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A Case of Septic Shock in Malaria Tertiana Relapse

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ABSTRACT

Malaria is a vector-borne parasitic disease that until today continous as a burden global health system, especially in tropical and subtropical regions. *Plasmodium vivax* was one of the five species infecting humans. It poses a unique challenge due to its ability to form dormant hypnozoites in the liver, which can reactivate and cause relapses long after initial infection. Clinical diagnosis is complicated by typically low parasitemia, non-specific symptoms and limitations in routine laboratory techniques. This case report presents a 27-year-old male who developed malaria caused by *P. vivax* after returning from Papua, an endemic area in Indonesia. The patient initially received dihydroartemisinin-piperaquine (DHP) and primaquine therapy in accordance with national guidelines, resulting in clinical improvement and parasitological clearance. However, 28 days after completing therapy, he returned with recurrent fever and laboratory confirmation of *P. vivax* with a parasitemia index of 1%, indicating a relapse. The patient was subsequently treated with oral quinine and responded favorably. This case underscores the complexity of managing malaria tertiana, especially in the absence of definitive biomarkers to differentiate relapse from reinfection. Diagnostic difficulties are compounded by the inability to routinely culture *P. vivax* in vitro. Clinicians must remain vigilant in assessing travel history, treatment adherence, and parasitemia recurrence timelines..

Keyword: *Plasmodium vivax, malaria relapse, malaria tertiana, hypnozoite, primaquine, artemisinin-based therapy*

1. INTRODUCTION

Malaria is a disease spreading through the bite of a female Anopheles mosquito infected with plasmodium parasites. Several types of Plasmodium that can cause malaria are *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium knowlesi* and *Plasmodium ovale*. The most common Plasmodium found in Indonesia is *Plasmodium falciparum* (55%) which causes tropical malaria, then *Plasmodium vivax* (45%) which causes malaria tertiana. While *Plasmodium malariae, Plasmodium knowlesi* and *Plasmodium ovale* are found in small amounts (Calderaro, 2013).

Malaria cases receive global attention due to their high morbidity and mortality rates in endemic areas. In 2021, World Health Organization (WHO) reported there were 247 million new cases of malaria, of which 2% were cases of malaria caused by *Plasmodium vivax* and a total of 619,000 malaria-related deaths in 84 malaria-endemic countries. In Southeast Asia region, there are 9 countries that are endemic for malaria and Indonesia ranks second after India with the most malaria cases (WHO, 2022). In Indonesia, malaria is quite often found in Eastern Indonesia, which is a malaria endemic area. Some cases are found in non-endemic areas as there is a previous history of traveling to endemic areas or during routine examinations to rule out differential diagnoses from fever symptoms. Kementerian Kesehatan Republik Indonesia in 2021 reported there were 304,607 cases of malaria in Indonesia with an Annual Parasite Incidence (API) was increasing to 1.1 per 1,000 population

(Kementerian Kesehatan Republik Indonesia, 2022).

Plasmodium vivax is the most widespread malaria-causing parasite in the world with 2.5 billion people at risk of its infection and >15 million cases recorded per year (Douglas, 2014). Chloroquine (CQ) has been used as first-line treatment in uncomplicated malaria tertiana. Failure of CQ therapy was first detected in Papua, Indonesia in 1989. Artemisinin combination therapy (ACT) is now recommended as first-line treatment for uncomplicated malaria. However, clinical assessment of drug effectiveness in malaria tertiana is complicated due to the challenge of distinguishing between treatment failure, re-infection (i.e., due to a new mosquito bite) or relapse (i.e., due to reactivation of dormant parasites in the liver). In particular, we do not have host biomarkers or parasite markers to confirm the reason for parasite recurrence (relapse, treatment failure or re-infection) (Price, 2014). In addition, it is difficult to assess *Plasmodium vivax* susceptibility in vitro because culture of *Plasmodium vivax* isolates cannot be routinely performed and ex vivo drug susceptibility tests are difficult to apply and difficult to interpret because *Plasmodium vivax* infections are usually not synchronous and parasite susceptibility is stage dependent (Popovici, 2019). Based on the previous explanation, the approach to diagnosis and management in malaria cases is still a challenge for clinicians, especially to distinguish cases of relapse, treatment failure, or mixed infection. In this case report, we will report a case of malaria relapse that occurred at Dr. Soetomo Hospital Surabaya.

Case Report

A 27-year-old male presented to the Emergency Department with a history of intermittent febrile episodes for a week, characterized by alternating febrile and afebrile days. The fever typically occurred around midday and persisted until midnight, preceded by chills and followed by sweating before the fever gone. Associated symptoms included nausea, vomiting, headache, and generalized weakness, particularly post-febrile episodes. There was no history of bleeding, and bowel and urinary remained normal.

The patient had recently stay in Papua for 1.5 months due to occupational duties as a mountain climbing guide. Fever began three days before leaving Papua and persisted upon his return to Surabaya, four days prior to admission. A colleague in Papua experienced similar symptoms. The patient did not take malaria prophylaxis and had close contact with a colleague diagnosed with malaria. He had no history of diabetes mellitus, hypertension or previous malaria infection.

He appeared weak but alert. His blood pressure was 113/67 mmHg, his heart rate was 96 bpm, his respiratory rate was 18/min, his temperature was 37.1°C and his oxygen saturation was 97% on room air. Mild scleral icterus was noted on head and neck examination. Abdominal examination revealed splenomegaly, Rumple-Leede test was negative.

Initial laboratory results: hemoglobin 12.6 g/dL, hematocrit 36.9%, leukocytes 3,820/mm³, platelets 83,000/mm³, BUN 12.6 mg/dL, serum creatinine 1.2 mg/dL, sodium 136 mmol/L, potassium 3.1 mmol/L, chloride 107 mmol/L, AST 23 U/L, ALT 20 U/L, albumin 3.7 g/dL, direct bilirubin 0.8 mg/dL, total bilirubin 1.7 mg/dL. Malaria rapid diagnostic test (ICT) was positive for non-falciparum species. Salmonella IgM, dengue IgM/IgG, and COVID-19 rapid test were negative. Chest radiography was normal. Urinalysis was within normal limits.

Microscopic examination of peripheral blood (thick and thin smear) identified *Plasmodium vivax* with a parasitemia index of 5% (Figure 1).

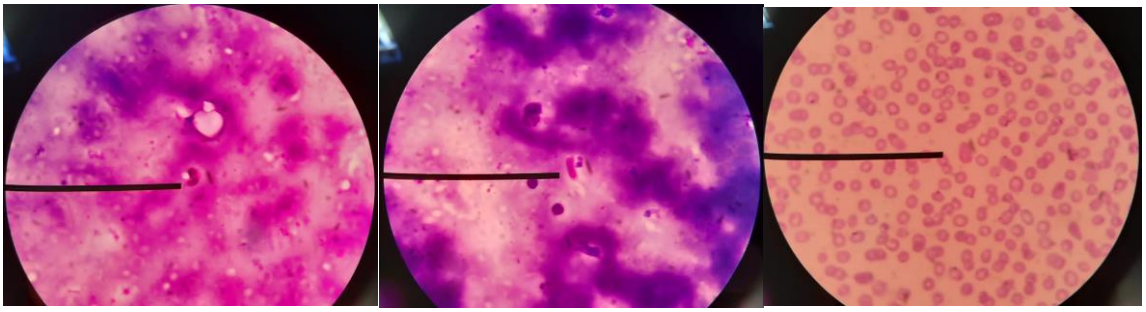

Figure 1. First peripheral blood smear shows *Plasmodium vivax* with parasitemia index of 5%

On the third day of hospitalization, the patient developed hypotension, blood pressure 71/37 mmHg, unresponsive to fluid resuscitation, need vasopressor support with norepinephrine, titrated from 50 to 100 ng/hour. Antimalaria therapy included Dihydroartemisinin-Piperaquine (DHP) 1 tablet four times daily for 3 days and Primaquine 1 tablet daily for 14 days.

There was no clinical evidence of bleeding or hemolysis. Serial complete blood counts showed stable hemoglobin and hematocrit levels (Hb 12 g/dL, Hct 37.2%, WBC 7020/mm³, platelets 98,000/mm³), and urine remained clear. The patient's

condition improved by day 5, with discontinuation of norepinephrine. Repeated peripheral smear was negative for Plasmodium. He was discharged on day 7th.

Follow-up blood smear at the end of primaquine therapy showed no parasitemia. However, 28 days post-treatment, the patient was readmitted with recurrent febrile episodes similar to previous pattern—diurnal onset preceded by chills, with milder intensity. He also reported nausea, vomiting, and fatigue. No history of travel to other endemic regions during this interval.

Repeated malaria ICT was positive for non-falciparum species. Peripheral blood smear confirmed *Plasmodium vivax* with a parasitemia index of 1% (Figure 2). The patient was managed with oral quinine (2 tablets three times daily) for 7 days. Follow-up peripheral blood smear post-treatment revealed no parasitemia.

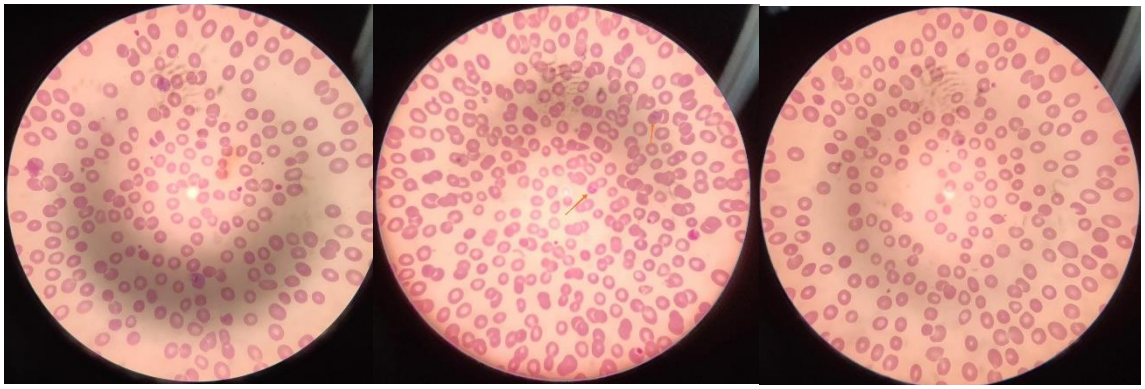

Figure 2. Second peripheral blood smear shows *Plasmodium vivax* with parasitemia index of 1%

2. DISCUSSION

The patient presented to the Emergency Department with a one-week history of intermittent fever occurring every 48 hours. The febrile episodes typically began during the day and persisted into the night, preceded by chills, followed by fever, profuse sweating and subsequent defervescence. Associated symptoms of nausea, vomiting and headache were also reported. Based on the clinical presentation, differential diagnoses for acute febrile illness were considered, including dengue fever, typhoid fever, leptospirosis, and malaria (Kementerian Kesehatan Republik Indonesia, 2013). Given the patient's travel history, malaria became a leading consideration. He had resided in Papua for approximately 1.5 months due to occupational responsibilities and began experiencing febrile symptoms three days prior to returning to Surabaya. He reported a colleague with similar symptoms and denied taking malaria chemoprophylaxis before or during his stay in Papua. Given these findings, a preliminary diagnosis of malaria was strongly suspected.

Upon presentation, the patient appeared weak, with a Glasgow Coma Scale (GCS) score of E4V5M6. Vital signs were within normal limits. Physical examination revealed mild scleral icterus, without conjunctival injection or calf tenderness. Rumple-Leede test was negative. Laboratory evaluation showed leukopenia (WBC 3,820/mm³) and thrombocytopenia (platelet count 83,000/mm³), with normal hemoglobin and hematocrit levels. Renal function, blood glucose, and chest radiography were within normal limits. Serological testing for typhoid (Tubex) and dengue (IgM/IgG) was negative. Malaria immunochromatographic testing (ICT) was positive, indicating non-falciparum species. Microscopic examination of thick and thin peripheral blood smears revealed *Plasmodium vivax* with a parasitemia index of 5%. Based on clinical presentation, epidemiological exposure, and laboratory confirmation, a diagnosis of *Plasmodium vivax* malaria was established.

Malaria is a parasitic infection transmitted to humans by the bite of infected female *Anopheles* mosquitoes. The causative organisms belong to the genus *Plasmodium*, which requires two hosts to complete its lifecycle: the human (intermediate host) and the mosquito (definitive host) (Carter & Escalada, 2016). Upon transmission via mosquito bite, Plasmodium sporozoites enter the human bloodstream and quickly migrate to hepatocytes, initiating the exo-erythrocytic (liver) stage. In the liver, they develop into schizonts, which release thousands of merozoites into the bloodstream after about two weeks. In infections caused by *P. vivax* and *P. ovale*, some liver-stage parasites become dormant hypnozoites, which may reactivate months or years later, leading to relapse. Once in the bloodstream, merozoites invade red blood cells (RBCs), initiating the erythrocytic cycle. Within RBCs, parasites develop through trophozoite and schizont stages, eventually causing cell rupture and the release of new merozoites. This leads to the cyclical symptoms observed in malaria. This asexual replication is termed schizogony. In the mosquito, when blood containing sexual forms (gametocytes) is ingested, fertilization occurs in the mosquito midgut. The resulting zygote develops into an ookinete, penetrates the gut wall, and forms an oocyst on the external gut surface. Sporozoites then mature within the oocyst and migrate to the salivary glands, completing the cycle (Kementerian Kesehatan Republik Indonesia, 2013).

Malaria pathogenesis is influenced by both parasite-related factors (transmission intensity, parasite load, virulence) and host-

related factors (immunity, genetic predisposition, nutritional status, and age) (Harijanto, 2006). Clinically, the patient exhibited hallmark features of uncomplicated malaria, including cyclical fever, chills, sweating, nausea, vomiting, and fatigue. The classic febrile paroxysm of malaria typically progresses through three stages: a cold stage (chills, rigors), a hot stage (high-grade fever, headache, vomiting, possibly seizures in children), and a sweating stage, with resolution of fever and intense fatigue. In *P. vivax*, these paroxysms generally occur every 48 hours (tertian fever pattern). Severe malaria, which can occur especially with *P. falciparum*, involves one or more of the following complications: cerebral malaria (altered mental status, seizures, coma), severe hemolytic anemia, hemoglobinuria, acute respiratory distress syndrome (ARDS), coagulopathy, hypotension, acute kidney injury (AKI), hyperparasitemia (parasitemia index >5%), metabolic acidosis, and hypoglycemia. In addition to the patient's clinical history, presenting symptoms, and physical examination findings, the diagnosis of malaria was confirmed through laboratory testing. A malaria immunochromatographic test (ICT) was positive, indicating the presence of non-falciparum Plasmodium antigens. Further confirmation was obtained through microscopic examination of thick and thin blood smears, which demonstrated the presence of *Plasmodium vivax* with a parasitemia index of 5%. Multiple diagnostic modalities are utilized for malaria detection, with the erythrocytic stage of the parasite life cycle being the ideal target for diagnosis. This is due to the high parasitemia and the expression of antigenic proteins, which elicit a measurable immune response and enhance detection accuracy (Krampa, 2020).

In malaria infections, *Plasmodium falciparum* typically exhibits a higher parasitemia index due to its ability to invade erythrocytes of all maturation stages. In contrast, *Plasmodium vivax* preferentially invades reticulocytes, which represent a smaller proportion of circulating red blood cells, thereby limiting the extent of parasitemia (Mueller et al., 2009). This biological characteristic aligns with our patient's observed parasitemia index of 5%, which is considered relatively high for *P. vivax* infection.

Although polymerase chain reaction (PCR)-based diagnostic methods offer superior sensitivity for malaria detection, they remain impractical for routine diagnostics, especially in remote or resource-limited settings due to equipment, cost, and infrastructure constraints (Tanner, 2015).

In the patient's complete blood count, thrombocytopenia was identified, with a platelet count of 83,000/mm³. While thrombocytopenia is more commonly associated with *P. falciparum* infections—often due to disseminated intravascular coagulation (DIC) and platelet-endothelial interactions—it may also occur in uncomplicated *P. vivax* malaria, although less frequently. In such cases, the etiology is multifactorial and may involve macrophage-mediated platelet destruction, cytokine-induced suppression, immune-mediated damage through antiplatelet IgG, oxidative stress, shortened platelet lifespan, and non-splenic sequestration. Additionally, pseudothrombocytopenia due to platelet clumping during sample processing should be considered (Katira & Shah, 2006).

Importantly, thrombocytopenia in *P. vivax* malaria is generally asymptomatic and does not necessitate specific treatment or platelet transfusion, as supported by clinical studies (Jadhav et al., 2004).

The patient was diagnosed with uncomplicated *Plasmodium vivax* malaria and managed in accordance with the Indonesian National Malaria Control Program guidelines. Treatment consisted of a radical antimalarial regimen: a fixed-dose combination of dihydroartemisinin-piperaquine (DHP), administered as four tablets once daily for three days, and primaquine, given as one tablet daily for 14 days. This regimen aims to eliminate all parasite stages in the human host, including gametocytes and hypnozoites, to prevent both transmission and relapse.

In Indonesia, the standard treatment protocol for malaria includes artemisinin-based combination therapies (ACTs), often combined with primaquine, to improve efficacy and reduce the risk of Plasmodium resistance to antimalarial agents (Nadia, 2019). The DHP formulation used in the national program contains 40 mg dihydroartemisinin and 320 mg piperaquine per tablet. The dosage is adjusted based on body weight, with dihydroartemisinin administered at 2–4 mg/kg body weight (BW) and piperaquine at 16–32 mg/kg BW, taken orally once daily for three consecutive days. Primaquine administration varies by species: it is given as a single dose on the first day for *P. falciparum* infections, but for *P. vivax* infections, a 14-day course is required to eradicate dormant liver forms (Nadia, 2019).

On the third day of hospitalization, shortly after the administration of the first dose of antimalarial therapy, the patient experienced an episode of acute hypotension, with a recorded blood pressure of 71/37 mmHg and pulse rate of 90 beats per minute. Despite an initial fluid resuscitation, there was no significant hemodynamic improvement. Capillary refill time was <2 seconds, suggesting preserved peripheral perfusion. Consequently, vasopressor support with norepinephrine was initiated, beginning at a rate of 50 ng/hour and later titrated to 100 ng/hour.

Immediate laboratory evaluation revealed: Hemoglobin 12.3 g/dL, Hematocrit: 37.2%, White blood cell count: 7,020/mm³, Neutrophils: 56.5%, Lymphocytes: 25.8%, Platelets: 98,000/mm³, Blood glucose: 131 mg/dL, BUN: 11.5 mg/dL, Creatinine: 0.89 mg/dL, Natrium 136 mmol/L, Kalium 4.4 mmol/L, Chloride 105 mmol/L. There were no signs of tissue hypoperfusion, no leukocytosis, and no biochemical indicators of organ dysfunction, making septic shock or severe malaria unlikely in this case.

While hypotension is more commonly associated with severe *Plasmodium falciparum* malaria, the mechanisms may offer insight into the hypotensive episode observed in this patient. Several theories have been proposed (Sivakorn, 2021):

1. Autonomic dysfunction, leading to relative bradycardia and impaired vascular tone regulation, may reduce diastolic blood pressure, especially upon positional changes.
2. Venous vasodilation, due to febrile responses and systemic inflammation, may redirect blood flow to peripheral tissues (e.g., skin and muscles), decreasing perfusion to vital organs such as the liver and kidneys, and lowering venous return and cardiac output.
3. Intravascular hypovolemia, commonly due to insensible fluid losses, vomiting, or inadequate intake during acute illness, can further exacerbate hypotension. Typical lab features include elevated urea-to-creatinine ratios, increased plasma osmolality, and reduced fractional sodium excretion.

While this patient's fluid balance parameters were not suggestive of severe hypovolemia, transient dehydration may still have contributed. Additionally, chloroquine—historically used in *P. vivax* treatment—has been associated with hypotensive and bradycardic effects, due to its venodilatory action mediated by endothelial nitric oxide release. It reduces systemic vascular resistance, decreasing both preload and afterload, which can lead to hypotension. It also demonstrates negative chronotropic effects on cardiac function (Capel, 2015). Though this patient was treated with dihydroartemisinin-piperaquine, this highlights a pharmacologic consideration relevant to antimalarial treatment-induced hypotension.

In the context of malaria, particularly in severe or complicated cases, fluid resuscitation must be conducted with caution due to the risk of pulmonary edema resulting from capillary leak and fluid sequestration. The initial fluid of choice is 0.9% sodium chloride, administered at a rate of 1–2 mL/kg body weight per hour, with continuous monitoring of vital signs and urine output. Should signs of pulmonary congestion develop, fluid administration should be restricted, and close hemodynamic monitoring is warranted. In cases of shock, defined by a mean arterial pressure (MAP) < 65 mmHg, a more aggressive approach is required. A fluid bolus of 5 mL/kg body weight of 0.9% NaCl should be administered, followed by the initiation of vasopressor support—typically norepinephrine. Simultaneously, other causes of shock such as hemorrhage or sepsis must be excluded. If there is clinical suspicion of sepsis, empirical administration of broad-spectrum antibiotics is recommended (Nadia, 2019). In this case, the patient's condition progressively improved by day five of treatment, allowing for tapering of norepinephrine. Follow-up examination of thick and thin peripheral blood smears showed no evidence of parasitemia, indicating parasitological cure. The patient was discharged in stable condition on the seventh day of hospitalization.

Approximately 28 days following the completion of primaquine therapy, the patient was readmitted with a recurrence of intermittent fever following the same cyclical pattern as prior, although the symptoms were milder in intensity. There was no history of recent travel to malaria-endemic regions, ruling out re-infection. Laboratory evaluation revealed a positive malaria ICT test for non-falciparum Plasmodium, and microscopic examination of thick and thin blood smears confirmed *Plasmodium vivax* infection with a parasitemia index of 1%. A distinguishing characteristic of *Plasmodium vivax* compared to *P. falciparum* is its ability to cause relapse due to the reactivation of dormant liver-stage hypnozoites. In tropical regions, *P. vivax* is known to produce frequent relapses, typically occurring within 3–6 weeks of initial infection, whereas in temperate climates, relapses are more sporadic and delayed (Baird, 2007). According to Indonesian national guidelines, relapse is suspected when a patient has completed primaquine therapy at a dose of 0.25 mg/kg body weight/day for 14 days, and subsequently presents with a recurrence of parasitemia between 4- and 52-weeks post-treatment, in the absence of re-exposure to endemic areas (Nadia, 2019). The pattern and frequency of *P. vivax* relapses are influenced by geographical and host-related factors. For instance, individuals of Melanesian descent tend to exhibit frequent relapses every 3–4 weeks, which may result in clinical tolerance, reflected by attenuated febrile responses in subsequent episodes (Anstey et al., 2009). Furthermore, the intensity of the initial mosquito inoculum, specifically the number of sporozoites transmitted, plays a critical role in determining the relapse timing and frequency. It has been suggested that systemic febrile illnesses themselves may serve as triggers for the activation of latent hypnozoites, contributing to the regularity of relapse episodes (White, 2011).

In cases of *P. vivax* malaria relapse, the patient should be retreated with an artemisinin-based combination therapy (ACT) regimen. However, the dose of primaquine must be increased to 0.5 mg/kg body weight/day for 14 days, to ensure eradication of hypnozoites. This higher-dose primaquine regimen must be preceded by screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency, as primaquine can induce hemolysis in G6PD-deficient individuals (Nadia, 2019). For patients who fail ACT therapy, the recommended second-line treatment is a combination of quinine sulfate and primaquine. Quinine is administered at a dose of 10 mg/kg body weight, three times daily for 7 days. One tablet contains 222 mg of quinine sulfate. Primaquine is continued at the appropriate dose to target hypnozoites (Nadia, 2019).

Treatment success and failure are classified based on clinical response and parasitological clearance over time:

- Cured: Resolution of clinical symptoms (e.g., fever) with no detectable asexual parasitemia up to day 28 of follow-up.

- Early Treatment Failure: Defined by one or more of the following:
    - Progression to severe malaria within days 1–3 of treatment with detectable parasitemia.
    - Parasite count on day 2 higher than on day 0.
    - Day 3 parasite count >25% of day 0.
    - Presence of asexual parasites with fever on day 3.
- Late Treatment Failure:
    - Development of severe malaria between days 4 and 28 with parasitemia.
    - Recurrence of asexual parasitemia with fever between days 4 and 28.
    - Reappearance of asexual parasitemia on days 7, 14, 21, or 28, even without fever.
- Recurrence: Reappearance of asexual parasitemia after completion of therapy. This may be further categorized as:
    - Relapse: Parasite recurrence after 28 days, originating from dormant liver-stage hypnozoites (*P. vivax* or *P. ovale*).
    - Recrudescence: Parasite recurrence within 28 days, due to survival of blood-stage parasites that were inadequately cleared by treatment.
    - Reinfection: A new infection from a subsequent mosquito inoculation, involving a new set of sporozoites.

In this case, the recurrence of febrile symptoms accompanied by detection of *Plasmodium vivax* with a parasitemia index of 1%, after prior confirmation of parasite clearance on days 7 and 14 post-treatment, supports the diagnosis of relapsed malaria. In countries with high malaria transmission rates, comprehensive malaria prevention strategies are critical. These include the use of insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), chemoprevention for pregnant women, and seasonal malaria chemoprevention (SMC) targeting children in regions with seasonal transmission. Furthermore, early diagnosis using rapid diagnostic tests (RDTs) and timely treatment with artemisinin-based combination therapies (ACTs) form the cornerstone of malaria control and case management (WHO, 2022). Natural immunity to malaria develops gradually through repeated exposure to *Plasmodium* infections. Immunity is acquired more rapidly in individuals exposed to more severe disease episodes. With increasing age and cumulative exposure, individuals tend to develop protection first against severe malaria, then against uncomplicated malaria, and eventually to asymptomatic parasitemia (Paton, 2021). A significant advancement in malaria control is the development of a malaria vaccine. The RTS,S/AS01 vaccine is the first and only malaria vaccine currently recommended by the World Health Organization (WHO). In 2019, it received national regulatory approval for pilot implementation in Ghana, Kenya, and Malawi, where it has been integrated into routine childhood immunization programs. The vaccine is indicated for children aged 6 weeks to 17 months, with a four-dose schedule: three doses administered at monthly intervals, followed by a fourth dose 18 months after the third (WHO, 2022).

3. CONCLUSION

This case highlights the ongoing clinical and diagnostic challenges posed by *Plasmodium vivax* malaria, particularly its capacity for relapse due to dormant liver-stage hypnozoites. Despite adherence to standard treatment protocols with ACT and primaquine, the patient experienced a recurrence of infection within one month, underscoring the limitations of current therapeutic and monitoring strategies. The inability to definitively distinguish between relapse, reinfection, and treatment failure without molecular tools complicates clinical decision-making, especially in non-endemic settings. Furthermore, the transient hypotension observed during treatment, though not indicative of severe malaria, raises awareness of potential complications during early therapy. This case reinforces the importance of comprehensive care in malaria management, including consideration of regional strain variations, access to G6PD testing, patient adherence to radical cure regimens, and the integration of advanced diagnostics. As malaria elimination efforts continue globally, addressing these challenges is essential to improving patient outcomes and reducing disease recurrence.

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