Chapter 9
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Study on Subjective Complaints of Malaria Related to Muscles and Joints

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ABSTRACT

Globally, malaria continues to be a major health problem and remains unsolved. Just like an iceberg phenomenon, WHO mentioned on their 2020 report that even though at the beginning of the third millennium there had been improvements, in the last three years (since 2017) there has actually been a plateau that seems to have slowed down efforts to eradicate global malaria. Poor access to medical service and proper treatment remains a problem in certain areas entangled in war and poverty. Other than that, persistent endemic areas with global and or regional travel of susceptible indidual to and from endemic areas increases the risk of morbidity and mortality.
Malaria causes a spectrum of signs and symptoms with classic *trias* consist of fever, anemia and splenomegali. Other sign that sometimes being complained by the patients is muscle and joint pain, a condition related to inflammation induced by the parasite. If that pain persistent during the course of the disease, it might probably be the untimely personalized complaint of rhabdomyolisis, a potentially fatal and lethal clinical condition that catagorized as complication of malaria or severe malaria. Without proper antimalaria treatment, the patient's condition may worsen and can be fatal.

Keywords: Blood protozoa; inflammation; fever; myalgia; arthralgia; endemic; imported malaria.

1. INTRODUCTION

The famous erythrocyte based parasite infection, a protozoan named malaria, is caused by insertion of *Plasmodium* spp parasite through the bite of a female mosquito *Anopheles* spp. [1,2]. So far, a total of 5 species of Plasmodium *spp*., have been known to infect humans, viz as stated by the name of the disease malaria *vivax,* malaria *falciparum*, malaria *malariae*, malaria *ovale*, and malaria *knowlesi* [3,4]. The region in the world which malaria disease is still most prevalent are some countries located in Africa, especially Sub Saharan and Asia, especially its southeast part including Indonesia [5,6]. Its persistent global number on morbidity and even mortality rate, especialy in the endemic area, still very high; according to WHO 2020 report, estimated 229 million malaria cases in 2019 in 87 malaria endemic countries, declining from 238 million in 2000. At the Global technical strategy for malaria 2016–2030 (GTS) baseline of 2015, there were 218 million estimated malaria cases [7].

Until nowadays, children and pregnant women are considered to be the most vulnerable group, but in addition to them, other vulnerable group also member of the military army and also travelers visiting to endemic 'high transmission' region [8,9]. This is known as imported malaria cases, especially when the clinical manifestations of malaria then the symptom become apparent clinically where they were back to their former hometown that usually is a malaria free zone [9-12]. Eventhough all doctors must also be aware that post travelling fever does not always caused by malaria [11].

Malaria transmission initially begins when a female *Anopheles* mosquito that contain sporozoites of malaria bites a susceptible person [1]. Through their proboscis, it injecting a number of *sporozoites*, successively through the host's skin and supporting tissue and carried away in the flow of the

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microvasculature bloodstream, then get stuck in the host's hepatocyte and stay there for sometime in resting condition or so called *hypnozoite*. The number of *sporozoites* grows by asexual multiplication *intra*-hepatocyte within the duration of 7 to 10 days, initially causing no obvious manifestation. But then after sometime, the merozoites launch into the erythrocyte stage of its evolution, by way of invading erythrocytes and multiply again *intra*-cellularly until the cells burst, this already multiply parasite invades more erythrocyte and causing repeated cycle of erythrocyte destruction and generate *intermittent* fever which occurs every time a parasite enters the bloodstream and occupy vulnerable erythrocyte [13,14].

Basically, malaria patients usually complaint some subjective condition, including high intermittent fever, lethargy, cefalgia, nausea/vomiting and arthralgia or myalgia, *etc*. [15]. To some extent, specific muscle related complaint is not always eminent, but sometime to certain individuals for certain individuals these complaints are felt and sometime being complained about [15] such complaints should not be ignored by doctors [15]. Pain is currently a mandatory evaluation criterion for patient's evaluation conducted by doctors. Pain is a prevailing symptom during the whole course of the disease, as well as how doctors manage to overcome the pain is compulsory for the patient. The painful experience and its coping and how medical staffs effort to help relieves the patient from the pain [15].

Malaria accompanied by persistent muscle and or joint complaints, the doctor should consider the possibility of rhabdomyolysis occurring in susceptible individuals [16]. The patient may be entering the earliest stage of more critical phase of malaria *falciparum*. Although this condition is very dubious, a context of rhabdomyolysis accompanied with with skeletal muscle necrosis and myoglobinuria, especially in the imunologically naive individual [14,15]. it sometime preceed the condition of acute tubular necrosis that culminates in renal failure, a very lethal impediment of untreated malaria *falciparum* [16]. this shows us that making correct diagnosis as early as possible and starting adequate anti-malarial treatment is very important in order to prevent malaria complication.

Here we present a summary of case report that already published previously [14]. The patient was a 21 years old female med student in Jakarta, Indonesia who just currently returned from her hometown, a small city named Timika, located in Papua, Indonesia. Geographically, this place is the easternmost region of Indonesia. She returned to Jakarta in the middle of July 2020. One week before she went to a doctor (July 28th 2020), she already felt ill and complaint of having high fever with chills, cephalgia with the persistent feeling of muscular deep pain. The fever felt intermittent, recurs every 48 hours or even less. When interviewed more deeply, actually the time gap between the occurence of fever and drops back to normal irregular, showing no lucid distinct periodicity. Her body temperature can reach 38.5^{0}C when the fever peaks accompanying with shivering due to high body temperature and massive *diaphoresis*, and this condition then gradually improves as the body temperature decreases and settle to normal and she felt finer.

As an additional complaint apart from fever, the most notable subjective complaint is continous muscle pain, which she conveyed as "*like she was beaten all over her body, and the pain was felt to the joints and bones*". This muscle related complaint being felt since the initial episodes of fever, and it did not resolved, even when the temperature back to normal. During the rise of the temperature she also had headache. Apart from these two additional complaints, the patient did not have any other complaints.

For initial symptomatic medication, she took over the counter medicine, Paracetamol 500mg, but unfortunately it did not provide satisfactory results. Except for antipyretics, the patient did not take any other drugs because she felt that she still could tolerated the complaints.

From the past medical history point of view, the patient already had chronicle of malaria since she was very little. As long as she can remember, the type of malaria she is suffering from is malaria *tropica*. As far as she can remember, she started experiencing her first illness when she was in elementary school many years ago. She was born in Timika and remained there until she finished senior high school, then she continued her higher education to a private faculty of medicine located in Jakarta, Indonesia. During her medical education (she was 3rd year medical student when this case

being presented) this muscle related complaint showed up repetitively, especially when she had unexplained hyperthermia. Beside complaining about hyperthermia and myalgia-arthralgia, actually she does not complain about any problems in other systems (*e.g* no gastro-intestinal derangement, no respiratory symptoms, *etc*).

During routine physical examination, her *status generalis* is as follows: during inspection, she seen unwell, moderately ill. Her vital sign as follows: temperature 38.5^0C (hyperthermia), blood pressure 110/80 mmHg, heart rate 84×/minute, and respiratory rate 20×/minute. The patient's height and weight: 158cm/63kg. Using BMI calculator, she is a little bit overweight (BMI = 25.2 kg/m2) .

Systematic review on the patient's major body system (respiratory, GI, neurology, *etc*) showed that actually all within normal range, except for the *musculoskeletal.* During close examination on her upper and lower extremity muscle *status localis* the result is as follows: the muscle strength 5555 in all of her extremity, the range of movement regarding those extremities are good and unlimited, but unfortunately there is muscle pain/*myalgia* (+). During the examination, the examiner can also notice about joints pain/*arthralgia* (+), especially in the upper extremity. Except for these two prominent complaint: the muscles and joints complaint, all other systems, from head to toe, were within normal limits and there were no clear signs of anemia (*e.g.*, pale looking or *pallorness* which usually found seen over lower conjuctiva *pars* palpebra, or angular cheilitis or *koilonichia*).

After carrying out a thorough physical examination, the doctor now want to conduct a supporting examination which is relevant to the *anamnesis* and the result of physical examination. From the *anamnesis* interview and and the results of her physical examination which help guide the doctor to suspect that the patient is experiencing a recurrence of malaria attack. The doctor asked the patient to have her blood being taken and malaria blood examination immediately created and subsequently being examined thoroughly in the laboratory of Parasitology, dept. of Parasitology, faculty of Medicine, Universitas Kristen Indonesia Jakarta, Indonesia.

The initial blood sampling withdrawn on July 28th 2020 when the patient consults the doctor for the first time, and at this time patient has suffer from fever. the second consecutive was withdrawn on July 29th 2020 and again, at that time the patient had a high grade fever. The third on August the 4th 2020. Thin and thick blood smear directly made from the blood taken and were smeared with giemsa stain. From the first and the second blood sampling, parasitologist can determine imature trophozoite of *Plasmodium falciparum* and the diagnosis of malaria *falciparum* (ring form/immature trophozoite) confirmed Parasitologically.

Actually, by the time the doctor found out that the patient is positive for malaria *falciparum*, the patient was immediately ordered to be admitted to the university hospital, so that appropriate anti-malarial drugs can be given *cito*. The main reasons for the doctor asked the patient being hospitalized was because in Jakarta as non-malarial endemic areas of Indonesia, anti-malaria drugs only accessible via provincial health office, so any positive malaria patient should be reported directly by the hospital, and only then the antimalarial therapy can be received by the hospital and then administered to the patient. As the government policy, malaria medication can only be given for hospitalized patient. But unfortunately, the patient refused to be hospitalized.

Beside refusal of hospitalization, patient also refuses to have a routine blood examination (Hemoglobin, Hematocrit, Thrombocyte, Leukocyte, diff count) and also routine urinalysis due to the financial limitation. The doctor already explain to the patient about the importance of those testings, but still she deny that.

The patient refuses to be admitted to the hospital and she was prefer to be outpatient. The reason for the refusal is because according to the patient, she was right in the middle of her final examination; she did not want to risk failing her final exam, if she has to be hospitalized for several days, then she may not be able to attend some class/lecture and that might prevent her to meet the attendance quota. and despite the patient's clinical circumstances, the patient still convince the doctor that she can still tolerate the condition and promises that if things get out of hand, she will be admitted to the hospital immediately. Due to the doctor's direction, the patient promised to have her blood drawn to

be re-checked exactly just as the doctor instruction. This repetitive blood smear checking intended for carefully assess the patient's response to antimalarial therapy. According to the patient's admission, she said that it had become a habbit for her to always bring typical anti-malaria drug wherever she goes (which she used to consume since she was still living in Papua); it seems this is a common practice for the patient because she already anguish malaria since she was still in elementary school.

According to the doctor's instruction, the patient start taking her medicine which is combo therapy of Dihydroartemisinin 40 mg and Piperaquine Phosphate 320mg (D-ARTEPP®, Guilin Pharmaceutical Co., Ltd, China Batch no. SQ190801, mfg. date 05/08/2019, exp. Date 04/08/2021). The amount of dosage is based on the calculation of the patient's body weight for 3 consecutive days consumption (D0, D1 and D2) with maximal adjusted dose recommended for her as many as 3 tablets daily single dose for patients weighing ≥ 41 kg, just as the manufacturer's instruction. Other Name for this preparat namely DHP. For supporting DHP, treatment with dihydroartemisinin piperaquine also added, a single dose of Primaquine (PQ) tablets of 0.75 mg/kg BW was provided on Day-3 using 15 mg base PQ tablets (local Indonesian product by PT Phapros, Tbk. Semarang, Indonesia). Additional generic Paracetamol 500mg given *pro renata*.

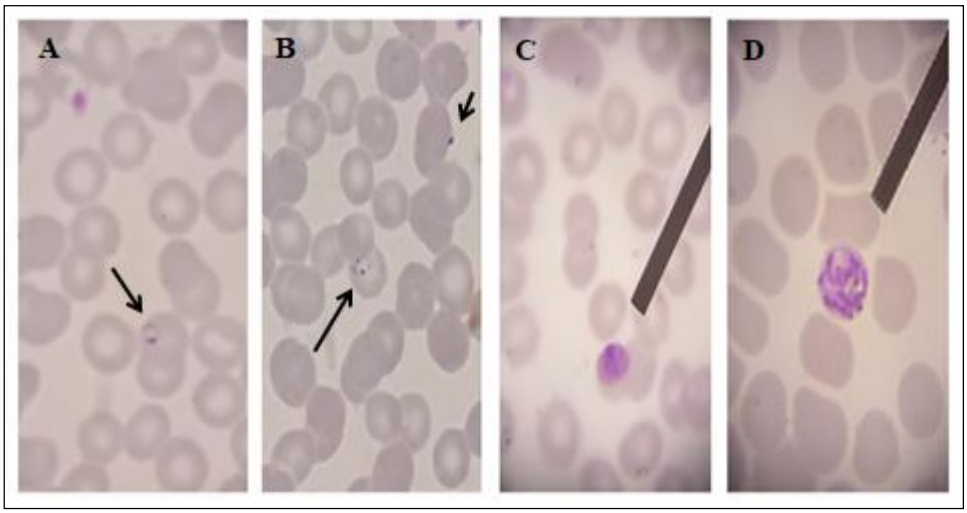

Fig. 1. Microscopic photographs of 100× objective amplification the thin blood film of *P. falciparum* infection. (A). The image of ring shape aspect of immature trophozoite *P. falciparum,* (B) impression of *accole* with double dots, still the shape of immature tropozhoite *P. falciparum*, (C) the appearance of developing gametocyte stage of *P. falciparum*, (D) mature schizont stage of *P. falciparum*. The slide (A) and (B) obtained from the 1st blood sample (obtained July 28th 2020). Slide (C) and (D) came from the 2nd blood sample (collected July 29th 2020). All slide belongs to our Laboratory of Parasitology.

The patient claim to experience a significant reduction in symptom intensity (reduced muscles and joints pain) after several hours she has taking the first medication (Day 1) of combo therapy DHP, her fever also started to get better (although she still didn't feel completely well). On Day 2, after several hours having the second regimen, all of her complain, including fever, pain, headache and chills diminished totally, according to her recognition. She continues to have the DHP until the third day (Day 3) where she said that she already feel healthy and recover. Analgesics and antipyretics medication (Paracetamol 500 mg) taken PO 3 times only in the first day, but Paracetamol adminisitered alone prior to anti-malarial therapy could not reduce the muscle or joints pain at all.

After completing taking the medication, the patient's blood is again drawn for examination. Parasitologically, examination on the third blood sampling can no longer find malaria parasites at any stage. Maybe it is already cleared away totally or in the sub microscopic condition. Parasitologist from our Department of Parasitology confirmed the result of the third examination was malaria negative. She already cured and revert after having and completing antimalarial medication exactly just as the doctor's instruction. The following paragraphs will discuss this condition more closely.

2. WHAT CAUSES THE MUSCULAR PAIN?

Among the several complications, the effects of malaria seem to target the skeletal muscle system, leading to symptoms, such as muscle aches, muscle contractures, muscle fatigue, muscle pain, and muscle weakness. Malaria cause also parasitic based clotting in small arteries/vessels, *e.g* coronary artery, that might caused occlusion [16-19]. It seems that there is a prominent role of cytoadherence to epithelial cells of the vasculature wall in disease pathogenesis and it is accompanied by sequestration of the infected erythrocyte [20].

Inflammatory cytokines play a crucial role in human immune responses to malarial disease [21,22]. Cytokines such as TNF-α, which is known to be increased in the plasma of malaria patients also contributes to disease severity [22]. Systematically, TNF-α and other cytokines up regulate adhesion molecules (e.g. ICAM-1) on vascular endothelium and thus modulate cytoadhrence, a common condition in infection, e.g malaria and dengue [18]. Excess production of TNF-α is likely to be involved in the appearance of such symptoms as fever and headache associated with *P. falciparum* infection only [20-23].

Past study revealed that there was Biochemical pathway of proof that malaria related skeletal muscle injury is ordinary, but the condition of obvious rhabdomyolysis appears to be sparse. Study conducted by Davis et al. [24] whose purpose was to find out the correlation between myoglobin levels vs the enzyme creatine kinase in serum. Beside that, Davis also observed the histology of the muscle and renal function in *P. falciparum* infections. Davis and his colleagues carefully observed 3 groups: the first group consist of 13 individuals who suffer from uncomplicated malaria, another group consist of 13 people with serious non-cerebral malaria, and the last group consist of 10 people with cerebral malaria. From each member of the group, specimen from muscle biopsy was collected for extensive observation under light microscopy and also electron microscopy. Result of examination is as follows: mean serum creatine kinase level obstained from the patient's blood were increased but somehow showed indistinguishable trends for all members of the three groups. The mean serum myoglobin concentration obtained from the patient's blood showed its highest in patient suffer from cerebral malaria, and then followed by in uncomplicated malaria and with the last serious non-cerebral malaria; and it was all corresponded with the mean serum creatinine concentration. Parasitologically, the amount or density of intravascular parasites, percentage of mature forms, and the reduced level of glycogen were notably highest in biopsy specimens that come from patients with cerebral malaria. Unfortunately, the appearance of myonecrosis was not detected. This group of researchers concluded that muscle, as body entity, apparently to be a crucial loci for the blood protozoan *P. falciparum* causing infected erythrocyte underwent sequestration, which in sequence of disease course would contribute to the worsening of metabolic and renal complications (multi-organ failure) [24].

Actually, based on literature study conducted recently, cases of the involvement of muscle and joints related malaria was under-reported. In Theory, while active malaria infection took place, microcirculatory derangement occured [24-26]. That condition characterized by the rise of blood viscosity, hindrance of multiple capillaries due to adhered infected erythrocyte to the cappilary wall, agglutinated and ruptured part of infected erythrocytes and, sometimes further more, the condition of intravascular coagulation also established in the small vessels [27-29].

This series of successive events lead to a certain changes to all organs that rely primarily on microvasculature for blood supply, including skeletal muscle. If this microvasculature blockade persist over time then necrosis occurs followed with myoglobinuria [17,25]. Any form of muscle damage—and by extension any entity that causes muscle damage—can initiate rhabdomyolysis. One of the most important treatment goals when rhabdomyolysis is suspected is avoiding acute kidney injury [23,26,28].

The liberation of myoglobin proteins from ruptured muscle cells (myocytes) is important to the sophisticated formation of rhabdomyolisis in certain muscles of the vulnerable patient; it is actually induced by the *Plasmodium*; and it is directly due to the formation and involvement of the immune complex [26]. The diagnosis is enforced based on the increased serum level of muscle enzymes named Creatine Phosphokinase (CPK) and the result of muscle enzyme examination should use in combination with previous clinical symptoms like myalgias [24].

Additional sign consist of sequestration of erythrocyte, decreased muscle mass due to the lysis of important contractile proteins inside the muscle cells. These are are some biomarkers which have the potency as predictor of damage situation of the skeletal and or cardiac muscles,. The result of the study conducted by Marrelli et al. [17] found out that underlying biomolecular route of malaria-induced muscle loss and damage, which focusing on some important key molecules, *e.g* genes and lipids, and its association that leads to muscle breakdown. These biomarkers might be useful clue for doctors in order to prevent long-term complications in severe malaria patient and determining the effectiveness of management and interventions which designed to preserve cardiac and skeletal muscles from irreversible malaria-induced damage [25].

With early and immediate appropirate antimalarial treatment, improvement of clinical condition and loss of subjective complaint soon can be occur. The patient's usually responded well to therapy given, and more severe complication can be prevented. Active controlling of the presence of antimalarial drug in the community is one way to prevent drug resistance.

3. CONCLUSION

This review once again presents the growing concern of muscle related manifestations related to P. *falciparum* infection. To the best of our knowledge, this might probably the earliest subjective warning to rhabdomyolisis occurring as one of the complication of severe malaria *falciparum*.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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