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Challenges of Severe Malaria Management in Patient Returning from Jayapura, Indonesia Presented with Severe Anemia: A Case Report

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ABSTRACT

We report a 55-year-old woman who presented to the hospital with intermittent fever for a month. The patient had a history of living in a malaria endemic area (Jayapura, Papua Province, Indonesia) for approximately 15 years. The hemoglobin level was very low (4.2 mg/dL). Furthermore, we conducted a follow-up supporting examination, Malaria *Rapid Diagnostic Test* (RDT), the result was positive for malaria tropica (*Plasmodium falciparum*). Blood smear test was also carried out to confirm the diagnosis, the result was that immature trophozoites (ring shape) were found. Thus, the patient was diagnosed with severe malaria tropica with clinical manifestations indicative of severe anemia. The patient was treated for 3 days with anti-malarial drugs and supportive drugs according to the symptoms in the hospital and was advised to follow up 7 days later. This case report describe the challenges of severe malaria management in patient returning from Jayapura with severe anemia.

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KEYWORDS:

Anti-Malarial Drugs, Severe Malaria, Severe Anemia

INTRODUCTION

Malaria is a tropical infectious disease caused by parasites named *Plasmodium*. Five species of *Plasmodium* were known to cause malaria: *P. falciparum, P. vivax, P. knowlesi, P. ovale,* and *P. malariae*. The transmission of this parasite occurs when a female Anopheles mosquito bites the host body. Globally, as many as 247,000,000 positive cases of malaria were reported in 84 malaria-endemic countries (2). Indonesia is one of the malaria-endemic countries with a relatively high number of cases, namely 443,530, and 89% of positive malaria cases were reported in Papua Province.

The malaria triad consists of three characteristic symptoms: fever, chills, and sweating. The majority of individuals affected by malaria seek medical assistance mostly due to the recurring symptom of intermittent fever, which persists for an extended duration. Given the multitude of disorders characterized by fever, diagnosing malaria becomes challenging for medical professionals. Nevertheless, a previous record of visiting endemic regions can facilitate the identification of malaria. Papua province is an area in Indonesia where malaria remains prevalent. Rapid Diagnostic Test (RDT) is used as a examination to confirm the diagnosis in patients suspected of having malaria, with a sensitivity of 95.2% and a specificity of 92.7%. If there were positive results following the RDT examination -or negative test results with highly suggestive clinical symptoms- the subsequent step is to do a blood smear test, which is considered a gold standard method for diagnosing malaria.

Malaria has the potential to progress into severe malaria when it impacts one or more systems. The criteria for severe malaria can be established by evaluating either the clinical symptoms or the findings from laboratory tests. Severe malaria, as defined by the *World Health Organization* (WHO), refers to cases of malaria caused by the asexual stages of the parasites *P. falciparum, P. vivax, and P. knowlesi,* which are accompanied by at least one complication. Prompt treatment of severe malaria is necessary in order to avert organ impairment and mortality. Practitioners face a dilemma in deciding the best course of action for severe malaria cases, given the persistently high malaria fatality rate in Indonesia- compromising of about 71 cases of mortality in 2022.

Hence, this study described the diagnosis and treatment of a severe case of malaria tropica (*P. falciparum*) in a woman exhibiting symptoms of severe anemia.

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CASE REPORT

A 55-year-old woman was admitted to emergency department, with a complaint of high intermittent fever for the past month. also complained of headaches, blurry vision, and general weakness. The subject had a history of residing in Jayapura, Papua Province, for 15 years before returning to Banjarnegara, Central Java Province this previous month.

The patient presented with intact consciousness, a blood pressure of 110/72 mmHg, a pulse of 102 beats/minute, a respiratory rate of 20 times/ minute, and a current body temperature of 36^0C. A review of systems was otherwise negative except for anemic conjunctiva. Physical examination of the thorax showed normal results. Physical examination of the abdominal also showed no abnormalities. Physical examination of the extremities was within normal limits.

Laboratory examination was significant for low hemoglobin count (4.2 g/dL), as seen in Table 1. Titers for Widal serological examination showed 1/320 for *S. Typhi* H and 1/80 for *S. Typhi* O. Another significant discovery from the laboratory analysis revealed that the patient's total bilirubin level was 3.84 mg/dL, with direct bilirubin measuring 0.34 mg/dL and indirect bilirubin at 3.50 mg/dL.

The RDT examination was conducted on the same day and yielded positive results for malaria tropica (*P. falciparum*). Subsequently, a blood smear specimen was obtained and examined under a microscope. The analysis revealed the presence of *immature trophozoites* (in the form of ring structures) of *Plasmodium sp.* in the thin blood smear, as depicted in Figure 1.

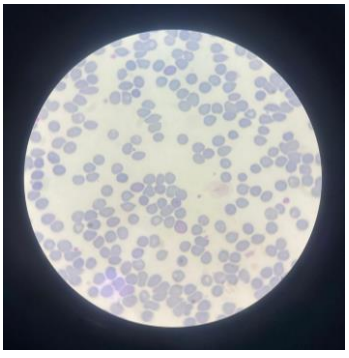

Figure 1. Subject's blood smear test prior treatment

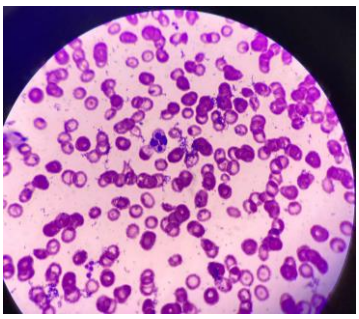

Figure 2. Subject's blood smear test after treatment

To treat anemia, the patient received medication in the form of a transfusion of three units of packed red blood cells (PRC). The other therapies include an infusion of 0.9% NaCl at a rate of 12 drops per minute, twice daily injections of Omeprazole at a dosage of 40 mg, twice daily injections of Paracetamol at a dosage of 1000 mg, oral administration of DHP (Dihydroartemisinin-Piperaquine) at a dosage of 3 tablets per day for three days, and a single dose of Primaquine at a dosage of 45 mg.

The subsequent assessment involved an abdominal ultrasound examination, which revealed no observable abnormalities in the liver, spleen, bladder, right kidney, left kidney, urinary bladder, pancreas, and aorta. No fluid accumulation in the abdomen, lumps in the abdominal or pelvic region, or abnormal tissue infiltration were observed. Additional assessments comprise thoracic radiography and electrocardiography. This examination is utilized to monitor the occurrence or non-occurrence of pulmonary edema, given that pulmonary edema leads to increased mortality in falciparum malaria even when positive pressure ventilation is applied (12).

Following the administration of 3 PRC blood transfusions, the patient's full blood test on the second day of treatment revealed an increase in hemoglobin level to 7.3 g/dL, as seen in Table 1.

The patient was admitted to the hospital for three days and showed improvement in both clinical and laboratory results. Subsequently, the patient was discharged and instructed to conduct a follow-up examination in the outpatient department after seven days. As part of the evaluation of treatment, a repeat blood smear examination was conducted during the control. Figure 2 demonstrates that no *immature trophozoites* were detected in the thin blood smears after seven days of treatment.

DISCUSSION

Globally, as many as 247 million positive cases of malaria were reported in 84 malaria-endemic countries (2). Indonesia is one of the malaria-endemic countries with a total of 443,530 cases, as much as 89% of positive malaria cases were reported from Papua Province (3). In 2022, the predicted number of deaths in Indonesia caused by malaria is 71 events (3).

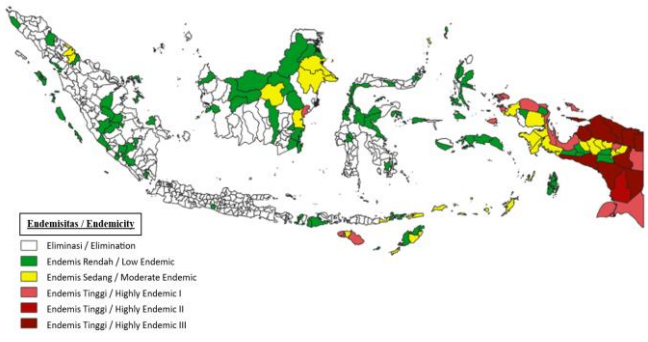

Figure 3. Malaria-endemic region

In this study, a 55-year-old woman who lived in Jayapura, Papua Province for 15 years before leaving for Banjarnegara, Central Java Province complained of intermittent fever one month after her arrival. Fever may not be a pathognomonic symptom of malaria (1). Diagnosing malaria can be assisted by a prior residence in a region where malaria is prevalent.

Other complaints encountered by patients include muscle pain, nausea and vomiting, blurred vision, and weakness. Malaria infection begins when a person is bitten by a female *Anopheles* mosquito so that the *trophozoites* (a form of *Plasmodium sp.*) enter the bloodstream. *Sporozoites* can reach the liver and reproduce asexually after the next 7–10 days. During this period, no manifestation emerged. When the parasite has become *merozoite*, symptoms will occur. *Merozoites* enter the bloodstream, invading erythrocytes and multiply within the erythrocytes, resulting in erythrocytes rupture, thus producing parasitic debris such as malaria pigments (*hemozoin* and *glycophosphatidylinositol*) and the putative malaria toxin. Symptoms of malaria can arise due to this process (4).

As previously described, the symptoms that appear are associated with malaria toxins, which activate mononuclear cells and stimulate the release of *cytokines* (5). The severity of symptoms depends on the balance between pro-inflammatory and anti-inflammatory *cytokines*, *chemokines*, growth factors, and effector molecules (4).

In this case, the patient's body temperature at first admission showed normal temperature. This is likely because the patient is in the afebrile phase, considering that fever in malaria is intermittent.

Clinical findings on physical examination include anemic conjunctiva, possibly due to the appearance of anemia in this patient. These clinical findings are based on the results of a complete blood test, where the patient's haemoglobin level was 4.2 g/dL. Therefore, this instance is categorized as a case of severe anemia. The criteria for severe malaria can be established by assessing either the clinical presentations or the laboratory findings. Severe malaria, as defined by the *World Health Organization* (WHO), refers to malaria caused by *P. falciparum*, *P. vivax*, and *P. knowlesi* in the asexual stage, accompanied by one or more clinical symptoms. These symptoms include reduced consciousness, muscle weakness, seizures, metabolic acidosis, pulmonary edema, shock, jaundice, abnormal spontaneous bleeding, low blood sugar, severe anemia, high parasite count in the blood, elevated lactate levels, and impaired kidney function. *P. falciparum* is the most common kind of malaria that leads to severe cases (12). According to these criteria, it may be concluded that this patient is suffering from severe malaria tropica (*P. falciparum*) with symptoms of severe anemia.

The presence of Plasmodium in erythrocytes results in the necessary destruction of red blood cells. Anemia in malaria is caused by the lysis of erythrocytes that harbor parasites. Nevertheless, the primary factor leading to anemia in malaria is the lysis of non-infected erythrocytes (4). Elevated extravascular hemolysis of erythrocytes and inadequate compensatory response by the bone marrow results in a substantial reduction in hemoglobin levels (11). Macrophages in the reticuloendothelial system are responsible for phagocytosing red blood cells that parasites have damaged. The spleen is the primary organ involved in this process of clearing the damaged cells. Following phagocytosis by macrophages, hemoglobin undergoes degradation into heme and globin. Subsequently, heme is further broken down into protoporphyrin, which is eventually transformed into indirect bilirubin. As hemolysis intensifies, there will be a corresponding increase in bilirubin metabolism, therefore necessitating the evaluation of bilirubin levels. The patient's bilirubin level showed a rise, specifically reaching 3.84 g/dL for total bilirubin, 0.34 g/dL for direct bilirubin, and 3.50 g/dL for indirect bilirubin. The elevation of bilirubin levels provides additional evidence of extravascular hemolysis in this patient.

The presence of bone marrow *dyserythropoiesis* during and immediately after an acute incident of malaria worsens the occurrence of hemolytic anemia. The duration of this period varies, contingent upon the initiation of malaria therapy. Initiating malaria treatment promptly reduces the duration of bone marrow *dyserythropoiesis* (12).

Rapid Diagnostic Test (RDT) for malaria sought to confirm the diagnosis. RDT detect the presence of the parasite *antigen Histidine-Rich Protein* 2 (HRP2) and *lactate dehydrogenase*. RDT has a sensitivity of 95.2% and a specificity of 92.7% (6). In this patient the RDT results showed positive results for tropical malaria (P. falciparum). This means that this patient has the HRP2 antigen.

Upon analyzing the blood smear, it was found that *immature trophozoites* (in the form of ring structures) of *Plasmodium sp*. were present. As practitioners, we must determine the most suitable treatment for patients suffering from severe malaria tropica caused by the *P. falciparum* parasite, who also exhibit severe anemia symptoms.

Considering the patient's past residence in a region with a high prevalence of malaria, together with the presence of severe anemia, positive results from Rapid Diagnostic Tests (RDT), and positive results from blood smears indicating tropical malaria, prompt therapy was administered to the patient. The treatment involves addressing both the symptoms and the underlying causes.

As stated in the 2023 Indonesian Malaria Management Guidebook, if RDT yields positive results, and there are accompanying symptoms and clinical signs consistent with malaria, along with a history of residing in a malaria-prone region, anti-malarial treatment can be initiated without waiting for the results of a blood smear examination. Prompt

initiation of treatment is crucial in order to avert deterioration and mortality associated with severe malaria.

An urgent intervention required for this patient is a blood transfusion, which will provide symptomatic relief. Anemia of such severity, characterized by a hemoglobin level below 5 g/dL, necessitates urgent transfusion as a critical measure to save a person's life (12). Hypohemoglobinemia, or low levels of hemoglobin in the blood, leads to a diminished ability of the blood to transport oxygen. Consequently, this results in a reduced delivery of oxygen to the tissues, leading to tissue hypoxia (9). Hence, it is imperative to address severe anemia promptly. Hemolytic anemia is the specific type of anemia that occurs in malaria. The recommended initial treatment for this condition is a blood transfusion.

The definitive therapy for this particular illness is the administration of anti-malarial medications, including DHP (Dihydroartemisinin-Piperaquine) and Primaquine. The rationale for selecting an artemisinin derivative as an anti-malarial medicine lies in its parasiticidal properties and superior efficacy compared to Quinine (13). However, it should be noted that parenteral artesunate is the preferred treatment for severe malaria, although its availability may be limited in certain regions. It is important to prioritize anti-malarial treatment over blood transfusion to avoid any delays (12).

Patients were administered a three-day course of DHP (Dihydroartemisinin-Piperaquine) and Primaquine as an anti-malarial medication (13). The patient's clinical progress is evident by the examination of the peripheral blood smear, as depicted in Figure 2. The first *immature trophozoites* observed upon the patient's arrival following administration of anti-malarial medication had undergone alterations. The administration of anti-malarial medication and blood transfusions resulted in a notable enhancement in patients with elevated hemoglobin levels, as seen in Table 1.

The patient was discharged with multivitamin medication containing Iron and Vitamin C. On the seventh day, when the patient returned for a follow-up visit, the patient experienced relatively adequate progress, and the patient's hemoglobin level increased to 9.7 g/dL.

Table 1. Laboratory Examination and Findings

Laboratory Testing	Result-1	Result-2	Result-3	Normal Range
Hemoglobin (g/dL)	4.2	7.3	9.7	12 - 16
Leukocyte (10^3/ uL)	5.7	1.90	1.90	4.8 - 10.8
Hematocrit (%)	12.4	20.7	28.6	37 - 47
Thrombocyte (10^3/ uL)	126	122	95	150 - 450
Erythrocyte (million/uL)	1.49	2.66	3.59	3.8 - 5.2
MCV (fL)	83.0	77.6	79.7	75 - 100
MCH (pg)	28.3	27.6	27.2	26 - 34
MCHC (g/dL)	34.0	35.6	34.1	32 - 36
RDW (%)	13.2	12.3	12.8	11 - 16
MPV (fL)	10.4	7.8	15	8 - 11
PDW (fL)	9.8	10.4	14.2	0.1 - 99.9
Lymphocyte (%)	92.7	86.2	91	15 - 40
Monocyte (%)	3.0	4.7	3.7	2 - 8
Granulocyte (%)	4.3	9.1	5.3	50 - 70
Ureum (mg/dL)	31.2	-	-	10 - 50
Creatinine (mg/dL)	0.62	-	-	0.6 - 1.3
Random Glucose (mg/dL)	115	-	-	70 - 150
Total Bilirubin (mg/dL)	3.84	-	-	0.2 - 1.2
Direct Bilirubin (mg/dL)	0.34	-	-	0 - 0.5
Indirect Bilirubin (mg/dL)	3.50	-	-	0.1 - 0.7
Widal		-	-	Negative
S. Typhi O	1/80			
S. Typhi H	1/320	-	-	Negative
RDT Malaria				
P. vivax	Negative	-	-	Negative
P. falciparum	Positive	-	-	Negative

CONCLUSIONS

The patient presented with clinical indications of malaria, and upon investigation, it was discovered that the patient had a history of residing in a region where malaria is prevalent. The physical examination revealed that the patient's state of awareness remained intact, although the clinical appearance

was pale, and their conjunctiva appeared anemic. The comprehensive blood test revealed a significantly low hemoglobin level. Malaria Rapid Diagnostic Test (RDT) yielded positive results, and the microscopic inspection confirmed the presence of plasmodium, namely young *trophozoites*. This patient can be diagnosed with severe malaria, exhibiting clinical manifestations indicative of severe malaria. The management for this patient involves administering a blood transfusion to address the anemia and prescribing anti-malarial medicines. Timely administration of anti-malarial medications is crucial, as any delay might have a detrimental impact on patient outcomes.

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