



Concurrent Infection of Dengue and Malaria: An Unusual Case Report

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ABSTRACT

Plasmodium knowlesi is one of the most common causes of Malaria in humans. Although several reported cases of dengue and Malaria occur together, only a few cases have been reported in Southeast Asia, including Indonesia. This study aims to provide additional insight into the epidemiology and clinical aspects of *Plasmodium knowlesi* (P. knowlesi) malaria infection and dengue fever that occur concurrently in Southeast Asia, particularly Indonesia. A 36-year-old male patient with a history of travel to the mountainous area of Lhoknga and a fever for five days sought treatment at the emergency department of Meuraxa Hospital. During 11 days of treatment, the patient underwent a routine haematology examination every 24 hours. The average platelet count during the first eight days was around 50,000, with an increase after anti-malarial treatment on the eighth day and marked clinical improvement. The patient was discharged on day 10 with no signs of bleeding or hemolysis during treatment. Diagnosis involved blood smears and hematologic examination, confirming dengue fever with P. knowlesi malaria infection. These findings emphasize the importance of thorough history taking, physical examination, and supporting investigations to diagnose these two conditions together. The results of this study may provide critical support for case management involving malaria infection and dengue fever, with a focus on platelet monitoring as an indicator of response to treatment in the Southeast Asian region.

Keywords: Dengue Fever, Malaria, Dengue Infection.

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INTRODUCTION

Plasmodium knowlesi is one of the most common causes of Malaria in humans. The definitive hosts of this parasite are *Macaca fascicularis* (long tail) and *Macaca nemestrina* (pigtail) in Southeast Asia. Since 2004, researchers have begun studying the increasing number of P. knowlesi infections in Kapit Division, Sarawak, Malaysia (Singh & Daneshvar, 2013). Since then, there have been many reports of cases of plasmodium infection in other countries in Southeast Asia. Several pieces of P. knowlesi malaria infection cases in Indonesia, especially in Kalimantan. There have only been 4 cases of severe and fatal knowlesi malaria infection in humans in the world (Ompusunggu et al., 2015)(Daneshvar et al., 2018).

Malaria is a protozoan infection caused by the genus *Plasmodium*. Currently, more than 150 species of *Plasmodium* infect mammals, birds and reptiles (Sato, 2021). Of the 20 species of *Plasmodium* that infect macaques, five can infect humans under natural or experimental conditions: P. simium, P. brazilianum, P. cynomolgi, P. inui and P. knowlesi. *Plasmodium knowlesi* (P. knowlesi) was first isolated in 1931 in India in a long-tailed macaque imported from Singapore. Sinton and Mulligan first studied morphological features in experimental infections in macaques.³ Around 1920-1950, P. knowlesi began to replace P. vivax in treating neurosyphilis by inducing fever. This treatment method was malaria therapy (Singh & Daneshvar, 2013).

The first case of *P. knowlesi* malaria infection in humans occurred in 1965 in an American citizen who had just returned from working in the forests of peninsular Malaysia. Initially, the patient was thought to have falciparum malaria infection. The second case occurred in 1971 when a Malaysian citizen was diagnosed using molecular methods. Initially, the patient was suspected of having malaria infection microscopically. Since then, there have been no more cases of natural disease with *P. knowlesi* in humans until 2004. This is probably because diagnosing *P. knowlesi* infection is challenging to establish and requires rhesus monkeys as experimental animals, so it is rarely studied anymore (Nelwan & Subbagian, 2013; Lee & Vythilingam, 2013).

Plasmodium knowlesi is a common plasmodium that infects long-tailed macaques, *Macaca fascicularis* (long tail) and pig-tailed macaques, *Macaca nemestrina* (pigtail) in Southeast Asia. *Plasmodium knowlesi* usually causes mild infection in *Macaca fascicularis* and severe infection in rhesus monkeys (*Macaca mulata*). Since 2004, Balbir Singh and colleagues began to study natural infection with *P. knowlesi*, which was increasing in incidence in Kapit Division, Sarawak, Malaysia.⁵ Since then, there have been many case reports of plasmodium *knowlesi* infection in other countries in Southeast Asia. In Indonesia, there have been several case reports of *P. knowlesi* malaria infection, especially in Kalimantan Island. To date, there have only been 4 cases of severe and fatal *knowlesi* malaria infection in humans in the world (Ompusunggu et al., 2015; Daneshvar et al., 2018).

Dengue fever and Malaria are endemic diseases that often occur in Southeast Asia, including Indonesia. However, only a few cases of malaria and dengue infections co-occurring in Southeast Asia have been reported (Sahu et al., 2016). The clinical manifestations in this case are generally more severe, accompanied by different laboratory images (Mushtaq et al., 2013). A thorough history, physical examination, and supporting studies are needed to diagnose these two conditions simultaneously. Diagnosis yang tepat dan cepat akan memberikan tatalaksana yang sesuai dan memberikan luaran pasien yang lebih baik. Precise diagnosis will provide appropriate treatment and provide better patient outcomes.

Plasmodium knowlesi, a causative agent of Malaria in humans, has attracted considerable research attention in recent years, especially in Southeast Asia. The novelty of this study lies in its focus on the emerging epidemiological patterns of *P. knowlesi* infections, particularly in regions like Kapit Division, Sarawak, Malaysia, where the prevalence has witnessed a noticeable rise since 2004. The investigation extends beyond the initial hotspot to explore the expanding geographic footprint of *P. knowlesi* infections in Southeast Asia, shedding light on its occurrence in Indonesia, precisely in Kalimantan.

Furthermore, the rarity of severe and fatal *P. knowlesi* malaria infections in humans globally adds another layer of novelty to the research. With only four documented cases worldwide, understanding the factors contributing to the severity of these infections becomes imperative from both clinical and public health perspectives.

The concurrent occurrence of dengue fever and *P. knowlesi* malaria represents an intriguing aspect of this study. While both diseases are endemic in Southeast Asia, reports of their simultaneous infections are scarce. The novelty of investigating coinfections lies in the potential exacerbation of clinical manifestations and distinctive laboratory findings, presenting a unique challenge in diagnosis and management.

By investigating the co-occurrence of these diseases, the study seeks to improve diagnostic precision, facilitating timely and appropriate treatment. Ultimately, achieving accurate diagnoses is expected to enhance patient outcomes, reduce morbidity and mortality rates, and inform public health strategies in the region. This research aims to contribute to understanding the epidemiology and clinical aspects of concurrent *P. knowlesi* malaria and dengue fever infections, particularly in Southeast Asia.

METHOD

A 36-year-old man came to the emergency room at Meuraxa Regional Hospital with a fever for the last five days. Fever tends to be high, fluctuating, and accompanied by chills and profuse sweating. Patients also complain of nausea, joint pain, pain throughout the body, and dizziness. History of spontaneous bleeding was denied. Micturition and defecation are normal. The patient has a history of travelling and staying overnight in the mountains in the Lhoknga area. No family members experienced complaints similar to the patient's. History of systemic diseases such as hypertension, type II diabetes mellitus, heart disease, kidney disease, and others are not found in this patient. His friends who travelled to the mountains also had complaints similar to the patients.

RESULTS AND DISCUSSION

On physical examination, hemodynamics was stable, but the temperature reached 38.5 degrees. The biological study revealed hyperemic conjunctiva, and signs of hemolytic anaemia, such as anaemic conjunctiva and icteric sclera, were absent. There were no signs of spontaneous bleeding, such as petechiae, hematemesis, or hematochezia. Laboratory examinations carried out in the emergency room gave Hb results of 13.4; erythrocytes 5.67 million; Ht 39.5; MCV 69.7; MCH 23.6; MCHC 33.9; leukocytes 6700; platelets 60,000; peripheral blood 3/1/76/14/6; GDS 147 mg/dL. On serological examination, it was found that NS-1 was reactive, and dengue IgG was positive.

The patient was diagnosed with dengue hemorrhagic fever grade 1. The patient was then given treatment in the form of bed rest, IVFD 20 drops per minute, and the administration of intravenous paracetamol 1 gr and intravenous omeprazole 40 mg. The patient is planned for hospitalization and routine haematological examination every 24 hours.

On the second day of treatment, the fever was felt to have disappeared. However, the patient complained more about pain throughout the body. Signs of bleeding, such as epistaxis and petechiae, were not found. The results of the physical examination were within normal limits. Second day's lab examination showed Hb 13.3; erythrocytes 5.58 million; Ht 38.5 ; MCV 69.0; MCH 23.8 ; MCHC 34.5 ; leukocytes 6100 ; platelets 56,000; peripheral blood 3/1/76/14/6 ; GDS 147 mg/dL

On the third day of treatment, the patient complained of fever again, accompanied by vomiting. Signs of bleeding, such as epistaxis petechiae, were not found. The results of the physical examination were within normal limits. The third day's lab examination showed Hb 13.3; erythrocytes 5.58 million; Ht 38.5; MCV 69.0; MCH 23.8; MCHC 34.5; leukocytes 6100; platelets 56,000; peripheral blood 3/1/76/14/6; GDS 147 mg/dL. SADT Results: Microcytic hypochromic anaemia + thrombocytopenia ec Plasmodium knowlesi and Malaria Examination Results (microscopic): Positive for Plasmodium knowlesi trophozoite, schizont, gametocyte stages.

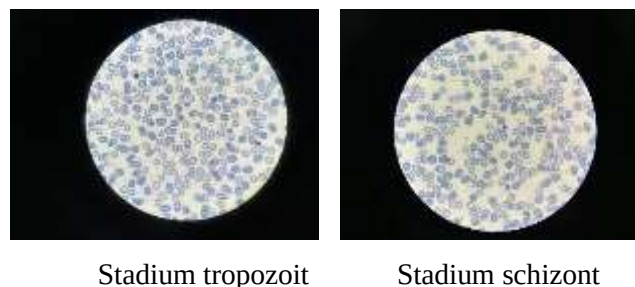


Figure 1. Microscopic Malaria

The patient complained of fluctuating fever and profuse sweating from the fourth to the eighth day of treatment. The patient's temperature was in the range of 37.8-38.5 degrees Celsius. There were no signs of bleeding on physical examination, such as epistaxis, hematemesis, hematochezia, or

bleeding from the gums. The following graphic depicts the patient's Hb and platelet values from days 1 to 11.



Figure 2. Platelet chart during treatment

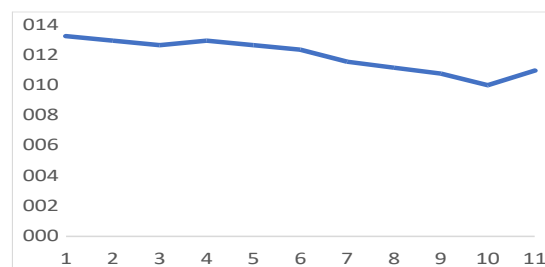


Figure 3. Hb chart during treatment

Because the fever did not improve and additional symptoms appeared, such as chills and sweating, on the eighth day of treatment, the patient had a blood smear. A picture of *Plasmodium knowlesi* in the trophozoite, schizont, and gametocyte stages was obtained.

From the eighth day of treatment, the patient was given an anti-malaria regimen in the form of DHF 1x4 tablets for three days and primaquine 1x1 tab. After administering the anti-malarial drug regimen, the patient's clinical course improved. Complaints of fever and sweating were reduced, and platelet and Hb values were also enhanced. The patient had a final diagnosis of dengue fever accompanied by Malaria Knowles. After being hospitalized for ten days, the patient improved and showed no complications.

Malaria and dengue are diseases spread through mosquito vectors, which play a significant role in the mortality and morbidity of tropical diseases (Chawla et al., 2014). Malaria is a parasitic infection caused by the plasmodium parasite and transmitted by the *Anopheles* mosquito. There are several Malaria species, but *Plasmodium knowlesi* is the most commonly found in Southeast Asia. Malaria will grow and reproduce in the human body in liver cells/hepatocytes and red blood cells (Shah & Mehta, 2017; Kotepui et al., 2020). Dengue is an ssRNA virus infection that is spread through the *Aedes Aegypti*. The dengue virus is divided into several serotypes, namely DENV 1, 2, 3, and 4, which are included in the flaviviridae family (Shah & Mehta, 2017; Kotepui et al., 2020).

Concurrent infection between these cases of dengue and Malaria can appear and provide similarities in clinical manifestation so that they are often underdiagnosed, which also causes undertreatment conditions. In some cases, The clinical images are more severe in concurrent infection conditions (Mushtaq et al., 2013). Several case reports found that many infections often occur due to dengue coinfection with other agents, including flavivirus, chikungunya, salmonella typhoid, shigella sonnet, and leptospira. The first case report of concurrent infection between dengue with plasmodium falciparum first appeared in 2005 after the patient travelled to Senegal and Guinea and was followed by the emergence of a case report of dengue coinfection with plasmodium vivax in 2006, which appeared in South Asia (India) (Mushtaq et al., 2013).

Based on a study conducted by Mohsin in 2013 in Guinea, it was found that the specificity level for concurrent infection between dengue and Malaria was 99%, which indicates a high rate of coinfection in that area (Garg et al., 2016). Dengue coinfection with Malaria is often found in Southeast Asia, such as Indonesia. Of the 36 cases of coinfection between dengue and Malaria, Indonesia is in fourth position in the number of reported cases (Mushtaq et al., 2013).

The clinical picture of malaria and dengue infections is similar. The symptoms that appear, especially in coinfection cases, are high fever accompanied by thrombocytopenia, which can occur in some cases of Malaria (Balaji et al., 2020). The symptoms that occur mainly in topics of coinfection are high fever and thrombocytopenia, which can appear in some cases of Malaria (Shah & Mehta, 2017; Sedger & McDermott, 2014). Anaemia is the main sign or symptom that occurs in malaria cases due to the malaria life cycle, which causes intravascular hemolysis (Balaji et al., 2020). Other clinical manifestations that can arise from Malaria are myositis, rhabdomyolysis, and acute renal failure. This is thought to be due to an increase in mediators in the form of TNF- α (tumour necrosis factor- α), which will trigger inflammatory processes in various areas and increase the synthesis of metabolic toxins and lactic acidosis which causes myositis, skeletal muscle necrosis, and myoglobinuria (Shah & Mehta, 2017; Sedger & McDermott, 2014).

In a case report conducted in Brazil, it was found that a patient with a case of dengue and malaria coinfection experienced severe thrombocytopenia and was still getting worse after being observed for several days (Tejo et al., 2023). However, after being given anti-malarial, both clinically and in terms of laboratory values, improvements were obtained. Using Hb as a coinfection marker is difficult because of the hemoconcentration effect, so Hb and Ht are incompatible (Magalhães et al., 2014).

Malaria and dengue give signs of high fever, although Malaria gives fever symptoms that last longer than dengue (Sahu et al., 2016). A haematological triad, such as atypical lymphocytosis, hemo concentration, and thrombocytopenia, is the main sign in diagnosing dengue based on blood findings. It also can be used as a consideration for malaria exclusion (Kotepui et al., 2020).

In most cases, the diagnosis of dengue is made based on the presence of IgM. In contrast, the diagnosis of Malaria must be based on a microscopic examination in the form of a blood smear (Assir et al., 2014). Several studies state that positive IgM antibody titers using ELISA in dengue cases can provide similar results in malaria cases. Apart from that, false adverse claims can also be found in secondary infections of dengue patients (Magalhães et al., 2014; Miri et al., 2021).

These two conditions have similar clinical manifestations. Careful anamnesis, physical examination, and supporting studies are needed to diagnose these two conditions simultaneously. Precise diagnosis will provide appropriate treatment and provide better patient outcomes.

CONCLUSION

Based on the results and discussion above, it can be concluded that the patient's clinical condition improved after starting the anti-malarial regimen, underscoring the importance of considering multiple infections in areas where dengue fever and Malaria are common. This case highlights the need for a comprehensive diagnostic approach, including a thorough history, physical examination, and supporting laboratory tests to accurately identify and treat coinfections, ultimately ensuring appropriate and timely treatment for better patient outcomes.

Additionally, this case highlights the challenges posed by the overlapping clinical manifestations of dengue fever and Malaria, making correct diagnosis critical. This study also emphasizes the limitations of relying on specific diagnostic markers alone, such as IgM antibody titers for dengue fever and microscopic examination for Malaria. In regions such as Southeast Asia, where both diseases are endemic, health practitioners must remain alert to the possibility of coinfection. This awareness and

multidimensional diagnostic strategies are critical to improving diagnostic accuracy, tailoring treatment plans, and preventing potential complications in patients suffering from dengue and malaria infections.

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