

Case Report: Covid-19 And Severe Malaria Co-Infection

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ABSTRACT: Background:*A mysterious pneumonia case was first reported in Wuhan, China in December 2019. The World Health Organization (WHO) later named this pneumonia Coronavirus Disease (Covid-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. The massive spread of Covid-19 increases the risk of co-infection with other pre-existing pathogens including malaria*

Case Report: *A 32 years old woman was admitted to the hospital due to complaints of jaundice, fever, dyspneu and andominal pain. On further examination of the malaria smear, plasmodium falciparum was found in the form of trophozoites and gametocytes, the parasite count was 119,902 U/L and a nasopharyngeal PCR swab was positive for SARS CoV-2. The patient conditionimprove after administering artesunate and oseltamivir.*

Discussion: *Several clinical manifestations are overlapping between Covid-19 and malaria, especially extrapulmonary manifestations of Covid-19 infection, including thrombocytopenia, elevated transaminase enzymes, increased bilirubin, and impaired kidney function. Management was carried out to deal with malaria and Covid-19 simultaneously and continuously.*

Keywords: *Covid-19, Malaria, Co-infection*

1. BACKGROUND

A mysterious pneumonia case was first reported in Wuhan, China in December 2019. The World Health Organization (WHO) later named this pneumonia Coronavirus Disease (Covid-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus.^(z1) This virus can be transmitted from human to human and has spread widely throughout the world, so that in March 2020 WHO declared Covid-19 as a pandemic. Until November 2020 there were 49,106,931 cases and 1,239,157 deaths worldwide. Meanwhile, in Indonesia, there have been 429,574 confirmed cases of Covid-19 and 14,442 deaths.⁽²⁾

The increasing number of Covid-19 patients around the world, including in Indonesia, is burdening the health system previously overwhelmed in controlling various diseases, both infectious and non-communicable diseases, including TB, HIV, and Malaria.⁽³⁾ Malaria is still included in the major global health problem with the number of patients reaching 219 million worldwide and an estimated 655,000 people died from malaria in 2017. Indonesia is one of the malaria-endemic areas with a number of 250,664 cases in 2019.

The massive spread of Covid-19 increases the risk of co-infection with other pre-existing pathogens. This case is confirmed by the existence of various reports regarding co-infection in Covid-19 with bacterial, viral, and fungal pathogens. However, case reports regarding Covid-19 co-infection and malaria are still very rare, to the best of the author's knowledge, there has been two reports regarding Covid-19 co-infection with malaria and in Indonesia there has been no report about this coinfection.⁽⁴⁾ This low incidence may correlate with a study conducted by Napoli *et al.* In the early phases of the Covid-19 pandemic the presence of endemic malaria appears to be sufficient to protect populations from the Covid-19 outbreak, especially in less developed countries.^(5,6) The case report concerns a patient co-infected with severe falciparum malaria with Covid-19.

2. CASE REPORT

A 32 years old woman, with no previous history of chronic disease, was admitted to the hospital due to complaints of jaundice since two days ago. She experienced a high fever since approximately one week ago. She got the fever not continuously accompanied by chills, and profuse sweating. She also felt upper right abdominal pain since ten days ago before being admitted to the hospital. The pain did not spread and did not penetrate backward with a twisting sensation. The pain came and stopped, followed by nausea and vomiting 1-2 times, not spraying the contents of water and food. The patient also complained of short breath experienced almost simultaneously with complaints of fever; the tightness was getting worse over time, not affected by weather and activity, and not accompanied by complaints of cough and chest pain. She also found her reddish-brown urine a few days before admission to the hospital. There was no pain when urinating; the urine volume was sufficient. Her defecation was normal. The patient previously lived in the Papua area and only lasted one month in Makassar. Her blood pressure was 130/80 mmHg; her pulse was 104 beats/minute; her breathing was 28 times/minute; her temperature was 38°C, and her O₂ saturation: 96%.

On physical examination, there was icterus, decreased breath sounds in the basal of both lungs, hepatosplenomegaly, tenderness in the right upper quadrant abdomen, and petechiae in the extremities. On laboratory tests, a white blood cell count was obtained $7.3 \times 10^3/\mu\text{L}$ (reference range: $4.0-10.0 \times 10^3/\mu\text{L}$), lymphopenia: $0.7 \times 10^3/\mu\text{L}$ (reference range: $1.0-3.0 \times$

$10^3/\mu\text{L}$), hemoglobin: 10.9 g/dL (13.0–17.0 g/dL) and thrombocytopenia with platelet count: $14 \times 10^3/\text{mL}$ (reference: 150–400/mL), direct hyperbilirubemia [total bilirubin of 12.82 mg/dL (reference range: 0.30–1.23 mg/dL) with direct bilirubin: 7.70 mg/dL (reference: 0–0.29 mg/dL)], SGOT 256 (reference: <35 U/L), SGPT 125 (reference: <45 U/L), C-reactive protein: 30.1 mg/L (reference: 0–5 mg/L), procalcitonin: 61.30 ng/L (reference: 0.5–2.0 ng/L), lactic acid: 2.4 mmol/L (reference: 0.5–2.2 mmol / L), elevated ferritin level: 3369.1 ng/ml (reference: 13–400 ng/ml) and high D-dimer: 2.25 mg/L (reference: 0.00–0.44 mg/L). Thoracic CT showed bilateral pneumonia and bilateral pleural effusions. The obtained abdominal CT scan was hepatosplenomegaly, no cholestatic features, and cholelithiasis.

On further examination of the malaria smear, plasmodium falciparum was found in the form of trophozoites and gametocytes, the parasite count was 119,902 U/L and a nasopharyngeal PCR swab was positive for SARS CoV-2. The patient was given fluid resuscitation and artesunate injection therapy of 132 mg at 0, 12, and 24 hours then continued administration 24 hours for 13 days. Then, the patient was given therapy in the form of oxygen 2-3 lpm via nasal cannula, azithromycin 500 mg/24 hours, oseltamivir 75 mg/12 hours, vitamin C 500 mg/24 hours orally, vitamin B Comp 1 tablet a day, zinc 20 mg/24 hours, Acecylsisten 1200 mg/24 hours IV, Albumin 2 caps/8 hours orally, and Lovenox 0.6cc/12 hours sc for five days. During the treatment, the patient's condition worsened so that she required intubation for ten days, then the patient's condition slowly improved, the malaria smear became negative, and the nasopharyngeal swab became negative twice, so the patient was expelled from isolation treatment. Laboratory investigations revealed normal white blood cell count of $8.8 \times 10^3/\mu\text{L}$, hemoglobin of 12.8 g/dL, improving platelet count of $171 \times 10^3/\mu\text{L}$, total bilirubin of 2.02 mg/dL, direct bilirubin of 1.59 mg/dl, SGOT of 67 U/L, and SGPT of 48 U/L.

3. DISCUSSION

Malaria is a parasitic infectious disease caused by plasmodium falciparum, plasmodium vivax, plasmodium ovale, and plasmodium malaria, which attacks erythrocytes and is characterized by the presence of asexual forms in the blood. Plasmodium falciparum is a malaria infection that often causes severe malaria with high mortality. This condition is caused by the Plasmodium Falciparum parasite undergoing sequestration in the small blood vessels in the body and the patient's immune process. This situation often occurs suddenly without any previous symptoms. The clinical manifestations of malaria can range from mild to life-threatening. The classic symptoms of malaria include high fever, chills, and profuse sweating. Prompt and accurate diagnosis is very significant in malaria management, especially in plasmodium falciparum infection which can cause various complications. Having a history of travel from malaria-endemic areas at least two weeks before the appearance of classic malaria symptoms is crucial information in suspecting a malaria case. ⁽⁶⁾ In this case, the patient was initially diagnosed with dengue fever, pancreatitis, and pneumonia. After taking a more in-depth history and physical examination, the suspicion of malaria was stronger, confirmed by DDR examination by obtaining Plasmodium falciparum in the patient's blood. The presence of jaundice accompanied by a picture of DIC provided a picture of severe malaria in this patient. Jaundice is one of the clinical manifestations often found in severe malaria with an incidence of 10-45%. ⁽⁷⁾ Several decades ago, cerebral malaria was the most common feature in severe malaria, but today the combination of hepatic

dysfunction with renal failure is the most common feature of severe malaria. Hypoalbuminemia elevated bilirubin levels, and elevated transaminase enzymes in these patients indicated hepatic dysfunction. The liver is the first organ to be exposed by plasmodium falciparum after the pre-erythrocytic phase of merozoite into the bloodstream. On liver biopsy, we can find hyperplasia of Kupfer cells, infiltration of mononuclear cells, and pigment deposits, but several studies have not shown any changes in the structure of the hepatic cells or only swollen hepatocytes. Broadly speaking, the causes of jaundice in malaria patients are multifactorial, such as: (9)

1. Intravascular hemolysis of red blood cells
2. Non-P red blood cell hemolysis
3. Microangiopathy hemolysis associated DIC
4. Hepatic dysfunction
5. Hemoglobinopathy
6. Hemolysis due to medication
7. G6PD deficiency

In this case, the cause of jaundice is most likely due to intravascular hemolysis and hepatic dysfunction.

The current spread of Covid-19 has increased the risk of co-infection with other pathogens. (4) In connection with the co-infection between Covid-19 and Malaria, there are two contradictory studies. Napoli *et al.* stated that there might be a protective effect of malaria infection on the risk of infection and worsening of Covid-19 while Alexandra Hogan *et al.* mentioned that there was an increased risk of infection and the number of deaths increased by 36% in malaria patients with Covid-19. (5,10)

Covid-19 is caused by the SARS-CoV-2 virus, an RNA virus that has a particle size of 120-160 nm. This virus is included in the genus betacoronavirus. The results of the phylogenetic analysis show that this virus is categorized in the same subgenus as the coronavirus causing the Severe Acute Respiratory Illness (SARS) outbreak in 2002-2004, namely Sarbecovirus. (10) Currently, the human-to-human spread of SARS-CoV-2 is the main source of transmission, so the spread has become more aggressive. Transmission of SARS-CoV-2 from symptomatic patients occurs via droplets released when coughing or sneezing. (11) Besides, it has been observed that SARS-CoV-2 can be viable to aerosols (generated through a nebulizer) for at least three hours. (12)

In this case, there were symptoms of asphyxiation not affected by weather and activity. There were no complaints of cough and chest pain, but there were several gastrointestinal manifestations, such as nausea accompanied by vomiting and the presence of abdominal pain. The manifestations of Covid-19 involved almost all organs having ACE receptors.

At the initial examination, the SARS-COV2 IgM and IgG antibodies were non-reactive, then after five days, the nasopharyngeal and oropharyngeal swab examinations were positive for Covid-19. The inactivity of the SARS-COV2 antibody does not necessarily rule out infection with SARS-CoV-2 at that time. False-negative results on virological tests can occur when specimens are collected in very early infection, or technical problems happen in the laboratory. The diagnostic test for detection of SARS-CoV-2 infection concerning symptom onset can be seen in Figure 2. (13)

Several clinical manifestations are overlapping between Covid-19 and malaria, especially extrapulmonary manifestations of Covid-19 infection, including thrombocytopenia, elevated transaminase enzymes, increased bilirubin, and impaired kidney function. In Covid-19 infection, the manifestations of hepatic disorders are caused by a direct viral infection of the liver cells characterized by the increased levels of aspartate aminotransferase and/or alanine aminotransferase.⁽¹⁵⁾ This increase was found in approximately 19-53% of Covid-19 patients (16,17). Also, a study reported that 30 out of 56 patients found an increase in gamma-glutamyl transferase and 1 patient had an increase in alkaline phosphatase.⁽¹⁸⁾ The increased levels of bilirubin and jaundice in COVID-19 patients are associated with a poor prognosis in these patients.^(15,19)

In this case, severe thrombocytopenia was found so that a platelet transfusion was necessary for its handling. This condition caused the patient's initial diagnosis of dengue fever. Thrombocytopenia, in this case, could be caused by malaria and Covid-19 infection. Severe thrombocytopenia in plasmodium falciparum infection is due to suppression of platelet production from megakaryocytes and is associated with poor mortality.^(20,21) Covid-19 causes thrombocytopenia through direct infection of the bone marrow so that the production of platelet cells will be reduced, which is exacerbated by damage to bone marrow progenitor cells as a result of the cytokine storm conditions that often occur in Covid-19 patients, destruction of platelet cells by the immune system, and aggregation platelets in the lungs increasing platelet and microthrombi consumption.⁽²²⁾

In this case, management was carried out to deal with malaria and Covid-19 simultaneously and continuously. Patients with severe malaria are often accompanied by high levels of parasitemia or some signs of organ disturbance so that the administration of antimalarial drugs is different from ordinary malaria. In severe malaria, the ability to kill parasites is needed which is faster and can last a long time in the blood to immediately reduce the degree of parasitemia.

Management of malaria therapy in this patient was the same as that in other severe malaria, namely eliminating malaria as quickly as possible by administering antimalarial drugs, in this case, artesunate 132 mg per 24 hours intravenously for 13 days. PRC transfusion and platelet concentrates were also executed because the Hb levels were <8 gr/dl.^(8,23,24)

The definite management of Covid-19 patient management is still changing frequently until today, as many drugs are currently in the clinical trial stage to deal with Covid-19 infection and its complications. In this patient, the antiviral administration of oseltamivir and the immunomodulatory effect of azithromycin was effective in the conversion of swab results. The most recent guidelines for pharmacological management of Covid-19 are divided by severity of infection

The provision of antimalarials as a treatment for Covid-19 is still a matter of controversy. At the beginning of the pandemic, several experts suggested the use of chloroquine and hydroxychloroquine as a therapy for Covid-19. Chloroquine and hydroxychloroquine were believed to have immunomodulatory effects and could inhibit cytokine production. Both effects can inhibit the effects of SARS-CoV2 on several target organs, such as the lungs, heart, liver, and intestines.⁽²⁶⁾

However, since the sizeable side effects and several RCTs (randomized controlled trials)

failed to prove the benefits of using chloroquine and hydroxychloroquine,(26)at this time, both drugs are no longer recommended.

4. CONCLUSION

This particular case discussed in this paper showed the co-infection of malaria and covid-19, some of which showed almost the same symptoms. Both of these infections could cause worsening of the patient. In our case, the patient's condition improved with the administration of artesunate, oseltamivir, and azithromycin.

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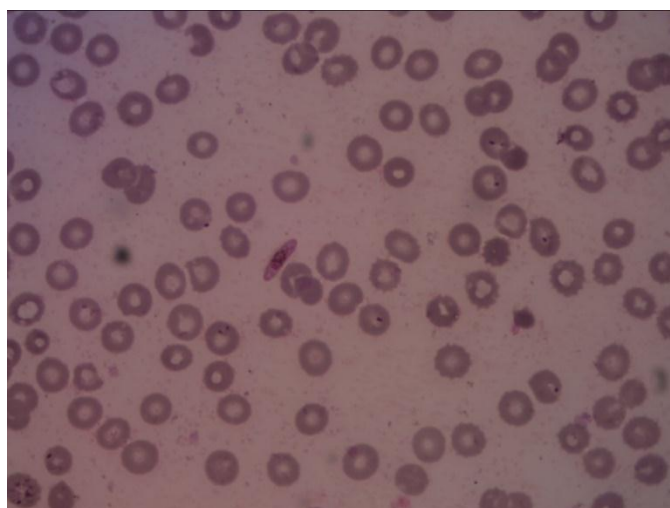


Figure 1: Malaria Smear with Plasmodium Falciparum

Figure 2: Thoracic CT

