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Case report: Malaria and Thrombocytopenia at Pimping Community Health Center, North Kalimantan, an Endemic Area in Indonesia

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ABSTRACT
Thrombocytopenia is one of the most frequent side effects of both Plasmodium vivax and Plasmodium falciparum malaria, despite the fact that it is not a sign of severe malaria. However, few studies said that thrombocytopenia would early recognition of severe malaria. Moreover, thrombocytes play a significant part in inflammatory response during malaria. In these cases, present malaria falciparum and vivax with thrombocytopenia without bleeding and any severe malaria. The case diagnosis with a rapid diagnostic test of malaria and peripheral blood examination.

Introduction

Malaria is a disease that causes serious problems in public health. Disease caused by plasmodium parasites transmitted by anopheles mosquitoes.(buku saku tatalaksana kasus malaria subdit malaria direktorat p2ptvz kementerian kesehatan republik indonesia 20, n.d.) According to WHO, the incidence of malaria in the world was 247 million cases in 2021 and 61900 deaths. While Southeast Asia occupies the second incidence rate in the world for malaria incidence rate around 3.4% of world cases. Meanwhile, Indonesia itself is a malaria endemic area where the incidence rate in 2021 is 304607 people. Patients with malaria have symptoms of fever, flu-like joint pain. If not treated immediately can be a serious complication that leads to death. (Buku saku tatalaksana kasus malaria subdit malaria direktorat p2ptvz kementerian kesehatan republik indonesia 20, n.d.; cdc - parasites - malaria, n.d.; malaria, n.d.) Plasmodium vivax and ovale are the cause of most severe malaria. Complications can include severe anemia, cerebral malaria with seizures, ARDS, kidney failure, circulatory failure causing shock, hemoglubinurea, spontaneous bleeding, thrombocytopenia, DIC (disseminated intravascular coagulation) and jaundice (Kumbhar et al., n.d.). Hemtological complications are the most common complications in malaria and one of them is thrombocytopenia (<150,000 mm3).(Naing & Whittaker, 2018) To determine the severity of malaria can be determined from hematologic abnormalities and thrombocytopenia is often underestimated is considered not to show the severity of malaria is not one of the markers of severe malaria by WHO, but based on some studies thrombocytopenia can be a marker of severe malaria at the beginning. (Hanson et al., 2015; Khan et al., 2012; Kumbhar et al., n.d.; Lacerda et al., 2011; Muwonge et al., 2013; Punnath et al., 2019; Saravu et al., 2011) However, in a

retrospective analyse conducted in Colombia on 846 cases of malaria, higher parasites were found in the blood leading to severe thrombocytopenia, but found no positive correlation on severity with thrombocytopenia, more positive correlation with liver function. (Martínez-Salazar & Tobón-Castaño, 2014). In addition, platelets have an important role to control parasitemia where platelets bind to red blood cells infected by plasmodium so that parasite lysis. (Kho et al., 2018)

Research Methods

Case 1 male 27 years old came with fever for a week at the same time of 09.00 to 11.00, at the time of fever, joint pain, nausea, heartburn, without accompanied by bleeding. The patient was infected with falciparum malaria last month in the Berau area. Physical examination showed GCS 15 blood pressure of 110/70mmhg, pulse rate of 68x/min, and current temperature up to 36°C, oxygen saturation of 100%. Heart and lung sounds within normal limits, at the time of palpation of the liver and spleen are not palpable. Laboratory Results, Hemoglobin 13 mg/Dl, platelets 34000mm3, leukocytes 5450mm3, glucose 98mg/Dl. Peripheral blood smears show plasmodium vivax and plasmodium falcifarum. RDT for malaria positive. Serological for dengue fever negative NS1 IgG and IgM. No symptoms of severe malaria, such as seizures, bleeding during hospitalization and getting primaquine 1x1 for 14 days and DHP for 3 days

Case 2 26 years old man came with complaints of joint pain, and fever since 3 days ago, the patient said fever also last week, but only a day, accompanied by nausea, heartburn. The patient had also been infected with malaria 2 months ago in Sekatak declared falciparum malaria. Physical examination showed GCS 15, blood pressure 115/76, pulse 104x/min, temperature 39°C, oxygen saturation 98%. Laboratory results of leukocytes 5500mm3 hemoglobin 15.5g/dl platelets 104000 mm3 glucose 118 90mg/dl. Heart and lung sounds within normal limits, when palpation of the liver and spleen is not palpable. Peripheral blood smears showed plasmodium vivax and falciparum, and RDT was positive. Serological for dengue fever negative NS1 IgG and IgM. There were no symptoms of severe malaria such as seizures, bleeding during hospitalization and receiving primaquine 1x1 for 14 days and dhp for 3 days.

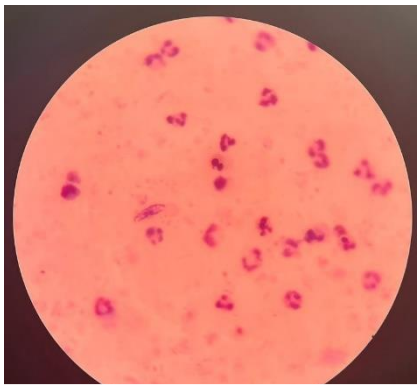

Figure 1 Peripheral blood smear showing the gametocyte form of *Plasmodium falcifarum*

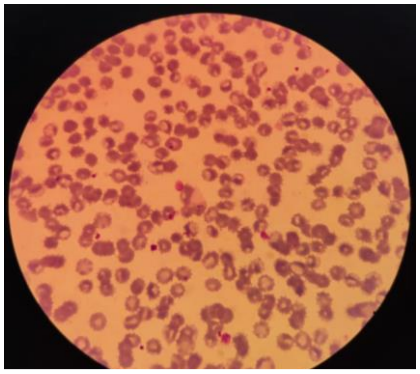

Figure 2 Peripheral blood smears showing irregular erythrocyte shape *Plasmodium vivax*

	Case 1	Case 2
Age	27	26
Sex	Male	Male
GCS	15	15
Gula	98 mg/Dl	118 mg/Dl
WBC	5450mm^3	5500 mm^3
PLT	34000mm^3	104000 mm^3
HB	13 g/Dl	15.5g/Dl
Antigen	Positif	Positif
Thick and Thin Blood Smears	P. Vivax dan P.Falsiparum	P. Vivax and P.Falsiparum
Duration in care	5 days	3 days
bat given	dihydroartemisinin-piperaquine and primaquine (14 Days)	dihydroartemisinin-piperaquine and primaquine (14 Days)

Results and Discussions

North Kalimantan is known to be an endemic area for malaria in Indonesia. However, in the northern part of Tanjung Palas, no cases have been reported for the past two years, from 2020 to 2022, except for imported cases from other districts. All patients sought medical care at Pimping Health Center through the general outpatient and emergency units.

All malaria cases experienced fever and chills, although the onset of fever was intermittent in some cases (Kumbhar et al., n.d.). For instance, in case one, the patient had a fever only in the morning, while in case two, the patient had high fever for three days, which subsided after receiving antipyretics. Both cases exhibited clinical and laboratory consistency with thrombocytopenia (Salim et al., 2021). Thrombocytopenia is often attributed to viral infections due to Indonesia's endemicity for dengue fever. To rule out dengue as the cause of thrombocytopenia, NS1 IgG and IgM dengue tests were performed, and the results were negative. Thrombocytopenia is a common complication of vivax and falciparum malaria, as well as mixed cases. In both patients, severe and mild thrombocytopenia were observed, with no spontaneous bleeding.

The exact cause of thrombocytopenia in malaria patients remains unclear, but several experts have proposed potential factors. These factors include immune complex reactions, bone marrow changes, excessive destruction of platelets by the spleen, oxidative stress, platelet aggregation, destruction through the process of Disseminated Intravascular Coagulation (DIC), and pseudothrombocytopenia due to clumping of erythrocytes infected with Plasmodium falciparum (Asaad Ma. Babker, 2020; Engwerda et al., 2005; Kelton et al., 1983; Lacerda et al., 2011). The spleen plays a vital role during acute malaria infection, as it contributes to parasite clearance, but this process can lead to anemia and the fragmentation of platelets during acute infection (“Depletion of Coagulation Factors in Drug-Resistant Plasmodium Falciparum Malaria,” 1967; Lacerda et al., 2011; Naing & Whittaker, 2018). IgG antibodies binding to the platelet surface, targeting glycoproteins found on malaria parasites, can lead to immune complex formation and subsequent thrombocytopenia. Inflammatory cytokines, including TNF-α,

IL-6, and IL-10 (Punnath et al., 2019), have also been implicated in thrombocytopenia during P. falciparum and P. vivax infections.

The mechanisms underlying thrombocytopenia in malaria involve platelet destruction by IgG antibodies, the release of adenosine diphosphate (ADP) by parasitized red blood cells undergoing hemolysis, dysmegakaryopoiesis, direct lytic effects of parasites on platelets, platelet phagocytosis, platelet adhesion to erythrocytes, and oxidative stress (Asaad Ma. Babker, 2020; Lacerda et al., 2011). While the exact mechanisms of oxidative stress-induced thrombocytopenia in malaria remain unclear, some studies have shown a negative correlation between platelets and lipid peroxide levels, suggesting increased activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase (Erel et al., 2001).

In most cases, platelet counts return to normal within seven days, as observed in the cases presented. Case one required three days of inpatient care, and after receiving malaria treatment, the patient's fever subsided, and the platelet count reached 50,000 without spontaneous bleeding by the fourth day. Case two was discharged on the second day after receiving antimalarial treatment, with a platelet count still around 100,000. Both patients were rechecked one week later, and their platelet counts had returned to normal.

Platelets play a significant role in inflammation in malaria cases, particularly related to changes in the endothelial cell layers of blood vessels. Studies have shown that platelet count is associated with Mean Platelet Volume (MPV), which increases in cases of malaria. Larger platelets are considered more active in malaria cases and are believed to play a crucial role in preventing bleeding (Dos-Santos et al., 2020; Lacerda et al., 2011). Thrombocytopenia can be used as an early marker for diagnosing malaria, with a sensitivity of 79.5% and specificity of 86.3% (Gebreweld et al., 2021).

Although thrombocytopenia is not considered a marker of severe malaria, it can be an essential indicator for assessing the severity of malaria and facilitating early diagnosis. This, in turn, can help reduce malaria-related mortality and alleviate the burden on public health.

Conclusion

Malaria remains a significant public health concern, with Indonesia, particularly Kalimantan Utara, being an endemic region for the disease. Although Tanjung Palas Utara had not reported any cases for the past two years, it's essential to remain vigilant due to the risk of imported cases from neighboring areas. Malaria-infected patients typically present with symptoms such as fever and chills, which may occur intermittently. Two cases were presented in this study, both showing clinical and laboratory evidence of thrombocytopenia, a common complication of both vivax and falciparum malaria, including mixed cases. No spontaneous bleeding was observed in these patients.

The exact cause of thrombocytopenia in malaria patients is not fully understood, but several factors have been implicated. These factors include immune complex reactions, bone marrow changes, excessive platelet destruction by the spleen, oxidative stress, platelet aggregation, destruction due to Disseminated Intravascular Coagulation (DIC), and pseudothrombocytopenia resulting from clumping of erythrocytes infected with Plasmodium falciparum. The role of the spleen is crucial during acute malaria infection as it plays a significant role in parasite clearance, and the subsequent destruction of infected red blood cells can lead to anemia. However, during acute infection, platelets are also broken down, contributing to thrombocytopenia.

It was observed that IgG antibodies adhered to platelets, targeting glycoproteins found on malaria parasites, leading to the formation of immune complexes that result in thrombocytopenia. Inflammatory cytokines, such as TNF-α, IL-6, and IL-10, were also identified as potential contributors to thrombocytopenia during P. falciparum and P. vivax infections.

Oxidative stress is another factor that may cause a decrease in platelets during malaria, although the exact mechanisms remain unclear. Some studies have reported a negative correlation between platelets and lipid peroxide levels, suggesting that increased antioxidant enzyme activity (glutathione peroxidase and superoxide dismutase) may play a role.

In most cases, platelet counts return to normal within seven days, as observed in the cases presented in this study. However, thrombocytopenia should not be underestimated, as it plays a crucial role in inflammation related to changes in endothelial cell layers in malaria cases. The study findings suggest that thrombocytopenia can serve as an early marker for malaria diagnosis, with a sensitivity of 79.5% and specificity of 86.3%.

While thrombocytopenia is not considered a severe malaria marker, it can be a vital indicator for determining the severity of malaria and enabling early diagnosis. This, in turn, can help reduce malaria-related mortality and alleviate the burden on public health systems.

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