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Plasmodium falciparum found in the bone marrow of a child in Manado City, East Indonesia: A case report

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ABSTRACT

In Indonesia, there are at least 1.3 million cases of malaria each year and *Plasmodium falciparum* appears to be the most common *Plasmodium*. The finding of *Plasmodium* is important for the diagnosis and management of malaria. This is a case of a 4-year-and-9-month-old male who lived in Manado, East Indonesia. He presented with a prolonged fever, was pale in appearance, and was easily fatigued over the last 3 weeks. Hepatosplenomegaly was found on the initial physical examination. Preliminary laboratory findings found pancytopenia and severe anemia. Before he was referred to our hospital, at the primary health center, the initial work-up was negative for *Plasmodium* with the serial Rapid Diagnostic Test and microscopic peripheral blood smears. Since there were signs and symptoms mimicking malignancy, the patient was referred to our hospital for further malignancy work-up. A bone marrow puncture was done and we incidentally found *Plasmodium falciparum* in a microscopic bone marrow smear. This was a rare case because *Plasmodium* was not initially found in the preliminary work-up (Rapid Diagnostic Test and Microscopic) and qPCR is not a routine work-up for *Plasmodium* suspected patients. Although the mortality rate of malaria is high, this condition can be treated if the clinician was aware of the clinical signs and symptoms in the early onset and prompt medical treatment is administered. In a severe case with an unclear etiology of fever and with signs and symptoms mimicking malignancy, qPCR is recommended. However, a bone marrow puncture can also be considered to exclude the possibility of a malaria infection.

1. Introduction

Each year, of Indonesia's 230 million people, there are at least 1.3 million cases of malaria caused by all five known species of human *Plasmodium*. The five species that cause diseases in humans are: *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. *P. falciparum* appears to be the most common *Plasmodium* species in Indonesia [1,2].

2. Case presentation

A 4-year-and-9-month-old male who lived in Manado, East Indonesia, visited his local hospital for primary care due to a fever. His medical systemic history was unremarkable and he was in overall good health prior to this visit. A routine

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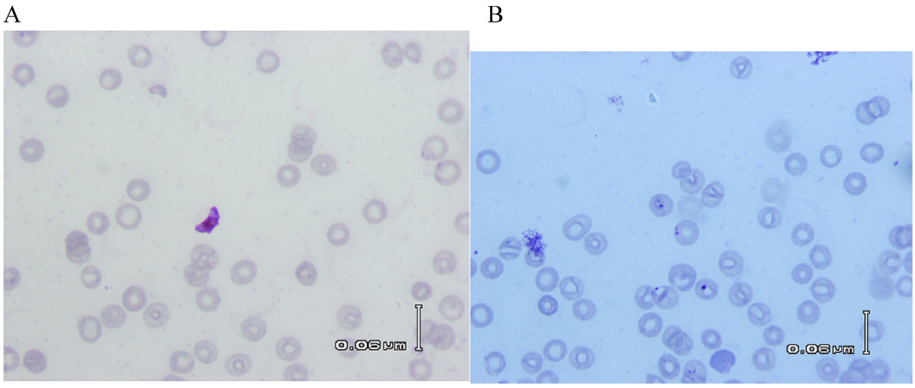

Figure 1. *P. falciparum* gametocyte, sexual stage (A) and trophozoite, asexual stage (B) in bone marrow with Giemsa stain.

laboratory work-up was performed including serial Rapid Diagnostic Test (RDT) and microscopic blood smear. Symptomatic medications and antibiotics were given, but the patient still persisted with a fever that lasted for more than 3 weeks. He was then referred to our hospital for further work-up. The fever was described as a high grade fever lasting for more than 3 weeks. The patient also complained of fatiguing easily. Hepato-splenomegaly was found on the physical examination as the liver was 2 cm below arcus costal and the spleen was at schüffner 2. Initial laboratory findings revealed pancytopenia, hemoglobin 7.2 g/dL, hematocrit 20.4%, leukocyte 3.8×10^3/uL, thrombocyte 53×10^3/μL, erythrocytes 2.57×10^6/μL, MCV 79.4 fL, MCH 28 pg, and MCHC 35.3 g/dL. A screening to rule out malaria was performed which yielded a negative result. Since there were signs and symptoms mimicking malignancy, a blood malignancy work-up was performed. The patient was then admitted into the Pediatric Hemato-Oncology Division of Professor Dr. R.D. Kandou Manado General Hospital. The malignancy work-up proceeded with a bone marrow puncture which surprisingly revealed *P. falciparum* in the bone marrow smear, both in the gametocyte and trophozoite phase. This was a rare case because no *Plasmodium* was found in the initial work-up, particularly in the peripheral blood smear. Hence, the patient was referred to the Pediatric Infection and Tropical Division and treated using artemisinin-based combination therapy, fixed dose combination with 2.5 mg/kg body weight (bw) per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 d and a single dose of 0.25 mg/kg bw primaquine. After completing artemisinin-based combination therapy and primaquine, the clinical manifestation subsided. Daily microscopic screenings were negative for *Plasmodium* every day while ongoing therapy and in the 3 consecutive days after therapy. The patient was discharged and cleared from all parasites. He had regular out-patient follow-up visits at the 4th, 7th, 14th, 21st and 28th day after discharged and in each follow up with negative microscopic finding. The anemia and hepato-splenomegaly was fully resolved after the 28th day after discharge.

3. Discussion

Our case presented with signs and symptoms mimicking malignancy. The child had a prolonged fever, hepato-splenomegaly, pancytopenia, fatiguing easily, and no other signs and symptoms were found. The patient underwent extensive work-up to exclude infectious diseases including malaria. In Indonesia, based on our guidelines, patients presenting with a fever or a history of a fever in last 48 h in endemic areas are malaria suspects and must be worked-up with RDT and microscopic evaluation every 24–48 h to exclude malaria as an etiology. Additionally, patients with a fever or history of a fever in last 7 d and have traveled to an endemic area or were in contact with a person who traveled there, must also be worked-up in the same way [3]. In our case, there were no positive findings during the peripheral blood examination according to our guidelines. The patient then underwent a baseline malignancy work-up. Surprisingly *P. falciparum* was found in the bone marrow smear both in the gametocyte and trophozoite phase (Figure 1). The demonstration of *Plasmodium* in peripheral blood smears is diagnostic of malaria, however, when repeated thin and thick smears fail to demonstrate *Plasmodium*, other diagnostic test may become necessary.

Cuartas *et al.* presented two similar cases in the Southern Medical Journal in 1972, although repeated examination of peripheral blood smears failed to reveal parasites, bone marrow aspiration confirmed the presence of *P. falciparum*. This report suggests that bone marrow aspiration is of value for the diagnosis of malaria [4]. Knowledge regarding parasite stages and their typical locations has progressed immensely since this report. In a study on parasite morphology of a small group of Gambian children, it was noted that they found asexual and mature sexual parasites in both the bone marrow and peripheral blood, in contrast, however, the prevalence and density of immature gametocytes was markedly greater in the bone marrow [5]. This case and its atypical presentation, testing the more concentrated blood found in bone marrow in similar presenting patients, especially ones with pancytopenia, would be helpful to determine the etiology. Later on, in the study by Aguilar and his colleagues, children with severe anemia were older and had a higher prevalence of sexual and asexual *P. falciparum* infection detected by microscopy in the bone marrow, as well as in peripheral blood, compared with non-severely anemic children. In *P. falciparum*-infected anemic children, immature gametocytes are more prevalent and abundant in bone marrow than in peripheral blood [6].

RDT for malaria works by detecting a specific protein in the blood of a person infected by malaria. RDTs are designed to target a protein called histidine rich protein 2 (HRP2). The blood test is typically administered at the point of care through a finger-prick and results are available within 15–30 min. RDT is routinely used as one of the diagnostic tools of malaria in Indonesia. However, Berhane *et al.* reported that out of the 50 *P. falciparum* infected blood specimens, only 10 were confirmed positive with all the lots of *P. falciparum* histidine rich protein 2

(*Pf*HRP2) detecting RDTs making the false negative rate 80% (41/51). The false negative result for RDT targeting *Pf*HRP2 antigen ranged from 65% (11/17) in Gash Barka region to 100% (12/12) in Northern Red Sea Region [7]. Our case also revealed that the negative results of serial RDT was possibly a false negative result.

In a systematic review and meta-analysis by Okell LC *et al*., they discuss how microscopy can miss a substantial portion of *P. falciparum* infections in surveys of endemic populations, especially in areas with a low transmission of infection. They also demonstrate that submicroscopic parasitemia is common in settings where transmission is low, indicating that those with little previous exposure are able to control parasite densities. This may be the result of clone specific immunity or partially successful treatment and could be important for maintaining immune responses [8]. It is not yet feasible to use PCR routinely also in our country, because of the resources required, however, rapid, simplified PCR methods are likely to become widely available in the near future and should be considered in studies where the true reservoir of infection needs to be estimated accurately.

In a study by Mirdha BR and his colleagues [9] they examined bone marrow for the diagnosis of malaria in patients with a persistent, prolonged fever. All marrow examinations of patients were examined microscopically and resulted in a diagnosis of malaria in 6.6% of the total patients studied. No cases of bacterial, mycobacterial, or fungal infections were diagnosed. The diagnostic efficacy of bone marrow for evidence of malaria was very useful in febrile individuals for whom the diagnosis was otherwise unknown.

The consideration to proceed in more invasive screening tests such as bone marrow puncture can be considered to exclude the possibility of a malaria infection in patients with a fever of unknown origin and other signs and symptoms mimicking malignancy. These other signs and symptoms include hepatosplenomegaly and severe anemia with a negative result on serial RDT, microscopic evaluations, qPCR and other possibility of bacterial, mycobacterial or fungal infection in peripheral blood.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] World Health Organization. *World malaria report 2015*. Geneva: World Health Organization; 2015. [Online] Available from: http://www.who.int/malaria/publications/country-profiles/profile_idn_en.pdf [Accessed on 2nd August, 2017]

[2] Elyazar IRF, Hay SI, Baird JK. Malaria distribution, prevalence, drug resistance and control in Indonesia. *Adv Parasitol* 2011; **74**: 41-175.

[3] Indonesian Ministry of Health. *Pocket book for management of malaria case*. Jakarta: Indonesian Ministry of Health; 2015, p. 23.

[4] Cuartas MF, Rothernberg MJ, Fecci MC, Gutterman J. Diagnosis of malaria by bone marrow aspiration. *South Med J* 1972; **65**(5): 523-546.

[5] Smalley ME, Abdalla S, Brown J. The distribution of *Plasmodium falciparum* in the peripheral blood and bone marrow of Gambian children. *Trans R Soc Trop Med Hyg* 1981; **75**(1): 103-105.

[6] Aguilar R, Magallon-Tejada A, Achtman AH, Moraleda C, Joice R, Cisteró P, et al. Molecular evidence for the localization of *Plasmodium falciparum* immature gametocytes in bone marrow. *Blood* 2014; **123**(7): 959-966.

[7] Berhane A, Russom M, Bahta I, Hagos F, Ghirmai M, Uqubay A. Rapid diagnostic tests failing to detect *Plasmodium falciparum* infections in Eritrea: an investigation of reported false negative RDT results. *Malar J* 2017; **16**(1): 105.

[8] Okell LC, Ghani AC, Lyons E, Drakeley CJ. Submicroscopic infection in *Plasmodium falciparum*-endemic populations: a systematic review and meta-analysis. *JID* 2009; **200**(10): 1509-1517.

[9] Mirdha BR, Samantray JC, Mishra B, Xess I. Bone-marrow examination for identifying malaria in fever of unknown origin. *J Assoc Physicians India* 1999; **47**(2): 177-179.