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Malaria-associated pulmonary edema

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Abstract:
Malaria-associated (MA) noncardiogenic pulmonary edema, or its more severe forms, i.e. acute lung injury and acute respiratory distress syndrome due to Plasmodium malariae, is a potentially fatal complication of malaria. It can mimic respiratory infections and present with concurrent malarial pulmonary edema and bacteriological respiratory infection. In our patient, malaria was diagnosed by microscopy (peripheral thick and thin Giemsa-stained blood smear) and bacteriological testing. The chest computed tomography showed interstitial edema and a pleural effusion. Bronchoalveolar lavage was performed, which was negative for both bacteria and hemozoin. After initiation of antimalarial treatment, the patient rapidly responded. Recognizing and promptly treating malaria is critical to reduce the mortality of MA pulmonary complications.

Keywords:
Acute respiratory distress syndrome, hemozoin, malaria, Plasmodium malariae, pleural effusion, pulmonary edema

Introduction

Malaria remains an important tropical disease, with 219 million malaria cases worldwide and 435,000 malaria deaths in 2018.[1] The prevalence of Plasmodium malariae is relatively low. The unique feature of P. malariae is that it can cause malarial attacks even decades after primary infection. The exact mechanism of this recurrence is currently unknown. In many patients, symptoms are fairly mild due to low parasite concentrations and mainly associated with anemia. We report a case of a patient presenting with severe anemia, intermittent fever, and exertional dyspnea in whom a chest computed tomography (CT) scan showed an interstitial lung pattern with a loculated pleural effusion.

Case Report

A 45-year-old female patient presented at our hospital with progressive dyspnea on exertion and general malaise for 3 weeks. The patient was born in Africa (Cameroon) and had been living in Europe for the past 17 years. Four months ago, she had visited Cameroon again and had taken malarial chemoprophylaxis (atovaquone/proguanil hydrochloride 250/100 mg daily). There were no other respiratory complaints. She had undergone laparoscopic Roux-en-Y gastric bypass surgery 9 years ago as bariatric procedure, after which she had chronic intermittent abdominal pain and iron-deficiency anemia. There was no history of tuberculosis or malaria in the past. Physical examination showed no abnormalities. There was a normal oxygen saturation on room air (SpO₂: 97%), no fever, no tachycardia, and a normal blood pressure. Lung and heart auscultation, as well as lung percussion, did not reveal abnormalities. There was no peripheral edema.

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and low brain natriuretic peptide (26 ng/l; normal limit <100 ng/l). An echocardiogram was not performed. A CT scan of the chest revealed bilateral pulmonary edema with a left-sided small pleural fluid collection (approximately 200 ml) and a right-sided small basal pleural fluid collection, without superimposed infiltrates of pulmonary embolism [Figures 1 and 2]. The pleural effusion was considered too small for safe thoracentesis. Pulmonary function testing including body plethysmography and CO diffusion capacity was normal. In the arterial blood gas analysis, there was no hypoxemia or hypercapnia. A bronchoscopy with bronchoalveolar lavage (BAL) in the medial lobe was performed. Macroscopically, no abnormalities were seen in the BAL (200 ml instillation, 120 ml recovery), cell counts including the CD4/CD8 ratio were within normal limits, and bacteriological cultures including both tuberculosis polymerase chain reaction and culture were negative. The cytology showed alveolar macrophages without inflammatory reactions. Four days after the bronchoscopy, the patient presented with abdominal pain at our emergency department. Due to the recent travel to Africa, malaria was considered. Microscopical examination of peripheral thick and thin Giemsa-stained blood smear showed some schizonts with some merozoites, gametocytes, and trophozoites. The serology testing with enzyme-linked immunosorbent assay and immunofluorescence antibody test showed strong positive reactions (1.04 and 640, respectively). We determined hemozoin in the BAL fluid, which was negative. After diagnosis of malaria with *P. malariae*, therapy with artemether and lumefantrine was initiated. There was complete recovery after treatment.

**Discussion**

We report a malaria-associated noncardiogenic pulmonary edema (MA-NPE) that was initially missed due to the suspected efficacy of antimalarial prophylaxis. If the diagnosis had not been made upon the second presentation, it may have progressed to MA-acute respiratory distress syndrome (ARDS). Pathophysiologically, these conditions are characterized by movement of excess fluid in the pulmonary alveoli due to pulmonary inflammation. The severity can range from the mildest form (MA-NPE) in outpatients to the most severe form (MA-ARDS) in hospitalized intubated patients with ventilatory support requirements. Whether the pulmonary edema always starts with the mildest stage and then progresses to the more severe stages of the disease is currently not known. This knowledge gap may be due to the lack of evidence relating to the rarity of pulmonary complications of malaria and also due to the frequent delay in diagnosing these patients. It is known that patients with pulmonary complications of malaria can present with ARDS within a relatively short period of time (few days).

Interestingly, hemozoin might play a crucial role in the pathogenesis of alveolar edema. The synthesis of hemozoin out of Hb is a vital pathway for the malaria parasite. In the process of digesting Hb, heme, that is toxic to parasites, is transformed into nontoxic hemozoin.[5] Concurrent bacterial infections can further aggravate the respiratory failure, and clinicians should, when in doubt, consider implementing broad-spectrum antibiotic therapy.[3,4]

However, hemozoin concentrations do not completely explain the pathogenesis of alveolar edema, because acute respiratory symptoms also can occur after clinical improvement with adequate antimalarial therapy, while the parasitemia is declining.[6] Hemozoin concentrations in the lung have been correlated with lung weight and alveolar edema and are mainly localized in phagocytes, infected erythrocytes, and occasionally in granulocytes.[7] In resection specimens of the lung, it correlates with MA-ARDS,
and in mice, it has been demonstrated to induce a strong pulmonary inflammatory response. To the best of our knowledge, hemozoin has not yet been determined in BAL fluid of a patient with pleuropulmonary manifestations due to *P. malariae* infection.

In the described case, BAL hemozoin was negative. This could be due to the mild pulmonary manifestation in our patient, with a suspected relatively low pulmonary parasite accumulation in this stage. Research has shown that the ARDS features in lung specimens, obtained from patients who died from severe malaria, coexisted with pulmonary edema and systemic bleeding. The severity correlated with the hemozoin level, the parasitized red blood cells, and the white blood cell accumulation in the lung. This could explain the negative hemozoin due to the absence of both erythrocytosis and leukocytosis in the BAL fluid of our patient. A possible explanation of the failed malaria protection of the routine prophylaxis in this patient could have been diminished drug absorption due to the Roux-en-Y gastric bypass.

**Conclusion**

Malaria may lead to life-threatening pulmonary complications sometimes being the first or dominant manifestation of malaria. Antimalarial prophylaxis may fail, especially after bariatric surgery, and thus, malaria should be considered even in those on prophylaxis. In case of suspected MA noncardiac pulmonary edema or ARDS, measurement of hemozoin level in BAL fluid may be considered.

In view of the increased traveling to endemic areas of malaria, maintaining a high index of suspicion is important, especially when pulmonary edema or ARDS is observed even in cases where chemoprophylaxis was used.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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