Falciparum malaria infection with invasive pulmonary aspergillosis in immunocompetent host – case report

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Abstract. Invasive pulmonary aspergillosis is an extraordinary rare in the immunocompetent host. Falciparum malaria contributes to high morbidity and mortality of malaria infection cases in the world. The impairments of both humoral and cellular immunity could be the reason of invasive pulmonary aspergillosis in falciparum malaria infection. Forty-nine years old patient came with fever, jaundice, pain in the right abdomen, after visiting a remote area in Africa about one month before admission. Blood films and rapid test were positive for Plasmodium falciparum. After malaria therapy in five days, consciousness was altered into somnolence and intubated with respiratory deterioration. Invasive pulmonary aspergillosis after falciparum malaria infection is life-threatening. There should be awareness of physicians of invasive pulmonary aspergillosis in falciparum malaria infection.

1. Introduction
Malaria is an important cause of morbidity and mortality worldwide. In 2015, it caused approximately 429,000 deaths in the world. Of five Plasmodium species known to cause malaria in humans; Plasmodium falciparum is lethal and responsible for severe disease. Transmission is initiated by anopheline mosquitoes injection that containing sporozoites into the skin during a blood meal. Pathology of malaria infection and associated clinical manifestations are predominantly attributed to asexual erythrocytic stages. Excessive and persistent inflammation during P. falciparum infections contributes to severe pathology and complications such as cerebral malaria and severe malaria. It can interfere immune response for other pathogens in infected persons and could be the key to opportunistic infection.

In immunocompromised patients, such as malignancies and high dose corticosteroid receiving, aspergillosis is a major cause of morbidity and mortality. It is caused by Aspergillus molds that easily found in the environment. There are two hundred species of Aspergillus, but only ten percent are pathogenic to humans. The most commonly isolated species is A. fumigatus, approximately ninety percent of systemic infection, followed by A. flavus, A. niger, and A. terreus. The transmission is via spores that inhaled through respiratory tract.

Human airways are under constant exposure to Aspergillus sp. with daily inhalation of several hundred spores. These asexual spinous conidia are usually harmless and readily cleared by the immunocompetent host, through defense mechanisms and systems involving macrophages, neutrophils, and antimicrobial peptides. However, in immunocompromised states, invasive pulmonary
aspergillosis can occur resulting in invasive, life-threatening septicaemia. Invasive pulmonary aspergillosis is the most common cases of invasive aspergillosis. Nevertheless, there are only some cases of aspergillosis with malaria. This is one of the limited cases of aspergillosis with falciparum malaria infection.

2. Case report
A 49-year-old man was admitted to one of the private hospitals in Tangerang, Banten, Indonesia. A week before admission, he was treated in Jeddah, Saudi Arabia and suspected of acute viral hepatitis and dyspepsia. The patient was a technician in a private airplane and had flown to a remote area in Africa about one month before admitted to hospital in Jeddah. He had neither previous medical history nor taken malaria prophylaxis. The patient was moved to Indonesia due to family demand.

On admission, he was sleepy but fully oriented, febrile, with yellowish skin, nausea, vomiting, and pain in the upper right abdomen. There were rhonchi in the lower right thorax. Blood pressure was 116/68mmHg, pulse rate 130/min, respiratory rate 24/min, and temperature 38.8°C. Initial laboratory result were Hb 9.6g/dl, WBC 11.1x10^3 cells/dl with 70% neutrophils, Platelet 64x10^3 cells/dl, hematocrit 27%, total bilirubin 19.1mg/dl, direct bilirubin 15.7mg/dl, GOT 80 U/L, GPT 158 U/L. Chest x-ray was bronchitis. Abdomen ultrasound was suspected of chronic cholecystitis and right basal pleural effusion. Serology for hepatitis A, B, C, and HIV was negative. Rapid test for malaria was positive, and blood films showed Plasmodium falciparum with parasitemia 12,760 parasites/µL. Sputum culture was Pseudomonas aeruginosa that is sensitive to levofloxacin.

![Figure 1](image-url) Figure 1. Chest x-ray of the patient after intubated with respiratory deteriorated.

Treatment for malaria was initiated with artesunate intravenous injection 2.4mg/kgBW and given three times in first 24 hours (0, 12, 24), continued once daily on the second day. On the third day, artesunate was switched with DHP 4 tablets/day orally for three days and primaquine one tablet for one day. Parasitemia was decreased to 1200 parasites/µL within the third day and undetectable on the sixth day.

On the seventh day, patient consciousness altered into somnolence and patient was delivered to ICU and intubated with respiration deteriorated. Chest x-ray was bronchopneumonia duplex with infiltrating that spread over both lungs. (Figure 1)

The blood sample was sent to Parasitology Laboratory, Faculty of Medicine, Universitas Indonesia, Jakarta, for advanced diagnostic. Blood film and PCR was negative for Plasmodium sp., but galactomannan serum detection was 1.24, with cut off 0.5. The patient was suspected of invasive
pulmonary aspergillosis. Fungi culture was not performed yet. Therapy with voriconazole was started immediately. The patient was also covered with a broad-spectrum antibiotic.

On the eight days of artificial ventilation, consciousness altered into a stupor with high fever and viscous mucus. Patient condition kept worsening on the next day with cardiopulmonary arrest. Resuscitation was not successful to save the patient.

3. Discussion
Fungal infection is uncommon during severe malaria because invasive aspergillosis is extraordinarily rare in immunocompetent patients. Invasive aspergillosis usually occurs in immunosuppression patients due to malignancies with prolonged neutropenia, transplantation, immunosuppressive agents, or AIDS, and has very poor prognosis.7

Falciparum malaria is associated with impairments of both humoral and cell-mediated immunity. Humoral immunity is impaired by reduction of specific antibodies, while cell-mediated immunity by inhibition of dendritic cells, T cell and macrophage function.3 6 11 It has been reported that splenic macrophage phagocytosis was decreased during acute malaria due to massive phagocytosis of erythrocytes. Hemozoin, hemoglobin degradation by parasites, plays a major role in immunity impairment. Macrophages, as well as circulating monocytes and leucocytes, are loaded with hemozoin and consequently lose their ability to phagocytose and kill microbes, including fungi. Inhibition of key enzyme involved in an oxidative burst by hemozoin contributes to the disruption of macrophage function. Phagocytes fail to generate reactive antimicrobial oxidants that impair oxidative burst. Abnormalities in antigen presentation may contribute to impairment of immune function. As macrophages function is disrupted by hemozoin, the availability of macrophages at the site of infection is questionable too.12 Since malaria infection, macrophage concentrates predominantly in the blood, including spleen, liver and bone marrow, but not the lung.

Pulmonary macrophages are the major line of defense for Aspergillus sp., as they are eliminating spores from the lung.7 Impairment of this function could be playing a role for invasive pulmonary aspergillosis in malaria falciparum infection. Studies from Deroost, et al. showed that hemozoin is associated with lung weight and alveolar edema, that it induces inflammation in the lungs. Malaria-associated acute respiratory distress syndrome (MA-ARDS) is a deadly complication of malaria. MA-ARDS is attributable to P. falciparum as a single or accompanied by additional complication, leading to multiorgan dysfunction. In this report, the patient also had respiratory symptoms and signs on admission, which might be associated with MA-ARDS.12

Unfortunately, fungi culture was not available in the hospital. Galactomannan was examined due to suspicious of supervisor in Parasitology Department, Medicine Faculty of Universitas Indonesia after showing an x-ray of the patient. Diagnosis of invasive aspergillosis remains difficult because of lacking conventional culture methods. Therefore, nonculture-based method, are important adjunctive tools. This assay has been included as microbiological criteria in the definitions of invasive fungal infections by the European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group. Diagnosis of Aspergillus-associated lung disease is based on a constellation of clinical observation, radiological findings, and immunological testing.7 Almost of invasive pulmonary aspergillosis cases were fatal. Nevertheless, early recognition and immediate treatment could save patients, but the diagnostic method that applicable and available is needed.

Only some cases of aspergillosis with malaria falciparum had been reported. Since lack of access to appropriate diagnostic tools could be the reason for under reported in development or under developed countries. This case should be a consideration for invasive pulmonary aspergillosis in malaria with respiratory deterioration.

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