December 2012 Critical Care Case of the Month: Sepsis-like Syndrome in a Returning Traveler

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History of Present Illness
The patient is a 56 year old male with a past medical history that is significant only for well controlled hypertension presenting with acute onset of fever, hematuria, jaundice and fatigue. He had been hospitalized in Mexico for the last 5 days. When he failed to improve his friends chartered an airplane and brought him to the U.S. Prior to his hospitalization in Mexico he had traveled to Sierra Leone related to his work as a geologist.

PMH, SH, FH
Past Medical History: Hypertension, gastroesophageal reflux disease
Past Surgical History: Vasectomy
Medications: Omeprazole, Lisinopril
Social History: Works as a geologist with recent travel to Sierra Leone, no history of alcohol abuse, intravenous drug abuse, or HIV

Physical Examination
Vital signs: Temperature 97.5° F, Pulse 87 beats/min, Respiratory Rate 18 breaths/min, Blood Pressure 111/84 mm Hg, and SaO2 89% on room air.
The patient was initially alert, oriented and appropriate.
His pulmonary examination revealed faint bibasilar rales.
His abdomen was obese, soft, non-tender and non-distended.
His skin had obvious jaundice and his sclerae were icteric.
He later decompensated, became altered and developed significant tachypnea.

Admission Laboratory Studies
Significant initial laboratory studies are as follows: Hemoglobin 11.5 g/dl, Hematocrit 35%, Platelet Count 25,000/uL, Chloride 115 mMol/L, CO2 17 mMol/L, BUN 35mg/dL, Creatinine 1.6 mg/dL, Albumin 1.5 g/dL, Total Bilirubin 13.2 mg/dL, ALT 38 IU/L, AST 97 IU/L, INR 1.7, Fibrinogen 270 mg/dL, D-Dimer 8.37 ug/ml, Venous Lactate 3.9 mMol/L, Urinalysis: Small Blood, 2 RBCs/HPF, Moderate Bilirubin, Urobilinogen 2.0 mg/dL.

As part of the workup for possible hemolysis a peripheral blood smear was obtained (Figure 1).
Figure 1. Peripheral smear of the patient’s blood.

Which of the following is the diagnosis?
1. Malaria
2. Babesiosis
3. Ehrlichiosis
4. Relapsing fever
5. American trypanosomiasis (Chagas disease)
Correct!
1. Malaria

Multiple laboratory studies exist to confirm the diagnosis of malaria but the best test is still the peripheral smear. Thick and thin preparations are often utilized in endemic areas. The thick smear allows a larger quantity of erythrocytes to be screened for the presence of the parasite; however, it lacks the sensitivity of the thin smear. The thin smear remains the “gold standard” for the diagnosis of malaria and it also has significant treatment implications. From the thin smear the species of plasmodium can be identified, the percentage of erythrocytes affected can be calculated and response to therapy can be monitored.

The patient’s peripheral smear displayed above reveals a diagnosis of Plasmodium Falciparum malaria. The rings shown are characteristic of falciparum. These rings are composed of double chromatin dots that resemble a “set of headphones” with some RBCs being multiply-infected. The RBCs are normal in size and shape when compared to other erythrocytes on the smear. This slide does not show the other stages of P. falciparum, but gametocytes, trophozoites and the rare schizont may be seen.

The WHO as well as the Centers for Disease Control makes treatment decisions based on the severity of illness and the species of Plasmodium. This patient is presenting with altered mental status, jaundice and increased serum creatinine which classify him as severely infected.

<table>
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<tr>
<th>Clinical Features</th>
<th>Laboratory Findings</th>
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<tr>
<td>Impaired Consciousness or Coma</td>
<td>Hypoglycemia &lt;40mg/dl</td>
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<tr>
<td>Generalized Weakness, Unable to Sit Up</td>
<td>Metabolic Acidosis with Bicarb &lt;15</td>
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<tr>
<td>Failure to Feed</td>
<td>Normocytic Anemia with Hgb &lt;5g/dl</td>
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<tr>
<td>Multiple Convulsions; &gt;2 in 24 hours</td>
<td>Hemoglobinuria</td>
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<tr>
<td>Respiratory Distress, Acidotic Breathing</td>
<td>Renal Impairment SCr &gt;265umol/l</td>
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<td>Circulatory Collapse, SBP &lt;70</td>
<td>Hyperlactatemia &gt;5mmol/l</td>
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<td>Jaundice and Evidence of Other Organ Failure</td>
<td>Hyperparasitemia &gt;2% in low Transmission areas or &gt;5% in high areas</td>
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<tr>
<td>Hemoglobinuria</td>
<td></td>
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<td>Spontaneous Bleeding</td>
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<tr>
<td>Pulmonary Edema</td>
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Table 1. WHO Classification of Severe Malaria, 2010

Which of the following drugs have been used to treat P. falcipirum malaria?
1. Chloroquine
2. Atovaquone-proguanil (Malarone®)
3. Quinine
4. Artesunate
5. All of the above
Correct!
5. All of the above

The Center for Disease Control and WHO have treatment guidelines/algorithms readily available on their websites. This patient had been diagnosed with malaria and was thought to be a treatment failure due to the chloroquine resistant malaria endemic to the area of Africa in which he had traveled.

Our infectious disease colleagues as well as the CDC were contacted when this patient arrived to the hospital. The patient received an initial 600 mg infusion of quinidine over 1-2 hours followed by a 2,880 mg infusion over 24 hours. This infusion was given in conjunction with doxycycline 100 mg IV x1. This was followed by artesunic acid therapy the next day.

Artesunic acid (Figure 2) has become the second parenteral drug available for the treatment of malaria in the United States after quinidine. It belongs to a class of medications known as the artemisinins. Artemesinins are derived from the plant Artmisia annua which has long been employed as herb in traditional Chinese medicine. This medication carries a “strong recommendation” from the WHO for initial treatment in patients with severe malaria. It is available in the United States only by contacting the CDC on their hotline; it is regulated by the FDA for investigational use only in the United States.

Figure 2. The investigational drug artesunic acid for chloroquine-resistant P. falciparum.

3.) Which of the following has been used as adjunctive treatment for severe P. falciparum malaria?
1. Inhaled nitric oxide
2. RBC transfusions
3. RBC exchange transfusion
4. Maintenance fluids only
5. All of the above
Correct!
5. All of the above

The patient became progressively more ill and decompensated into respiratory failure and a sepsis like syndrome. The patient then received a red blood cell exchange transfusion that evening administered by the Red Cross. This is thought to be beneficial by removing the parasite-infected cells and replacing them with donor non-affected cells. There are no prospective studies evaluating this therapeutic modality but retrospective studies show there may be some benefit. This therapeutic maneuver is also a recommendation by the CDC once the parasite load reaches greater than 10% or if there are indications of impending renal failure.

A few hours after the exchange transfusion the patient became progressively more tachycardic and then progressed into severe shock with his lactate climbing to 9.9 mmol/L, pH dropping to a nadir of 6.98, and requiring support with norepinephrine and phenylephrine. He received multiple boluses of normal saline throughout the evening but his vasopressor requirement did not diminish. This hypotension was thought to be possibly a side effect of intravenous quinidine therapy, which he was receiving at the time. Early the next morning the patient was still requiring significant doses of norepinephrine and phenylephrine. The patient was bolused with 1 liter of 5% albumin and the phenylephrine was able to be weaned off that morning and norepinephrine over the next two days. This coincided with the discontinuation of quinidine and the institution of artemesunate. The issue of volume resuscitation in the setting of severe malaria is continually debated; most recently in the FEAST trial published in NEJM October 6, 2011.

Case Outcome

The malarial percentage on his initial smear was 8.5% on day 1, on day 2 it declined to 0.18% and on day 3 it was undetectable on the peripheral smear. He finished his artemesunate therapy which was followed by atovaquone/proguanail for the next 3 days. He unfortunately did develop some sequelae from his acute malarial infection including splenomegaly with a small hematoma and renal failure which was treated by continuous renal replacement therapy then later transitioned to intermittent hemodialysis. The patient spent 7 days with us in the ICU and total of 3 weeks in the hospital before he was transferred back to a hospital in his hometown in Mexico.

References