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Acute Respiratory Distress Syndrome Caused by *Plasmodium falciparum* Infection

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Acute Respiratory Distress Syndrome Caused by *Plasmodium falciparum* Infection

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Case Report

A 23-year-old male was admitted to an inpatient facility in June for the evaluation of a fever that was not responding to antibacterial therapy. The patient had presented at a local clinic 2 days previously with a nonproductive cough and fever of 24-h duration. Left basilar crackles were heard on physical examination. Chest X ray revealed no significant findings, and vital signs were normal with the exception of slight tachycardia (76 beats per minute) and a fever of 101.7°F. The patient was diagnosed with bronchitis/early community-acquired pneumonia and sent home on a 1-week regimen of levofloxacin.

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The patient had been in good health, with past medical history significant only for a hernia repair as an infant. The patient was a nonsmoker. He resided with his parents and reported good health for his parents and two siblings. A third sibling was recently diagnosed with mononucleosis. One month prior to admission, the patient spent 12 days on a mission trip to Cameroon. Vital signs upon admission included a spiking high-grade fever (T_{max} of 105°F), increased tachycardia (105 beats per minute), slight tachypnea (22 breaths per minute), and blood pressure of 114/56. Pulse oximetry was 96% on room air. His illness was also characterized by ongoing fatigue, myalgia, increased thirst, diminished appetite, and nonshaking chills. No altered mental status was observed. Initial laboratory data were significant for decreased platelets (60,000/μl; lower limit of normal, 150,000/ml), decreased electrolyte levels (sodium, 125 mmol/liter; potassium, 3.3 mmol/liter; chloride, 91 mmol/liter [lower limits of normal, 136 mmol/liter, 3.5 mmol/liter, and 100 mmol/liter, respectively]), elevated total bilirubin (2.4 mg/dl; upper limit of normal, 1.2 mg/dl), and slightly elevated serum transaminases (AST, 99 U/liter [upper limit of normal, 40 U/liter]; ALT, 75 U/liter [upper limit of normal, 60 U/liter]). A peripheral leukocyte count was within normal limits, yet the differential showed 87% neutrophils.

On hospital day 2, the patient began to experience shortness of breath. Pulse oximetry was 95% on 4 liters of supplemental oxygen. The patient continued to have no significant cough, sputum production, or hemoptysis. Over the next 2 days, the patient developed acute respiratory failure, requiring mechanical ventilation. A computed tomography scan of the chest with contrast (Fig. 1A) revealed extensive, relatively symmetric, bilateral lower lobe opacification and patchy airspace disease in the perihilar portion of each lung. Cultural studies produced no clinically significant microbial etiologies of infection.

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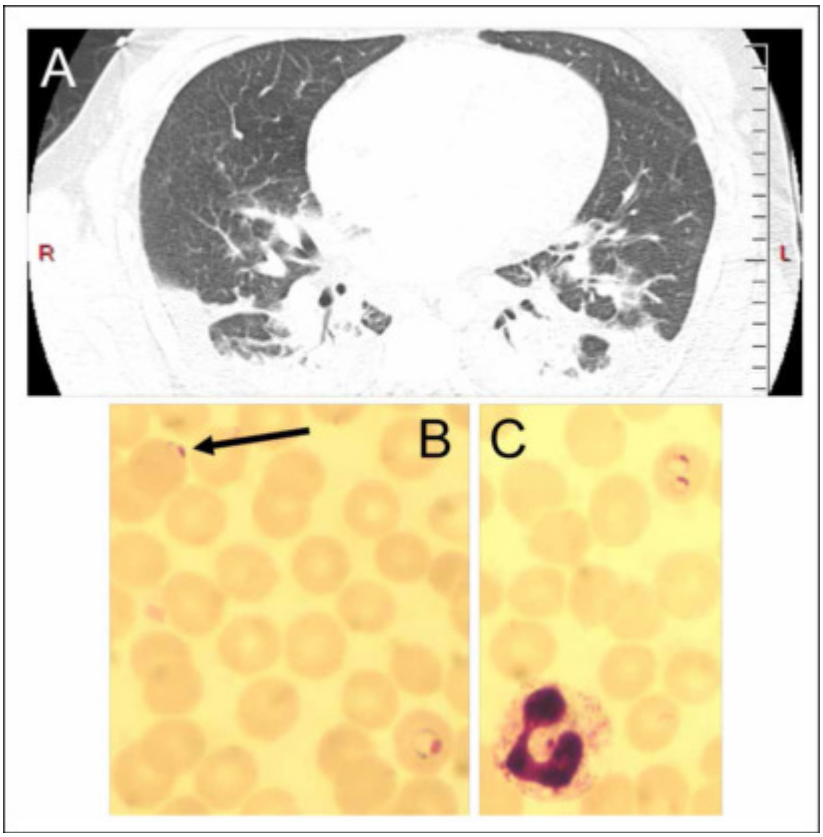

Figure 1. (A) Chest CT scan with contrast (transverse section). (B and C) Giemsa stain, peripheral blood smear; x1,000 total magnification.

However, significant data were generated from microscopic examination of a peripheral blood smear. Normocytic erythrocytes were infected by parasites (Fig. 1B). Thin and delicate trophozoites (ring forms) possessed one or two chromatin dots. Some ring forms were observed on the periphery of erythrocytes (appliqué forms [Fig. 1B, arrow]). Several erythrocytes were infected by more than one ring form (Fig. 1C). Schüffner's dots were not observed. The preliminary microscopic diagnosis of *Plasmodium falciparum* infection (parasitemia was estimated at 1 to 2%) was confirmed by a real-time PCR performed by the Wisconsin State Laboratory of Hygiene with melting curve analysis[1] on EDTA-treated venous blood.

An initial antimalarial regimen (oral atovaquone/proguanil) was not tolerated by the patient. After subsequent verbal consultation with the Centers for Disease Control and Prevention (CDC), and in accordance with guidance documents,[2] a treatment plan that used intravenous doxycycline and quinidine gluconate was produced, which resulted in progressive patient improvement. The patient's parasitemia was estimated at 0.01 to 0.1% on hospital days 3 to 6 and was not detected by hospital day 7. Hemoglobin determinations,

which were within normal limits upon admission (15.9 g/dl; lower limit of normal, 13.0 g/dl), fell outside normal limits beginning on hospital day 3, reached a nadir of 11.4 g/dl on hospital day 7, and returned to normal on hospital day 10. The patient was slowly weaned from ventilation over several days, extubated without complication, and discharged on hospital day 11.

Discussion

Malaria surveillance data for 2012 published by the CDC[3] showed that of the 1,056 documented U.S. malaria cases imported from Africa, 83.7% were caused by *P. falciparum*. The CDC defines severe malaria as *Plasmodium* sp. infection with one or more of the following manifestations: severe anemia, renal failure, neurologic symptoms, jaundice, ≥5% parasitemia, or acute respiratory distress syndrome (ARDS).[3] The 2012 malaria surveillance report indicated that 231 (14%) of all reported malaria cases in the U.S. were severe. Approximately 75% of the reported severe malaria cases were attributed to *P. falciparum*, and the two most commonly reported manifestations were severe anemia (22%) and renal failure (16%). *P. falciparum*-related ARDS incidence in the U.S. was only 7% of the severe malaria cases.[3]

In the context of *P. falciparum*-related ARDS, a role of the infected erythrocyte has been investigated.[4,5] This entity may bind to capillary endothelial cells, with the basis for respiratory distress being associated edema, leukocyte tropism, and capillary narrowing. Aitken et al.[6] have developed a murine/*Plasmodium berghei* lung ultrastructure model that mimics pathology exhibited in humans with fatal *P. falciparum*-associated ARDS. With this model, they describe additional endothelial basement membrane thickening and distended cytoplasmic extensions. The capillaries were congested, and the alveolar spaces contained blood cells, cellular debris, and edema.

In regions of the world with increased malaria endemicity, *Plasmodium vivax* infection has also been associated with a significant incidence of ARDS. A 3-year surveillance report from Pakistan[7] indicated that 37.5% and 51.1% of reported *P. vivax* and *P. falciparum* patient cases, respectively, were severe. Among these cases, 21 to 26% of patients developed ARDS. A report from India[8] documented 16.9% and 36.3% delineations of severe *P. vivax* and *P. falciparum* malaria, respectively, over a 4-year interval. Among these severe cases, 35.3% of *P. vivax* and 25.2% of *P. falciparum* malaria patients developed ARDS. Interestingly, these data contribute to an evolving paradigm that challenges the "benign clinical course" of *P. vivax* malaria.[9]

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In summary, this case report describes ARDS as a manifestation of *P. falciparum* infection that is rarely seen in the U.S. In addition, this respiratory distress course, which is not caused by typical bacterial, viral, or fungal etiologies, emphasizes the importance of obtaining a complete social and travel history when triaging patients.

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