Case Report: Acute Respiratory Distress Syndrome in a Case of *Plasmodium ovale* Malaria

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Abstract. Acute respiratory distress syndrome is a well-known complication in *Plasmodium falciparum* infection. It is less frequently described in *Plasmodium vivax*, and only one case is reported in *Plasmodium ovale*. Here we present the second description of this pulmonary complication in a *P. ovale* acute infection.

INTRODUCTION

Malaria is the most frequent parasitic disease in the world, with 500 million cases and >1 million deaths every year overall in children younger than 5 years of age in Africa. It can be caused by four *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. The prevalence rate of *P. ovale* infection may be 0.5–10.5% of all malaria cases and is restricted to sub-Saharan Africa, the islands of the western Pacific, and rarely on the mainland of southeast Asia.1 Acute respiratory distress syndrome (ARDS) is a well-known complication in *P. falciparum* infection and less frequently described in *P. vivax*. *P. ovale* usually causes mild disease without complications, and only one case of ARDS has been reported up to now in the medical literature.2 Here we present the second description of this pulmonary complication in a *P. ovale* acute infection.

CASE REPORT

A 43-year-old Nigerian man returned from a 3-month trip to Nigeria visiting relatives without taking malaria prophylaxis. He had been living for 5 years in Spain, and he had a history of hypertension and diabetes mellitus for 13 years. His daily treatment was irbesartan and insulin. Three days after returning, he began with fever, chills, headache, malaise, and vomiting. On admission, he was febrile (40.5°C), supine blood pressure was 104/62 mm of Hg, cardiac rate was 88/min, and oxygen saturation breathing room air was 96% assessed by pulsoximetry, with a normal respiratory rate. Physical examination showed only mucosal dryness, and lung auscultation was clear.

Laboratory results showed a white blood cell count of 5,700/µL (56% neutrophils, 1% bands, 41% lymphocytes, 2% monocytes), hemoglobin of 9.8 g/dL, and platelet count of 56,000/µL. Serum creatinine was 1.8 mg/dL, glucose was 243 mg/dL, albumin was 2.7 g/dL, aspartate aminotransferase was 77 IU/L, alanine aminotransferase was 77 IU/L, gamma glutamyl transpeptidase was 88 IU/L, lactate dehydrogenase was 950 IU/L, total bilirubin was 1.9 mg/dL, and ferritin was 2,462 ng/mL. Serum electrolytes, coagulation, creatine phosphokinase, haptoglobin, and urine analysis were within normal range. Chest radiography was normal without cardiomegaly. An electrocardiogram showed an incomplete left bundle block.

Trophozoites and gametocytes of *P. ovale* with a parasitemia of 6,000/µL were detected by an expert microscopist in the thick film, and a malaria antigen test (NOW Malaria KT test, Binax Inc., Scarborough, ME) was positive for the aldolase (malaria antigen common to the four species) band and negative for HRP/2. Multiplex polymerase chain reaction (PCR)3 performed in a reference laboratory (Laboratorio de Malaria del Centro Nacional de Microbiología, Spain) confirmed this diagnosis and was negative for other *Plasmodium* species.

The patient was started on oral chloroquine therapy for 3 days, paracetamol, and insulin. During the first 2 days, 1,500 and 2,500 mL of 0.9% saline were infused, respectively. Forty-eight hours after admission, fever continued, creatinine worsened to 2.4 mg/dL with sodium fractional excretion of 0.09%, and he developed progressive dyspnea, tachypnea, and hemoptysis. Bibasal crackles were heard on auscultation, and jugular venous pressure was not elevated. Arterial blood gases showed pH 7.52, PCO2 of 26.7 mm of Hg, PO2 of 38 mm of Hg, bicarbonate of 22.3 mmol/L, and hemoglobin dropped to 7.8 g/dL. Bilateral extensive alveolar infiltrates were seen in chest radiography (Figure 1). He was admitted to the intensive care unit (ICU) and was intubated and ventilated. Ceftriaxone and levofloxacin were added as empirical treatment, and two packed red cell units were transfused. Arterial blood gases during mechanical ventilation with 50% oxygen and 10 cm H2O PEEP were pH 7.43, PCO2 of 36 mm of Hg, PO2 of 90 mm of Hg, and bicarbonate of 24.4 mmol/L. The PaO2/FiO2 ratio remained <200 for 10 days. Central venous pressure (CVP) was 20 cm H2O initially. Pulmonary capillary wedge pressure (PCWP) was not measured. Noradrenaline infusion was needed for 48 hours because of a hypotensive episode on the fourth day of ICU, which did not respond to fluids and the development of progressive generalized edema. Negative fluid balance was achieved on Day 5 in the ICU after being hemodynamically stabilized. Echocardiogram performed on Day 30 from admission showed an important left ventricular hypertrophy with normal systolic function. Thick film performed on the second day of chloroquine treatment showed only gametocytes and 5 days later was negative. Multiple urine and blood cultures were negative. Bronchoscopy on the first day in the ICU showed diffuse inflammatory signs with intense bloody secretions. Bronchoalveolar aspirate was negative for bacteria, mycobacteria, and fungi. Lactic acid and rheumatoid factor were normal. Antineutrophil, antineuclear, and antibasal membrane antibodies were negative. Abdominal ultrasound was normal, and abdominothoracic...
CT with intravenous contrast on Day 13 in the ICU showed bilateral alveolar infiltrates with pseudonodular appearances, pleural effusions, and atelectasis in the lower lobules. Urinary *Legionella* antigen and human immunodeficiency virus (HIV), hepatitis C virus, hepatitis A virus immunoglobulin M, syphilis, *Brucella*, and *Leishmania* serology were all negative, and serologic evidence of a previous infection by hepatitis B virus was seen. Stool parasites were negative. *Mansonella perstans* was detected in the blood. *Acinetobacter baumannii* grew in another bronchoalveolar aspirate taken 15 days after ICU admission, and intravenous colistin and amikacin were added. A 14-day oral primaquine treatment was completed after confirming a normal level of glucose-6-phosphate-dehydrogenase.

Sustained fever persisted for 14 days after chloroquine initiation, but infiltrates, oxygenation, and renal function improved progressively. Extubation was achieved on Day 21 in the ICU, and he was transferred to the internal medicine ward. Finally he was discharged 40 days after admission. Ten months later, he was asymptomatic, and a thoracic computed tomography scan showed normal lungs.

**DISCUSSION**

In this patient, pulmonary edema is consistent with criteria of ARDS after a *P. ovale* infection with acute onset of bilateral infiltrates on chest radiography, absence of clinical evidence of left atrial hypertension, and a PaO₂/FiO₂ ratio ≤ 200.¹ Fluid infusion during the first 48 hours to improve prerenal acute renal failure might have worsened the pulmonary distress, adding a component of fluid overload to a patient with hypertensive cardiomyopathy and possible diastolic dysfunction beside a lung with enhanced vascular permeability injured by *P. ovale* infection. Renal function deteriorated initially because of low intravascular volume and saline expansion, and vasopressure drugs were necessary. CVP is not a reliable method to measure left atrial pressure overall on mechanical ventilation with PEEP. PCWP would have given complementary information in this case but was not used. The radiographic feature and slow infiltrates resolution were also more consistent with ARDS. Other factors that might have contributed to pulmonary edema were anemia, fever, and hypoalbuminemia with low oncotic pressure.

The possibility of mixed infection with *P. falciparum* was ruled out by PCR analysis. Community acquired pneumonia or sepsis from another source were unlikely because of initial negative microbiological analysis including results from the first bronchoscopy. Ventilator-associated pneumonia by *Acinetobacter* was not related with the acute lung injury but a late nosocomial infection with favorable outcome. Diffuse pulmonary hemorrhage is described in ARDS, and other etiologies may be excluded by the absence of connective tissue disease signs, negative laboratory tests, and good evolution without immunosuppressive drugs.

The clinical evolution of this patient was similar to previous reports of *P. vivax* and *P. ovale* ARDS. Almost none had significant respiratory symptoms or x-ray abnormalities at presentation,⁵ and worsening resulted several days after initiation of specific treatment of malaria. A better clinical evolution and lower mortality has been described in *P. vivax* than in *P. falciparum*–related ARDS. Mortality of ARDS without mechanical ventilation may exceed 80% in falciparum malaria, but in those patients who survive, clinical recovery is often rapid.⁶ Fever resolution can be delayed from initiation of therapy despite good parasitologic response,⁷ probably as a consequence of intense inflammatory response post-treatment. Low parasitemia is nearly a constant in these species of *Plasmodium*. Complications are most often described in non-immune individuals,⁶ which our patient can be considered because he has been living in a non-malarious country for 5 years. Diabetes mellitus as a cause of immunosuppression could have been a factor for more severe infection as might be seen in HIV patients with malaria.

The pathophysiology of acute pulmonary edema in malaria is not clear, and the mechanism may be different in *P. falciparum*, *vivax*, or *ovale*. In the case of falciparum, infected red cells cytoadhere to the microvascular endothelium causing mechanical obstruction of pulmonary vasculature. Inflammatory cells like neutrophils and mononuclears are activated increasing pulmonary phagocytic cell activity with intense liberation of cytokines. Alveolar capillary permeability increases, and intravascular fluid is spread into the lungs leading to an ARDS feature.⁸ A possible role of impaired pulmonary NO bioavailability has been postulated as a cause of higher risk of developing ARDS.⁹ A component of hydrostatic edema may be facilitated by fluid overload so that the recommendations in malaria are to maintain the CVP and PCWP at relatively low levels.

In series of severe falciparum malaria, pulmonary edema occurred in 9–21%. Pulmonary edema in *P. vivax* infection is a rare complication, but in the last years has been more frequently reported.⁵ Because of its clinical and microbiological similarities with *P. ovale* malaria, it might provide more insights into the pathophysiology of our reported case. It is known that altered pulmonary function is common in uncomplicated falciparum, vivax, and ovale infection.¹⁰ In a recently published study comparing uncomplicated vivax and falciparum malaria, the functional lung alterations suggested that *P. vivax*–infected erythrocytes may also be sequestered within the pulmonary microvasculature,¹¹ but it is unknown whether *P. ovale* can sequester in the lung. Moreover, host response seems to be stronger at lower parasitemia in vivax and ovale than in falciparum infection,¹² and progressive alveolar-
capillary dysfunction after treatment of vivax malaria is also consistent with this greater inflammatory response,\(^1\) a phenomena not seen in uncomplicated falciparum infection.\(^1\)

Marked increase in pulmonary phagocytic activity was also measured in a patient with \(P.\) ovale 1–2 days after starting chloroquine.\(^1\) Some formation of rosettes has also been shown in vivax and ovale\(^1\) that may support the sequestrating hypothesis. More virulent strain of \(P.\) ovale cannot be excluded in this case. Until now, there were very few autopsy studies in patients with vivax and ovale infection without clear conclusions on mechanisms of pulmonary injury.

An increasing number of patients from West Africa is seen in our area, and \(P.\) ovale infections represented 7% of our malaria cases,\(^1\) including one locally acquired case.\(^1\) Although it is a rare complication, it is important to be aware of the possibility of developing ARDS in malaria other than falciparum infection. Careful monitoring of fluid replacement must be recommended for the treatment of severe malaria of any species. Finally, it must be stressed that all travelers to malarious areas and especially African people visiting relatives and friends must be counseled about taking adequate malaria prophylaxis.

Received March 13, 2008. Accepted for publication June 4, 2008.

Disclosure: The authors state that they have no conflict of interest.

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