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INTERMITTENT FEVER IN MALARIA FALCIPARUM AND DENGUE HAEMORRAGHIC FEVER CO-INFECTION AT DIAN HUSADA HOSPITAL MOJOKERTO, CASE REPORT

Ihwan Arifiyanto[1], Ardan Mulyarajasa Hanifullah[2], Nugroho Setyawan Sobaa[3], Deo Sanjaya[4], Chabib Fachry Albab[5], Almas Talida Habibah[6]
arifiyantointerna@gmail.com[1], ardanmh31@gmail.com[2], nugrohosetyawan8@gmail.com[3], deosanjaya1009@gmail.com[4], fachryalbab55@gmail.com[5], almastalida56@gmail.com[6]
Dian Husada Hospital Mojokerto[1234], Kedungadem Clinic, Bojonegoro[5], Ibnu Sina Hospital, Bojonegoro[6]

ABSTRACT

Fever is a clinical sign of illness in reaction to infection. Dengue infection has a pattern depends on the phase meanwhile intermittent fever is fever for several hours during the day seen in Malaria. Malaria falciparum has quotidian pattern. Mr.MG 19-years-old Papuan native came to ER of Dian Husada Hospital presented with features of dengue hemorraghic fever grade I. He was treated with fluid therapy and supportive but there aren't significant changes until 3rd day of treatment. The internist decided to check microscopy of blood smears revealed Plasmodium falciparum. The patient was treated anti malarial gradually improved. Fever is a symptom of many diseases. As a clinician, we have to understand the pattern of fever to guide us for diagnostic procedure.

Keyword: *Intermittent fever, Malaria Falciparum, Dengue Hemorraghic Fever*

INTRODUCTION

Fever is a clinical sign in reaction to infection. It can from bacterial, viral, or parasite. Dengue infection has a pattern depends on the phase febrile, critical, and recovery [Ogoina, 2011]. Meanwhile intermittent fever is fever for several hours during the day seen in Malaria [Ogoina, 2011]. Malaria falciparum has quotidian pattern, plasmodium ovale and vivax has tertian pattern, Plasmodium malariae has quartan pattern. [Ogoina, 2011].

This case was very unique because in Mojokerto has low rate of endemicity of Malaria but already found because of easiness from citizen's mobilization especially Papua province. Papua had high annual parasite incidence up to 48,1 / 1000 citizen [Kemenkes, 2011]. Additionally, there was coinfection with Grade I dengue hemorrhagic fever that had already been detected initially. It made unique because the clinician gave the patient dual therapy (anti parasite and supportive for viral infection).

CASE PRESENTATION

Patient Mr. MG, male, 19 years old, came with his family to the emergency room of the hospital Dian Husada Mojokerto on June 4, 2021 at 16.30 with complaints of high fever and chills since 5 days ago, getting worse at night and getting better after taking fever-reducing medication, but it didn't last long. In addition, the patient also complained of joint pain, throbbing dizziness, nausea, vomiting with a frequency of more than 6 times, lower left abdominal pain, last bowel movement 3 days ago, last urination this morning dark yellow, reddish patches on the skin (-), nosebleed (-), bleeding gums (-). The patient is a native of Papua, standing 5,9 feet tall and weighing 180 pounds, blood type A rhesus +. He had at least five previous cases of malaria infection. He's 1st child in his family, he has parents and 2 brothers. All family member already infected with malaria. His parent don't have comorbid like diabetes, hypertension, stroke and cardiac disease. He is a college student in Malang who routine playing basketball everyday, active smoker, and non-alcoholic.

Physical examination revealed good general condition, compos mentis consciousness with *Glasgow Coma Scale* (GCS) E4V5M6. Blood pressure 122/70 mmHg, pulse 115 beats/minute, respiratory rate 20 times per minute, body temperature 39°C axilarry and oxygen saturation 99% on room air. On physical examination of the head and neck showed no anemic conjunctiva, no icteric sclera, no cyanosis, no dyspneau.

On chest examination, the chest was symmetrical and there was no retraction, pulmonary examination revealed vesicular breath sounds in both lungs, no crackles or wheezing were found, on cardiac examination, a single S1 S2 sound was found, regular and no murmurs or gallops, on abdominal examination the abdomen was found soepel, tympanic sound, normal bowel sounds, on examination of the extremities red warm without oedema, capillary refill time < 2 seconds. Obtained > 5 petechie when the rumple leede examination was performed so the rumple leede (+).

Laboratory results in the ER showed haemoglobin 16.1 g/dl, hematocrit 46.3%, platelets 29,000/µL, leukocytes 9,200 /L, erythrocytes 5.710,000 /L with lymph count 7%, mid 8%, granulocytes 85 %, random blood glucose levels are 101 mg/dl, COVID-19 rapid antigen is negative. From the anamnesis, physical examination and supporting examination, the patient was diagnosed with Dengue Haemorraghic Fever grade I. Plan of diagnosis: serial blood count and IgM dengue. Therapeutic plan is Ringer's lactate infusion 1500 cc/24 hours, injection of 3 x 500 mg / 2 ml of metamizole sodium, injection of pantoprazole sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondansetron HCl dyhidrate 3 x 4 mg / 2 ml. Monitoring plan: complaints, vital signs (VS), serial full blood count results, dengue IgM results. *Planning education*, the patient is explained about the disease experienced by the patient, the course of the disease, things that aggravate and relieve, examination and treatment that may be carried out depending on the condition and objective signs that exist in the patient.

On the second day of treatment (5 June 2021) patient had normal body temperature and just little bit dizziness, GCS E4V5M6 was obtained, blood pressure 110/70 mmHg, pulse: 80 beats/minute, body temperature 36°c axillar, SpO2: 98% room air, serial full blood count → haemoglobin 14.2 g/dl, hematocrit 37.8%, platelets 34,000/µL, leukocytes 10,500 /L, erythrocytes 5.110,000 /L with lymph count 9%, mid 3%, granulocytes 87.5%, while dengue IgM is (+). The therapy was given by infusion of Ringer's lactate 1500 cc/24 hours, injection of 3 x 500 mg/2 ml of metamizole sodium, injection of pantoprazole sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondansetron HCl dihydrate 3 x 4 mg/2 ml.

Third day of treatment (6 June 2021) patient had normal body temperature but in the afternoon the patient had fever and dizziness. GCS E4V5M6, blood pressure 100/70 mmHg, pulse: 89x/min, body temperature 36.4°c axillar (body temperature in the morning), SpO2: 98%, serial full blood count results obtained haemoglobin 13.9 g/dl , hematocrit 39%, platelets 30,000/L, leukocytes 12,600 /L, erythrocytes 4.910.000 /L with lymph count 7%, mid 8%, granulocytes 85%, therapy given Ringer lactate infusion 1500 cc/24 hours, injection metamizole sodium 3 x 500 mg/2 ml, injection pantoprazole sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondansetron HCl dihydrate 3 x 4 mg/2 ml. Extra Injection metamizole sodium 1x500 mg/2ml at 16:45 because the patient complained of chills and the body temperature increased to 39°c axillar. Body temperature stagnated at 39°c axillar at 20.24 extra 1 gram paracetamol injection.

Fourth day of treatment (7 June 2021) the patient had high fever in the morning and dizziness. GCS E4V5M6, blood pressure 130/90 mmHg, pulse: 80x/minute, body temperature 36.4°c axillar, SpO2: 98%, serial full blood count results obtained haemoglobin 12.6 g/ dl, hematocrit 33.9%, platelets 38.000/µL, leukocytes 8.900 /L, erythrocytes 4.620.000 /L with lymph count 15%, mid 4%, granulocytes 81%. given infusion of Ringer lactate 1500 cc/24 hours, injection of 3 x 500 mg/2 ml of metamizole sodium, injection of pantoprazole sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondancetron HCl dihydrate 3 x 4 mg/2 ml, at 08.00 in the morning the patient has a fever up to 39°c axillar extra injection of 1 gram of paracetamol. After 3 days of DHF treatment but there's no significant changes, the internist advised to blood smear (thick drops), ICT and full blood count. Diagnostic challenge in this case is limitation of facilities for ICT dan dengue IgM, it needs to send the sample to the laboratory at Surabaya.

Fifth day of treatment (8 June 2021): patient had high body temperature but in the early morning and dizziness. GCS E4V5M6, blood pressure 120/80 mmHg, pulse: 110x / minute, body temperature 39.7°c axillar, SpO2: 98%, serial full blood count results obtained haemoglobin 11.9 g/ dl, hematocrit 33.1%, platelets 26.000/µL, leukocytes 7.600 /L, erythrocytes 4.270.000 /L with lymph count 16%, mid 4%, granulocytes 80% treated with Ringer lactate infusion 1500 cc/24 hours , injection of metamizole sodium 3 x 500 mg/2 ml, injection of pantoprazole sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondansetron HCl dihydrate 3 x 4 mg/2 ml, body temperatures at 4 am 39.7 to 36.0 at 8 am.

Malaria ICT results reporting Plasmodium falciparum (+), Plasmodium vivax (-), blood smear (thick drops) → Mauer dot (+). Anti-malaria therapy, DHP Frimal 40 mg 1x4 tab, primaquine phosphate 15 mg 1x1, Planning of treatment: drip paracetamol 3 x 1 gram. Injection Metamizole sodium 3x1 stop.

Sixth day of treatment (9 June 2021): patient had normal body temperature and dizziness (-). GCS E4V5M6, blood pressure 100/70 mmhg, pulse: 89x/min, body temperature 36.4°c axillar, SpO2 98% room air, serial blood results obtained haemoglobin 11, 3 g/dl, hematocrit 31%, platelets 32,000/µL, leukocytes 5,200 /L, erythrocytes 4,250,000 /L with lymph count 28%, mid 9%, granulocytes 63%. DHP Frimal therapy 40 mg 1x4 tab, injection of pantoprazole

sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondansetron HCl dihydrate 3 x 4 mg/2ml, drip paracetamol 3 x 1 gram

Seventh day of treatment (10 June 2021): patient had normal body temperature and dizziness (-) GCS E4V5M6, blood pressure 100/70 mmHg, pulse: 89x/min, body temperature 36.4°c axillar, SpO2: 98%, serial full blood count showed haemoglobin 11.6 g/dl, hematocrit 33.1%, platelets 63,000/µL, leukocytes 6,200 /L, erythrocytes 4.220,000 /L with a lymph count of 42%, mid 10%, granulocytes 48%. DHP Frimal therapy 40 mg 1x4tab, drip 3 x 1 gram, injection of pantoprazole sodium sesquihydrate (powder) 1 x 40 mg diluted in 5 cc water of injection, ondansetron HCl dihydrate 3 x 4 mg / 2ml.

Eighth day of treatment (11 June 2021) patient had normal body temperature and dizziness (-). GCS E4V5M6, blood pressure 100/70 mmHg, pulse: 89x/min, body temperature 36.4°c axillar, SpO2 98% room air, there are no complaints and an evaluation is carried out on the patient, the results of the patient have recovered so they are sent home as well as being educated for control to the internal medicine poly at Dian Husada Hospital. Evaluation inpatient treatment did everyday based on clinic presentation, blood smear (thick drop) until negative microscopy. Evaluation at 7^{th},14^{th},21^{st}, 28^{th} day [Kemenkes,2017].

DISCUSSION

The pyrogenic and anti-pyretic properties of numerous exogenous and endogenous chemicals are necessary for the initiation, symptoms, and modulation of the fever response. Exogenous (made outside the host) and endogenous (formed within the host) pyrogens are two different categories of pyrogens. Exogenous pyrogens are bacteria or their parts or by products, such as toxins. In reaction to exposure to external pyrogens, immune cells such neutrophils, macrophages, and lymphocytes as well as endothelial cells, astrocytes, and glial cells create endogenous pyrogens [Ogoina,2011].

Although the pathogenic mechanism of DHF has not yet been fully understood, it is generally agreed that the level of viremia correlates with the severity of the disease. A putative process called antibody-dependent enhancement (ADE) of infection may cause higher levels of viremia. A sudden, high-grade fever of about 40 C that typically lasts two to seven days happens during the febrile phase. Around 6% of instances of fever are saddleback or biphasic, especially in individuals with DHF and severe dengue. It is described as a fever that subsides for at least one day before the subsequent fever spike begins and lasts for at least another day [Soegijanto,2018].

Plasmodium falciparum /ovale /vivax undergoes an erythrocytic cycle that lasts 48–72 hours before releasing parasites into the circulation in the case of malaria. Every 48–72 hours, pyrogenic cytokines that are activated by released parasites cause fever cycles. However, unlike other species, Plasmodium falciparum has the ability to infect many red blood cells non selectively, and each infection has its own distinct erythrocytic parasite life cycle. Consequently, this parasite's fever is typically quotidian in nature (daily fevers spikes). Young and senescent erythrocytes are infected with Plasmodium vivax/ovale and Plasmodium malariae which cause them to rupture and release merozoites (pyrogens) after 72 and 96 hours, respectively. The cyclical character of fever in these malarial fevers is partially explained by these occurrences. After frequent exposure to pyrogens like LPS, cytokine release may be downregulated, which may cause fever to subside or become intermittent [Ogoina,2011].

When two agents are simultaneously infected, the symptoms of the sickness may overlap, making it difficult for the treating physician to make a diagnosis. Accurate clinical diagnosis and treatment are challenging without laboratory confirmation due to the closeness in symptoms and differential diagnoses of these infections, which frequently match those of dengue [Soegijanto,2018].

Viral infection commonly results in thrombocytopenia. In a region where malaria is not

widespread, dengue infection is frequently accompanied with an acute febrile illness with thrombocytopenia, particularly when the platelet count is less than 150.000 per microliter of blood. However, in the clinical course of dengue infection, the recovery phase is distinguished by the absence of fever, an increase in platelet count and return to normal, and reabsorption of fluid excess on days 6-7 following the beginning of fever. When fever and a low platelet count after day 7 continue, other diagnoses besides dengue illness should be taken into account [Nelda et al,2021]. According to a review by Lacerda et al. (2011), thrombocytopenia has been observed in 70 out of 90 patients with malaria falciparum, with prevalence rates ranging from 24 to 94%. The platelet count in both cases of malaria was typically between 25.000 and 50.000 [Nelda et al,2021].

The supply of fluids orally to prevent dehydration is the only difference between the therapy of the febrile phase of DHF and the treatment of DD, which is symptomatic (anti pyretic, etc) and supportive. The transition stage, or days 3-5 of the febrile phase when the temperature lowers, is the crucial moment. Patients need to be cautiously watched for any potential shock episodes based on Kemekes RI 2017 "Pedoman dan Pencegahan Demam Berdarah Dengue di Indonesia" meanwhile treatment for Plasmodium falciparum infection based on Kemenkes RI 2017 "Buku Saku Malaria", it can be based on weight or age.

In this situation, the prognostic is dubia ad bonam. Frequently grade dengue hemorrhagic fever since the patient received fluid therapy to prevent shock, which can lead to severe dengue fever [Suardamana, 2018]. This patient wasn't in severe malaria and already gotten anti malarial drug. Early diagnose can lead us to minimize complication such as cerebral malaria, respiratory failure, acute kidney injury, blackwater fever, hipoglycemia, icterus, severe anemia [Kemenkes,2017]. Native Papuan have already developed robust immune system to Malaria.

The adverse in this case we admitted that the diagnostic of Malaria delay because full blown of the Dengue, the most physician dan clinician in The Java always diagnosed with dengue fever based on incidence rate.

Medical's history is one of important thing for clinician. It can support the clinician to diagnose based on medical's history, physical examination, and laboratory to diagnose the patient. As we know fever is clinical sign of illness, it can be from bacterial, viral and parasite. This patient is Papuan native who lived in Mojokerto. His background support the clinician to check his microscopy of blood smears revealed Plasmodium falciparum after 3 days of DHF grade I treatment but there aren't significant changes for fever and thrombocytopenia. 3 days of treatment it means fever 8th day, if this is only DHF grade I, it may there are significant changes based on the phase of febrile in Dengue Hemoraghic fever and increasing of thrombocytopenia. After the patient got anti-malarial and fluid therapy there are significant changes from body temperature and thrombocyte. As a clinician, we have to understand the pattern of fever to guide us for diagnostic procedure.

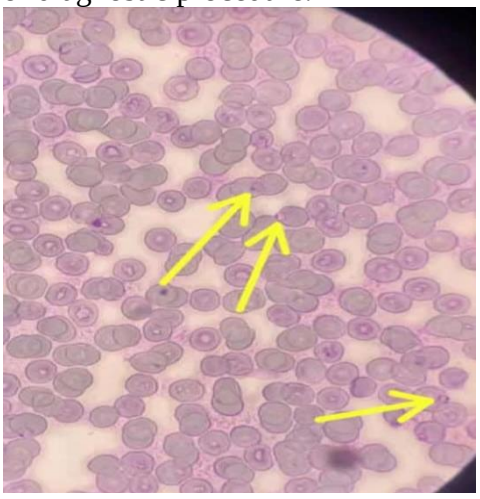

Figure 1. Microscopy of blood smears revealed Plasmodium falciparum, Mauer dot (+).
References: Private Supporting data, 2021

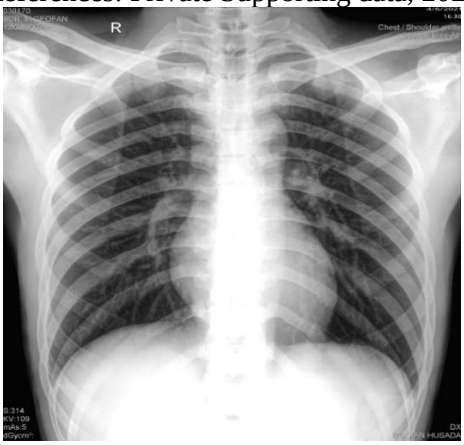

Figure 2. Thorax Photo of the patient (normal)
Refrences: Private supporting data, 2021

CONCLUSION

It has been reported 19 years old male with fever for 10 days, he is a Papuan native. After check the medical history, physical examination, laboratory test, radiology test, the patient diagnosed dengue haemoraghic fever grade I and malaria infected by Plasmodium falciparum and inpatient for 8 days at Dian Husada Hospital Mojokerto. The patient got the therapy for dengue haemorraghic fever grade I and malaria. During treatment, patient has significant improvement satisfied during the treatment because the doctor aware and care about his condition, The patient's condition has been steadily getting better, which is proof of this. Even though a few days of evaluation are needed to determine the main caused.

The strengths of this case report are having possess boundaries so it has detail information about specific patient, a clear scope, methodical and structured mindset. The limitation of this case report can't generalized. The lesson that we can got from this case, as a clinician we have to understand the pattern of fever to guide us for diagnostic procedure. Every aspect of the patient must be taken into consideration in order to make an accurate diagnosis and administer the proper treatment. The patient's condition can be prevented from getting worse with prompt and appropriate therapy. So, we as a clinician have to think "out of the box".

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