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An 85-Year-Old Man With Recurrent Fever and Multiple Splenic Infarcts

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An 85-year-old man with a history of benign prostatic hyperplasia, hyperlipidemia, and Guillain-Barré syndrome in 1989 presented in September 2017 for the third time in 2 months with intermittent fever, chills, and night sweats. In July, he presented with a 5-day history of intermittent fever, with a temperature of 103°F and chills. The urinalysis and chest x-ray were normal, and 2 sets of blood cultures showed no growth. A computed tomography (CT) scan of the abdomen and pelvis was performed (Fig. 1A). The leukocyte count was 4200/μL (69% neutrophils), hemoglobin (Hb) 11.0 g/dL, and platelet count 63,000/μL. Patient received 3 days of azithromycin and was discharged with 2 days of oral cefpodoxime and azithromycin to complete a 5-day course of treatment.

The patient was readmitted to the hospital 4 days later with fever of 104°F associated with chills and sweating. Intravenous vancomycin, cefepime, and metronidazole were given. The leukocyte

count was 7800/μL, Hb 11.0 g/dL, and platelet count 386,000/μL. Blood cultures and CT of the abdomen and pelvis were negative. The patient was discharged from the hospital on day 4 without antibiotics when fever subsided.

In mid-September, 2 months after the initial presentation, the patient was readmitted to the hospital for recurrent fever for 10 days, with worsening fatigue, malaise, and anorexia. The leukocyte count was 6100/μL, Hb 7.6 g/dL, and platelet count 130,000/μL, with lactate dehydrogenase 849 U/L, alanine aminotransferase 53 U/L, aspartate aminotransferase 70 U/L, and alkaline phosphatase 41 U/L. The erythrocyte sedimentation rate was 115 mm/h, and C-reactive protein was 10 mg/dL. Blood cultures and echocardiogram were normal. Repeat CT scan of the abdomen and pelvis is shown in Figure 1B. The patient denied travel outside New York. He is originally from Greece and has lived in Brooklyn, NY, for 50 years. He did not recall any insect or tick bites, and no other family members had a similar illness. The patient denied any dental procedures in the past year. Patient's home medications were finasteride and pravastatin. What is your diagnosis?

FIGURE 1. A, Computed tomography of the abdomen and pelvis taken on July 2017. B, Computed tomography of the abdomen and pelvis taken on September 2017.

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Written informed consent for the release of radiological imaging and peripheral blood smear of the patient was obtained.

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Part 2

Diagnosis: *Babesia* Infection Caused by *Babesia microti*

Our patient presented with intermittent fever of unknown origin, and tick-borne disease was not included in the differential diagnosis initially. Thus, peripheral smears for parasites were not done in his previous 2 admissions. The initial CT scan showed a normal liver and spleen size (Fig. 2A). A subsequent CT scan 2 months later revealed numerous new splenic infarcts with hepatosplenomegaly (Fig. 2B). As mentioned, blood cultures and echocardiogram were nondiagnostic. On further questioning, the patient recalled that he had visited family in Greenport, Long

FIGURE 2. A, Computed tomography of the abdomen and pelvis taken on July 2017. Spleen size 92.4 mm. B, Computed tomography of the abdomen and pelvis taken on September 2017. Blue arrows point at splenic infarcts. Spleen size 140.6 mm.

Island, for the fourth of July weekend, 5 days prior to the onset of his febrile illness. Peripheral blood smear showed intraerythrocytic and extraerythrocytic ring inclusions consistent with babesiosis (Fig. 3) with 0.3% parasitemia. Polymerase chain reaction for *Babesia microti* was positive. Our patient was immediately started on azithromycin plus atovaquone, and the temperature normalized within 48 hours. He was discharged home on hospital day 7.

Splenic infarction is a rare complication of *Babesia* infection. To date, only 2 cases of splenic infarction in association with *Babesia* infection in humans have been published in the literature.¹ Interestingly, azithromycin as monotherapy at a higher dose resulted in a significant reduction in *Babesia* parasitemia and prolongation of survival when compared with controls in hamster models.² Our patient's initial improvement in fever and thrombocytopenia after his first hospitalization was likely due to azithromycin therapy. There has been evidence of drug resistance to azithromycin-atovaquone with relapse of *Babesia* infection in immunocompromised patients after initial exposure to azithromycin as monotherapy.³ However, our patient remained afebrile and has been doing well 3 months after completion of a 10-day course of azithromycin plus atovaquone therapy.

Babesiosis is a tick-borne infection caused by intraerythrocytic protozoa of the genus *Babesia*, transmitted by the *Ixodes* tick. *Babesia microti* is the most predominant strain in the Northeastern and upper Midwestern region of the United States.⁴ The most common route of transmission is via direct inoculation from *Ixodes scapularis* ticks. Blood transfusion and rarely transplacental transmission have also been documented.⁴ The peak acquisition of disease occurs between May and September. Although tick activity and tick-borne diseases are common in warmer months, *I. scapularis* is active throughout the year, when ambient-air temperature is greater than 4°C (40°F).⁵ Thus, babesiosis should be considered and investigated appropriately even during the months not typical for increased tick activity.

Clinical manifestations of *Babesia* infections are variable, depending on the *Babesia* species and the immune status of the host. Clinical presentation of babesiosis includes febrile hemolytic anemia due to parasite-mediated lysis of red blood cells in the circulation.⁶ *Babesia* infections may induce cycles of disease by varying antigen expression and by displaying new outer-surface proteins during the disease course. The antigenic variants are referred to as serotypes and prevent the elimination of the protozoa by the immune system. This may contribute to the recurring nature of relapsing fever.⁷

Immunocompetent individuals typically have subclinical illness, associated with low-level parasitemia (<4%) and may present with a gradual onset of nonspecific flulike symptoms. Babesiosis in immunocompromised patients is often severe, with a complication rate of 40% to 60%, including acute respiratory failure, congestive heart failure, renal failure, and disseminated intravascular coagulation.^{8,9} Patients may present with splenic infarction as in our patient. Proposed mechanisms of splenic infarction in

FIGURE 3. Peripheral blood smear showing intraerythrocytic and extraerythrocytic ring inclusions.

human babesiosis include microthrombus formation and local release of vasoactive factors caused by red blood cell lysis leading to infarcted necrosis of splenic tissue.¹⁰ Moreover, during infection, proinflammatory cytokines are released, specifically tumor necrosis factor, interleukin 1, interleukin 6, and interferon, leading to increased expression of adhesion molecules on the surface of the vascular endothelium. This in turn results in cytoadherence of the infected erythrocytes to the vascular endothelium.¹⁰ The parasitized erythrocytes also lack the deformability needed to transit the splenic sinusoids, causing their sequestration by resident macrophages and obstruction of the vascular flow within the spleen.¹

Our patient presented with fever of unknown origin and new splenic infarcts secondary to *Babesia* infection. Our case reinforces the importance of taking a detailed history including travel history when evaluating a patient with fever of unclear etiology. Our patient did not think that it was relevant to mention during his earlier admissions to the hospital that he traveled to Greenport, Long Island (Suffolk County), for a weekend. Furthermore, babesiosis should be included in the differential diagnosis in a patient who presents with nonspecific flulike symptoms, hematological manifestations, and new splenic infarcts on radiographic imaging. Physicians should ensure timely diagnostic testing and appropriate initiation of treatment in a patient with babesiosis and splenomegaly to prevent further progression to splenic infarct or rupture, which may lead to a fatal outcome.

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