Splenic Infarction in Human Babesiosis: Two Cases and Discussion

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We describe 2 patients with Babesia infection who presented with fever and multiple splenic infarcts. There were no other conditions present that could potentially be causes of splenic infarction. Although retinal infarction has been described rarely in patients with babesiosis, splenic infarction has not been reported previously in association with this infection in humans.

Babesiosis is a tick-borne zoonosis caused by intraerythrocytic protozoa. In the United States, human infections are caused predominantly by Babesia microti; infections due to Babesia duncanii nova species [1] (previously called WA1-type and CA1-type) and MO1-type infections have been reported in the Northwest and Midwest, respectively. New England, New York, Missouri, Minnesota, Virginia, Maryland [2, 3], and New Jersey [4] are considered to be areas of endemicity, and cases have been reported from Pennsylvania [5]. Most infections are asymptomatic, but older or immunocompromised persons may develop severe or even fatal disease [2, 3, 6].

Splenic infarction, a recognized complication of malarial infection, has not previously been reported in association with human babesiosis. We describe 2 patients with splenic infarction and Babesia infection.

Patient 1. A 58-year-old Indonesian man presented in July 2005 with fever, chills, myalgias, and left upper quadrant pain on deep inspiration. He reported similar episodes lasting 3–4 days at 6–8-week intervals during the preceding 6 months that had subsided without treatment. The patient visited a physician 3 days before hospital admission and was treated with unspecified antibiotics, but he remained febrile, with complaints of fatigue, anorexia, and a 5-kg weight loss over a 1–2 week period. He denied rashes, nausea, vomiting, diarrhea, chest pain, dyspnea, or cough.

The patient lived in an urban area in New Jersey. He was born in Bali and had immigrated to the United States 35 years before presentation. He had visited Bali since his immigration but not within the previous 9 years. His past medical history included treatment for malaria at 6 years of age. He had frequent contact with 2 dogs and a cat at his ex-wife’s home, but he denied any tick bites.

The findings of an initial physical examination were notable for fever (38.4°C), slight abdominal distension, and left upper quadrant tenderness. Laboratory results included a total leukocyte count of 8000 cells/mm³, a hemoglobin level of 13.6 g/dL, a platelet count of 209,000 platelets/mm³, an erythrocyte sedimentation rate of 81 mm/h, an aspartate aminotransferase level of 102 U/L, and an alanine aminotransferase level of 121 U/L. Chest and abdominal radiograph findings were normal. CT with contrast of the abdomen and pelvis showed a normal liver and mildly enlarged spleen with a regular contour and multiple massive hypodense areas consistent with acute infarcts (figure 1). The patient was admitted to the hospital with presumed subacute endocarditis. Three sets of blood samples were obtained for culture, and treatment was initiated with ampicillin-sulbactam (3 g every 6 h intravenously) plus gentamicin (65 mg every 8 h intravenously). No vegetations, masses, or patent foramen ovale were found on transesophageal echo- cardiograms. All blood cultures were without growth, but the patient continued to be febrile. Blood samples submitted for parasitologic evaluation showed intraerythrocytic ring-like structures with different morphologies and many multiply infected erythrocytes. A preliminary report of “Plasmodium species, not speciated, 0.5% parasitemia” was made, and treatment was initiated with doxycycline (100 mg every 12 h) and quinine (650 mg every 8 h). When thin smears were reviewed the next morning, the report was modified to Babesia species because of the pinform appearance of the rings and the presence of extraerythrocytic parasites (figure 1). Treatment was switched to oral atovaquone (750 mg every 12 h) plus azithromycin (500 mg every 24 h). Doxycycline therapy was continued for possible coinfection with Borrelia species or Anaplasma species. A serum
enzyme immunoassay for Lyme disease had a positive result, but a Western blot test did not confirm infection. The results of Western blot tests for reactivity to *Anaplasma phagocytophilum*, performed at the New York State Department of Health Laboratories (Wadsworth Center, Albany, NY) were positive for both IgM (48 kDa protein band) and IgG (44 kDa, 48 kDa, and 68 kDa protein bands) antibodies. A blood sample referred to the New York City Department of Health and Mental Hygiene and the Centers for Disease Control and Prevention (Atlanta, GA) for molecular testing confirmed infection with *B. microti* and excluded coinfection with *Plasmodium* species. The patient improved, and his liver function test results normalized. He was discharged on day 7 after hospitalization with a hemoglobin level of 12.0 g/dL and a hematocrit of 36.2% with normal indices.

**Patient 2.** A 75-year-old woman who resided in Manhattan, New York, was admitted to the hospital in August 2005 with fever, night sweats, and fatigue. Her medical history included hypertension and colon cancer treated 5 years earlier, without evidence of current disease. She had not traveled recently but had close contact with her daughter’s dog, which traveled frequently to the Pocono Mountains. She denied tick bites, but she recalled seeing a tick on the floor of her home. An outpatient evaluation included CT without contrast of the abdomen and pelvis, which demonstrated a marked increase in spleen size to 17 cm in length (a prior CT had shown the spleen to be 12 cm in length) and a subcapsular hypodensity and an area of low attenuation in the splenic parenchyma but no evidence of malignancy or adenopathy.

At admission to the hospital, the patient’s temperature was 39.8°C, her blood pressure was 100/60 mmHg, and her heart rate was 103 beats/min. The findings of a physical examination were remarkable for splenomegaly and lower extremity edema up to the mid-calf. Laboratory values were notable for pancytopenia, with a total leukocyte count of 1700 cells/mm³ (61% neutrophils and 13% bands), a hemoglobin level of 8.7 g/dL, a platelet count of 55,000 platelets/mm³, a random distribution of red cell distribution width (RDW) of 19.6%, a reticulocyte percentage of 3.51%, an aspartate aminotransferase level of 123 U/L, an alanine aminotransferase level of 119 U/L, an alkaline phosphatase level of 161 U/L, an alkaline phosphatase level of 161 U/L, and a lactate dehydrogenase level of 2435 U/L. Chest radiograph findings were normal. Blood
and urine samples were obtained for culture, and treatment with ceftazidime, filgrastim, and eopoietin alfa was initiated. The initial peripheral blood smears were reported to be negative for malaria and babesia. A bone marrow examination demonstrated a mildly hypercellular marrow with increased erythroid precursors but no malignancy. The patient remained febrile, and although her total leukocyte count and transaminase levels improved, she remained anemic. Multiple cultures of blood, bone marrow, and urine samples were without growth. An additional CT with contrast, obtained 25 days after the initial CT, showed multiple wedge-shaped peripheral splenic infarcts. Because of the persistent anemia and fever, additional peripheral blood smears were evaluated, and rare ring forms suspicious for *Babesia* species were reported. Treatment was started with azithromycin (250 mg every 24 h) and atovaquone (750 mg every 12 h) but was changed to quinine (650 mg administered orally every 8 h) and clindamycin (1200 mg administered intravenously every 12 h) plus doxycycline (100 mg administered orally every 12 h) because of gastrointestinal intolerance. After 7 days, the patient defervesced, her anemia improved, and her other abnormal laboratory findings resolved. An additional blood smear was negative for *Babesia* species, and the patient was discharged from the hospital after 10 days of therapy. Serological tests performed at Quest Laboratories (Teterboro, NJ) for Lyme disease and human granulocytic anaplasmosis had negative results, but the results of evaluation for *Babesia* antibody were borderline positive for IgG at 16 (normal level, <16). A blood specimen sent to the Centers for Disease Control and Prevention for molecular testing was reported to be negative for *Babesia* species, but the sample had been obtained after 5 days of anti-*Babesia* species treatment.

Ten days later, the patient was readmitted to the hospital with spiking fevers, chills, fatigue, weakness, and recurrent pancytopenia. Two blood smears were reported to have findings suspicious for *Babesia* species, and treatment with clindamycin and quinine was restarted. The patient did not improve, and azithromycin and atovaquone were added to the treatment regimen. The patient’s hospital course was complicated by aspiration pneumonia, sepsis, and multiorgan failure, and she died 6 weeks later. Autopsy revealed an enlarged spleen weighing 1160 g with a focally thickened and fibrotic capsule and many large, firm, yellow areas in the parenchyma, consistent with multiple large infarcts. The splenic vessels were unremarkable. On microscopic examination, many *Babesia*-infected erythrocytes were noted within the spleen, liver, and lymph nodes.

**Discussion.** A number of mechanisms have been documented to lead to infection with *Babesia* species, including blood transfusion [7, 8] and transplacental transmission [9, 10], but infection with *B. microti* is most often seen following a tick bite in a person visiting or living in an area of endemicity. One of our patients resided in New Jersey, an area recently recognized as an area of babesiosis endemicity [4], and had contact with animals that could have provided a source of exposure to infected ticks. Our second patient did not live in an area of endemicity and had not traveled, but she had contact with a potentially exposed dog.

*Babesia* infection may be asymptomatic or may present with symptoms ranging from a mild flu-like illness to acute, severe, and sometimes fatal disease [2, 3, 6]. Most patients with symptoms present 1–6 weeks after a bite from an infected tick with malaise, fatigue, myalgia, and anorexia, followed by nausea, vomiting, fever, and shaking chills [2, 3, 6]. However, longer incubation periods of 3 months have been described, and chronic or persistent infection is thought to occur both in humans and animals [2]. Older persons and persons who are even mildly immunocompromised (e.g., because of pregnancy or diabetes) are more likely to develop symptomatic and severe disease. Patients who are asplenic are particularly vulnerable, presumably because of a reduced ability to clear the parasite. Our patients were both older; at 58 years of age, patient 1 was within the age range (50–60 years of age) that is associated with the highest incidence of babesiosis requiring medical intervention [2]. His 6-month course prior to presentation and moderate anemia at diagnosis are consistent with a subacute or chronic presentation. Of note, he also had evidence of human granulocytic anaplasmosis, which may have contributed to the prolonged course of his illness. Coinfection with *A. phagocytophilum* has been reported to moderate the severity of *Babesia divergens* infection in splenectomized calves [11].

Symptoms recurred in patient 2 despite an initial improvement and apparent clearance of parasitemia after treatment that included a 7-day course of intravenous clindamycin plus quinine, which is the currently recommended regimen for severe babesiosis [12]. In this case, relapse was most likely associated with delayed clearance of parasitemia, which has been observed in a substantial proportion of treated patients [13]. In a prospective study, DNA evidence of parasitemia persisted after 7 days of treatment in ~40% of subjects who received azithromycin plus atovaquone and in ~50% of subjects who were treated with clindamycin plus quinine [14]. Pancytopenia may also have contributed to the severity of illness in this case; the etiology of the pancytopenia was unclear. In addition, extensive infarction of the patient’s spleen could have further impaired her ability to clear the parasite.

Hatcher et al. [3] have reported a 41% complication rate among hospitalized patients with severe babesiosis, including acute respiratory failure, acute renal failure, congestive heart failure, and disseminated intravascular coagulation. Myocardial infarction has been described, most likely as a consequence of decreased oxygen-carrying capacity. Although obstruction of vessels by parasitized erythrocytes, with subsequent infarction, is not generally associated with human infections due to *B.
microti or B. divergens, retinal nerve fiber layer infarcts and retinopathy, possibly as a consequence of microobstruction, have been described in 2 patients with babesiosis [15, 16]. We have been unable to find any previous report of splenic infarcts in patients with babesiosis.

Splenic infarctions may be caused by embolic occlusion of the splenic artery or its branches or may be nonembolic, caused by focal stasis and thrombosis [17]. For patient 1, the presumed diagnosis at hospital admission was subacute bacterial endocarditis, but the absence of positive blood culture results or supportive findings on transesophageal echocardiographic examination made this diagnosis unlikely. There was no evidence for other diagnoses commonly associated with splenic infarction, including other embolic disorders, hematological disorders, or autoimmune diseases.

Patient 2 also was without evidence for other causes of splenic infarction, and autopsy findings clearly demonstrated Babesia organisms in vessels in the spleen but no signs of thrombosis or embolism.

In malaria, splenic infarction can occur in patients with splenomegaly caused by chronic infection or in patients who have an underlying hemoglobinopathy in addition to malaria. Splenic infarction is also a rare complication of acute malaria and can occur even at low levels of parasitemia [18].

In both of our patients, levels of peripheral parasitemia were low. Although splenic infarction has not previously been reported in human babesiosis, multifocal coagulative necrosis was observed in the spleen and other organs of Syrian hamsters infected experimentally with the WA1 babesial variant [19]. A number of mechanisms, including microthrombus formation and local release of vasoactive factors caused by RBC lysis, have been proposed [20]. In Plasmodium falciparum, Babesia bovis, and possibly Babesia canis infections, parasitized erythrocytes can be sequestered in small vessels by the interaction of vascular endothelial receptors with erythrocyte “knobs” formed from capping of parasite-derived antigens. However, knob formation has not, to date, been described in B. microti infection. Sequestration may also be a consequence of the inflammatory response. In animal models, Babesia species–infected erythrocytes trigger an acute inflammatory response and activate the coagulation system, leading to increased erythrocyte adhesiveness to the capillaries [21].

Splenic infarction in acute malaria may be under-recognized and under-reported; only 8 cases were reported prior to the case described by Bonnard et al. [18]. If splenic infarction occurs in babesiosis with a frequency similar to that with which it occurs in malaria infection, this complication may be recognized more often as the incidence of Babesia infection increases. We recommend that babesiosis be considered in the differential diagnosis of splenic infarction in patients from areas of endemcity.

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References


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