

*Jurnal Kedokteran dan Kesehatan: Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya*  
Volume 8, No.3, 2021/DOI: 10.32539/JKK.V8I3.13814  
p-ISSN 2406-7431; e-ISSN 2614-0411

## A Case Report of Moderate COVID-19 and Malaria Falciparum co-infection with Thrombocytopenia

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Received 20 Feb 2021; accepted 25 Mei 2021

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### Abstract

The COVID-19 pandemic that attacks the world has made the attention of all medical personnel focused on this disease. The clinical picture is similar to other infectious diseases such as malaria, dengue, influenza, etc., which often leads to misdiagnosis. We report the case of a man, 31 years old, with a history of travel and complaints of high fever persisting for more than 7 days. On physical examination, the temperature was 39-40 C, others were within normal limits. Initial platelet count was  $69 \times 10^3/\mu\text{L}$ , leukocytes was  $15.52 \times 10^9/\text{L}$ , CRP was 96 mg/L. The blood smear found *Plasmodium falciparum*, and PCR SARS-CoV-2 was positive. Chest X-ray showed pneumonia. Dihydroartemisinin-piperazine and primaquine therapies were administered for malaria, as well as favipiravir, azithromycin, and other symptomatic therapy for COVID-19. Platelets decreased to  $38 \times 10^3/\mu\text{L}$  while D-dimer level increased ( $> 20 \text{ mg/L}$ ). Anticoagulant was delayed. On monitoring after therapy, the platelets returned to normal, the D-dimer level decreased, and there was no bleeding. The co-infectious conditions of malaria and COVID-19 should be suspected in patients with suggestive symptoms and travel history from endemic areas, therefore both examinations should be performed. This co-infection has the potential to cause hyper inflammation and hypercoagulation and this is associated with a poor prognosis. Appropriate treatment is needed.

**Keywords:** SARS CoV-2, *Plasmodium*, low platelet

### Abstrak

Pandemi COVID-19 yang menyerang dunia telah membuat perhatian seluruh tenaga medis terfokus pada penyakit ini. Gambaran klinisnya yang mirip dengan penyakit infeksi lain seperti malaria, dengue, influenza, dll, sering menyebabkan kesalahan diagnosis. Kami melaporkan kasus seorang laki-laki, 31 tahun, dengan riwayat perjalanan dan keluhan demam tinggi menetap lebih dari 7 hari. Pemeriksaan fisik didapatkan suhu 39-40 C, lain-lain dalam batas normal. Hitung trombosit awal  $69 \times 10^3/\mu\text{L}$ , leukosit  $15.52 \times 10^9/\text{L}$ , CRP 96 mg/L. Apusan darah dijumpai *Plasmodium falciparum*, dan PCR SARS-CoV-2 positif. Rontgen thorax menggambarkan pneumonia. Terapi dihidroartemisinin-piperakuin dan primakuin untuk malaria, serta favipiravir, azitromisin dan terapi simptomatik lain diberikan untuk COVID-19. Trombosit sempat turun hingga  $38 \times 10^3/\mu\text{L}$  dan peningkatan D-dimer  $>20 \text{ ug/mL}$ . Antikoagulan ditunda. Setelah pemantauan, trombosit kembali ke normal, D-dimer turun, dan tidak dijumpai perdarahan. Kondisi ko-infeksi malaria dan COVID-19 harus dicurigai pada pasien dengan gejala yang mendukung dan riwayat perjalanan dari daerah endemis, sehingga harus dilakukan pemeriksaan laboratorium untuk memeriksa kedua penyakit ini. Ko-infeksi ini berpotensi menimbulkan hiperinflamasi dan hiperkoagulasi dan ini dihubungkan dengan prognosis yang buruk. Terapi yang tepat dibutuhkan.

**Kata kunci:** SARS CoV-2, *Plasmodium*, trombosit

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## 1. Introduction

Since the declaration as a global health emergency on January 30, 2020, then as a global pandemic on March 11, 2020, the coronavirus infectious disease, or popularly known as COVID-19, has not shown any signs of its disappearance. The number of cumulative active cases and deaths keep climbing up, especially in Indonesia. On February 11, 2021, the confirmed case has reached 1,191,990 cases with 32,381 deaths in Indonesia.<sup>1</sup>

Although dominantly causing damage to the lung, the clinical features of COVID-19 show similarity with other infectious diseases like dengue infection or malaria. Fever, mild cough, headache, arthralgia, myalgia, fatigue, nausea, and sometimes vomiting, can be found as typical symptoms in these three diseases that bring patients to seek medical advice. Laboratory finding like thrombocytopenia is also common in these diseases and sometimes leads to misdiagnosis. High suspicion of COVID-19 nowadays has also made other infectious diseases as other differential diagnoses of fever were left behind for further investigations. The holistic approach including careful anamnesis especially traveling history, the onset and pattern of fever, physical examination, and choosing appropriate laboratory investigations should be applied.

## 2. Case report

A 31-year-old man, presented to the emergency unit in the hospital with high-grade fever accompanied by chill, shiver, headache, mild cough, mild diarrhea, and nausea. The fever started seven days before, at night, right after he arrived home after traveling by plane from Timika, Papua. He stayed and worked there for two months on a construction project. On the second day from the onset of fever, he went to the secondary level hospital and was admitted there and diagnosed with dengue fever because of low platelet count. From day 4 until day 6

from the onset of fever, the temperature was normal and the platelet count was around  $60 - 75 \times 10^3/\mu\text{L}$ . He was discharged on day 7 with a diagnosis of ITP (Idiopathic thrombocytopenic purpura) and was planned for further workup from the outpatient clinic. But at night, the fever, chill, and shiver returned, he then went to our tertiary level hospital. He had no history of chronic medical conditions.

At the current presentation, the temperature was 39.0 C, respiratory rate was 20 x/m, heart rate was 92 x/m, normal blood pressure with 97% oxygen saturation on room air. The physical examination revealed relatively normal, no hepatosplenomegaly. Initial laboratory examination showed significant thrombocytopenia with platelet count  $69 \times 10^3/\mu\text{L}$ , leucocytosis with WBC count  $15.52 \times 10^9/\text{L}$ , 85% of neutrophil and 9% of lymphocyte, and elevated level of C-reactive protein (CRP, 96 mg/L). According to the patient, when he traveled by plane, the result of the rapid antibody test for SARS-CoV-2 was non-reactive both for IgM dan IgG. He was sent to the isolation ward for COVID-19 because his condition met the criteria for a suspected case of SARS-CoV-2 infection. The PCR SARS-CoV-2 swab test was ordered as well as thick and thin blood film tests for malaria and rapid antigen test for malaria were also performed. Malaria smear was positive for *Plasmodium falciparum*, with ring form trophozoite and banana-shaped gametocyte. The rapid antigen test was also positive for *Plasmodium falciparum*. The nasopharyngeal PCR for SARS-CoV-2 was also positive with a CT value of 13.52 detected for gene orf1ab. Further laboratory examination showed slight elevation of creatinine (1,24 mg/dL) and total bilirubin 1,50 mg/dL, and normal PO<sub>2</sub>/FiO<sub>2</sub> (448,4 mmHg). Chest X-ray revealed pneumonia.

Dihydroartemisinin-piperazine for three days and primaquine for one day were administered to treat malaria. Favipiravir 1600 mg bid day 1 – 600 mg bid day 2-5 orally, and azithromycin 500 mg orally, both for five days,

as a treatment protocol for COVID-19, were given to the patients, along with vitamin C 1000 mg orally, N-acetylcysteine 200 mg three times daily orally. In follow-up laboratory examination, day 1 after administration of antimalarials and antivirals, D-dimer level was high, >20,00 mg/L with normal fibrinogen, while platelet count dropped to the level of  $38 \times 10^3/\mu\text{L}$  and CRP increased (150 mg/dL). *Plasmodium falciparum* was still detected. The patient was in a hypercoagulable state and anticoagulant therapy enoxaparin 40 mg subcutaneous was considered to be given in caution if D-dimer did not decrease with definitive therapy with antimalarials and antiviral because platelet was very low. On further follow-up, D-dimer decreased to 11,60 mg/L then to 1,22 mg/L on day 4 after definitive treatment started. The platelet was  $63 \times 10^3/\mu\text{L}$ , and enoxaparin was postponed. Blood smear evaluation on day 4 showed negative *Plasmodium falciparum*. The patient did not experience fever, nausea, and headache anymore, he was discharged from the hospital for self-isolation from COVID-19 on day 7.

On day 14, the patient came to the outpatient clinic for follow-up. He complained of no symptoms. The platelet level returned to normal,  $407 \times 10^3/\mu\text{L}$  and *Plasmodium falciparum* was not detectable on the blood smear. The PCR SARS CoV-2 swab test was not evaluated and he was recovered from COVID-19 after completing self-isolation.

### 3. Discussion

Thrombocytopenia is frequently found as a result of viral infection. In a non-endemic area of malaria, like Palembang, South Sumatera, an acute febrile illness with thrombocytopenia is associated with dengue infection, especially when the platelet count is below 150.000 per microliter of blood. But in the clinical course of dengue infection, the recovery phase is characterized by no fever, the platelet count increases and returns to normal, and reabsorption of fluid overload on days 6-7 since

the onset of fever.<sup>2</sup> Other diagnoses besides dengue infection should be considered whenever fever and low platelet count after day 7 persist.

Thrombocytopenia in malaria has been shown in many studies, ranging from 24-94% as reviewed by Lacerda et al, 2011.<sup>3</sup> Recent study conducted by Gupta et al, in 2013 revealed 100 cases of thrombocytopenia in 130 malaria vivax positive patients. While from 90 malaria falciparum-positive patients, thrombocytopenia was seen in 70 cases. In both malaria, the platelet count was mostly between 25.000 and 50.000.<sup>4</sup> Although thrombocytopenia is not regarded as a clinical manifestation of severe malaria, some studies reported its association with severe malaria, especially in the pediatric population.<sup>3,5</sup> Several mechanisms were proposed as the pathogenesis of malarial thrombocytopenia, including coagulation disturbances, splenomegaly, bone marrow alterations, antibody-mediated platelet destruction, oxidative stress, and platelet aggregation.<sup>3</sup> Despite its frequent occurrence, the severe bleeding incidence is relatively low, probably because of the enhancement of hemostatic responses by hyperactive platelets. Another possible mechanism is that larger platelets as a compensation for low platelets in the periphery can preserve primary hemostasis and avoid severe bleeding.<sup>3,4,6</sup>

Thrombocytopenia itself is one of the hematological changes commonly found in COVID-19, together with reduced lymphocyte count and elevated D-dimer level. The mechanisms of thrombocytopenia in COVID-19 patients are described in several hypotheses. It is speculated that hematopoiesis in the bone marrow can be inhibited through certain receptors by SARS-CoV-2. The destruction of the hematopoietic progenitor cells in the bone marrow of patients with SARS-CoV-2 pneumonia is speculated to happen after the cytokine storm. These mechanisms lead to decreased primary platelet production. After the storm, many blood cells are swallowed, then peripheral blood platelet count decreases. COVID-19 may also increase levels of

autoantibodies and immune complexes, resulting in specific destruction of platelets by the immune system. Platelet consumption is also increased. In COVID-19 lung tissues and pulmonary endothelial cells are damaged. This then activates the aggregation of platelets to form microthrombi. It is supported by the finding that most patients with COVID-19 have thrombocytopenia together with elevated D-dimer levels and impaired coagulation time.<sup>7</sup>

In this patient, besides low platelet count, a high D-dimer level was also found. This finding is in line with the above statement. COVID-19 can induce pro-coagulant state, as indicated by increased D-dimer and fibrin degradation product levels, and prolonged prothrombin time and these are associated with a poor prognosis. Malaria itself also associated with a pro-coagulant state, with activation of the coagulation cascade, mediated by TNF-alpha and IL-6. The complications of microthrombosis are most commonly described. If bleeding and DIC are seen, they are associated with high mortality. Another mechanism proposed which can promote a pro-coagulant state is the lysis of activated platelets, along with the release of tissue factor from damaged vascular endothelial cells, and this is similar to in COVID-19. Thus, greater degrees of coagulopathy and more severe disease with poor prognosis should be anticipated in malaria and COVID-19 co-infection rather than either infection alone.<sup>8,9</sup> Fortunately, there was no bleeding or thrombosis incidence happened in this patient. After concurrent antimalarial therapy with dihydroartemisinin-piperaquine-primaquine and antiviral therapy with favipiravir, the patient showed clinical and laboratory improvement.

The source of malaria infection was suspected as an imported case from Papua since Palembang itself is not a malaria-endemic region. While the source of COVID-19 infection is still confusing. Whether it was acquired during the patient's travel from Papua to Palembang, or during the previous hospitalization for suspected dengue fever a week earlier.

The case of COVID-19 and malaria co-infection with thrombocytopenia was rare to find. The similar case was published by Sardar et al, 2020, in Doha, Qatar, of a man with jaundiced suffering from COVID-19 and *Plasmodium vivax* malaria co-infection.<sup>10</sup> In Indonesia, similar case was reported by Junaedi M et al, 2020 from Makassar. He reported a woman who previously lived in Papua with severe malaria falciparum and COVID-19 co-infection and was successfully treated with artesunate and oseltamivir.<sup>11</sup>



**Figure 1. Banana-shaped gametocyte (black arrow) of *Plasmodium falciparum* from the patient's blood smear**



**Figure 2. The chest X-ray shows bilateral infiltrates of pneumonia**

#### 4. Conclusion

The co-infection of malaria and COVID-19 is very likely to happen and should be considered especially in patients with a traveling history from the malaria-endemic region and with suggestive symptoms for both conditions such as fever, fatigue and headache. Laboratory tests for both malaria and COVID-19 should be performed then to minimize the potential of missing either of them.<sup>12</sup> Although thrombocytopenia and hypercoagulant state are common findings in malaria and COVID-19 and associated with poor prognosis, appropriate therapy at the right time for both infections can improve better outcomes in patients.

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