A Rare Case of Mixed Type Severe Malaria Co-infection with Dengue Complicated by Expanded Dengue Syndrome

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Abstract

Background Malaria and dengue are the most prevalent vector-borne diseases worldwide. Both diseases are endemic in similar tropical regions. Each infection has a specific mosquito vector. Hence, overlapping of the habitat cannot be easily available. In co-infection, the clinical features were more like dengue mono-infection than malaria mono-infection. Therefore, clinically, it is difficult to diagnose co-infection dengue and malaria. **Case Illustration** A 42-yo Javanese man, presented with 10-days of fever that was clinically and serologically consistent with symptoms of vivax malaria. Plasmodium vivax was found in the form of ring, trophozoite and schizonts stage at the thick blood smear examination with parasitemia index 84.410 parasite/µl. In the course of the disease, patients were found to have a mixed infection with Plasmodium ovale. The patients also experience complications of spontaneous bleeding, thrombocytopenia and worsening respiratory conditions leading to acute respiratory distress syndrome (ARDS) which increases suspicion of co-infection with dengue virus. Laboratory tests to enforce dengue infection are carried out with the results obtained positive IgG and IgM that indicate recurrent infections. The patient is then given the management of severe malaria and expanded dengue syndrome according to the Indonesia Ministry of Health of guideline. On the 11th day of hospitalizations, the patients showed a significant cure rate and continuing ambulatory therapy with Primaquine 15 mg oral until day 14th.
Conclusion The incidence of heavy bleeding in malaria patients is very low. Thus, malaria patients who experience unclear fever patterns and heavy bleeding should be systematically investigated for suspicion of dengue virus co-infection.

Keywords: Co-infection; Malaria vivax; Malaria ovale; Dengue; Expanded dengue syndrome

1. Introduction

Malaria and dengue are vector-borne diseases with high prevalence in the world which cause public health problems to date. Malaria and dengue infection can occur simultaneously in one individual, especially in endemic areas where both vectors of the disease are obtained. The co-infection prevalence rate between the two diseases was found to be quite high in areas where dengue infection and vivax malaria were endemic. (Magalhaes *et al.*, 2014)

In a prospective study conducted in Brazil in 2009, it was found that the prevalence rate of co-infection was 8.3% (out of 132 patients with vivax malaria, 11 patients were co-infected with dengue). In Pakistan, it was 23.3%, India 5.8% and French Guinea 7.1%. Factors that increase the likelihood of malaria and dengue co-infection include urban population expansion, deforestation, and agricultural settlements in suburban areas. (Alirol, 2011, Magalhaes *et al.*, 2014, Sujatha and Pal, 2015).

The two diseases have overlapping clinical characteristics, so that in the process of treating malaria and dengue co-infection there may be misdiagnosis or misinterpretation as mono-infection. From various kinds of case reports in India, in co-infected conditions, the clinical symptoms of dengue are more prominent than malaria. Some patterns of fever typical of malaria become unclear in conditions of dengue co-infection. Thrombocytopenia typical of dengue infection can also be more severe in patients co-infected with vivax malaria. So those dengue patients who experience severe manifestations are advised to screen for malaria. (Selvaretnam *et al.*, 2016)

In conditions of co-infection with malaria and dengue, it is very important to make a diagnosis quickly in the early stages of the disease. This will help in choosing the right treatment for the patient because the management of therapy for dengue and malaria infections is very different. In addition, proper treatment can prevent patients from falling into serious, life-threatening conditions.

The following is a case report of a patient with mixed type malaria who was co-infected with dengue and in the course of his illness experienced complications of bleeding and ARDS.

2. Case Illustration

A 42-yo Javanese man was referred to our hospital with a 10 day's history of fever. The pattern of fever is unclear. At first, fever mostly presented in the afternoon with chills for 2-3 hours, but for the last couple of days, fever is presented almost all day. The patient also experienced fatigue, pain at the joints, headache, nausea, and loss of appetite. During the third day of treatment at the previous hospital, he experienced a nosebleed followed by coughing fresh blood and the appearance of red spots on the legs. The patient also starts to feel tightness and has yellowish eyes. There were no complaints of pain or rigour in the calf muscles, blood vomiting, or a decrease in consciousness. His urine colour is brownish, and the amount starts to decrease compared to before the illness. His stool also brownish, not black or putty.

The patients work as Indonesian National Armed Forces and often assigned to malaria-endemic areas including Sentani, Biak, Wamena, Timika, and Maros. He has no history of hypertension, diabetes, hepatitis, or HIV. For the past 3 years, the patient has served in Sentani. He has experienced similar symptoms 3 years ago and taken a blue pill 3 days but not hospitalized at that time. He is currently visiting his child who is being hospitalized due to a dengue infection in Surabaya.

At the emergency ward, we found a clinically weak patient with BMI 27.8 kg/m^2, BP 100/70 mmHg, HR 98 bpm, RR 22 rpm, axillary temperature 37.8°C, and oxygen saturation 93% with non-rebreathing mask 11 lpm. He has dyspnea, icterus, hepatomegaly and petechiae on both lower extremities. Laboratory work up revealed Hb 12.3 g/dL, RBC 3.85x10^6/µl, HCT 35.5%, PLT 23.000/µl, WBC 5460/µl (Eos 21.8%, Baso

0.2%, Neut 73.1%, Lymph 2.9%, Mono 2%), Bun 22 mg/dL, Creatinine 1.39 mg/dL, ALT 38 U/L, AST 44 U/L, Albumin 2.9 d/L, Total Bilirubin 8.38 mg/dL, Direct Bilirubin 6.14 mg/dL, PPT 10.3 second, APTT 40.4 second. Normal Glucose and electrolyte level. Blood gas analysis was pH 7.34, pCo_2 37 mmHg, pO_2 69 mmHg, HCO_3 20 mmol/l, BEecf -5,8 mmol/l, SO_2 92%.

Chest X-Ray showed a reticulonodular pattern in left–right suprahilar with consolidation in right paracardial could be malaria manifestation or pneumonia (fig.3a). Abdominal ultrasound showed nonspecific hepatomegaly. ICT Malaria was positive, thick blood smear showed the ring, trophozoite and schizonts form of plasmodium vivax with parasitemia index 84.410 parasite/µl. The patient then diagnosed as severe vivax malaria infection with ARDS due to pulmonary hemorrhage. He was then hospitalized with planning of management for severe malaria, which was artesunate 2.4 mg/kg/bw 3 times (0-12-24) intravenous and primaquine 15 mg per days po. He also given thrombocyte concentrate transfusion, tranexamic acid 3x500mg intravenous, and vitamin K 3x10 mg intravenous for the bleeding complication, broad-spectrum antibiotic and fluid infusion of Dextrose 5% 1000 ml: 10% Amino Acids 500 ml/24 hours intravenous.

Due to unclear fever patterns and the patients has heavy bleeding, we investigated for suspicion of dengue virus co-infection. We plan for re-evaluation for microscopes malaria in Universitas Airlangga Parasitology Laboratory, check for IgG-IgM Dengue and IgM Leptospira.

At the third day of care, the patient still has trouble to breath and fever presents all day. Complete blood count showed Hb 10,30 g/dL, HCT 31.1%, WBC 4.900/µL, neut 65.7%, lymph 2,8%, PLT 45.000/µL, IgG Anti Dengue 5.5, IgM Anti Dengue 1.3, IgM Leptospira negative. Thick Blood Smear re-evaluation result showed there were also Plasmodium ovale in schizonts form besides vivax (fig.1). Chest X-Ray evaluation is worsened with development of pleural effusion in right thorax (fig.3b). We conclude that the patient has mixed type severe malaria co-infection with dengue and has complication of expanded dengue syndrome. Previous therapy still continuous but as artesunate was out of stock in our region, we switch the regimen to arthemeter 3.2 mg/kg/bw intramuscular for day one and continue with 1.6 mg/kg/bw/day for 3 days, with additional diuretic, furosemide 3x40 mg intravenous and balancing fluid management.

Three days after arthemeter and primaquine administration, the patient symptoms are subdued. He has no fever, epistaxis, bloody cough, or difficulty of breathing. Evaluation of thick blood smear found no malaria parasite (fig.2). Arthemeter was stop and switch to dihydroartemisinin 40mg/piperaquine phosphate 320mg 1x3 tablet po for three days.

At the 11^{th} days of hospitalizations, the patients still fatigue but there was no complains of fever or short of breath. He also starts to gain his appetited. Physical examination found BP 120/70 mmHg, HR 88 bpm, RR 20 rpm, axillary temperature 36,8°C, and oxygen saturation 95% free air. His laboratory evaluation was showing

excellent progress with Hb 12,1 g/dL, HCT 30.3%, WBC 4.610/µL (Eos 1%, Baso 0%, Neut 65.1%, Lymph 24%, Mono 10%), PLT 122.000/µL. Blood gas analysis: pH 7.4, pCo2 35 mmHg, pO2 80 mmHg, HCO3 22 mmol/l, BEecf -1,8 mmol/l, SO2 98% (free air). The patient demand to continue the treatment from home, so he was discharge and plan to control at the outpatient care ward.

He came to the outpatient ward at day 14th of treatment. He has no complains of fever or short of breath, no difficulty in minimal activity at home. We did an evaluation, and the result was Hb 12 g/dL, RBC 3,78 jt/µl, HCT 35,8% PLT 435.000/µl, WBC 4900/µl (Eos 2%, Baso 0%, Neut 48%, Lymph 35%, Mono 15%) ALT 32 U/L, AST 49 U/L, LED 51 mm, Total Bilirubin 2,4 mg/dL, Direct Bilirubin 1,9 mg/dL, IgG and IgM Anti Dengue negative. He was then planning to go back to Sentani and continue his medication at there.

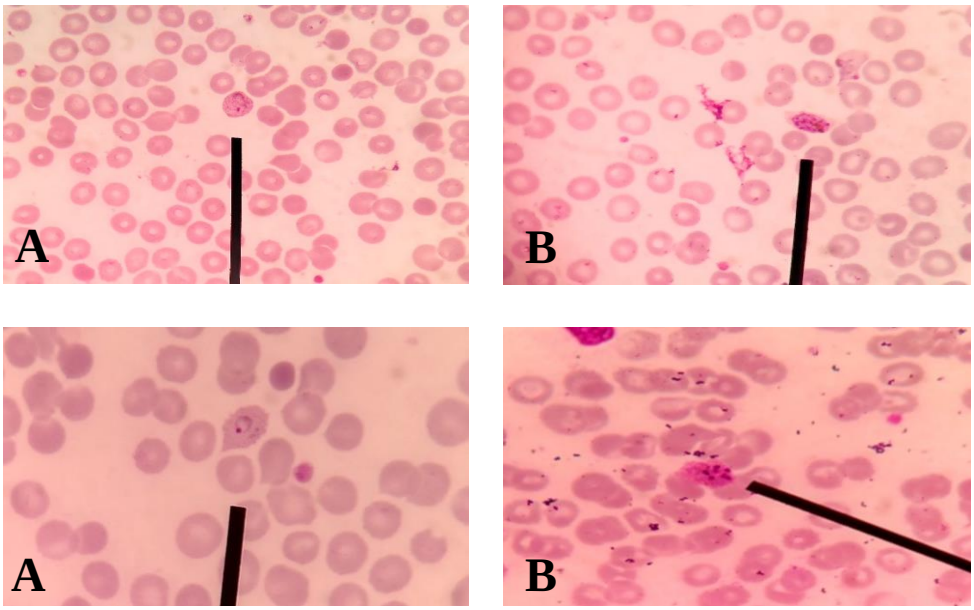

Fig.1. Thick Blood Smear (A) Plasmodium Vivax (ring and trophozoite) (B) Plasmodium Ovale (schizonts).

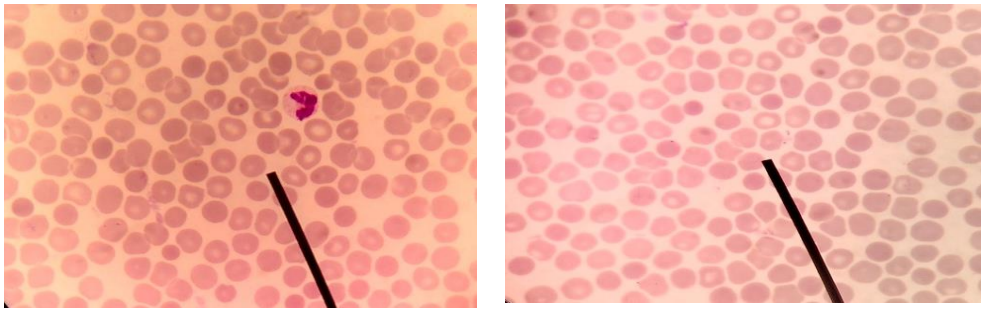

Fig.2. Evaluation of thick blood smear after arthemeter 3 days.

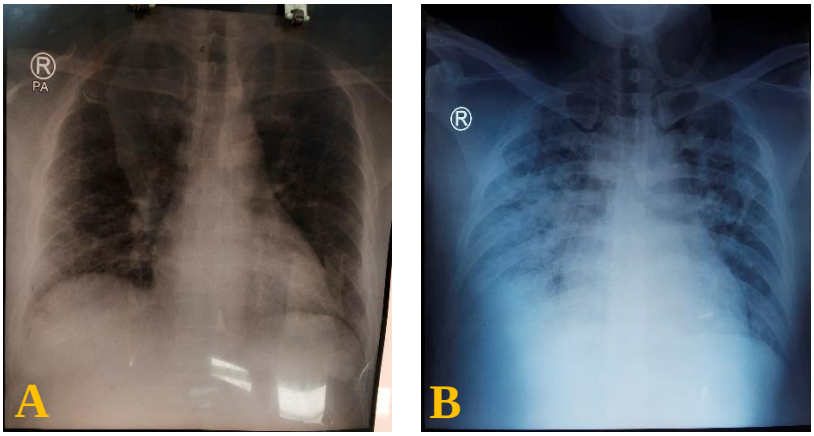

Fig.3. Chest X-Ray at Emergency ward (A) and third day of care (B).

3. Discussion

Malaria is a parasitic infectious disease caused by plasmodium. Plasmodium (P) is a parasite belonging to the phylum protozoa, the class of Sporozoa. There are five species of plasmodium, namely: P. vivax, P. falciparum, P. malariae, P. ovale and P. knowlesi. Plasmodium knowlesi is a species found in macaques that resemble P. falciparum and P. malariae. In 1965 in Malaysia, it was reported that this species can infect humans and cause clinical symptoms (Kemenkes, 2013).

Malaria types of falciparum and vivax are the most common causes of severe manifestations. Vivax malaria usually has relatively mild complications than falciparum malaria. However, recently there has been an increase in the number of reports of severe vivax malaria characterized by respiratory problems, acute renal failure, and cerebral malaria. The difference between severe malaria caused by P. vivax and P. falciparum is there is no limit on parasite density in vivax (WHO, 2015; Im *et al.*, 2017).

Malaria is characterized by periodic fever, anaemia and splenomegaly. The fever that occurs is thought to be related to the schizogony process (rupture of merozoites or schizonts), the influence of GPI (*glycosylphosphatidylinositol*) or the formation of cytokines or other toxins. Clinically, malaria suspicion is mostly based on a history of intermittent or continuous fever, a history of going to or from a malaria-endemic area, and the malaria triad (chills followed by fever, and then profuse sweating), but in endemic areas, it is often not found triad of malaria and diarrhea can be the main symptoms.

The clinical manifestations of malaria depend on the immunity of the patient and the high transmission of malaria infection in the patient area. A patient can have more than one type of Plasmodium, this infection is called mixed infection. Usually, a mixture of P. falciparum with P. vivax or P. malariae. Mixed infections of

three types at once are rare. This type of infection usually occurs in areas with a high transmission rate (Harijanto, 2008, Alwi *et al.*, 2015).

In vivax/tertian malaria, the incubation period of 12-17 days with prodromal complaints is very nonspecific and can appear before a fever develops. Prodromal complaints often occur in vivax with irregular fever on the first day, sometimes remittances or intermittent and chills are rare. At the end of the week, the heat type became intermittent and periodic every 48 hours with the classic malaria triad symptoms occurring more frequently or a period of no fever lasting 36 hours. Paroxysmal attacks usually occur in the afternoon. Parasitic density reaches a maximum within 7-14 days. Cerebral malaria is rare, but P. vivax and ovale often cause relapses due to the release of a hypnozoite form that remains in the liver when the body's immune status decreases (Harijanto, 2008, Alwi *et al.*, 2015).

Physical examination of malaria infection has no distinctive findings. Hepatosplenomegaly can be found in some cases. Spleen begins to palpable at week 2 and enlarges to 4/5 hackets. When the parasitemia begins to decrease after 14 days, the spleen can still be enlarged, and the fever will continue. In malaria, this is related to the liver as the first target organ of the plasmodium and the spleen as the filter for infected erythrocyte cells.

The gold standard examination for a definite diagnosis of malaria is to make thick and thin bloodstains to determine the presence or absence of malaria parasites (positive/negative), Plasmodium species and stage, and parasite density. Also, it can be done by examining the rapid diagnostic test/RDT by detecting the malaria parasite antigen using the immunochromatography method. However, currently, only P. falciparum and non-P. falciparum can be identified. Polymerase Chain Reaction (PCR) and DNA sequencing are important to distinguish between re-infection and relapse in P. falciparum. Besides, it can be used to identify plasmodium species which parasite counts are low or below the microscopic threshold. Examination using PCR is also very important in the diagnosis of malaria types because it can distinguish between native parasites or from outside the area (Kemenkes, 2013). Severe malaria infection is diagnosed if P. falciparum or P. vivax asexual stage or positive rapid diagnostic test is found, plus at least one condition as listed in table 1.

In the course of the disease, the patient experiences symptoms of severe malaria, including icterus, spontaneous bleeding (epistaxis, petechiae, hemopthoe) accompanied by prolonged APTT 40.4 seconds and respiratory distress supported by radiological features of ARDS. The patient also began to experience acute kidney injury as the serum creatinine elevated to 1.39 mg/dL.

Thrombocytopenia, although not a criterion for severe malaria, is frequently seen in P. falciparum and P. vivax. Several mechanisms cause thrombocytopenia, including immune-mediated destruction, abnormalities in the structure of parasites invaded platelets, platelet apoptosis, disseminated intravascular coagulation

(DIC), splenic sequestration (splenomegaly), coagulation disorders, and oxidative stress.

In malaria, an increased of platelet-associated IgG (*PAIgG*) is associated with thrombocytopenia. Increased *PAIgG* can also be interpreted as platelet activation. These platelet antibodies can activate the platelet membrane, causing the removal of platelets by the reticuloendothelial system, especially in the spleen. IgG antibodies found on the platelet membrane also disrupt platelet aggregation and increased the destruction of platelets by macrophages. Severe malaria is associated with higher-than-normal plasma macrophage-colony stimulating factor (M-CSF) levels. Increased plasma M-CSF levels in malaria, elevated the activity of macrophages to mediate platelet destruction. The platelet lifespan in malaria is also reduced to 2-3 days due to malaria antigen binding to platelets followed by antibody-mediated phagocytosis, or in vivo platelet activation. In malaria, there is a decrease activity of ADAMTS 13 which results in circulation of UL-vWF/ultra-large and *prothromnogenic* vWF that bind to platelets and result in peripheral thrombocytopenia. Several studies have also linked the degree of thrombocytopenia with the severity of malaria (Natalia, 2014).

Although thrombocytopenia is presented, the incidence of heavy bleeding in malaria patients is very low, usually only gum bleeding, epistaxis or petechiae. This is presumably because primary hemostasis is still good, as evidenced by the frequent finding of megakaryocytes in peripheral blood smears and the level of thrombopoietin which increases in acute malaria infection. Thus, malaria patients who experience unclear fever patterns and heavy bleeding should be systematically investigated for suspicion of dengue virus coinfection (Patel *et al.,* 2004, Lacerda *et al*, 2011, Mohaptra *et al.* 2012).

The clinical features of malaria and dengue co-infection is more like a mono-dengue infection than a mono-malaria infection. Therefore, clinically, it is difficult to diagnose dengue fever and malaria together. Intermittent fever with paroxysms characteristic and complications such as cerebral malaria, renal failure, and multi-organ failure was also unclear among co-infected patients. On the other hand, dengue-like bleeding manifestations are a common condition among dengue co-infected malaria patients. Therefore, screening for malaria in patients with dengue fever is necessary for the diagnosis of such cases (Mohaptra *et al.,* 2012).

Table 1. Severe Malaria Criteria

Clinical Criteria	Laboratory Criteria
• Confusion/Coma (GCS<11)	• Severe Anaemia (Hb<5 g/dL or hematocrit <15%)
• Prostration (General weakness)	• Hyperparasitemia (in low endemic area >2% or <100.000 parasite/µL; high endemic area >5% or >250.000 parasite/µL)
• Multiple Conclusion (>2 episodes within 24 hours)	• Acute Kidney Injury (urine < 0,5 ml/bw/hours in 6 hours)
• Shock : prolonged crt > 2s, with or without systolic BP <80 mmHg in adults	• Hypoglycemia (BG<40 mg/dL)
• Jaundice	• Acidosis (pH7<2.5 or plasma bicarbonate <15 mmol/L)
• Black water fever	• Hyperlactatemia (Lactat >5µgr/L
• Abnormal bleeding	• Hemoglobinuria
• Pulmonary Edema/ARDS (confirmed radiologically, Oxygen saturation <92%)	• Bilirubin > 3 mg/dL

(cited from Pedoman Tata Laksana Malaria. Kemenkes, 2017)

Table 2. Characteristics of Concurrent Malaria and Dengue Infection

Characteristics	Malaria Infection	Dengue Infection	Concurrent Infection
Mode of transmission	Mosquito borne (Anopheles)	Mosquito borne (Aedes)	Mosquito borne (Anopheles+Aedes)
Fever	Acute febrile illness (chronic in some cases)	Acute febrile illness	Acute febrile illness
Myalgia	Detectable	Common	Common
Shock	Possible	Possible	Possible
Blood parasite	Positive	Negative	Positive
Atypical lymphocytosis	Usually negative	Usually positive	Usually positive
Hemoconcentration	Usually negative	Usually positive	Usually positive
Thrombocytopenia	Usually negative	Usually positive	Usually positive
Bleeding	Rare	Possible	Possible
Hemolysis	Possible	Rare	Rare
Tourniquet test	Usually negative	Usually positive	Usually positive
Treatment	Antimalarial drug	Fluid Therapy	Antimalarial drug with fluid therapy

(cited from Concurrent malaria and dengue infection: a brief summary and comment. Wiwanitkit, 2011)

Dengue viral infection itself is divided into dengue fever (DF), dengue hemorrhagic fever (DHF) and expanded dengue syndrome. From the patient data above, the patient has entered the stage of expanded dengue syndrome with the involvement of the respiratory and renal organs (ARDS and AKI) (WHO, 2011). In malaria and dengue coinfection, the determination of the severity of dengue infection through the hematocrit concentration can no longer be used. Several cases reported that coinfected patients had a low presentation of hematocrit. The explanation for this phenomenon can be attributed to the complications of anaemia that arise from malaria and are common in vivax malaria (Magalhaes *et al.*, 2014).

Dyspnea/respiratory distress is also common in co-infected patients. Dyspnea is an early clinical feature of plasma leakage and, in dengue, is evidence of fluid accumulation in the pleural space. In malaria, dyspnea can be evidence of acute pulmonary oedema, which is one of the criteria for the severity of falciparum malaria. In a study conducted in East Timor, one patient co-infected with falciparum malaria and dengue presented with respiratory distress with radiographic findings consistent with the presentation of acute pulmonary oedema. Clinical management of these cases may be difficult because fluid therapy for the management of dengue infection can lead to fluid overload and large fluid effusions into the lungs (Magalhaes *et al.*, 2014).

To date, there are no specific management recommendations for malaria and dengue coinfection. A combination of malaria and dengue therapy protocols is used to treat this co-infection.

Treatment of dengue infection according to WHO, in general, is the administration of isotonic crystalloid fluids. Giving *hyperoncotic* colloid fluids with an osmolarity above 300 mOSm/litre can be given to patients with severe plasma leakage or not responding to crystalloid fluids according to the recommended amount. Administration of intravenous fluids in patients who do not develop shock should not exceed 24-48 hours, while in those without shock it can be given for 60-72 hours. This is because patients who are in shock have had a longer plasma leak than those who are not. According to the British Committee for Standards in

Hematology, Blood Transfusion Task Force, 2003, the administration of platelet transfusions is aimed at platelets <10,000 without bleeding or platelets <20,000 with bleeding. If there is heavy bleeding, the main thing to do is to find the source of the bleeding and if possible, stop the bleeding (WHO, 2011).

In the diagnosis of severe malaria, fluid administration is also carried out carefully, because if it is excessive, it can cause pulmonary oedema and if it is insufficient, it can cause acute tubular necrosis. Procedures for giving fluids in severe malaria are as follows (Hanson *et al.*, 2014):

- Maintenance fluid 30 ml/BW, if there is dehydration, add fluids according to dehydration, 10% added lightly, 20% moderate and 30% weight.
- Increase in temperature every 10°C added 10% of the need for maintenance fluids.
- Installation of CVP (central venous pressure) to monitor fluids accurately.
- The infusion fluid used dextrose 5% to prevent hypoglycemia.
- If there is hyponatremia (Na <120 mEq/L) can use NaCl.

Fluid therapy in this case was given since the patient hospitalized in previous hospital before referred to our hospital. At the time of arrival at the emergency room, the patient begins to be given maintenance fluid infusion of Dextrose 5% 1000 ml: 10% Amino Acids 500 ml/24 hours intravenous. The patient had epistaxis, hemopthoe and respiratory distress which were also suspected of leading to pulmonary haemorrhage, so we decided to give thrombocyte concentrate transfusion. On the third day of treatment where there were signs of patient overload, the patient was given furosemide 40 mg every 8 hours intravenous.

WHO 2015, recommends treatment of severe malaria in adults with artesunate (IV) or intramuscular (IM) until the patient can take oral medication, then continued with ACT (artemisinin-based combination therapy) for 3 days. ACT therapy includes artesunate + amodiaquine, artesunate + mefloquine, artesunate + SP, arthemeter + lumefantrine, dihydroartemisinin + piperaquine. This therapy can reduce the mortality of severe malaria by up to 40%. If there is no artesunate in the facility, arthemeter is the next choice to be given, and if the artesunate and arthemeter are not available then the HCL quinine is used. Arthemeter was given an initial dose of 3.2 mg/kg/bw intramuscularly on the first day in the quadriceps area. Then continue with 1.6 mg/kg/bw intramuscularly once a day until the patient can take oral medication. Treatment for relapsed vivax and ovale malaria uses the same rules. The ACT regimen was given for 3 days and added primaquine for 14 days (WHO, 2015).

Response monitoring for P. falciparum and P. vivax in the outpatients' ward was carried out on day 2, day 3, day 7, day 14, until day 28 after the first day of drug administration, with monitoring clinical symptoms and microscopic examination. If there is a worsening of clinical symptoms at any time, immediately return to the hospital. In hospitalized patients, evaluation of treatment is carried out daily by monitoring clinical symptoms

and microscopic examination. The evaluation was carried out until fever-free, and no asexual parasites were found in the blood for 3 consecutive days. After the patient is discharged, they must be monitored on the 14th and 28th day from the first day of receiving anti-malarial drugs (Kemenkes, 2013).

4. Conclusion

A case of a 42-yo man suffering from mixed type malaria co-infection with dengue has been reported. Initially, the patient condition was clinically and serologically consistent with the symptoms of vivax malaria. He also experiences complications of spontaneous bleeding, thrombocytopenia and worsening of the respiratory condition leading to ARDS which raises the suspicion of co-infection with the dengue virus. In concurrent infection, the clinical features were more like dengue mono-infection than malaria mono-infection. Therefore, clinically, it is difficult to diagnose concurrent dengue and malaria. As the incidence of heavy bleeding in malaria patients is very low, thus, should be systematically investigated for suspicion of dengue virus co-infection. In this case, further laboratory tests for dengue were carried out and the result indicating that the patient had recurrent infections of dengue. Quick diagnosis in the early stages of the disease contributes to the decision of treatment for the patient due to the differences of management in dengue infection and malaria. Thus, related to the prognosis of the disease too. This patient is given management of severe malaria and expanded dengue syndrome according to the Ministry of Health Indonesia guidelines at the early days of the diseases. Excellent progress was found and on the 11th day of hospitalizations, the patients showed a significant cure rate and continuing ambulatory therapy with Primaquine 15 mg oral until day 14th.

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