Successful of oral antimalaria therapy in severe malaria: Cerebral malaria and black water fever, A case in rural area of Waingapu, East Sumba

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Abstract

Introduction: Cerebral Malaria (CM) and Black Water Fever (BWF) are examples of severe malaria. Severe malaria has a mortality rate of > 5% and increases the risk of death by 50%. According to WHO, the first line therapy for severe malaria is parenteral artesunate. However, in rural areas such as Waingapu, East Sumba, parenteral artesunate is not always available, so oral anti-malarial drugs are used as a substitute treatment. In this case, we present an adult case with Cerebral Malaria and Black Water Fever who responded well to oral anti-malarial.

Case Report: A 38 year old man, with complaints of decreased consciousness starting with fever symptoms 4 days before hospitalization, accompanied by chills, cold sweat, headache, muscle aches and decreased appetite. Blackish red urine (coca-cola colored urine). The patient was treated in the ICU for 2 days and given DHP therapy for 3 days, because enteral anti-malarials were not available. On the third day of treatment the patient showed clinical improvement.

Conclusion**:** DHP oral anti-malarial therapy and supportive therapy provided good results in this patient.

Keywords: *anti-malarial drug, black water fever, cerebra malarial.*

I. Introduction

Malaria is an infectious disease of global concern. This disease is still a public health problem because it often causes outbreaks, has a broad impact on the quality of life and the economy, and can result in death.[1]Based on the WHO malaria case report in 2022, it is estimated that globally there was 247 million malaria cases in 2021 in 84 malaria endemic countries. This incidence increased compared to 2020, amounting to 245 million cases. The countries experiencing an increase in cases came from the African Region.[2] The incidence of malaria among the Indonesian population in 2013 was 1.9 percent, a decrease compared to 2007 (2.9%), but Papua experienced a sharp increase in the number of malaria sufferers. The five provinces with the highest incidence and prevalence are Papua (9.8% and 28.6%), East Nusa Tenggara (6.8% and 23.3%), West Papua (6.7% and 19.4%), Central Sulawesi (5.1% and 12.5%), and Maluku (3.8% and 10.7%).[1]

If left untreated, malaria can develop into severe malaria and result in death. Cerebral Malaria (CM) and Black Water Fever (BWF) are examples of severe malaria. Severe malaria has a mortality rate of > 5% and increases the risk of

death by 50%.[3] Clinical symptoms of CM are associated with impaired consciousness without other causes such as hypoglycemia, seizures, drug use, with coma characteristics that can be seen from the Glasgow Coma Score < 11.[4] BWF is hemoglobuminoria condition caused by intravascular hemolysis which can result in acute renal failure and hepatosplenomegaly.[5] In intervention trials on adults in Asia and children in Africa, it was found that 54% of adults and 34% of children experienced CM. Of the children who survive, 10-20% experience a series of neurological disorders that impact cognition, behavior, vision, hearing and smell.[6] According to WHO, the first line therapy for severe malaria is artesunate given parenterally.[2] However, parenteral artesunate is not always available in remote areas, so oral anti-malarial drugs are used as a substitute. In this case, we present an adult case with Cerebral Malaria, Black Water Fever who responded well to oral anti-malarial drugs.[7]

II. Case

A 38 year old man was brought to the Emergency Room (ER) of the Lindimara Christian Hospital (RSKL) by his family with complaints of decreased consciousness since the morning. Initially, the patient complained fluctuating fever for 4 days before entering the hospital, accompanied by chills, cold sweat, headache, muscle aches and decreased appetite. Other complaints such as coughing, runny nose, shortness of breath, nausea, vomiting, indigestion, seizures, bleeding such as nosebleeds or bleeding gums and bleeding spots on the skin were denied. Since the morning the patient has become increasingly weak, unable to sit or stand, unable to eat and unable to interact such as minimal eye contact and unable to answer questions. The patient had never experienced similar complaints before. In the patient's neighborhood, no one experienced similar complaints. Previous history of malaria infection or consumption of anti-malarial drugs was denied. Denied history of chronic disease.

The patient appeared weak, pale, with delirium, Glasgow Coma Scale was E2V3M4 (GCS 9). Vital signs showed blood pressure 90/60 mmHg (hypotension), pulse 130 times/minute (tachycardia), strong lift, respiration rate 20 times/minute, afebrile temperature 36.8◦C, oxygen saturation 99% room air, estimated body weight 60 kg. From physical examination, the eyes were found to have anemic conjunctiva, no jaundice on the sclera and both pupils were isochoral. Chest examination was within normal limits. On abdominal examination, no enlargement of the spleen or liver was found. On examination of the extremities, the acral was cold. Neurological examination revealed no abnormalities.

A urinary catheter was installed and the urine was blackish red (coca-cola colored urine). Laboratory examination found Hb 11.9 g/dL, WBC $14.65x10^3$ /µL with an increase in neutrophils 79.8%, PLT $29x10^3$/uL, MCV 93.5 fL, MCH 28.1 pg, HCT 31.3%. A peripheral blood smear for malaria was examined with positive results for plasmodium falciparum with a parasite count of 4185 parasites/µL. Blood sugar was 130 mg/dL, urea 40 mg/dL, creatinine 1.1 mg/dL, and electrolytes within normal limits.

The patient was treated in the ICU for 2 days. The patient was hospitalized with a diagnosis of Severe Malaria: Cerebral Malaria, Black Water Fever, accompanied by Sepsis Shock. The diagnosis is made based on the patient's signs and symptoms as well as laboratory tests. Initial treatment for the patient in the emergency room was fluid therapy loading with 500 cc of 0.9% NaCl followed by 30 tpm of 0.9% NaCl maintenance fluid as initial treatment for septic shock. Due to the unavailability of parenteral anti-malarials, the patient was given oral anti-malarials, namely Dihydroartemesin + piperaquin (DHP) 1x4 tablets for 3 days, Primaquin 1x1 tablet single dose, via nasogatric tube (NGT). Other drugs given

were Ceftriaxone 1x2 grams intravenously, Paracetamol 3x750 mg intravenously. The patient also had a urinary catheter installed to monitor urine production and changes in color. After loading 500 cc of 0.9% NaCl, blood pressure evaluation was carried out, there was an increase in blood pressure to 100/70 mmHg. However, after 11 hours in the room the patient's blood pressure decreased to 70/40mmHg so he was loaded with 1500cc of 0.9% NaCl fluid, but the blood pressure remained at 80/40 mmHg so the patient was given a vasopressor, namely Vascon with a starting dose of 0.1mcg/kgBW with MAP target > 65 mmHg, uptitrate the Vascon dose every 15 minutes. Monitoring urine production for 24 hours showed urine production of 1ml/kgBW/hour. Patients were monitored for Complete Blood Count and Peripheral Blood Smear for malaria.

Table 1. Follow up on Patient's Vital Signs during Hospitalization

Parameter	1st Day	2nd Day	3rd Day	4th Day	5th Day
GCS	E2V3M4	E3V3M5	E4V5M6	E4V5M6	E4V5M6
Blood Pressure (mmHg)	90/60	70/40	112/72	120/80	120/90
Pulse (times/minute)	130	110	85	96	80
Respiratory rate (times/minute)	20	22	20	22	22
Oxygen saturation (%)	99	94	96	97	96
Temperature (◦C)	36,8	38,4	37,3	36,6	36

On the second day under ICU treatment, the patient experienced clinical improvement in the form of the patient's consciousness starting to improve, there was a change in urine color and the patient's blood pressure was stable without vasopressors with an average MAP of 80 mmHg. So on the third day the patient was treated in a regular inpatient room, and the NGT was removed.

On the fifth day the patient no longer showed symptoms such as decreased consciousness, dark urine, muscle weakness, fever accompanied by chills or decreased appetite, so the patient was allowed to go home.

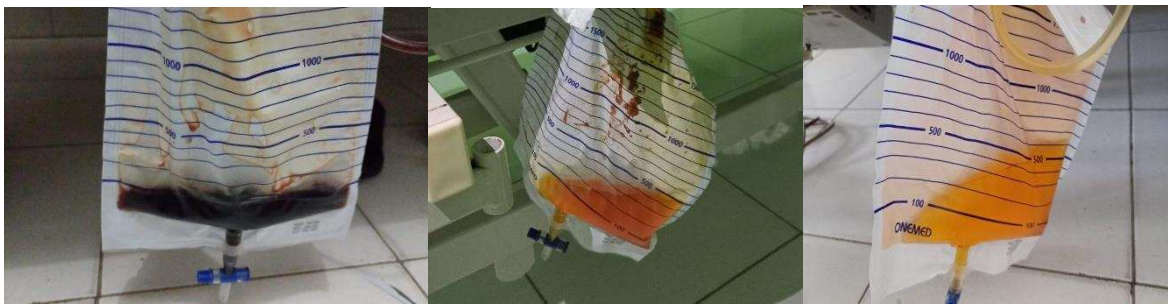

Figure 1. Monitoring Urine Color

Table 2. Follow up Evaluation of Patient Laboratory Results during Hospitalization

Parameter	1st Day	2nd Day	3rd Day	4th Day	5th Day
Complete Blood Count					
WBC (x10^3/µL)	14.6	10.84	11.55	9.12	7.65
Neu%	79.8	86.2	77.4	66.2	59.8
Lym%	11.1	7.3	15.7	21.3	25.0
Mon%	6.5	4.2	4.1	6.4	10.3
Eos%	0,6	1.8	1.6	4.7	4.2
Bas%	2.0	0.5	1.2	1.4	0.7
RBC(x10^6/uL)	4.24	3.57	3.4	3.19	3.07
HGB(g/dL)	11.9	10	9.5	8.7	8.5
HCT (%)	39.6	33.2	31.3	29.2	28.1
MCV (fL)	93.5	93	92.2	91.7	91.5
MCH (pg)	28.1	28.1	27.9	27.4	27.7
PLT(/uL)	29	26	46	66	112
Blood Smear					
Parasite/µL	4,185	497	Negative	Not performed	Not performed
Kidney Function					
Urea	40	52	Not performed	Not performed	Not performed
Creatinin	1.1	1.7	Not performed	Not performed	Not performed
eGFR (mL/mnt/1,73m^2)	74,9	45,3	Not performed	Not performed	Not performed

III. Discussion

Malaria is caused by Plasmodium which is transmitted through the bite of an infected Anopheles mosquito. Among the 5 types of plasmodium that cause malaria (plasmodium falciparum, malariae, ovale, vivax and knowlesi), plasmodium falciparum is the most pathogenic and life-threatening.[7] To diagnose malaria, you can look at clinical symptoms, physical examination and supporting examinations. Clinical symptoms of malaria appear in the erythrocyte phase of the malaria parasite. Usually characterized by paroxysmal fever (fever preceded by chills, followed by an increase in body temperature and profuse sweating), followed by headache, muscle aches, dry cough, nausea, vomiting, diarrhea, fatigue, etc. Physical examination usually reveals an axillary body temperature ≥37.5◦C, pale conjunctiva or palms, icteric sclera, enlarged spleen or liver (splenomegaly or hepatomegaly). Laboratory tests that can be used are (1) examination using microscopy, namely examining thick or thin blood smears to determine the presence or absence of malaria parasites,

species and plasmodium, as well as parasite density, (2) Rapid diagnostic test to detect malaria antigens by immunochromatography method. A history of traveling or living in endemic areas can also be a clue to diagnosing malaria.[8.9]

Clinical manifestations of malaria can vary from mild to severe. If left untreated it can become severe malaria causing death. According to WHO 2015, severe malaria is the presence of asexual stage Plasmodium Falciparum with at least one of the following clinical manifestations or laboratory results:[8,10]

Table 3. Clinical manifstations and laboratory result of severe malaria

Clinical Manifestations	Laboratory Results
1. Alteration of consciousness (GCS < 11) 2. Muscle weakness, unable to sit or walk 3. Recurrent seizures of more than 2 episode in 24 hours 4. Respiratory distress 5. Circulatory failure or shock: capillary refill time >3 seconds, systolic pressure <80 mmHg (in children <70 mmHg) 6. Jaundice (bilirubin >3 mg/dL and parasite densiity >100.000) 7. Hemoglobinuria 8. Abnormal spontaneous bleeding 9. Pulmonary edema (radiology, oxygen saturation <92%)	1. Hypoglycemia (blood sugar <40mg %) 2. Metabolic acidosis (plasma bicarbonate <15 mmol/L) 3. Severe anemia (HB <5gr% for highly endemic. <7gr% for moderately-low endemic), in adults HB <7 gr% or hematocrit <15% 4. Hyperparasitemia (parasite >2% eritrocyte or 100.000 parasite/µl daerah endemis tinggi) 5. Hyperlaktaemia (asam laktat >5mmol) 6. Hemoglobinuria 7. Impared kidney function (serum creatinin >3mg%)

The patient had symptoms of paroxysmal fever, decreased consciousness with GCS of 9, muscle weakness, symptoms of shock and hemoglobinuria, lived in an endemic area and had a peripheral blood smear examination which showed positive for Plasmodium falciparum malaria so that the patient could be diagnosed as Severe Malaria.

CM is a serious/fatal neurological complication of P. falciparum infection, which can be defined as the presence of peripheral plasmodium falciparum parasitemia and coma without other causes, characterized by reversible encephalopathy. It has a mortality rate of 100% in untreated patients, and 15-20% with anti-malarial therapy and adequate ICU care. Among adult patients who successfully recover, less than 1% experience serious neurological symptoms such as hemiplegia, ataxia, speech disorders and epilepsy, resulting in neurological deficits and even death.[11,12]

The pathogenesis of CM is not fully understood, but is thought to involve (1) decreased tissue perfusion leading to microvascular blockage by infected red blood cells (RBC), (2) excessive proinflammatory release due to hyperactivation of host immune cells and (3) associated coagulopathy caused by an immune reaction. The unique characteristic of plasmodium falciparum infection compared to other plasmodium is the sequestration of erythrocytes in

veins in many organs, especially the brain, this causes many complications, especially in the nervous system, resulting in inflammation in the brain and endothelial damage.[13]

There is no gold standard for diagnosing CM, so it can be diagnosed clinically which includes (1) a comatose state (unable to localize a painful stimulus) for more than 6 hours starting with fever 1 to 4 days before the onset of symptoms, after experiencing generalized seizures, (2) detection of the asexual stage of P. Falciparum in a peripheral blood smear (thick or thin), and (3) exclusion of other causes of encephalopathy.[11,14] In adults, coma occurs gradually, starting with drowsiness, disorientation, delerium and agitation, improving in 2-3 days. There are differences in the symptoms of cerebral malaria in children and adults. Clinical manifestations of CM include CNS symptoms, retinopathy, and Non-CNS symptoms. CNS symptoms consist of seizures, coma, nervous disorders and nervous reflexes. Retinopathy in CM is characterized by white retina (change in color of retinal blood vessels from pink to orange or white), retinal hemorrhage and papilledema. Non-CNS symptoms can include anemia, hypoglycemia, hyponatremia, jaundice, metabolic acidosis, and respiratory distress.[11,15] In this case, the patient experienced a decrease of consciousness with GCS 9 after experiencing fever for 4 days without anti-malarial administration. The detection of P. Falciparum in the blood smear was 4,185 parasites/µL and there was mild anemia. CT scans, MRI or CSF (cerebrospinal fluid) were not carried out to rule out other possible causes of encephalopathy due to limited diagnostic tools and the patient's unstable condition.

BWF is a complication of malaria, which is characterized by the clinical syndrome of intravascular hemolysis, hemoglobinuria which causes dark urine, and acute kidney injury. Most often caused by P. Falciparum infection. However, it can also be caused by P. Vivax, P Malariae or mixed infections.[16]

The pathogenesis of BWF is very complex and the mechanism is not yet known with certainty. Apart from being associated with infection by P. Falciparum, there are several risk factors for the occurrence of BWF such as immune inadequacy against malaria, recurrent malaria infections, misuse of amino-alcohol anti-malarial (quinin), use of atermicin derivatives and G6PD deficiency which are associated with the incidence of BWF. Amino alcohol anti-malarials and G6PD deficiency have almost the same mechanism, both producing oxidative stress that causes intravascular hemolysis. There are no clear predictive risk factors for BWF, and this syndrome is often diagnosed only after malaria patients undergoing treatment are found to have dark colored urine.[16,17] Based on research conducted by Mahopatra et al, as many as 90% of BWF patients experienced anemia with average hemoglobin was 7.4 and hematocrit was 29.9. Laboratory examination also found leukocytosis with an average of WBC was 17.1. Leukocytosis is suspected because of another infection. In this case, the patient did not have any of the above risk factors. The patient was diagnosed immediately after the discovery of dark colored urine when installing a urinary catheter.

According to WHO, first line therapy for severe malaria such as CM and BWF is artesunate which is given parenterally at a dose of 2.4 mg/kgBW 3 times at 0, 12, 24 hours. Next, it is given 2.4 mg/kgBW intravenously every 24 hours until the patient is able to take oral medication. If the patient is able to take oral medication, then treatment is continued with a dihydroartemisinin-piperaquine regimen or other ACT for 3 days + primaquine (according to the type of plasmodium) with a dose according to body weight. Meanwhile, artemether and quinine are second-line therapy. Enteral administration of artesunate can reduce mortality by 25-35% compared to quinine, because artesunate quickly eradicates young ring forms, preventing maturation and parasite sequestration. However, single administration of

anthermicin can result in drug resistance, so it is recommended to administer Artemisinin-based combinations (ACTs), to improve clinical outcomes, reduce mortality, prevent long-term neurological deficits and slow down artemisinin resistance.[9,18] In this case, the patient was given oral anti-malarials in the form of DHP 1x4 tablets for 3 days, Primaquin 1x1 tablet single dose according to the type of plasmodium and body weight. Patients also underwent therapy monitoring and regular blood tests. This is due to the unavailability of parenteral artesunate. However, clinical improvement occurred within 2 days according to theory. This can be caused by the patient's low parasite density. In plasmodium falciparum infection, the mortality rate can be influenced by parasite density. Mortality increased at a parasite density of 100,000/µl and mortality reached 50% at a parasite density of 500,000/µl.[9.19]

IV. Conclusion

CM and BWF are examples of severe malaria. There is no gold standard for diagnosing CM and BWF. CM can be diagnosed clinically which includes (1) a comatose state (unable to localize a painful stimulus) for more than 6 hours followed by fever 1 to 4 days before the onset of symptoms, after experiencing generalized seizures, (2) detection of asexual stage P Falciparum in peripheral blood smear (thick or thin), and (3) exclusion of other causes of encephalopathy. Meanwhile, BWF is often diagnosed after malaria patients undergoing treatment are found to have dark urine. According to WHO, first line therapy for severe malaria such as CM and BWF is artesunate given parenterally. However, the unavailability of parenteral antimalarials makes oral antimalarials an alternative therapeutic option, with close monitoring and adequate supportive therapy. DHP oral anti-malarial therapy and supportive therapy provided good results in this patient.

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