Severe malaria vivax with sepsis bacterial: a case report

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Abstract. Malaria cases are often misdiagnosis by clinicians in tropical areas like Indonesia. Some cases show overlapping signs and symptoms of another infection that are common in the tropical areas such as typhoid, dengue, and leptospirosis. It can be misdiagnosed in practice and led to a wrong management that can end fatally. Severe malaria is usually caused by Plasmodium falciparum. P. vivax can also cause severe malaria but the cases reported are uncommon. Since infections with severe P. vivax that generally results in serious disease is quite uncommon in Indonesia, their identification and management are important. We report a case of severe malaria with sepsis, renal injury and hepatic impairment associated with malaria in a 70-year-old male. Clinical manifestations included anemia, sepsis, and elevated serum creatinine, urea, total bilirubin, and procalcitonin. The rapid diagnostic test for malaria and microscopic examination of blood smears were positive for P. vivax. The patient was treated as severe malaria with intravenous artesunate for six days, followed by oral treatment of primaquine for 14 days. Intravenous fluid therapy, antipyretic, anti-malaria and antibiotic treatment were administered. The patient was stable and then discharged from the hospital. The prognosis depends much on early diagnosis and appropriate supportive treatment.

1. Introduction
Malaria cases are often misdiagnosis by clinicians in tropical areas like Indonesia. Malaria has overlapping symptoms and sign with other tropical disease infection, such as typhoid, dengue, and leptospirosis. Malaria is still a general health problem worldwide, especially in Indonesia. Five types of Plasmodium have been found to infect human: Plasmodium vivax (P. vivax), P. ovale, P. malariae, P. falciparum and P. knowlesi1 Infections by P. vivax and P. falciparum represent the two most frequent types found. Although infection by P. falciparum is more likely to show more severe clinical manifestations than P. vivax, P. vivax can also cause severe disease in several cases. About 2.5 billion people are at risk of infection by P. vivax1. The latest WHO estimation, released in December 2016, said that there were 212 million cases of malaria in 2015 with 429,000 deaths. In Indonesia, malaria disease is still a highly infective disease, particularly in the east region of the country. According to the basic health research of Indonesia (RISKESDAS) in 2013, the prevalence of malaria in 2013 was 6%. In North Sumatera, the prevalence was 5.2 %3. Data from the North Sumatera health department profile also showed that in 2013, North Tapanuli, an area in the province, had 463 of suspected malaria cases, with 38 to be found malaria positive4. From that data, it was found that the incidence of malaria in North Tapanuli was 8.21%5. Severe malaria is life-threatening and can cause mortality and morbidity. Treatment of malaria according to leaflet product, artesunate injection 2.4mg/kgBW
intravenously on the first day followed by 1.2mg/kgBW for 6 days. Sepsis is one of the conditions that increased the morbidity and mortality to the patients with malaria vivax. Serum procalcitonin (PCT) levels are correlated well with the severity of sepsis and the later outcome. PCT is a prohormone of calcitonin that is found elevated in any bacterial infection\(^9\). Serum PCT levels increase during severe generalized bacterial, parasitic or fungal infections with systemic manifestation. In severe viral infections or inflammatory reactions of non-infectious origin, serum PCT levels do not increase at all or only increasing moderately\(^10\). PCT cut-off point in malaria disease is 10.0ng/ml with sensitivity 67%, specificity 94%. Higher procalcitonin over 10.0ng/ml indicates that bacterial infection involved to this situation. The higher increase of PCTs related to fatal outcome\(^9\).

2. Case report

A 70-year-old male, Indonesian, admitted to Haji Adam Malik Center hospital in August 2017 with a history of 14-day intermittent fevers, headaches, rigors, and chills, and a history of 1-day nausea, vomiting, yellowish on sclerae, and diffuse abdominal pain, and also previous hospital admission. When he subsequently developed fever and chills symptoms, he came to the hospital. Antibiotic history for this patient was ceftriaxone for 4 days uses. In admission, the patient was alert and well oriented. The temperature was 38.2°C, heart rate of 90x/min, blood pressure of 110/70 mm/Hg, and respiratory rate of 28x/min. Physical examination findings were significant for diffuse abdominal tenderness and yellowish in sclera orbital. Laboratory studies showed a white blood cell (WBC) count of 12280/µL, hemoglobin of 10g/dL, and a platelet count of 15000/µL. The total bilirubin concentration was 9.8mg/dL. Elevated for urea 261mg/dl, creatinine 4.16mg/dl and procalcitonin was 24.48ng/ml. Transaminases were normal with serum aspartate aminotransferase (AST) level of 22U/L, an alanine aminotransferase (ALT) of 20U/L, and an alkaline phosphatase level of 64U/L. Examination of a thin blood smear revealed ringed trophozoites and schizont typical of the \( P. \) vivax. Density plasmodium malaria of the patient, performed by light microscope, was +++ (found 1-10 parasites in the high-power field) in malaria vivax blood checked. Abdominal ultrasound showed a thickened gallbladder wall diameter common bile duct, but showed no gallstones or biliary ductal dilatation. Cholecystitis was diagnosed.

![Figure 1. Trophozoit & schizont Plasmodium vivax.](image)

Treatment was begun with Intravenous (IV) fluids, injection antibiotic ampicillin-sulbactam 1.5gr/8hr, Omeprazole 40mg/12h, artesunate 2.4mg/kgBW on the first day and then 1.2 mg/kgBW for six days, and also oral primaquine 15mg one time daily. Over 3 days after initiation of antimicrobial therapy, the patient’s clinical condition improved. Injection of Ampicillin-Sulbactam was discontinued after the patient’s procalcitonin level decrease, falling 90% from base line. By the fourth day of treatment, the bilirubin level decreased 5.3gr/dl. By the fifth day of treatment, platelet began to rise up to 85000mg/dl, creatinine had declined to 2.82mg/dl and by the ninth day creatinin to
2.00mg/dl. A repeated blood smear on the third day after treatment with artesunate showed clearance (negative) of parasitemia. The hemoglobin concentration, however, declined to 7.4, by the fifth day it began to rise up to 8.3g/dl. In the seventh day of treatment, the clinical symptoms started to improve and had finally resolved completely by the ninth day. The patient was discharged with instructions to complete a 2-week course of oral treatment of primaquine. The patient condition showed in table-1. We gave antibiotic for ESBL as empirical treatment (ampicillin-sulbactam) regarding our calculation for risk factor patient got ESBL infection by Italian score/duke score (table 2 we see the Italian score). This is one of the scores to identify if patients had related to extended-spectrum β-lactamase (ESBL), the percentage is 80% if the scores 8 or above were from the patient's history the Italian score was 10. It means that this patient was suspected to the ESBL and need antibiotic against this ESBL. We made a choice to ampicillin-sulbactam 1.5gr/8hr for six days. Procalcitonin as an indicator to us to see the effect antibiotic to the patient, and the result is PCT is a decrease from 24.48 to 1.48 and the patient discharged from the hospital.

### Table 1. Patient condition.

| Day | Density of Plasmodium | Haemoglobin | Platelet Count | Creatinine | Bilirubin total | Procalcitonin | Sofa score |
|-----|-----------------------|-------------|----------------|------------|----------------|--------------|-----------|
| 1   | +++                   | 10          | 1500           | 4.16       | 9.8            | 24.4         | 10        |
| 2   | +                     | 10.6        | 1300           | 4.05       | 8.2            | 6            | 10        |
| 3   | -                     | 7.4         | 1500           | 4.44       | 7              | -            | 10        |
| 4   | -                     | 7.6         | 5200           | 4.10       | 5.3            | 9.8          | 10        |
| 5   | -                     | 8.3         | 8500           | 2.82       | 3.4            | 4.05         | 10        |
| 7   | -                     | 10.3        | 120,00         | 2.82       | 2.6            | 8.96         | 7         |
| 14  | -                     | 11.1        | 170,00         | 1.4        | 1.48           | -            | 7         |

### Table 2. Italian score.

| Attribute                                      | No. of points |
|------------------------------------------------|---------------|
| Recent antibiotic therapy with β-lactams and/or fluoroquinolones<sup>a</sup> | 2             |
| Previous hospitalization<sup>b</sup>           | 3             |
| Transfer from another healthcare facility      | 3             |
| Charlson Comorbidity Score of ≥4              | 2             |
| Recent history of urinary catheterization<sup>c</sup> | 2             |
| Age ≥70 years                                  | 2             |

<sup>a</sup>During the three months preceding the index hospitalization.
<sup>b</sup>During the twelve months preceding the index hospitalization.
<sup>c</sup>During the thirty days preceding the index admission.

3. Discussion

Based on WHO 2015 Guideline for Treatment of Malaria, diagnose severe malaria consists of one or more of the following below: impaired consciousness (Glasgow coma scale <11), prostration (generalized weakness so that the person is unable to sit, stand or walk without assistance), multiple convulsion (more than 2 episodes within 24 hours), acidosis (plasma bicarbonate level <15mmol/L or venous plasma lactate >5mmol/L), hypoglycemia (plasma glucose <40mg/dl), severe malaria anemia (Hb ≤7g/dl or Hematocrit ≤20%), renal impairment (serum creatinine >3mg/dl), jaundice (serum bilirubin >3mg/dl), pulmonary edema, significant bleeding (recurrent or prolonged bleeding from
nose, gums, or venipuncture, hematemesis or melena), shock (systolic blood pressure <70mmHg), hyperparasitemia (Parasitemia >10%) with no parasite density threshold.

These signs and symptoms could lead to life-threatening episodes. In this patient, we met the criteria by the malarial anemia, jaundice, renal impairment, and parasitemia in blood and sepsis.

Severe malaria could occur in human, and it is caused by its pathogenesis in the human tissues and blood. As the schizonts rupture, from 4 up to 36 daughter merozoites, depending on the Plasmodium species, released into the circulation and invade fresh red blood cell (RBC) to perpetuate the asexual life cycle. At the same time, a large toxin and parasite products are also released and cause the activation of the innate immunity. Symptoms associated with malaria-like fever could cause the release of inflammatory mediators. After 1–1.5 days, the merozoites mature from the ring stage to the trophozoite stage. Infected red blood cell (IRBC) then adhere to the endothelial cells in the microcirculation of various organs. This phenomenon, termed “sequestration,” is believed to occur mainly to avoid splenic removal of IRBC. Sequestration can cause microcirculatory obstruction, impaired tissue perfusion, and inflammatory cells activation. It is mainly linked to the severity of the disease. Matured forms of parasites (asexual stage and gametocytes) can adhere to the vascular endothelium of several organs (lung, heart, brain, liver, and kidney), the subcutaneous adipose tissues and the placenta. This phenomenon is called “cytoadherence,” which is the ability of parasites to adhere to the vascular endothelium. One of the forms of cytoadherence during late stages of IRBC is called “rosetting.” This process is when the IRBC adhere to non-parasitized red blood cells or platelets. These three phenomenon are the pathogenesis of malaria that leads to the severity of the disease.

According to Surviving Sepsis 2016, sepsis is defined as life-threatening caused by dysregulated host response to infection. The severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions. The predominant score in current use is the Sequential Organ Failure Assessment (SOFA) (originally the Sepsis-related Organ Failure Assessment). A higher SOFA score is associated with an increased probability of mortality. Sofa score patient at the admission was 10 and decrease to 1 when patient discharge.

Table 3. SOFA score ≥2 means organ dysfunction.

| System                      | Score | 0 | 1 | 2 | 3 | 4 |
|-----------------------------|-------|---|---|---|---|---|
| Respiratory                 |       |   |   |   |   |   |
| PacVsFiO2, mm Hg (kPa)      |       | ≥400 (53.3) | <400 (53.3) | <300 (40) | <200 (26.7) with respiratory support | <100 (13.3) with respiratory support |
| Coagulation                 |       |   |   |   |   |   |
| Platelets, 10^11/L          |       | ≥150 | <150 | <100 | <50 | <20 |
| Liver                       |       |   |   |   |   |   |
| Bilirubin, mg/dL            |       | <1.2 (20) | 1.2-1.5 (20-32) | 2.0-5.5 (33-101) | 6.0-11.5 (102-204) | >12.0 (204) |
| Cardiovascular              |       |   |   |   |   |   |
| MAP ≥70 mm Hg               |       | MAP <70 mm Hg | Dopamine <5 or ephedrine <1 or norepinephrine <0.1 | Dopamine 5.1-15 or ephedrine 1-10 or norepinephrine 0.1-0.3 | Dopamine >15 or ephedrine >1 or norepinephrine >0.1²⁸ |
| Central nervous system      |       |   |   |   |   |   |
| Glasgow Coma Scale score²⁹ |       | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Renal                       |       |   |   |   |   |   |
| Creatinine, mg/dL           |       | <1.2 (110) | 1.2-1.9 (110-170) | 2.0-2.4 (171-299) | 2.5-4.9 (200-440) | >5.0 (440) |
| Urine output, mL/d          |       | <500 | <200 |   |   |   |

Abbreviations: \( \text{FiO}_2 \): fraction of inspired oxygen, \( \text{MAP} \): mean arterial pressure, \( \text{Pac}_V \): partial pressure of oxygen. ²⁸: Catecholamine doses are given as \( \mu \text{g} / \text{kg} / \text{min} \) for at least 1 hour. ²⁹: Glasgow Coma Scale scores range from 3-15, higher score indicates better neurological function.
Sudhir et al. in their research had a result that higher SOFA score levels were associated with significantly higher serum PCT concentrations (P<0.05). Serum PCT proved to be the best indicator of sepsis in critically ill patients, with sensitivity of 94% which is normally not found in the blood stream. Procalcitonin is a prohormone of calcitonin that is found increased in any bacterial infection. In severe viral infections, or inflammatory reactions of non-infectious origin, serum PCT levels commonly are not elevated, or if it is, only moderately. In malaria, the PCT is elevated due to the parasitic infection. The PCT cut-off point in malaria disease is 10.0ng/ml with sensitivity 67%, specificity 94%. The higher increase of procalcitonin is associated to fatal outcome.

According to the Italian score which is a model to identify patient infected with extended-spectrum β-lactamase (ESBL), 80% of scores 8 or above were associated with the disease. The carbapenem antibiotic is still the first choice of treatment for serious infections with ESBL-producing E. coli and K. pneumonia, but with the emergence of carbapenem-resistant Enterobacteriaceae, the choice to treat this is difficult. There are some drugs which can be used to treat this bacteria, fosfomycin, colistin, ticagrelol, ampicillin/subbactam, piperacillin-tazobactam.

Many guidelines showed how to treat malaria. According to second edition WHO guidelines for treatment of malaria, the artesunate doses to treat severe malaria is 2.4mg/kgBW/IV/IM at 0, 12 hours, then daily until they could tolerate oral therapy, complete treatment with 3 days of an ACT (artemisinin-based combination therapies), but in this case we chose the regimen by the leaflet on the product of artesunate for injection from Guilin pharmaceutical Co., Ltd.

3. Conclusion

We reported a case of severe malaria vivax with sepsis in 6 days length of stay in Adam Malik Hospital and patient got discharged. The prognosis usually depends on early diagnosis and treatment.

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