4% (reference range 0.5-1.5%), peripheral blood smear didn't show sign of hemolytic anemia with no polychromasia and normoblast. Serum iron 90ug/dL (reference range 65-175ug/dL), total iron binding capacity 210ug/dL (reference range 250-450ug/dL), ferritin 1025ng/mL (reference range 28-365ng/ml). He has microalbuminuria with albumin-creatinin ratio was 41.19ug/mg (reference range <30ug/mg). Last urinalysis showed no proteinuria. Blood smear for malaria remained negative for plasmodium until day 7. He was discharged on day-11 and on follow up time he remained afebrile and the blood smear on day-14 and day-21 remained negative. The last blood ureum was 51.82mg/dL, blood creatinin was 2.04mg/dL. He was still slightly anemic with hemoglobin level was 10.2g/dL. He was still on tappering down of prednisone tablet. He didn't show up on day-28 of follow up for the evaluation of hemoglobin, kidney test, and the last microscopic malaria test.

3. Discussion

Malaria presentation is very unspesific so alternative and more frequent diagnoses should be excluded such as severe pneumonia, meningitis, hemorraghic fevers, salmonellosis, viral hepatitis, and dengue. Fever is common. Additional symptoms include chills, headache, malaise, nausea, vomitting, diarrhea, abdominal pain and myalgia. Splenomegaly is an inconstant finding. In practice, malaria should be suspected in any febrile individual returning from tropics, especially if coexisting anemia, thrombocytopenia, or cytolisis [4]. The renal failure of malaria must be distinguished from renal impairment due to other febrile illnesses such as leptospirosis, traditional herbal medicines, snakebite, glomerulonephritis and hypertension. The jaundice and hepatomegaly of malaria should not be confused with that of viral hepatitis (A, B and E), yellow fever, cytomegalovirus and Epstein–Barr virus infections, leptospirosis, biliary disease, drug-induced diseases and alcohol [3]. Diagnosis malaria is made by direct demonstration of parasites in blood [4]. According to the program by Ministry of Health, Republic of Indonesia, diagnosis should be made based on the gold standard blood microscopic test (thin and thick) [2].

Our patient presented with symptoms history 3-4 days of febrile illness that had been treated as malaria with oral DHP plus primaquine. The laboratory test from other fascility 1 day prior admission to our hospital showed no malaria nor dengue fever. We have excluded another common causes of acute febrile illness with similar symptoms to malaria such as typhoid fever, leptospirosis, hepatitis B and C with all serologic test returned negative. We still strongly suspected our patients having malaria even though the latest laboratory results showed negative for malaria. We therefore repeated the tests and came back positive for Plasmodium falciparum. The test in Sumba was performed with a puncture blood at the fingertips without knowing the species of plasmodium. This may be due to limited facilities in remote areas of Sumba. By knowing the species of plasmodium then it can increase our awareness against the possibility of severe malaria.

Our patient had severe falciparum malaria manifested as acute kidney injury with creatinin>3mg/dL, met one criteria from WHO for severe malaria falciparum[5]. Diagnosis of severe malaria is made when one of clinical and laboratory findings is found, including muscle fatigue (without neurological disorder), impaired consciousness, acute respiratory distress syndrome, repeated convulsions,

circulatory collapse, pulmonary edema (proven by radiograph), spontaneous bleeding, jaundice, hemoglobinuria, hyperpyrexia (adults 40^0C, children >41^0C), severe anemia (Hb <5 g/dl atau Ht <15), hypoglycemia, acidosis, renal dysfunction, hyperlactatemia, hyperparasitemia >5% in hypoendemic area (non-immune) [2].

Any form of complicated or severe malaria must therefore be regarded as a life-threatening medical emergency [3]. Principles of severe malaria management are preventing and minimizing the risk of death. It can be achieved by performing early diagnosis as well as prompt and appropriate treatment. Adequate treatment includes supportive treatment, causal (anti-malarial) treatment and management of complications [2]. All patients of severe malaria should be treated with parenteral artemisinin derivatives or quinine due to presence of widespread chloroquine-resistant P falciparum in South-East Asia [5]. The artemisinine derivatives have the broadest time window of antimalarial effect (from ring forms to early schizonts). These compounds prevent maturation of ring stages, thus reducing subsequent cytoadherence responsible for severe disease [6].

One of the drug of choice for severe malaria that available in Indonesia is artemisinine derivative, intrravenous artesunate. As WHO recommendation [5], our patient received treatment with artesunate IV 2.4mg/kgBW on admission (time 0) repeated at 12h and 24h then every day until patient is able to tolerate oral intake. On day 4 he was switched from IV artesunate to dihydroartemisinin-piperaquine (DHP) 4 tablets once daily. No fever noted during admission. Parasitemia should be determined initially, at D3, D7, and D28 to assess severity, therapy monitoring and late failures detection [4]. As in our patient, we checked the microscopic malaria every day until undetected and on day 7,14,21,28. The plasmodium falciparum was first time undetected on day 3 and remained undetected on day 7,14, and 21.

One manifestation of severe malaria caused by P.falciparum is kidney involvement. Clinical manifestations of kidney involvement in malaria include proteinuria, microalbuminuria and urinary casts, reported in 20 to 50% of cases. Nephrotic syndrome has also been described in the infection by P. falciparum, but it is rare [7]. In malaria-endemic regions, AKI can occur in up to 40 % of adult patients with severe P. falciparum malaria, and it is associated with a mortality as high as 75 % when renal replacement therapy (RRT) is not started in time. In non-immune travellers with severe P. falciparum infection, AKI is reported to occur in 34 to 52 % of cases [8].

Our patient presented with signs of moderate to severe dehydration, kidney injury with blood creatinin more than 11mg/dL, blood ureum more than 200mg/dL, proteinuria and urine production was 0.3ml/kgBW/hour. We assumed the kidney injury was acutely associated malaria based on history taking of patients never having previous kidney impairment. We do not have baseline data on the patient's blood ureum and creatinine. He had abdominal ultrasound by 2015 and showed normal results in both kidneys.

The mechanism that leads to AKI in malaria is complex and includes mechanic and immune factors, cytokines release and acute phase response. New kidney injury biomarkers have been investigated in malaria by P. falciparum, including neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), which have the advantage of detecting AKI earlier than traditional markers, such as creatinine[7]. The pathogenesis of AKI in malaria is still not clearly understood. Blockage of renal microcirculation due to sequestration of infected erythrocytes, immune-mediated glomerular injury and volume depletion are some of the proposed hypotheses. The main histopathological finding in malaria-associated AKI is acute tubular necrosis (ATN) with reports of interstitial nephritis and glomerulonephritis [8].

Severe malaria can cause disease in glomeruli, tubules and in the interstitial region. Kidney disease in malaria is primarily due to erythrocyte abnormalities. Parasitized red cells tend to adhere to healthy erythrocytes, blood platelets and capillary endothelium, leading to formation of rosettes and clumps, which impair microcirculation, and these events are probable contributing factors for kidney injury, in association with hemodynamic instability, including hypovolemia and shock [7].

Treatment of malaria-associated kidney disease includes appropriated antimalarial drugs, besides all supportive measures that AKI requires (hydroelectrolytic disturbances corrections, fluid replacement

and dialysis. Renal replacement therapy (dialysis) should be considered in AKI treatment, with hemodialysis being more effective. Dialysis is required in 46 to 76% of cases, and complete renal function recovery is reported to occur in approximately 64% of cases in both P. falciparum and P. vivax malaria-associated AKI. Antimalarial drugs are not adequately depurated in hemofiltration dialysis, so dialysis does not interfere with the specific treatment of malaria. Early initiation of dialysis, for any AKI cause, has been associated with better outcomes, and a recent meta-analysis found a 25% reduction in all-cause mortality and 30% increase in renal recovery among patients with AKI receiving early renal replacement therapy, so we recommend early dialysis initiation for AKI associated with severe malaria [7].

Along with treatment for malaria, our patient was also managed for his kidney injury with IV hydration and monitoring fluid balance, serial hemodyalisis and high dose methylprednisolone with suspicion of rapid progressive glomerulonephritis.

He remained stable during follow up, except for dizziness. The blood smear remained negative for plasmodium on day 21. He was still slightly anemic with hemoglobin level of 10.2g/dL. His urine production was normal with last blood creatinine was 2.04mg/dL. He didn't show up on follow up day 28.

4. Conclusion

We have reported one case of severe falciparum malaria complicated with kidney injury requiring serial hemodyalisis. Diagnosis of malaria should be made based on the gold standard blood microscopic test (thin and thick) to determine the spesific of plasmodium as the cause of malaria. An increasing awareness of severe malaria caused by P.falciparum on early diagnosis and treatment may prevent the progression to severe stages and a prompt intervention in critical situation can reduce the risk of complications. In malaria-associated kidney injury, rapid initiation of hemodialysis proves useful in the restoration of renal function.

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