BRIEF REPORT

Complications of Coinfection with Babesia and Lyme Disease After Splenectomy

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The patient is a 58-year-old man who had a trauma-related splenectomy 25 years ago. In August 2002 he presented to the office with several days of fluctuating fevers of 102° F or higher, rash, malaise, chills, and sweats. He spent a week at Cape Cod before a trip abroad to Brazil, from which he had just returned. His symptoms developed after the first week in Rio de Janeiro, Brazil. He recalled having no mosquito or other insect bites while in Brazil or Cape Cod. His temperature was 100.5° F and he had an eyrthema multiforme-like macular rash on his back and abdomen. An infectious disease specialist was consulted. Laboratory studies were notable for bandemia of 11%, mildly elevated liver injury tests, normal bilirubin, negative babesiosis, ehrlichia, Rocky Mountain Spotted Fever and typhus immunoglobulin IgG and IgM antibody titers, negative hepatitis A and hepatitis B titers, and a negative thick smear for intra-erythrocytic parasites. He was prescribed doxycycline but did not improve. Twelve days after presentation he noted myalgias with associated difficulty walking and was seen in the emergency department. Intra-erythrocytic parasites were noted on a thick blood smear; malaria was diagnosed and the patient was prescribed oral chloroquine.

One day later the diagnosis was changed to babesiosis and treatment was changed to oral clindamycin and quinine. Several days later the patient was hospitalized with dark-colored urine and *Babesia* parasitemia of 4%. He initially received intravenous quinine and clindamycin, but he did not respond and treatment was changed to atovaquone, azithromycin, and a 2-week course of doxycycline. He developed adult respiratory distress syndrome, presumably from a *Babesia* parasitemia now up to 16%; this necessitated an exchange transfusion. The myalgias and weakness worsened and primary demyelinating polyneuropathy was diagnosed on electromyography. A magnetic resonance image of the brain was normal but serum IgM and Western Blotting were positive for Lyme disease. Despite a 1-month course of ceftriaxone, neuropathic symptoms did not improve until he received a 5-day course of intravenous immune globulin (IVIG). Five years later, the patient still has mild residual lower extremity sensory neuropathy but is otherwise well. He did not recall previously receiving vaccinations for encapsulated bacteria and was given meningitis, Haemophilus, and pneumococcal vaccines.

Discussion

At the initial presentation the patient's visit to Cape Cod was not mentioned and the differential diagnosis focused on his history of travel to Brazil. However, because July and August are winter months in South America, the transmission of mosquito-borne diseases in Brazil was, in hindsight, unlikely. Knowing this might have directed the diagnosis back to infectious sources from the United States and may have changed empiric therapy to treatment of babesiosis (known to be a potentially fatal infection in a splenectomized patient). Coinfection with *Babesia* and Lyme disease is common.[1] Some suggest that ticks may host multiple infective agents and that this may increase the number of diseases a patient may present with after a tick bite.[2,3] This patient presented with symptoms and signs of 2 diseases. His fever and malaise were most likely caused by babesiosis; his rash is best explained by stage 2 Lyme disease (note that rash is not a feature of babesiosis or malaria). Given his

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Table 1. Ixodes Tick-Bborne Infections[1]

Disease	Agent	Target Tissues	Vector (Ixodes species)	Prevalence of Infection	Timing of Infection	Early Clinical Features	Diagnostic Tests	Treatment (in Nonpregnant Adults)
Lyme disease	*B. burdorferi*	Systemic bacterial infection	North America (high prevalence in Northeast, Wisconsin, Minnesota, West Coast), Russia, Europe	*Ticks*: 20% to 40% in New England; 0% to 14% in California; 0 to 4.6% in Southern United States	Spring and summer	7–14 day incubation after tick detaches *Stage I*: erythema migrans lesion in 70% of cases (malaise, headache, and fatigue may accompany EM) *Stage II*: generalized annular rash, severe malaise and fatigue, migratory joint pains, neurologic symptoms (meningitis, facial palsies, radiculoneuritis) in 15% of untreated patients, and cardiac conduction abnormalities	Antibodies to *B. burdorferi* *IgM*: positive as early as 2 weeks after infection *IgG*: postitive 6 weeks after infection; Western blotting	*Stage I*:Doxycycline 100 mg; Cefuroxime 500 bid; or Amoxicillin 500 mg tid for 14 days *Stage II*:Ceftriaxone 2 g IV bid for 14 days
Babesiosis	*B. microti*	Red blood cells	North America (high prevalence in Northeastern and Pacific Northwestern United States)	*Ticks*: 20% to 40% in New England *Humans*: 1% to 5%	Peaks in June	Incubation, 1 to 3 weeks Gradual onset of flu-like syndrome: malaise, anorexia, chills, myalgias, arthralgias, nausea, vomiting, cough, abdominal pain, sore throat Fever up to 40° C, hepatosplenomegaly Lymphadenopathy, rashes Anemia, thrombocytopenia, mild leukopenia, atypical lymphocytosis, elevated sedimentation rate, elevated liver injury markers Dark urine in severe cases. Intravascular hemolysis, hemoglobinuria, and proteinuria Increasing severity in patients older than 50, medical comorbidities Asplenia: ARDS, CHF, ARF, DIC Fatality rate of 20% to 40%	*Peripheral blood smear*: intraerythrocytic parasites, **thin** smears required to distinguish trophozoites of babesia vs. Malaria. Maltese cross arrangement of trophozoites uncommon but pathognomonic Indirect immunofluorescent antibodies become positive at least a week after onset of illness IgM: sensitivity, 91% specificity, 99% IgG: Sensitivity, 88% to 96% Specificity, 90 −100% PCR amplification can detect parasitemia at levels as low as 3 parasites per 50 μL of blood	Atovaquone 750 mg bid and azithromycin 250 mg qd for 10 days or clindamycin 600 mg po tid or 300 to 600 mg IV q6 hours and quinine 650 mg poq 6 to 8 hours Exchange transfusion for parasitemia >10% or significant hemolysis, renal, pulmonary, or hepatic compromise
Human granulocytic anaplasmosis	A. phagocytophilum	Neutrophils	Ixodes species			Fever, chills, headache Thrombocytopenia, leukopenia, elevated liver injury tests Increasing severity in immunosupression, chronic inflammatory illnesses and underlying malignancy	*Peripheral blood smear*: intragranulocytic inclusions Acute and convalescent phase antibodies	Doxycycline 100 mg bid for 10 days rifampin 300 mg bid for 10 days

medical and travel histories, a peripheral blood smear showing intra-erythrocytic parasites was most suggestive of babesiosis. Peripheral blood smear is the definitive method of diagnosis of babesiosis, but **thin** blood smears are usually required to distinguish between the trophozoites of *Babesia* and *Malaria*. Polymerase chain reaction amplification can detect parasitemia at levels as low as 3 parasites per 50 μL of blood, which can provide a diagnosis within 24 hours. IgM and IgG indirect immunofluorescent antibody tests have adequate sensitivity and specificity for diagnostic purposes (IgM, 91% to 99%; IgG, 88% to 96% and 90% to 100%, respectively). However, antibodies do not develop for at least a week after the onset of illness, rendering serology less useful in the early diagnosis of acute infection. Treatment failures are common in babesiosis and Lyme disease, thus the need to change antibiotics during treatment is an anticipated complication.[4]

Although neuroborreliosis may respond to IVIG, it is not known by what mechanism patients respond. IVIG has an off-label indication for therapy of neuroborreloisis. In the last published report on this topic, Crisp and Ashby[5] proposed that the immune-modulating properties of IVIG might ameliorate Lyme disease by any of the following mechanisms: inhibition of cytokines, competition with autoantibodies, inhibition of complement deposition, interference with Fc receptor binding on macrophages or B-cells, or interference with T-cell recognition of antigens.[5]

This case highlights the importance of a precise and detailed travel history in the febrile traveler and, in particular, one who has a history of splenectomy. Patients with immunocompromised systems are at greater risk for a more prolonged and severe courses of illness, especially with multiple infectious etiologies, illustrated here with Lyme disease and babesia.[6] In these patients, reasoning to the single most likely cause of illness may not be the best approach to diagnosis and empiric treatment. Familiarity with tick-borne diseases is important and may become more so as the habitats of humans and ticks increasingly intersect.[7] Knowledge of which supporting and confirmatory laboratory tests to order is useful in expediting diagnosis and treatment. Finally, when treating any disease it is valuable to know which treatments are based on reliable research, such as the antibiotic choices for babesiosis and Lyme disease, and those which are anecdotal, such as IVIG treatment of neuroborreliosis.

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