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**Two Cases of Co-Infection with Babesiosis and Lyme Disease**

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**Case 1**

The patient is a 71-year-old female with past medical history significant for hypothyroidism and hyperlipidemia who presented to Thomas Jefferson University Hospital (TJUH) with complaints of myalgias for 6 weeks duration. The patient stated that she had begun an exercise program to lose weight and had subsequently noticed body aches and increased fatigue. She had presented to an outside hospital with these complaints, was told that the etiology was musculoskeletal, and was prescribed naproxen for pain relief. The pain did improve slightly with the naproxen but she noticed a rash and hives after starting the medication and stopped taking it. Her symptoms continued for about 6 weeks and she decided to come to our emergency department when she was unable to obtain an appointment with her primary care physician. She also noted that 2 days prior to admission she had an increase in her temperature to 100˚ F. She had been feeling fevers since this time coupled with chills and sweating. The fevers were not cyclic in nature.

On presentation the patient noted that her body aches were diffuse and constant. The pain itself was a “dull” pain and “soreness”. There was no radiation or exacerbating or alleviating factors. There were no other associated symptoms except the fevers mentioned above. She denied any joint pains or swelling, as well as any tenderness to palpation of her muscles or joints. She did note that she had mild nasal congestion but no rhinorrhea, coughing, or shortness of breath. She also had had “tea-colored” urine about 1 day prior to admission but no dysuria. She denied any abdominal pains, constipation, nausea, vomiting or diarrhea. Her review of systems was positive for malaise, increased fatigue and headache, all noted above. She denied any respiratory symptoms, abdominal symptoms or urinary symptoms. There was no focal muscular pain, joint pain, or swelling.

The patient had hypothyroidism controlled with levothyroxine, hyperlipidemia controlled with ezetimibe, simvastatin and Omega-3-acid ethyl esters, seasonal allergies controlled with fexofenadine, and depression controlled with duloxetine. She had been stable on these medications and there were no new medications started. She was allergic to sulfamethoxazole/trimethoprim and naproxen, with both causing a rash.

She originally immigrated to the United States from Columbia in 1972 and had not travelled outside of the United States recently. She denied any sick contacts. She worked as a weaver in the past but currently worked as a home health aide at a farm in rural Pennsylvania. She did report tick and mosquito bites in the past but did not recall any new rashes on her body. Her family history was significant for a mother with hepatocellular carcinoma, deceased, and a father with end-stage renal disease, also deceased.

Her physical exam was positive for scant bibasilar crackles that cleared with coughing. She did not have any lymphadenopathy. Her skin exam revealed no rashes or target lesions. She had full strength in all her extremities and did not have a gait disturbance. She did not have any meningeal signs or any focal neurological deficits.

Given the nature of her symptoms, the acute nature of her fevers, and the time of year, influenza was initially suspected. There was also a concern for subacute endocarditis and as a result she was admitted to the hospital for further testing. Her influenza A and B viral polymerase chain reaction (PCR) tests were negative, as was her respiratory viral panel assay. Blood cultures and hepatitis B and C serologies were negative. Laboratory results (total bilirubin 1.8 mg/dl, direct bilirubin 0.3 mg/dl and lactate dehydrogenase 325 U/L on admission) were concerning for hemolysis, and, given her history of tick exposure, thick and thin blood smears were evaluated for parasites. Giemsa staining demonstrated inclusion bodies in the red blood cells, with a total parasitemia level of 0.07%. She was also found to have a positive Lyme antibody, confirmed with PCR. This overall clinical presentation was consistent with Babesia (*B. microti* later confirmed with PCR) and Lyme co-infection. She was prescribed atovaquone 750mg twice a day for 10 days and azithromycin 250mg once a day for 10 days for treatment of Babesiosis and doxycycline 100mg twice a day for 30 days to treat her Lyme disease. Two weeks after discharge she had completed her antibiotic course, her strength had returned to normal, and all her previous symptoms had resolved.

**Case 2**

A 44-year-old female from suburban Southeastern Pennsylvania presented to TJUH with fevers and headache. Her past medical history was significant for type 2 diabetes mellitus, obesity, pancreatic mucinous cystic neoplasm of the tail of the pancreas status post distal pancreatectomy and splenectomy 3 years ago. The patient reported that intermittent fevers began 8 days prior to presentation, but she was unsure of a pattern or cyclical nature. She stated her temperature maximum at home was 103˚ F. Her fevers were associated with intermittent headaches that she described as “pounding” in quality and located both at the back of her head and behind her eyes. She did not describe it as the worst headache of her life. She had occasionally been taking acetaminophen and ibuprofen with minimal to no relief of pain. She denied abdominal pain, nausea, vomiting, and rash.

The patient reported travel one month prior to the mountains of Northeastern Pennsylvania, where she spent a significant amount of time outside in wooded areas. She denied finding ticks or bite marks on her body, and had not had any rash since that time. Travel history was also notable for a trip to North
Carolina 6 months prior to admission and travel to China 10 years ago.

Physical examination was significant for fever with temperature maximum of 103.1°F, tachycardia with heart rate 119 bpm, and blood pressure 98/51 mmHg. Skin exam, including inspection of scalp, revealed no rash. Examination was otherwise significant for obesity. Pupils were equally round, reactive to light and anicteric. Neurological examination revealed cranial nerves 2 through 12 to be intact. Motor function was grossly normal, sensation intact throughout.

Laboratory studies revealed leukocytosis with bandemia, thrombocytopenia and hemolysis. Electrolyte panel was within normal limits. There was a slight transaminitis in a mixed hepatocellular/cholestatic pattern. Given her headache and fever, lumbar puncture was performed and cerebrospinal fluid analysis was unremarkable. A preliminary review of blood smear revealed intra-erythrocyte ring forms with an initial parasite load of 18%. Polymerase chain reaction for Babesia microti deoxyribonucleic acid was positive, confirming suspicion for Babesia infection. Serology for HIV, Ehrlichia, Rocky Mountain Spotted Fever, Rickettsia yphi, and anaplasmosis was negative. Lyme immunoglobulin G and immunoglobulin M antibodies were positive. The overall clinical picture was consistent with a co-infection of both babesiosis and Lyme disease. Further, given her relatively large parasite burden it was determined to treat this patient as severe babesiosis.

Treatment plan included a course of clindamycin and quinine for her severe babesiosis, as well as doxycycline to cover Lyme disease. The patient’s blood parasite level was monitored, and on the second hospital day it increased to 36% from 18%. In response to this rapid rise in the parasite burden exchange transfusion was implemented; she tolerated this procedure without any complications. On the following day her parasite load decreased to 0.07% and remained stable around this level. Patient was deemed stable and discharged home to finish her antibiotic regimen.

Discussion

Babesiosis is an infectious disease caused by parasitic protozoa of the genus Babesia. Human beings are only accidental hosts—Babesia is normally maintained amongst rodent reservoirs and dependent on the Ixodes scapularis tick for transmission. As a result, infection typically involves residence in, or travel to, locations common to the Ixodes tick: the Northeastern and upper Midwestern United States (Figure 1). Most cases are reported during the summer and spring months when the protozoa is in its nymph or adult stage.

Clinical manifestations follow an incubation period of 1-6 weeks and initially mimic an acute viral infection with gradual onset of fever, fatigue and malaise. Unlike Lyme disease, there is no rash associated with babesiosis. Laboratory evaluation may reveal evidence of hemolysis (low haptoglobin, elevated lactate dehydrogenase and indirect bilirubin); a subsequent thin peripheral smear will display the characteristic intraerythrocytic parasites (Figure 2). Interestingly, the pathognomonic "maltese cross" sign (Figure 3) is a relatively rare formation but can be appreciated if an erythrocyte is found when the parasite in an asexual reproduction.

In select patients, progression to severe disease can be rapid and can include disseminated intravascular coagulation, acute respiratory distress syndrome, kidney and heart failure and myocardial or splenic infarction. Risk factors for severe disease include patient age > 50 years, immunocompromise, co-infection with human immunodeficiency virus and, more pertinent to our cases, previous splenectomy (Case 2) and co-infection with Borrelia (both cases).10

Several sources corroborate the poor outcome associated with asplenia, both functional or post-splenectomy.3,8,10,11 In their
landmark study, White et al. showed that 10 of 16 (63%) patients post-splenectomy experienced severe disease compared to only 42 of 121 (34%) patients in the control group. A European study found that babesiosis almost exclusively affects those without a functional spleen. The exact mechanism by which asplenia contributes to severe disease has not yet been elucidated, but Vannier et al suggest that the spleen allows for compartmentalization of the inflammatory reaction (largely IFN-γ and TNF-α based) necessary to activate antiprotozoal macrophages. In the absence of this compartmentalization, systemic inflammation can develop. The spleen is also necessary for removing senescent and malformed erythrocytes. In malaria Plasmodium falciparum manages to avoid widespread splenic removal of its infected erythrocytes through cytoadherence (red blood cell sequestration in the capillaries of distant organs). This process has been demonstrated in Babesia bovis, but is not known to occur in Babesia microti, and as a result the spleen may play a much larger role in this disease response.

Another risk factor for severe disease, co-infection with Borrelia burgdorferi is also well-documented—unsurprising given that up to 1 in 3 New Jersey ticks carry Borrelia burgdorferi and 1 in 11 carry Babesia microti. In a recent study, 14 of 70 patients (20%) with serologic evidence of babesiosis also had evidence of Lyme disease. Co-infected patients experienced more severe clinical manifestations and a longer duration of symptoms. While Borrelia remains the overall more common pathogen, newer trends show that the incidence of Babesia is on the rise.

Krause et al reported a four-fold increase in new babesiosis cases relative to Lyme disease in Rhode Island. Expansion of human habitats into areas where the tick and rodent population is high will likely lead to continued zoonotic infections, and thus co-infection.

It is important to assess for these risk factors because the presence of severe disease changes the treatment paradigm. While mild illness can be treated with a combination of azithromycin and atovaquone, the recommendation for severe disease is paired clindamycin (300-600mg IV every 6 hours) and quinine (650 mg by mouth every 6 to 8 hours). Doxycycline (100 mg by mouth every 12 hours) is added to cover confirmed Borrelia. Baseline and follow-up electrocardiograms are important in trending the corrected QT interval while on quinine. Daily hemoglobin, hemolysis labs and blood parasite levels should be monitored while the patient remains hospitalized. Significant hemolysis, severe disease and/or parasitemia > 10% are all indications to begin exchange transfusion therapy. As clinical status improves and parasite levels remain low, the transition can be made to outpatient therapy. There are no specific guidelines for the duration of therapy, but in Case 2, the patient was treated with 2 weeks of clindamycin/quinine and 3 weeks of doxycycline following documented parasite clearance.

References

"Love Park"
photograph by Soham Vakil, MD

"Love Fountain Sky"
photograph by Paurush Shah, MD