A case report: a 38-year-old man with vivax relapse malaria

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ABSTRACT

INTRODUCTION

Malaria is a parasitic disease caused by blood protozoa of Plasmodium genus derived from the species P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi. The disease is naturally transmitted through the bite of a female Anopheles mosquito. Indonesia is still an endemic area, especially in the eastern regions. About 40% of malaria cases in the world are caused by Plasmodium vivax. Tertiana or vivax malaria can cause relapse because it has a hypnozoite stage that is dormant in the liver. This case report will discuss a case of relapse vivax malaria with thrombocytopenia.

Case Illustration: A 38-year-old man came to the emergency room consciously with a fever complaint since 4 days before entering the hospital. Fever occurred throughout the body, disappeared, accompanied by chills and sweating. On the second day the fever began to decrease somewhat but the next day the fever began to increase. The patient has a history of serving in Papua and contracted malaria 3 months before entering the hospital. While in Papua, the patient worked as a supporter for the 2021 PON event and malaria treatment was not complete. A complete blood examination found thrombocytopenia and microscopic examination of thin drops of the presence of ring-shaped Plasmodium vivax. The patient is diagnosed with vivax relapse malaria. The patient was treated with antimalarial therapy with DHP 4 tablets in a day for 3 days and primaquine 2 tablets in a day for 14 days. Monitoring therapy was done on the eighth day, with microscopic examination, and the result was negative malaria plasmodium.

Conclusion: This case report discusses vivax relapse malaria and proper management to irradicate the hypnozoite stage which has an important role in the recurrence phase.

Keywords: malaria, plasmodium vivax, relapse.


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severity of malaria. Research in Bangkok showed platelet levels were significantly lower in severe malaria cases than uncomplicated malaria.\(^7\) Research in Bengkayang Regency, West Kalimantan stated that a decrease in platelet counts is often found in people with severe malaria. Complications of thrombocytopenia can lead to bleeding. The bleeding found in malaria patients is usually in the form of petechiae, spontaneous bleeding in the form of gum bleeding, epistaxis, retinal hemorrhage, gastrointestinal bleeding, hematomas can occur in tropical malaria infection.\(^8\)

Cases of vivax malaria around the world, when compared to other types of malaria, are around 70 – 80 million per year.\(^2\) *Plasmodium vivax* can cause relapse due to the presence of a hypnozoite stage in the liver that can one day redevelop. According to WHO, about 40% of malaria cases in the world are caused by *Plasmodium vivax*. *Plasmodium vivax* is the most dominant parasitic species in Southeast Asia, Eastern Europe, North Asia, central and South America.\(^2\) This case report will discuss a case of relapse vivax malaria with thrombocytopenia.

**CASE ILLUSTRATION**

A 38-year-old male patient, a Javanese tribe, came to the emergency room of RSAD Udayana with a fever complaint. Fever had occurred since 4 days ago at 12.00 WITA. Fever was said to occur throughout the body and disappeared, accompanied by chills. After the body temperature decreased, the patient was said to begin to develop sweating. On the second day the fever began to decrease somewhat but on the next day it was said that the body temperature began to increase and measurements were taken at the patient’s home measuring 39°C. Complaints of fever interfere with activity. The patient also had complained of headaches since 4 days ago. Complaints of headache arose simultaneously with fever. The headache felt pressing. The patient’s appetite and drinking are still said to be good. Complaints of nausea and vomiting are absent. A history of nosebleeds, bleeding gums, bruises on the body, defecation and black TUB are refuted. A history of allergies to food, drugs and others was refuted. A history of chronic diseases is refuted. The patient had a history of malaria in September 2021 while working in Papua, but treatment was not completed. It was said at that time, the patient only took malaria medicine for 11 days. Before the patient went to the emergency room at RSAD Udayana, the patient had time to take heat-reducing drugs obtained at the pharmacy, but it had little effect on relieving fever. A family history with the same complaints was refuted. A family history of chronic diseases was refuted. Patient worked as a vendor tenant at an event. In September 2021, the patient was transferred to Papua as tenant of PON 2021. The patient had no history of taking malaria prophylactic drugs. Social habits were said to have no habit of smoking or drinking alcohol.

On physical examination the patient appeared to be moderately ill, awareness was obtained *compos mentis* with **Glasgow Coma Scale** (GCS) E4V5M6, blood pressure 120/80 mmHg, pulse rate 90 times per minute, measured temperature 37.6°C, breath rate 20 times per minute with peripheral oxygen saturation of 99% of the room air.

From the physical examination of the face and neck, it was found that the eyes and neck looked normal, no enlargement of the glands around the neck was found. From the examination of the gums there was no bleeding. Examination of the ears, nose and throat was within normal limits. Physical examination of the pulmonary heart of the impression was within normal limits. From the physical examination of the abdomen, no abnormalities were found, either enlarged organs or disorders of intestinal peristalsis. Examination of the extremities palpable was warm with no edema.

On a complete blood support examination, leukocyte values were obtained 6.70 x 10^3 / μL, neutrophils 71.5%, lymphocytes 14.5%, monocytes 12.7%, eosinophils 1.0%, platelets 74 x 10^4 / μL, hematocrit 39.6%. Blood chemical results SGOT value 16 U/L, SGPT 19 U/L, creatinine 0.6 mg/dL. The results of the Malaria Rapid Diagnostic Test (RDT) were obtained positive for vivax malaria. The patient was checked with microscopic thin thick drops found ring-shaped *plasmodium vivax* (Figure 1).

Based on the results of anamnesis, physical examination and support, the patient was then diagnosed as relapse vivax malaria. The patient was then hospitalized with a plan of administering Ringer Lactate infusion fluid 20 drops per minute. Patient was also given paracetamol 500 mg every 8 hours PO, DHP 4 tablets a day for 3 days, primaquine 2 tablets a day for 14 days. On the fourth day of hospitalization, the patient had no complaints. Physical examination obtained sufficient general condition, awareness *compos mentis* with GCS E4V5M6, blood pressure 120/70 mmHg, pulse rate 66 times every minute, breath rate 20 times every minute, temperature 36°C, oxygen saturation 99% room air. The physical examination of the face and neck seemed normal. Physical examination of the heart, lungs and abdomen within normal limits. Examination of the extremities of the accrual was warm, there was no edema. The patient was re-examined for complete blood with platelet results of 160 x 10^9 / μL, hematocrit 38.2%. The patient was scheduled to follow up in the Internal Medicine Polyclinic on day 8.

The patient came to the Internal Medicine Poly with no complaints and the patient was still taking primaquine medicine. Physical examination of the general state was sufficient with awareness of *compos mentis* GCS E4V5M6, blood pressure 110/80 mmHg, pulse rate 80 times per minute, breath rate 20 times per minute,
temperature 36°C, oxygen saturation 99% of the room air. Physical examination of the face and neck within normal limits. Examination of the heart, lungs, abdomen normal impression. Examination of the extremities of the accrual was warm, there was no edema. The patient was subjected to microscopic re-examination of malaria thin thick drops with the result that no malaria plasmodium was found. From the results of anamnesis, physical examination and supporting examination, the patient was diagnosed with relapse vivax malaria with improvement. The patient continued primaquine therapy 2 tablets in a day and spent for 14 days.

DISCUSSION

Malaria is a disease caused by intracellular obligate protozoa of the genus Plasmodium and transmitted by female anopheles mosquitoes. The diagnosis of malaria can be established based on anamnesis, physical examination and supporting examination. Anamnesis that is often complained of is fever accompanied by chills and sweating. In addition, the presence of headaches, nausea, vomiting, diarrhea and muscle aches or aches. The malaria paroxysm consists of three stages. The first stage is a 15-60 minute cold stage characterized by chills and a feeling of coldness. The second stage, namely the hot stage lasts 2-6 hours, sometimes fever reaches 41°C, redness, dry skin and frequent headaches, nausea and vomiting. The last stage of sweating lasts 2-4 hours where the fever drops rapidly and the patient feels sweaty. In all types of malaria-causing causes, the periodic fever response is caused by the rupture of an adult schizont. In severe malaria, it can be enforced based on WHO criteria, 2015, namely found asexual stage Plasmodium falciparum with at least one of the clinical manifestations such as loss of consciousness, muscle weakness, recurrent seizures, respiratory distress, circulatory failure or shock, jaundice, haemoglobinuria, abnormal spontaneous bleeding and pulmonary oedema or laboratory results were found such as hypoglycaemia, metabolic acidosis, severe anemia and impaired kidney function. In the case, the patient was a 38-year-old male, complaining of fever lasting 4 days. Fever is said to occur throughout the body. At first shivering then suddenly the body temperature rises and finally the patient begins to develop sweat. In addition, on the second day the fever is said to begin to decrease but the next day the fever begins to increase. The basis for enforcing the diagnosis is the presence of a fever attack with paroxysm, which goes through three stages, the cold stage lasts 15-60 minutes where the patient shivers, the fever stage lasts 2-6 hours where the patient's body temperature increases accompanied by headaches, the third stage lasts 2-4 hours the patient develops sweating when the body temperature decreases. In all types of malaria, the feverish period is caused by the rupture of adult schizonts. Plasmodium vivax schizonts become adults every 48 hours so that the periodicity of fever is tertiana (tertiana malaria). In the presence of complaints of fever disappearance accompanied by headaches in patients, it may be the basis of a clinical diagnosis of malaria. In patients, there were no complaints that led to severe malaria.

The patient has a history of traveling to an endemic area, namely Papua, 3 months before entering the hospital. This is in accordance with research conducted in China in 2016 that men aged 21-50 years have risk factors for developing malaria and this is related to a history of travel to endemic areas due to work. It was also found that eastern Indonesia is still an endemic area for malaria. In this case, the patient 3 months ago was exposed to malaria but it was said that malaria treatment was not complete. So it is suspected that the patient has a relapse. In theory, vivax malaria and ovale malaria will experience recurrence. Pasien that originally came with Plasmodium vivax infection was 1.5 times more likely to come back with malaria compared to patients initially infected with other species of Plasmodium. On physical examination of mild malaria generally the axillary body temperature ≥ 37.5 °C with other vital signs still within normal limits. However, if malaria is severe, it is found that the icteric sclera, conjunctiva and palms are pale, splenomegaly, hepatomegaly and the presence of tea-like urine. In addition, there is also a decrease in consciousness. In cases, the patient comes in a conscious state, body temperature 37.6 °C and other vital signs are still within normal limits. Physical examination from head to toe found no signs leading to severe malaria.

Laboratory examination that can be used to establish a diagnosis with microscopic examination and RDT (Rapid Diagnostic Test). The RDT examination has weaknesses, namely sensitivity and specificity, especially in low parasitemia. Usually used in cases of extraordinary events that require quick results in the field. To determine the presence or absence of malaria parasites, species, plasmodium stage and density of parasites can use a microscope examination with blood preparations removed thick and thin. The golden standard in diagnosing malaria is to use thick and thin blood preparations. The patient's blood sample was taken when the patient had a fever and had not been given anti-malarial drugs in order to find the parasite if the patient was infected with malaria. P there is a basis RDT works by capturing the target antigen in the patient's blood produced by Plasmodium falciparum (HRP-2) and Plasmodium vivax (pLDH), with specific single clone antibodies (anti-HRP-2, anti-pLDH and control), which are affixed to nitrocellulose paper. If the-asién blood contains HRP-2 and or contains pLDH, the antigen will be captured by antiHRP-2 or anti-pLDH on nitrocellulose paper, so that in a positive result it will cause a red color on the nitrocellulose paper. Because the patient has a history of traveling to endemic areas, RDT and microscopic checks of thin thick drops are carried out. On the RDT examination, a positive result of vivax malaria was found. After that the patient is carried out an examination of thin and thick blood smears to confirm the diagnosis. A morphological picture of ring-shaped vivax malaria was found. This can be established in the diagnosis of vivax malaria, which is found to be positive for vivax malaria on examination of blood preparations.

The results of a complete blood examination in cases of found thrombocytopenia. This is appropriate because in the case of malaria it will cause thrombocytopenia, especially in...
Plasmodium vivax and Plasmodium falciparum. It is suspected that platelets will induce clots of red blood cells infected with Plasmodium falciparum in patients with cerebral malaria in vitro while in Plasmodium vivax there will be clots in endothelial and placental cells ex vivo. Thrombocytopenia is associated with several cytokines such as TNFa, IL-6, and IL-10. Thrombocytopenia in Plasmodium vivax there is an increase in IL-10 levels while in Plasmodium falciparum cytokine changes increase the occurrence of malaria with complications. As a pro-inflammatory cytokine TNFa is in charge of eliminating plasmodium infections and the number varies depending on the type and number of pathogens, patient immunity and other immunity. It is suspected that increased TNFa will trigger platelet trapping and inflammation in the blood vessels. To reduce its production, IL-10 is needed which is an immunoregulatory and plays a role in controlling inflammation of infectious events. But indirectly related to the incidence of thrombocytopenia in Plasmodium falciparum and Plasmodium vivax. In addition, platelets are associated with the process of clumping infected erythrocytes so that the more erythrocytes infected, the more platelets are used and this triggers the occurrence of thrombocytopenia. It can be said that the more and longer the parasitemia is in the body, it affects the lightweight of thrombocytopenia.18

Based on the anamnesis, physical examination and supporting examination the patient is diagnosed with relapse vivax malaria. It is said to be a relapse because the patient had a history of malaria 3 months ago in Papua and the patient said the treatment of malaria in Papua was not complete. This is in accordance with the theory where in Plasmodium vivax there is a reactivation of the hypnozoite phase that is dormant in the liver, giving rise to a new stage of infection that usually occurs several months after the first infection. The number of sporozoites inoculated by mosquitoes, as well as the geographical origin of the parasite are the main determinants of the periodicity of recurrence. In the tropics, the risk of early relapse is high (more than 80%) with subsequent relapses occurring every 3-4 weeks. While in temperate climates and some subtropical regions, the risk of recurrence is much lower and there may be a long incubation period or latency between early infection and recurrence lasting 8-12 months.19

Malaria management in this case is DHP 4 tablets in a day for 3 days, primaquine 2 tablets in a day for 14 days. This is in accordance with the management of malaria without complications, especially malaria, which causes Plasmodium vivax using DHP and primaquine. The dose of malaria vivax depends on the patient's body weight. In cases of relapse malaria, it is given with the same ACT regimen but the primaquine dose is increased to 0.5 mg/kgBB/day.15

Patients with Plasmodium vivax need to be radically treated with primaquine for 14 days with supervision to irradiate the dormant or hypnozoite stage, but previous studies in this population showed that if not supervised, then the effectiveness is very poor.13 The recurrence in question reappears in the form of asexual parasites in the blood up to 6 months after the post-therapy monitoring period. Recurrence may occur as a result of the presence of drug resistance, failure of therapy, non-compliance with treatment and its reactivation of the hypnozoite stage. It is said that clinical malaria will be aggravated due to the relationship of poor inflammatory response with high parasitemia. Host activation of the immune system is mainly T lymphocytes which are the core factors of severe malaria pathogenicity associated with a high and disproportionate increase in pro-inflammatory cytokines, which can be observed in the erythrocytic life cycle. In vivax malaria, increases in TNF, IFN-γ and IL-10 have correlated with the development of the disease towards severe clinical.20

While in Papua, the patient only took anti-malarial drugs for 11 days. It is reported that the recurrence of vivax malaria resulted from the failure of primaquine treatment. The recommendation of anti-malarial therapy especially in vivax malaria is a combination of chloroquine taken for 3 days and primaquine taken for 14 days. Primaquine is given for its hypnozoite cidal activity. Combining chloroquine and primaquine as a treatment of Plasmodium vivax can reduce recurrence by 90% because there is a synergistic activity of primaquine with chloroquine against parasites at the asexual blood stage and its hypnozoitisidal activity. Compliance with the administration of the drug and the exclusion of the possibility of recurrent infection, showed a cure rate of 86% after the standard treatment of vivax malaria (chloroquine with primaquine) in Brazil to eliminate parasitemia and prevent recurrence for an average of 6 months. Relapse occurs between day 33 and day 137 after the initials of therapy. No failure of therapy was found during the first 28 days indicating a high cure rate with chloroquine and primaquine treatment. But the failure of more than 28 days was the failure of primaquine to kill hypnozoites. Ebasic fication of primaquine to prevent recurrence varies between different geographical strains. An important risk factor that needs to be identified is the dose that depends on body weight, gender, early parasitemia and the duration of the symptoms. Research shows that the most powerful factor associated with recurrence is low dose primaquine kg/mg. In cases, patients often forget to take antimalarial drugs obtained due to their work so that it is suspected that insufficient doses and insufficient adherence to treatment can trigger a relapse.19

Basically the main therapy of vivax malaria is a combination of schizonticide antimalariais and hypnozoitisidals. First irradiate the parasitic stage in peripheral blood to eliminate fever and finally irradiate the hypnozoite reservoir, preventing subsequent relapsing infections and their subsequent transmission. In most countries, chloroquine remains the main treatment at the stage of Plasmodium vivax. However some endemic areas of the vivax plasmodium are resistant to chloroquine. The highest chloroquine resistance occurs in New Guinea (Indonesia and Papua New Guinea).19 In 2006, Indonesia was one of the first countries to adopt a first-line policy of using uncomplicated malaria dihydroartemisinin–piperaquine (DHP) in either Plasmodium falciparum or Plasmodium vivax. Given that previously there have been reported cases of failure of therapy with chloroquine. The risk
of recurrent parasitemia within 42 days was 4.1% in Plasmodium falciparum and 10% in Plasmodium vivax. In a study conducted in Papua (2015) with DHP therapy (40 mg of dihydroartemisinin and 320 mg of piperaquine) was given once a day for 3 days at a weight dose. Patients with vivax malaria were given primaquine (0.5 mg/kgBB/day) for 14 days. The efficacy of using DHP in vivax malaria is almost 100%, only 1.8% have recurrent infections, compared to the 90% efficacy reported in 2005. The proportion of parasitemia patients fell rapidly, more than 98% apathymetric in 48 hours and no patients remained parasitemia at 72 hours. So far, there are no severe side effects. Primaquine is a hypnozoitisidal cell capable of irradiating the hypnozoite stage in Plasmodium vivax and preventing recurrence. However, this drug can cause severe drug-induced hemolysis in individuals with glucose-6-phosphate (G6PD) deficiency. Primaquine is also contraindicated in pregnant women and nursing mothers because it has a risk of hemolysis in the fetus and newborns. In malaria endemic areas, a DHP treatment strategy is needed to irradiate the asexual stage in all Plasmodium species and then combined with hypnozoitisidal agents such as primaquine to irradiate the hepatic stage of Plasmodium Vivax and Plasmodium Ovale. Prevents recurrence of parasitemia and can reduce the morbidity and mortality of malaria.

Judging from the geographical distribution of recurrence latency, in North America, Europe and Russia before elimination, Plasmodium vivax has a long latent phase with an estimated incubation period of 9 months or with an incubation period of 2 weeks for primary infection and then a relapse interval of about 9 months. In contrast in Southeast Asia and Oceania, Plasmodium vivax has a short latent phase where relapses occur approximately 3 weeks after antimalarial treatment (artesunate, quinine) and 6-7 weeks after antimalarial treatment such as mepracine, chloroquine, mefloquine or piperaquine.

To date, there is no solid evidence of the management of malaria patients with thrombocytopenia. Indication of platelet transfusion if the number of platelets is below 10,000 / mm³ and it is proven that there is a disorder in the bone marrow. In most cases, conservative approaches such as providing appropriate antimalarial therapy and clinically treating patients can raise platelet counts to the normal range.

In this case, the patient was treated with antimalarial drugs and paracetamol according to his fever complaints. Monitoring of treatment is carried out by clinical examination and microscopic examination. In outpatients, treatment evaluation is carried out after treatment is completed (day 3), day 7, 14,21 and 28 while inpatients treatment evaluation is carried out daily until no parasites were found in the blood preparation for 3 days in a row and after it was evaluated like an outpatient. In the case, the patient was carried out a microscopic examination on day 7 and found negative for malaria. The patient continued the primaquine treatment for up to 14 days.

CONCLUSION

The vivax relapse malaria has been reported. The patient had classic clinical symptoms such as a fever disappearing accompanied by chills and sweating. The patient had a history of traveling to endemic areas. On the RDT examination, a positive result of vivax malaria was found and on examination of thin and thick blood smears, it was found a ring-shaped vivax malaria morphological picture. Based on the results of a complete blood examination in this case, thrombocytopenia was found. Relapse vivax malaria obtained from the patient was suspected because the patient had a history of going to an endemic area 3 months ago but did not complete treatment. The patient was treated with DHP for 3 days and primaquine for 14 days. From the results of patient monitoring on day 7, a microscopic examination was carried out and a negative result of malaria was obtained. However, the patient continued the primaquine treatment in order to irradiate hypnozoites in the liver.

CONFLICT OF INTEREST

There is no conflict of interest in the writing of this paper.

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ETHICS IN PUBLICATION

The patient’s parents have signed the informed consent and agreed that the medical data would be published in the form of case reports in medical scientific journals.

AUTHOR’S CONTRIBUTION

All authors contributed to writing this paper, starting from patient examination, data collection, and report writing.

REFERENCES


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