Symptomatic Babesiosis in Systemic Lupus Erythematosus
Report of a Case and Review of the Literature

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Symptomatic babesiosis is a complication of a disease transmitted to immunocompromised patients via tick-borne inoculation or through blood transfusion. We report a case of a 43-year-old African American woman with severe systemic lupus erythematosus that required renal transplantation and hemodialysis for renal failure and multiple transfusions for massive hemorrhaging from a colonic arteriovenous malformation. For treatment of persistent SLE activity, the patient was maintained on low-dose prednisone, hydroxychloroquine, and azathioprine. The patient developed high fevers and was found to have a hemolytic anemia with intraerythrocytic ring-shaped trophozoites characteristic of babesiosis. The patient was successfully treated without serious complications or relapse. Due to her history of multiple recent blood transfusions and lack of travel out of New York, it was believed that the disease was contracted from transfusions. Since babesiosis is a curable disease if recognized, and the fact that the blood supply is not screened for this parasite, the diagnosis should be entertained as another cause of opportunistic infection in systemic lupus erythematosus (SLE). A case is made for blood bank screening in endemic areas.

Case Report
A.D. is a 43-year-old female New York resident of West African descent who was diagnosed with systemic lupus erythematosus (SLE) in 1995. She was living in Africa and working in the Peace Corps when she developed a fever 104° F accompanied by shaking chills. Originally she was thought to have malaria, but the diagnosis was excluded after extensive testing of her sera at the Center for Communicable Diseases in Atlanta. Over the course of the next 5 years, she developed arthritis, a malar rash, Raynaud’s phenomenon, positive ANA, and dsDNA, and despite treatment with high-dose steroids and several courses of intravenous cyclophosphamide, she developed rapidly progressive nephritis and renal failure. She received a cadaveric renal transplant in 2000 and was maintained on tacrolimus and oral prednisone therapy. In 2002, within months of stopping tacrolimus, the graft failed, necessitating hemodialysis 3 days a week which continues to this day. In 2005, she became short of breath and was diagnosed with interstitial pneumonitis, either secondary to lupus or to lung injury induced by previous cyclophosphamide treatments. There was no evidence of opportunistic infection or tuberculosis. In 2008, she required a total of 60 units of packed red blood cells transfused (the last transfusion in December, 2008) at another institution because of massive gastrointestinal bleeding secondary to a colonic arteriovenous malformation, which was obliterated successfully by laser. Because of presumed increase in lupus lung activity, she was treated with prednisone 40 mg daily which was tapered to 10 mg daily due the development of steroid myopathy. Azathioprine 100 mg daily and hydroxychloroquine 200 mg twice daily were added as steroid-sparing agents. Her activity was mostly restricted to a wheelchair with continuous oxygen 3 L/min by nasal canula at rest and sleep, increased to 4 L/min for walking. The patient has not left her home in Manhattan for many years and has never visited the coastal areas of Long Island, Connecticut, or Massachusetts.

In January 2009, the patient developed fever and shaking chills that persevered when she was seen for outpatient dialysis 2 days later. The patient was sent to
the emergency room at Tisch Hospital of the New York University-Langone Medical Center and noted to be febrile (103.9°F) and tachycardic (138 bpm) and with an oxygen saturation of 88% on 3 L that improved to 98% on 5 L oxygen by nasal cannula. ECG revealed sinus tachycardia and a chest radiograph showed no acute findings. She had a white blood cell (WBC) count of 3,100 µL with 59% neutrophils (37% bands), a hemoglobin and hematocrit of 10.2 g/dl and 31.8, respectively, and a platelet count of 87,000 µL. Serum electrolytes were significant for a BUN of 15 mg/dl and a creatinine of 3.0 mg/dl (stable from baseline). Serum LDH was 1432 U/L. At presentation, a lupus flare was suspected due to the presence of high fevers, respiratory insufficiency, and lab results suggestive of hemolytic anemia. However, an incidental review of thin and thick smears showed intraerythrocytic ring-shaped trophozoites characteristic of babesiosis (Fig. 1) occupying 4.7% of examined red blood cells. Due to these findings, the diagnosis of babesiosis was made and the patient was started on a 6-day course of azithromycin 500 mg IV daily and atovaquone 5 mg orally every 12 hours. Tests for serum Lyme antibodies were negative, thus ruling out concomitant Lyme infection. There was no evidence to suggest ehrlichiosis. However, an incidental review of thin and thick smears showed intraerythrocytic ring-shaped trophozoites characteristic of babesiosis (Fig. 1) occupying 4.7% of examined red blood cells. Due to these findings, the diagnosis of babesiosis was made and the patient was started on a 6-day course of azithromycin 500 mg IV daily and atovaquone 5 mg orally every 12 hours. Tests for serum Lyme antibodies were negative, thus ruling out concomitant Lyme infection. There was no evidence to suggest ehrlichiosis. However, an incidental review of thin and thick smears showed intraerythrocytic ring-shaped trophozoites characteristic of babesiosis (Fig. 1) occupying 4.7% of examined red blood cells. Due to these findings, the diagnosis of babesiosis was made and the patient was started on a 6-day course of azithromycin 500 mg IV daily and atovaquone 5 mg orally every 12 hours. Tests for serum Lyme antibodies were negative, thus ruling out concomitant Lyme infection. There was no evidence to suggest ehrlichiosis. However, an incidental review of thin and thick smears showed intraerythrocytic ring-shaped trophozoites characteristic of babesiosis (Fig. 1) occupying 4.7% of examined red blood cells. Due to these findings, the diagnosis of babesiosis was made and the patient was started on a 6-day course of azithromycin 500 mg IV daily and atovaquone 5 mg orally every 12 hours. Tests for serum Lyme antibodies were negative, thus ruling out concomitant Lyme infection. There was no evidence to suggest ehrlichiosis. However, an incidental review of thin and thick smears showed intraerythrocytic ring-shaped trophozoites characteristic of babesiosis (Fig. 1) occupying 4.7% of examined red blood cells.

**Discussion**

Human babesiosis is a tick-borne parasitic infection that can result in an intraerythrocytic infection and hemolytic anemia. Many patients may carry the parasite but have minimal or no symptoms. In the United States, most cases are caused by the parasite *Babesia microti*, which is most often carried on the tick species *Ixodes scapularis*. Considering that *I. scapularis* is also often the vector of *B. burgdorferi* (the primary parasite for Lyme Disease) and *A. phagocytophilum* for human ehrlichiosis, it is common for persons afflicted with Babesia to have concurrent infections. This is particularly true along the coastal states of the Northeastern United States south of Massachusetts. A study from 2002 showed a co-infection rate among patients presenting with symptoms suggestive of a tick-borne infection, confirming a 1992 study showing a 23% co-infection rate among New York State residents. Concomitant *Babesia microti* and Lyme Disease have been reported as far west as Minnesota and Wisconsin, with a similar increased prevalence during the spring and summer months.

Despite the similar geographical distribution and transmission of *B. burgdorferi* and *Babesia microti*, determining the prevalence of babesiosis is more difficult to ascertain. Whereas Lyme disease may have a characteristic manifestation that is pathognomonic for that disease (i.e., the rash of *erythema chronicum migrans*), babesiosis is often asymptomatic or can present with non-specific flu-like symptoms, such as fever and chills (as were seen in our patient) as well as fatigue, sweats, or myalgias. Additionally, in co-infected patients, the symptoms of babesiosis are often attributed to the more common Lyme disease, and the diagnosis can be missed. For these reasons, the true incidence of babesiosis is probably vastly underestimated. When suspected, a CBC showing anemia and thrombocytopenia, as well as a blood smear showing intraerythrocytic parasites can confirm the diagnosis. The use of IgM antibody to babesiosis as well as PCR can also be used to confirm the diagnosis.

Of the patients that are symptomatic from babesiosis, the majority are elderly or immunocompromised, either with a concurrent infection such as HIV, have a malignancy, are being treated with immunosuppressive therapy, or are asplenic. The manifestations of symptomatic babesiosis in immunocompromised patients are generally similar to those of immunocompetent patients; however, these individuals are also at risk for severe *Babesia* complications including a prolonged and relapsing course, respiratory failure, DIC, congestive heart failure, renal and liver failure, or death. There are a few cases of symptomatic babesiosis reported in transplant patients on immunosuppressive therapy. Only two of the reported cases (those which were post-renal transplantation) received azathioprine, similar to our patient. This further supports the hypothesis that immunosuppressive agents such as azathioprine increase the risk of developing symptomatic babesiosis.
The link between symptomatic babesiosis and asplenia has also been documented, including one case of a surgically asplenic SLE patient who developed symptomatic babesiosis. It has been said that SLE itself is a condition of functional asplenia, in that there is impairment in the clearance of circulating immune complexes, in some cases due to chronic hemolysis, splenic infarction, rupture or atrophy. Babesiosis, in turn, may cause a functional asplenia through similar mechanisms. Additionally, there are reported cases of symptomatic babesiosis associated with sickle cell anemia, a hemolytic disease known to cause splenic infarction. One of the important mechanisms postulated for prevention of malaria is the effect of anti-malarial drugs on cell membranes, preventing the parasite from cellular penetration. Indeed, quinine was in the original protocol for the treatment of babesiosis, but the high rate of adverse drug reactions and persistence of infection despite therapy, makes this a poor therapeutic choice for babesiosis. The beneficial mechanism of action of hydrochloroquine in SLE is not fully understood, but possibly there is resistance to immune complex activation on the cell membranes of target cells. Of interest, hydroxychloroquine in our case did not prevent cellular penetration and hemolysis by the Babesia parasite. The prevailing treatment protocol for babesiosis in both immunocompromised and immunocompetent patients is atovaquone and azithromycin, which have shown to be superior to clindamycin and quinine, with equal efficacy and greatly reduced incidence of adverse drug reactions.

The presence of asymptomatic carriers makes babesiosis a public health problem, as the blood supply is not routinely screened. Red Cross guidelines state that those with a history of babesiosis are ineligible to donate blood. However, this restriction fails to prevent those with asymptomatic infections from donating blood. As a result, blood transfusion remains a significant mode of spread of babesiosis, and the risk of transmission is increased with multiple transfusions. The medical literature is replete with reports of babesiosis contracted from infected blood transfusions. Additionally, numerous cases have linked the spread of Babesia microti from one donor to multiple recipients. The US Food and Drug Administration reports 70 cases of transfusion-transmitted babesiosis since 1997, with 9 deaths since 1998. Since infection with Babesiosis does not require federal or state notification, this incidence rate is most likely a gross underestimation. Considering that our patient has not visited any wooded or coastal areas in years and considering her numerous recent transfusions, she is most likely a case of transfusion-transmitted babesiosis.

We, therefore, conclude that our patient’s development of symptomatic babesiosis was most likely multifactorial, including an immunosuppressed state due to SLE and azathioiprine treatment. While our patient’s presentation and treatment was uncomplicated and her recovery was full, babesiosis remains a potentially fatal infection for immunosuppressed patients. Current Red Cross guidelines only prohibit donation by known previously-infected persons. We, however, feel that all blood obtained from endemic areas should be screened for the Babesia microti.

Disclosure Statement
The authors have no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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