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South Sudan to Martha's Vineyard: Malaria

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PRESENTATION

A summer vacation came to a sudden, dramatic end when a 52-year-old woman had a witnessed seizure at a social event. The patient, who had spent the previous 4 days visiting Martha's Vineyard, an island off the coast of Massachusetts, was brought by ambulance to a community hospital. Over the course of the previous week, she had complained of worsening malaise, headaches, anorexia, and intermittent fevers. She had no significant medical history, and she did not take any medications. She was a regular smoker and drank alcohol socially, but she did not use recreational drugs.

The patient's usual place of residence was a large urban center in Western Europe. Yet, for the past 18 months, she had been working for an international development organization in South Sudan. She left that country approximately 1 month before her presentation. While in South Sudan, she had not taken malaria prophylaxis. She reported having regular access to prepared food and clean water. Since arriving in the United States, she had spent time outdoors but had not noticed any insect bites.

ASSESSMENT

At the community hospital, the patient was disoriented and appeared ill. Her clothing was soaked with urine. She was febrile to 101.1°F (38.4°C) and tachycardic. Initial laboratory values were significant for thrombocytopenia, profound hyponatremia, acute kidney injury, elevated transaminase levels, hyperbilirubinemia, and anemia (Table 1). Computed tomography of her head and a plain film of her chest produced unremarkable results. A thick smear of her peripheral blood was notable for intraerythrocytic parasites. She was treated empirically with atovaquone, doxycycline, and clindamycin for tick-borne infections endemic to Eastern Massachusetts, while a quinidine gluconate infusion was initiated for malaria. Hypertonic saline was also administered to correct her hyponatremia.

On arrival to this hospital, the patient was afebrile but had developed hypotension with a blood pressure of 80/48 mm Hg. She was diaphoretic, photophobic, somnolent, and ill-appearing. Her skin was diffusely jaundiced, and conjunctival icterus was present. Thin and thick blood smears showed *Plasmodium falciparum* parasites with an estimated parasite density of 50% (Figure 1).

DIAGNOSIS

Although endemic malaria was eliminated from the United States more than 50 years ago, the annual number of imported cases continues to climb. In 2011, the Centers for Disease Control and Prevention (CDC) reported 1920 imported cases of malaria among people in the United States—the most since 1971.[1] The parasites *P. falciparum* (64%) and *Plasmodium vivax* (28%) accounted for the majority of these infections, with the largest proportion occurring among travelers to Africa (69%); travelers to Asia (22%) and the Americas (8%) accounted for almost all remaining cases.

To avoid unnecessary treatment delays, clinicians must maintain a high index of suspicion when evaluating a febrile patient with a history of travel to an area endemic for malaria. The risk for infection varies according to the region visited.[2] Our patient spent 18 months working for an international development organization in South Sudan, a country with one of the highest malaria burdens in Sub-Saharan Africa.[3]

A large, retrospective review of more than 30,000 returning travelers found that fever or a history of fever significantly increased the likelihood of a malaria diagnosis (likelihood ratio [LR] 5.1; 95% confidence interval [CI] 4.9-5.3), whereas an absence of fever made malaria less likely (LR 0.12; 95% CI 0.10-0.15).[2] Some physical examination

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Table 1 Selected Laboratory Values over the Patient's Hospital Course

Laboratory Value	Normal Range	Outside Hospital	Admission	Hospital Day 1	Hospital Day 2	Hospital Day 3	Hospital Day 6
Sodium (mmol/L)	133-145	117	122	128	120	122	135
Carbon dioxide (mmol/L)	22-31	18	16.4	13.8	14.7	15.4	20.7
Urea nitrogen (mg/dL)	6-20	100	100	86	100	98	63
Creatinine (mg/dL)	0.5-1.0	4.74	4.87	3.90	5.11	5.33	2.88
Glucose (mg/dL)	70-105	77	73	126	153	100	113
White blood cells (k/uL)	4.5-11.0	6.3	5.0	3.5	5.9	5.0	5.1
Bands (%)	0-10	—	22.0	36.8	8.1	5.3	0
Hemoglobin (gm/L)	12.0-16.0	10.3	7.7	10.2	9.0	8.7	7.8
Platelets (k/uL)	150-450	8	8	10	22	13	41
SGPT/ALT (u/L)	0-33	64	50	45	60	64	54
SGOT/AST (u/L)	10-35	86	90	117	127	92	40
Alkaline phosphatase (u/L)	35-104	167	145	85	85	88	105
Total bilirubin (mg/dL)	0-1.2	2.7	5.3	7.4	2.2	1.8	0.7
Direct bilirubin (mg/dL)	0-0.4	—	4.3	6.1	1.3	1.2	0.3
Lactate (mmol/L)	0.5-2.2	2.9	3.3	2.3	1.9	1.0	—
PT-INR	0.9-1.1	1.0	1.1	1.2	1.1	1.1	1.1
Fibrinogen (mg/dL)	150-400	—	184	124	137	117	118
Parasite density (%)	0	—	50	13	3.9	0.8	0

SGPT = serum glutamic-pyruvic transaminase; ALT = alanine aminotransferase; SGOT = Serum glutamic oxaloacetic transaminase; AST = aspartate aminotransferase; PT-INR = prothrombin time - international normalized ratio

findings, such as the presence of splenomegaly, jaundice, or pallor, increased the probability of malaria, but the absence of these findings only marginally decreased the odds of malaria. The most predictive laboratory results seem to be hyperbilirubinemia (LR 7.3; 95% CI 5.5-9.6) and thrombocytopenia (LR 5.6; 95% CI 4.1-7.5).[4]

At presentation, our patient was postictal, febrile, and jaundiced. Her initial laboratory results were remarkable for hyponatremia, acute kidney injury, hyperbilirubinemia, and severe thrombocytopenia. Together with her travel history and lack of chemoprophylaxis, her symptoms, examination findings, and laboratory results placed malaria high on the differential diagnosis.

The clinical picture and travel history, however, were also concerning for human babesiosis. Our patient had vacationed in a highly endemic area of Massachusetts, with potential exposures to the primary vector, *Ixodes scapularis*, also known as the deer tick. In the New England states, parts of New York, and the upper Midwestern states, *Babesia microti* is an increasingly recognized pathogen, causing a broad range of syndromes, from subclinical infection with nonspecific symptoms to severe and even fatal illness with features such as acute respiratory distress syndrome, disseminated intravascular coagulation, and acute kidney injury.[5] Risk factors for severe disease include asplenia, immunosuppression, cancer, and hemoglobinopathy.[6] Lower on the differential diagnosis, but still possible, was co-infection with another endemic tick-borne infection, such as anaplasmosis or Lyme disease.

In this case, our patient was assumed to be immunocompetent. Thus, her high burden of parasitemia would argue against a *B. microti* mono-infection. We did consider that our patient could be co-infected with both malaria and *B. microti*, so careful examination of her smears was required. Differentiating between malaria and *Babesia* infection on a thin smear, however, can be challenging (**Table 3**). *B. microti* trophozoites are pleomorphic round, oval, or pear-shaped ring forms that can be found in both intra- or extra-erythrocytic forms. Immediately before the lysis of erythrocytes, merozoite tetrads may be visible under the microscope, though they are rarely seen. When these cross-shaped arrangements resembling the

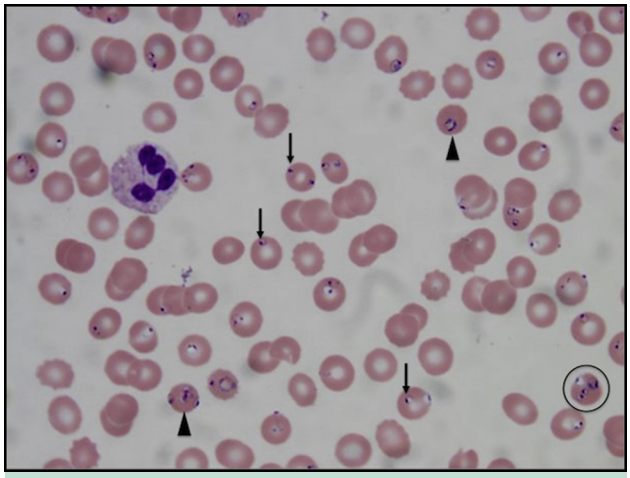

Figure 1 A peripheral blood smear obtained from the patient on admission demonstrated approximately 50% parasitemia. Note the early ring-form trophozoites (arrows), mature trophozoites (triangles), and developing schizont (circle). Photograph courtesy of J. Chu.

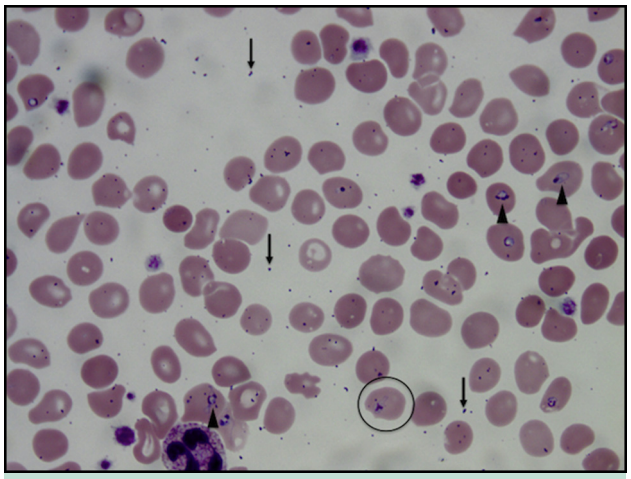

Figure 2 This example of a blood smear shows intra-erythrocytic (triangles) and extra-erythrocytic (arrows) forms of *B. microti*. Note the developing tetrad (circle), which may eventually appear as the pathognomonic "Maltese cross".

Maltese cross (**Figure 2**) are found, they are a pathognomonic finding.[7] By comparison, the *P. falciparum* species have no extracellular forms, and pathognomonic findings for *P. falciparum* include banana-shaped gametocytes.

MANAGEMENT

Patients diagnosed with malaria are generally categorized as having either uncomplicated or severe infection (**Table 2**). Uncomplicated malaria is usually treated with oral antimalarials, the choice of which is guided by the *Plasmodium* species and its susceptibility to antimalarial drugs in the region of infection.[8] Patients with severe malaria, who represent an estimated 10%-15% of imported cases, require parenteral therapy, intensive monitoring, and frequent reassessment, because recent case fatality rates among returning travelers range from 1% to 5%.[1,9]

Our patient had many findings consistent with severe malaria, including seizures, jaundice, hypotension, metabolic acidosis, hyperparasitemia, hyperlactatemia, and acute kidney injury. Thus, she was treated empirically for both malaria and tick-borne infections. Additionally, an 80% exchange transfusion was initiated, and 9 units of packed red blood cells were administered.

Since 1991, quinidine gluconate, derived from the bark of the cinchona tree, has been the only parenteral antimalarial drug available in the United States. Quinidine works against the intra-erythrocytic stages of *P. falciparum* malaria. Once the parasite density is <1% and the patient can tolerate oral therapy, treatment can be completed with an oral regimen,

Table 2 Criteria for Severe Malaria

Criterion	Definition
Impaired consciousness	A Glasgow coma score <11 in adults or a Blantyre coma score <3 in children
Acidosis	A plasma bicarbonate of <15 mM or venous plasma lactate >5 mM
Hypoglycemia	Blood or plasma glucose <40 mg/dL
Severe anemia	Hb <5 g/dL or a Hct of <15% in children <12 y of age Hb <7 g/dL or a Hct <20% in adults
Acute kidney injury	Plasma or serum creatinine >3 mg/dL or blood urea >20 mM
Jaundice	Serum bilirubin >3 mg/dL, together with a parasite count >100,000/μL
Pulmonary edema	Radiologically confirmed pulmonary edema or SpO2 <92% on room air with a respiratory rate >30/min
Significant bleeding	Recurrent or prolonged bleeding from nose, gums, or venipuncture sites; hematemesis or melena
Shock	Compensated shock is defined as capillary refill ≥3 but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults with evidence of impaired perfusion
Hyperparasitemia	*P. falciparum* parasitemia >10%

One or more of the above must occur in the absence of an alternative cause and in the presence of *P. falciparum* asexual parasitemia.

Adapted from: Severe malaria. *Trop Med Int Health*. 2014;19(suppl S1):7-131.

Table 3 Key Morphologic Findings of P. falciparum and B. microti on Thin Smear

Parameter	*P. falciparum*	*B. microti*
Size of infected RBCs	Normal	Normal
Trophozoite characteristics	Small and delicate rings less than 1/3 the diameter of the RBC; double chromatin dots ("head phones")	Small, delicate, pleomorphic rings 1/3 to 1/6 the diameter of the RBC
Presence of RBC inclusions	Mauer's clefts (small red dots over the cytoplasm)	None
Extracellular forms	Rare	Vermicules common
Pigment	Brown-black	No
Pathognomonic finding	Banana-shaped gametocytes	Maltese cross

Adapted from: Mayo Clinic Medical Laboratories. Laboratory diagnosis of tick-borne infections. Available at: www.mayomedicallaboratories.com/articles/hottopics/2010-07a1-tick-borne-pt1.html. Accessed June 3, 2015.

RBC = red blood cell.

such as quinine combined with doxycycline, tetracycline, or clindamycin for a 7-day course.

The therapeutic window of parenteral quinidine is quite narrow. Cardiac arrhythmia is the most feared complication: quinidine slows conduction and prolongs the QT interval in a dose-dependent manner. Because of this risk, quinidine should be administered in an intensive care setting with continuous cardiac monitoring.

In recent years, quinidine has become less widely available because its use as an antiarrhythmic drug has declined, and many hospitals no longer maintain the drug on formulary. As an alternative to quinidine, intravenous artesunate, an investigational agent, is available through the CDC. However, certain guidelines and eligibility requirements must be met to enroll a patient in the treatment protocol. Healthcare providers should telephone the CDC Malaria Hotline for information (770-488-7788; or after hours, 770-488-7100).

Our patient received quinidine for 4 days without adverse events. Doxycycline was continued for 7 days for tick-borne coverage, whereas clindamycin was discontinued after 3 days. The level of parasitemia fell to 13% after completion of the exchange transfusion and to 0.8% by hospital day 3, at which point she was transferred to a general medicine unit. Additional laboratory tests for tick-borne organisms were performed, including evaluations for *Borrelia burgdorferi*, the culprit in Lyme disease, *B. microti*, *Anaplasma phagocytophilum*, and *Ehrlichia* species. All were negative. Her hyponatremia, acute kidney injury, elevated transaminase levels, and thrombocytopenia improved (**Table 1**), although she had persistent anemia with a hemoglobin level of 7.8 g/dL at the time of discharge on hospital day 7.

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