Case Report

Pulmonary Edema in Malaria

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Two patients, hospitalized in New York City with malaria caused by Plasmodium falciparum, developed pulmonary edema while responding to antimalarial therapy. These cases serve as a timely reminder of this serious pulmonary complication of malaria.

CASE REPORTS

Patient 1

A 33-year-old Australian woman, who had been stationed in Liberia for 4 months, flew to New York City for vacation. Several days later, she developed fever, rigors, lower back pain, and headache. On the third day of symptoms, she was acutely ill and was admitted to The New York Hospital where a peripheral blood smear showed characteristic ring forms of P. falciparum (Figure 1). She had discontinued chloroquine and proguanil prophylaxis due to gastrointestinal intolerance 10 weeks before admission. Initial laboratory studies included white blood cell (WBC) count of 4800/mm³; hemoglobin, 11.9 g/dL; hematocrit, 34%; platelet count, 43,000/mm³; lactic dehydrogenase (LDH), 399 IU; prothrombin time (PT), 14.7 seconds (control 12.0 s); and partial thromboplastin time (PTT), 35.1 seconds (control 38 s). Admission chest examination and roentgenogram were normal (Figure 2, A).

After 18 hours of treatment with oral quinine and doxycycline, parasitemia was reduced from 2.1 to 1.2%. However, 12 hours later, the patient developed acute respiratory distress with severe hypoxemia (arterial PO₂, 38 mmHg, while receiving 100% oxygen). Bronchial breath sounds and rales were heard over both lower lung fields. Fever to 39°C persisted, although parasitemia was less than 0.1%. The patient developed evidence suggesting coagulopathy or disseminated intravascular coagulation (DIC) with a further increase in PT to 15.4 seconds and a positive D-dimer test. Repeat chest x-ray was consistent with pulmonary edema (see Figure 2, B). In the 24 hours prior to the onset of respiratory distress, the patient had received normal saline intravenously at a rate of 150 cc per hour. Serial electrocardiograms (EKG), cardiac enzymes, transthoracic echocardiogram, and a ventilation-perfusion scan were all normal.

Although the patient had no clinical evidence of fluid overload, she received furosemide and responded with a diuresis of 2 liters of urine over 24 hours. Despite this, there was essentially no improvement in oxygenation (arterial PO₂, 63 mmHg, while receiving 100% oxygen). Two days later clinical and radiographic findings began to improve and evidence of coagulopathy began to resolve. Antimalarial therapy was stopped after 7 days, and the patient was discharged on day 8 with a normal chest roentgenogram.

Patient 2

A 35-year-old French-Haitian woman, who lived in New York City, presented to The New York Hospital with 2 days of high fever (40°C), rigors, drenching sweats, and headache. Her symptoms started 7 days after a 5-day trip.
with her husband to a remote beach resort in Haiti. The patient's husband also had been hospitalized 2 days earlier, with similar symptoms caused by *P. falciparum* malaria. On admission, she was acutely ill appearing, with a WBC count of 3,400/mm³; hemoglobin, 14.0 g/dL; hematocrit, 43%; platelet count, 110,000/mm³; LDH, 510 IU; PT, 12 seconds; and PTT, 36 seconds. Admission chest examination and chest x-ray were normal. Her peripheral blood smear showed *P. falciparum* infection (0.1% parasitemia), and a total of 2.5 g of oral chloroquine phosphate was given over the next 48 hours.

On the second hospital day, parasitemia was less than 0.05%; however, the patient complained of progressive dyspnea and cough and was found to have diminished breath sounds at the lung bases. Chest roentgenogram showed diffuse infiltrates extending from the hilum with a normal cardiac silhouette. Because of the possibility of fluid overload, she was treated with furosemide with prompt diuresis. Despite a negative fluid balance of 2.1 liters, she developed acute respiratory failure on the fourth hospital day (PO₂, 48 mmHg, while receiving 100% oxygen) and required mechanical ventilation and positive end-expiratory pressure (15 cm H₂O). Repeat chest x-ray showed a pulmonary edema pattern and normal heart size, consistent with the adult respiratory distress syndrome (ARDS). At this time, blood studies revealed hemoglobin, 8.2 g/dL; platelet count, 62,000/mm³; PT, 13.6 seconds; and elevated fibrin degradation products (FDP) suggesting coagulopathy. Serial EKGs, cardiac enzymes, transthoracic echocardiogram, and pulmonary capillary wedge pressure were all normal.

After 48 hours of mechanical ventilation, the patient started to show improvement. Her hospital course was extended, owing to a left pneumothorax and *Serratia marcescens* nosocomial pneumonia. On discharge, her chest roentgenograph had returned to normal. The patient's husband, who responded promptly to chloroquine therapy, had an uneventful hospital stay.

**DISCUSSION**

Since the turn of the century, respiratory complications in patients with acute *P. falciparum* malaria have varied from minor symptoms consistent with bronchitis to full-blown respiratory failure, and even fatal pulmonary apoplexy. The overall incidence of respiratory complications in this infection ranges from 3% to 10%. Pulmonary complications during the course of malaria historically bear a high mortality rate. In one series of 12 cases, mortality was 75%, with more than half the deaths occurring during the first 24 hours. In surviving patients, clinical Improvement occurred 72 to 96 hours following the onset of the acute respiratory episode. In Africa, patients with cerebral malaria due to *P. falciparum* appear more likely to develop respiratory complications, observations in Far East Asia also have suggested a separate association between DIC and ARDS in *P. falciparum* malaria.

The earlier concept of renal insufficiency combined with fluid overload as the cause of respiratory failure in *P. falciparum* malaria has been replaced by the notion of a capillary-alveolar leak phenomenon. Fein and colleagues reported a well-documented case of acute non-cardiogenic pulmonary edema during the early phase of *P. falciparum* therapy, thereby supporting, as also illustrated by the two cases herein described, the current hypothesis of primary lung injury as a cause of respiratory compromise during malaria. High circulating levels of inflammatory cytokines, such as tumor necrosis factor-α, may be a target for additional treatment. Whether the use of heparin for malaria-associated coagulopathy and DIC or corticosteroids for cerebral malaria has a beneficial effect on concomitant ARDS is not clear.

In the majority of the reported malaria cases in which an ARDS-like scenario developed, respiratory failure...
occurred during or immediately following an adequate antiparasitic response to treatment.\textsuperscript{2-10} Both of the patients described in this case report demonstrated this timing. The typical onset of respiratory complications is within 5 to 7 days of first malarial symptoms; rarely, pulmonary complications may be delayed.

The management of ARDS related to malaria does not differ from ARDS associated with other disorders except for giving proper therapy for malaria itself.\textsuperscript{14,15}

No association has been found with the degree or duration of the initial parasitemia and subsequent pulmonary complications.\textsuperscript{5-10} These two patients developed respiratory failure in the presence of nearly undetectable levels of parasitemia.

REFERENCES