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Severe Falciparum Malaria with Multiple Complications in Sanglah Hospital Denpasar

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ABSTRACT

Malaria is caused by *Plasmodium*, which is transmitted through the bite of infected female Anopheles mosquitoes. *Plasmodium falciparum* causes the most severe form of malaria and can be life-threatening. A 63-year-old male with decreased consciousness, fever, chills, vomiting, and joint pain. The patient works in the Ivory Coast, malaria-endemic areas. Physical examination found clouding of consciousness and jaundice. Laboratory examination results are leukocytosis with eosinophilia and thrombocytopenia, increased of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), total bilirubin, direct and indirect bilirubin, Blood Urea Nitrogen (BUN), creatinine, decreased of estimated Glomerular Filtration Rate (e-GFR), decreased random plasma glucose. Urinalysis showed macroscopic hematuria, positive blood, and protein are found, and erythrocyte sediment is increased. A blood gas analysis examination revealed metabolic acidosis. Rapid Diagnostic Test (RDT) showed positive for *Plasmodium falciparum*. The blood smear showed leukocytosis with eosinophilia and thrombocytopenia and the ring-form trophozoites stage of *Plasmodium falciparum*. The definitive diagnosis of falciparum malaria is confirmed by microscopic peripheral blood smear and malaria RDT for antigen detection. An overall investigation concluded the patient diagnosed is severe falciparum malaria with various complications including hypoglycemia, jaundice, and acute kidney failure. The patient died on the first day after being treated in Sanglah Hospital, Denpasar.

Keywords: Severe malaria, *Plasmodium falciparum*, complicated malaria

INTRODUCTION

Malaria is a disease caused by *Plasmodium*, a single-cell organism belonging to the Protozoa group. Malaria is transmitted through the bite of a female Anopheles mosquito containing *Plasmodium. Plasmodium* lives and breeds in human red blood cells.[1] According to the World Health Organization (WHO) in 2018 there were 228 million malaria cases in the world with the most cases from Africa, South East Asia, and East Mediterranean. Countries in Africa had the highest mortality rates due to malaria (94%) and most were due to *Plasmodium falciparum*. Six countries with the most malaria cases in the world were: Nigeria (25%), Democratic Republic of Congo (12%), Uganda (5%), and Ivory Coast, Mozambique, Nigeria (4% each).[2]

Five species are known to cause malaria, namely *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*, and *Plasmodium knowlesi*. From these 5 species, *Plasmodium falciparum* is the most common to cause severe malaria causing death.[3] Malaria with complications is usually classified as severe malaria, which by WHO is defined as *Plasmodium falciparum* with one or more complications such as cerebral malaria (coma), metabolic acidosis, severe anemia, hypoglycemia, acute kidney failure or acute lung edema.[4] Patients suspected of severe malaria may be treated immediately according to the results of a malaria Rapid Diagnostic Test (RDT). The prognosis of severe malaria is based on the speed and accuracy of diagnosis dan treatment.[5]

CASE

RLM, a 63-year-old male patient was brought to the Sanglah Hospital Emergency Room with the main complaint of a decrease of consciousness. The patient was referred from a private hospital with the diagnosis of severe malaria. The patient's family stated that the patient couldn't communicate with his wife for 2 days before admittance. The patient could open his eyes spontaneously, but could not give the appropriate answer when spoken to. The patient had a fever five days before admittance, it was a sudden high fever of 39°C, accompanied by shivering and vomiting, consisting of food that had

been eaten. The fever dropped with medicine. There was pain in the joint that caused the patient to not be able to resume regular activity. The patient also complained of gum bleeding a day before admittance. History of hematuria or melena was denied. Bowel movements were within normal limits. History of seizures or fainting were both denied.

There was no known prior history of malaria. History of hypertension, kidney disease, heart disease, and diabetes was denied. The patient's wife had a history of malaria. The patient came from Australia and worked at Ivory Coast for 20 years ago. The patient smoked and drunk alcohol since he was 20 years old.

The patient arrived with a decrease of consciousness and GCS E4V3M5, he was weak and seemed severely ill, had a temperature of 36.8°, heart rate of 120 x/minute, respiratory rate of 24 x/minute, blood pressure 150/90 mmHg and pain 0/10. Physical examination of the head revealed icteric sclera; while there were no abnormalities on the neck, chest, abdomen, and extremities.

Complete blood count showed leukocytosis with a differential count showing eosinophilia and thrombocytopenia as shown in Table 1. Hemostasis results were within normal limits as shown in Table 2.

Table 1. Hematology results

Parameter	01/11/2019	Reference Range
Leukocytes (10^3/µL)	14.93	4.1-11.0
% neutrophil	43.32	47-80
% lymphocyte	20.25	13-40
% monocyte	3.03	2.0-11.0
% eosinophil	32.90	0.0-5.0
% basophil	0.50	0.0-2.0
Erythrocyte(10^6/µL)	4.92	4.5-5.9
Hemoglobin (g/dL)	15.07	13.5-17.5
Hematocrit (%)	49.27	41.0-53.0
MCV (fL)	100.20	80.0-100.0
MCH (pg)	30.64	26.0-34.0
MCHC (g/dL)	30.59	31-36
RDW (%)	14.82	11.6-14.8
Thrombocytes (10^3/µL)	39.40	150-440
MPV (fL)	14.83	6.80-10.0

RDW = Red Cell Distribution Width; MPV = Mean Platelet Volume

Table 2. Coagulation laboratory results

Parameter	31/10/2019	Reference Range
aPPT (seconds)	29.9	24.00 – 36.20
PT (seconds)	14.2	11.80 – 14.40
INR	1.1	0.8 – 1.2

INR = International Normalized Ratio

Urinalysis results showed blood and protein in the urine. There was an increase in erythrocyte sediments and bacteria was also found in the urine as shown in Table 3.

Table 3. Urinalysis results

Parameter	31/10/2019	Reference Range
Urinalisis		
Color clarity	Yellow clear	Yellow (bright-dark)
pH	6.0	5.0 – 8.5
Specific gravity	1.020	1.000 – 1.030
Leukocyte	Negative	Negative
Blood	Positive (+)	Negative
Protein	Positive (+)	Negative
Glucose	Negative	Negative
Urobilin	Negative	Negative
Urobilinogen	Negative	Negative
Bilirubin	Negative	Negative
Keton bodies	Negative	Negative
Nitrit	Negative	Negative
Sediments		
Leukocytes	1-2/HPF	1 - 2/HPF
Erythrocytes	5-6/HPF	0 – 1/HPF
Epithelial cells: Squamous	1-2/HPF	1 - 2/HPF
Renal tubulus	0/HPF	0/HPF
Casts	Negative	Negative
Crystals	Negative	Negative
Others: bacteria	Positive (+)	Negative

Clinical chemistry results showed an increase in AST, ALT, total bilirubin, direct and indirect bilirubin, Blood Urea Nitrogen (BUN), and creatinine. There was also a decrease in e-GFR and random blood glucose as can be seen in Table 4.

Table 4. Clinical chemistry laboratory results

Parameter	01/11/2019	Reference Range
AST (U/L)	227.7	11.00-33.00
ALT (U/L)	96.80	11.00-50.00
Total bilirubin (mg/dL)	7.93	0.30-1.30
Direct bilirubin (mg/dL)	5.29	0.00-0.30
Indirect bilirubin (mg/dL)	2.64	
Albumin (g/dL)	3.50	3.40-4.80
BUN (mg/dL)	56.60	8.00-23.00
Creatinine (mg/dL)	2.60	0.70-1.20
e-GFR (mL/min1.73m^2)	25.12	>= 90
Random blood glucose (mg/dL)	34	70-140

AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; BUN = Blood Urea Nitrogen; e-GFR = estimated Glomerular Filtration Rate

Blood gas analysis and electrolyte examinations showed a decrease in blood pH, bicarbonate (HCO3-), and a decrease in pCO2 compensation. There was also a sodium decrease as shown in Table 5.

Table 5. Blood gas analysis and electrolyte results

Parameter	01/11/2019	Reference Range
pH	6.60	7.35-7.45
pCO2 (mmHg)	30.3	35.00-45.00
pO2 (mmHg)	184.80	80.00-100.00
HCO3- (mmol/L)	2.90	22.00-26.00
SO2c (%)	96.4	95%-100%
TCO2 (mmol/L)	3.80	24.00-34.00
Natrium (Na) (mmol/L)	131	136–145
Kalium (K) (mmol/L)	5.56	3.50-5.10
Cloride (Cl) (mmol/L)	103	96-108

Malaria laboratory examinations consist of RDT and microscopical thick and thin blood smears. *Plasmodium falciparum* was positive in the Malaria RDT showing two lines, one in the control area (C) and one in the *Plasmodium falciparum* (F) as seen in Figure 1.

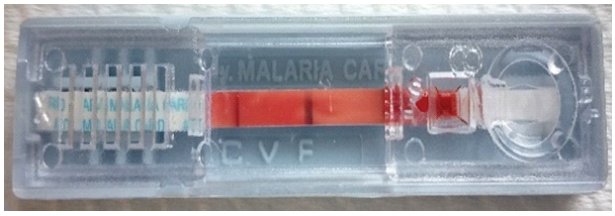

Figure 1. Positive *Plasmodium falciparum* RDT examination

Microscopical thick blood smear found *Plasmodium falciparum* malaria parasites (ring form) with parasite density (++++) using a semi-quantitative method as shown in Figure 2. No quantitative parasite count was carried out in this patient because there was a huge number of parasites.

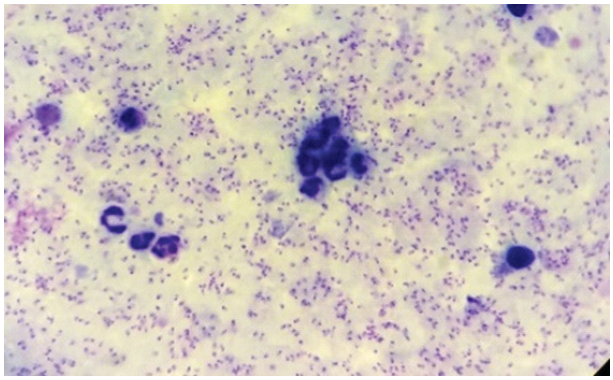

Figure 2. Thick blood smear

Microscopical thin blood smear as seen in Figure 3 found.

Erythrocyte: normochromic normocytic, there were *Plasmodium falciparum* malaria parasites in the ring form with (++++) parasite density.

Leukocyte: seems to increase in number, differential count of eosinophilia, no immature granulocytes, no toxic granules, and no vacuolization.

Thrombocyte: seems to decrease in number, positive giant platelets, normal distribution

Conclusion: Leukocytosis with thrombocytopenia and the presence of the ring form of *Plasmodium falciparum*

Radiology examinations consisted of an AP chest photo showing no abnormalities in the heart and lungs. Head CT scan without contrast showed no visible intracranial bleeding/infarction/ mass/infection.

The patient was diagnosed with severe falciparum malaria with various complications. Management of this patient was given nasal cannula oxygen 4 liters/minute, intravenous 0.9% Sodium Chloride: Dextrose 5% 20 drops/minute, artesunate 200 mg intravenously (at 0, 12, and 24 hours) continued every 24 hours, paracetamol 500 mg/oral every 8 hours (if temperature > 37.50C) and soft food diet 1800kcal/day.

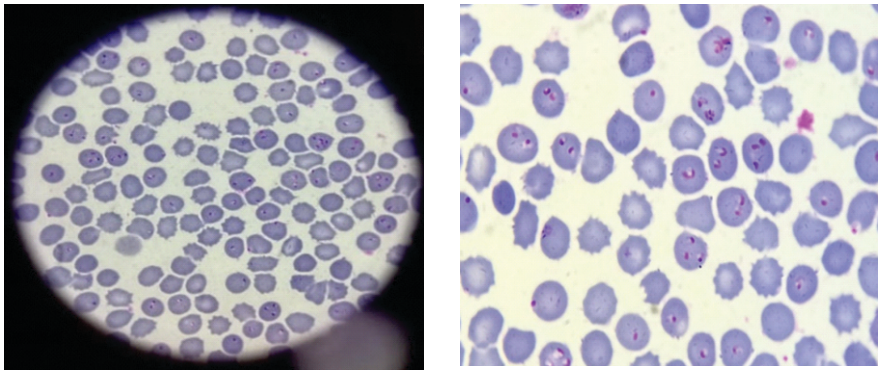

Figure 3. Thin blood smear

DISCUSSION

Severe malaria is defined as finding an asexual stadium of *Plasmodium falciparum* or *Plasmodium vivax* with one or more of the following clinical manifestations: decrease of consciousness, muscle weakness, continuous seizures (more than two episodes in 24 hours), respiratory distress (in children), lung edema, circulation failure or shock, icterus, hemoglobinuria and abnormal spontaneous bleeding or laboratory findings such as hypoglycemia, metabolic acidosis, severe anemia, hyper-parasitemia, hyperlactatemia, hemoglobinuria, and kidney function disorder.[3]

Decrease of consciousness in severe malaria can be caused by cerebral malaria, hypoglycemia, meningitis, or encephalitis. In patients with a decrease of consciousness (apathetic with GCS E4V3M5), the patient could not communicate with his wife for two days before admission. The patient could spontaneously open his eyes, but could not respond when being talked to, there was already a decrease in random blood sugar caused by an increase in blood glucose in the tissue due to an increase of glucose use by the malaria parasites.[6] Consciousness disorder due to cerebral malaria and meningitis or encephalitis could be excluded because there were no neurological symptoms such as seizures and on head CT scan without contrast, there were no signs of intracranial bleedings/ infarcts/mass/infections.

The patient had a fever for five days prior to hospitalization, it was a sudden high fever at 39°C, accompanied by chills, joint pain, and vomiting. These symptoms support the diagnosis of the patient, as they are clinical manifestations of malaria. The patient is an Australian citizen working in the Ivory Coast, which is an endemic place for Malaria. Mild symptoms are usually diagnosed as other infections such as typhoid or dengue fever, but the patient has been examined for anti-dengue IgG and IgM and *Salmonella typhi* IgM examination with negative results eliminating the differential diagnosis.[3]

Eosinophils are a type of leukocytes that play a role in the body's immune system and attack multicellular parasite infections and specific infections. An increase in eosinophils can be caused by allergies to a parasite infection. A complete blood count will show leukocytosis with a high diff count of eosinophils and thrombocytopenia. The increase of Plasmodium in the blood will cause an increase in the number of eosinophils so they can kill parasites by depositing cationic protein on the surface of the parasites.[7] Gum bleeding in patients may be caused by thrombocytopenia. Platelet-associated IgG/PAIgG increases in malaria and is interpreted as platelet activation. The antiplatelet antibody can activate the thrombocyte membrane causing the disposal of thrombocytes by the reticuloendothelial system (RES), especially in the spleen. IgG antibodies found on the thrombocyte membrane can also cause a thrombocyte aggregation disorder and increase the destruction of thrombocytes by macrophages, malaria infection also causes induction of radical hydroxyl (OH) release from the liver that is responsible for the induction of oxidative stress and apoptosis. Platelet membranes are less resistant to oxidative stress, so an increase in oxidative stress is estimated to increase platelet lysis.[8]

Definite diagnosis of malaria must be established by blood smear microscopical examination or rapid diagnostic test such as RDT malaria antigen. A blood smear must be made to see whether there are parasites in the blood of a patient. The blood smear must use Giemsa staining. Emersion oil is used to help examine the blood smear with 100x objective lenses. If a malaria parasite is found, the patient is declared positive for malaria. This patient had a positive *Plasmodium falciparum* RDT test, and the results of microscopic examination of thick blood preparations found trophozoite stage or ring form *Plasmodium falciparum* malaria parasites with parasite density (++++) and thin blood preparations found trophozoite stage *Plasmodium falciparum* or ring form.[9]

Acute Kidney Injury (AKI) is a rapid decrease of Glomerular Filtration Rate (GFR) (in hours to weeks) that is usually reversible, followed by failure of the kidney to excrete nitrogenous waste, with or without disturbance of fluid and electrolyte balance.[10] The three pathophysiology of AKI are a decrease in kidney perfusion (prerenal), an intrinsic kidney disease (renal), and acute renal obstruction (post-renal).[11] Acute kidney injury complications in malaria, happen when serum creatinine > 3 mg/dL with urine production < 0.5 mL/kg/day. The most common cause of AKI in malaria is pre-renal kidney failure due to dehydration (>50%).[6] Kidney function tests in this patient showed an increase in BUN and serum creatinine, a decrease in e-GFR, and a decrease in urine production (250 mL) indicating the patient had stage 2 AKI (where there is a 100 – 199% increase of creatinine or urine output < 0.5 mL/hour during 12–14 hours).[10] Acute kidney injury was caused by decreased blood flow to the kidney (pre-renal) shown by the BUN/SC ratio > 20:1 causing ischemia with disruption to the

microcirculation of the kidney reducing glomerular filtration.[11]

Chemical urine tests showed positive blood parameters and microscopical urine examination showed positive erythrocytes, ruling out hemoglobinuria as the cause.[12] Urinalysis results of this patient showed macroscopical hematuria, with positive blood and protein, there was also increased erythrocyte sediment indicating hematuria. In malaria patients with AKI, proteinuria indicates developing nephropathy. Proteinuria associated with hematuria suggests glomerular disease and a mixed pattern of glomerular-tubular excretion causing the need for more specific laboratory tests to investigate the cause.[13]

Metabolic acidosis is one of the acid-base disorders with clinical features of confusion to coma, weakness, bone pain, abdominal pain, and difficulty of breathing. Typical laboratory findings in metabolic acidosis are decreased blood pH, decreased bicarbonate (HCO3-), and a compensatory decrease in pCO2. Metabolic acidosis is caused by one of these three mechanisms: increased non-volatile acid production, decreased renal excretion of acid and loss of alkali. In this patient, based on the clinical presentations, namely feeling confused, weak body and bone pain, as well as the results of blood gas and electrolyte analysis, it was found that blood pH, HCO3- and pCO2 decreased, there was hyperkalemia, and an increase of anion gap, indicating that the patient had metabolic acidosis. This was due to the kidney's disability to efficiently excrete sulfate, phosphate, and organic acid anions. Hyperkalemia commonly occurs in AKI with metabolic acidosis due to the displacement of potassium out of cells.[14]

Physical examinations showed icteric sclera. Clinical chemistry examination found an increase in AST, ALT, total bilirubin, and direct and indirect bilirubin, which indicates impaired liver function due to complications of malaria. This is due to the process of sequestration and cytoadherence, which causes microvascular obstruction resulting in decreased blood flow to the liver and also because the malaria parasite enters the liver through the blood vessels causing damage to hepatocyte cells.[6] However, it can also be caused by acute viral hepatitis and leptospirosis, so other laboratory tests are needed to rule out the differential diagnosis, but none have been done on this patient.[3]

CONCLUSION

A male patient with severe malaria falciparum with various complications naming hypoglycemia, icterus, and acute kidney failure. Laboratory examinations show eosinophilia, thrombocytopenia, and an increase in AST, ALT, total, direct, and indirect bilirubin, BUN, and creatinine. A decrease in e-GFR and RBG. Urinalysis showed hematuria. Rapid diagnostic test for malaria showed positive *Plasmodium falciparum*. Microscopical examinations found a trophozoite (ring form) stage of *Plasmodium falciparum* with a (++++) parasite density. The patient's condition worsens since hospitalized and died a couple of hours after. Malaria cases in Denpasar are rare, so patients from endemic areas should get the proper laboratory examinations for accurate and rapid diagnosis to prevent complications.

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