Fatal Babesiosis in an Immunocompetent Patient

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ABSTRACT

Human babesiosis is an emerging infectious disease with a progressively rising number of cases in the Northeast over the last few decades. We report a case of fatal babesiosis in a 48-year-old male without significant risk factors for a severe presentation. Clinicians should be aware that even in patients without the classic risk factors of asplenia, advanced age, and immunocompromised status for severe presentations of babesiosis, a deadly case can present. There is a need for further research regarding optimal treatment options for severe babesiosis considering the questionable efficacy of red blood cell exchange (RCE) transfusion in patients who do not improve on the current first-line antimicrobials.

KEYWORDS: babesia, babesiosis, red cell exchange, exchange transfusion, therapeutic apheresis

ABBREVIATION: RCE: red blood cell exchange

INTRODUCTION

Babesiosis is an intraerythrocytic infectious disease caused by the protozoa of the genus Babesia. The parasitic infection results in hemolysis of red blood cells (RBCs) with infection severity ranging from asymptomatic to mild-moderate characterized by a febrile hemolytic illness, and severe fulminant disease which can ultimately lead to death. It is typically transmitted by an arthropod vector, most commonly the *Ixodes scapularis* tick, but can also be transmitted uncommonly by blood transfusion, organ transplantation, and transplacentally. *Babesia microti* is the principal species causing the human disease in the United States, which is primarily seen in the northeastern and upper midwestern states.[1]

Severe human babesiosis is characterized by a parasitemia ≥4%, pronounced laboratory abnormalities, and complications that can include hemodynamic instability, encephalopathy, renal failure, disseminated intravascular coagulation (DIC), hepatic failure, acute respiratory distress syndrome (ARDS), myocardial infarction (MI), and death. The main risk factors for severe babesiosis are asplenia, an immunocompromised state including those with HIV/AIDS, malignancy, chronic kidney disease, on immunosuppressive therapy, and individuals age >50.[2-4] Current first-line treatment entails a dual antimicrobial regimen of azithromycin and atovaquone. In the minority who do not respond to antimicrobials, RCE transfusion is weakly recommended by the Infectious Disease Society of America (IDSA) for severe babesiosis, often with parasitemia >10% or with mild/moderate parasitemia with severe hemolytic anemia (hemoglobin <10 g/dL), and/or severe renal, pulmonary, or hepatic impairment.[5]

Here, we present a case of severe babesiosis that proved fatal in an individual lacking significant risk factors, who did not receive an RCE.

CASE REPORT

A 48-year-old male with a past medical history of type 2 diabetes (recent hemoglobin A1c of 13.5%), obesity, and mild intermittent asthma presented to the emergency department (ED) in July with a two-week history of worsening fatigue, generalized weakness and intermittent subjective fevers. The patient endorsed headaches, vision changes, nausea, nonbloody emesis, nonbloody diarrhea, and dark urine. He denied chest pain, dyspnea, abdominal pain, arthralgias, myalgias, rashes or chills. Of note, the patient worked as a landscaper. He denied any known recent tick or animal exposures, any recent travel, or previous blood transfusions.

On arrival to the ED, the patient was tachycardic, afebrile, and normotensive. Physical exam was notable for an ill-appearing male who was fully oriented with jaundiced skin,

Figure 1. Patient's peripheral blood smear demonstrating small ring-form parasites, consistent with babesiosis.

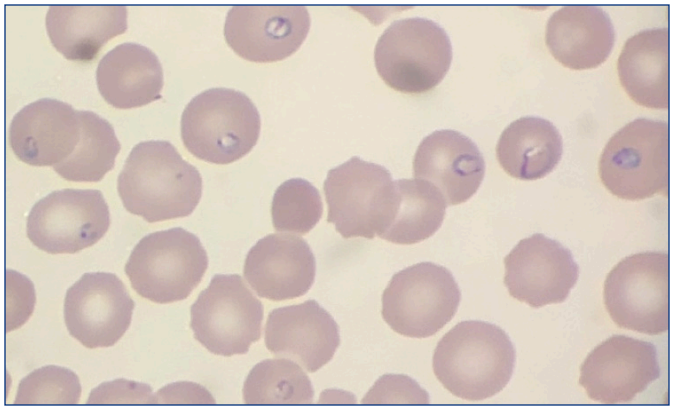


Figure 2. Initial presenting results from patient's blood parasite blood smear, accordant with severe babesiosis (≥4% infected RBCs).

BLOOD PARASITES	
Blood Parasite Path Review	see below * c !
Blood Parasite Prep	POSITIVE * !!
Number Infected RBC	901,630
Percent Infected RBC	25.19
Thick Smear for Bld Parasite	POSITIVE !!

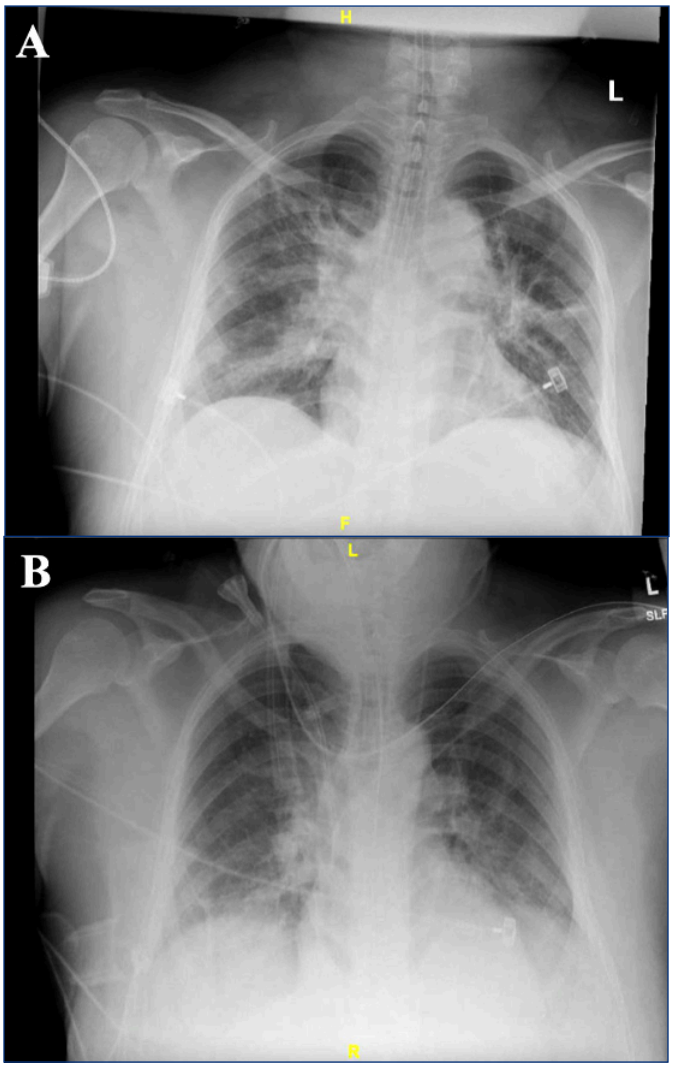
icteric sclera, clear lungs, soft abdomen without organomegaly, and no rashes. Blood parasite smear returned with small ring-form parasites (**Figure 1**) with 25% RBCs infected consistent with babesiosis (**Figure 2**). Complete blood count revealed a hemoglobin of 11.1 g/dL, white blood cell count of 12.4 x10^9/L, and platelet count of 11x10^9/L. Basic metabolic panel was notable for creatinine of 5.96 mg/dL (patient's baseline creatinine was 0.9–1.0 mg/dL), blood urea nitrogen of 108 mg/dL, and anion gap of 20. Hepatic function panel was remarkable for aspartate aminotransferase of 314 IU/L, alanine transaminase of 107 IU/L, alkaline phosphatase of 137 IU/L. Lactate was 5.8 mEq/L. Azithromycin and atovaquone were started for babesiosis treatment, as well as doxycycline to cover possible co-infection with Lyme disease and anaplasmosis (both later returned negative).

Following admission to the medical intensive care unit, the patient was tachypneic and hypoxic, requiring supplemental oxygen. Repeat parasite blood smear two hours following the initial smear returned with 17.5% of RBCs infected. The Transfusion Medicine service was then consulted for RCE consideration, who recommended deferring an exchange transfusion.

The next day, the patient required endotracheal intubation with mechanical ventilation after developing altered mental status and worsening tachypnea. A chest X-ray was obtained and revealed multifocal bilateral airspace opacities suggestive of pulmonary edema (**Figure 3**), consistent with a diagnosis of ARDS. Total bilirubin returned at 24.4 mg/dL, direct bilirubin at 19.6 mg/dL, and phosphorus at 10.2 mg/dL. The patient soon became hypotensive and required vasopressor support. Transfusion Medicine and Infectious Disease services recommended against RCE due to the patient's hemodynamic instability and RCE's limited efficacy. Shortly after, the patient was started on continuous venovenous hemofiltration due to his renal failure, worsening acidemia and hemodynamic instability.

The patient's hemodynamics continued to deteriorate, requiring three vasopressors to maintain adequate perfusion pressures. This was further complicated by episodes of atrial fibrillation with rapid ventricular response, requiring synchronized cardioversion. During this time, the patient developed worsening hemolytic anemia, worsening acidemia and new acute liver failure, despite a reduction in parasitemia

Figure 3. Patient's chect X-rays revealing worsening multifocal bilateral airspace opacities and pleural effusions.
(**A**) hospital day 2; (**B**) hospital day 3.



(10%). At this point, the patient's family requested that he be transitioned to comfort measures only and the patient passed soon after.

A few days following the patient's death, babesia studies returned with PCR positive for *B. microti* and positive antibody findings (IgG 1:128 and IgM 1:160) confirming the babesiosis diagnosis.

DISCUSSION

Human babesiosis is an emerging infectious disease with a progressively rising number of cases in the Northeast, including Rhode Island, over the last few decades.[1] The incubation period of *B. microti* following a tick bite is typically between one to four weeks. Tick-borne babesiosis in the United States is predominantly seen between May and September.[6] Patients whose daily lives require frequent

exposure to high grass, such as our patient, should be educated on the importance of wearing long sleeves and using tick repellant for primary prevention of tick-borne illness.

Severe human babesiosis from *B. microti* is typically seen in an adult with at least one of the three main risk factors: asplenia, immunosuppressed state, or age >50.[2-4] Notably, our patient did not have any of these risk factors. In regard to babesiosis, an immunosuppressed state has been previously defined as one due to an immunodeficiency disorder, malignancy with or without active chemotherapy, immunosuppressive therapy for solid-organ or stem-cell transplantation, or tumor necrosis factor-alpha inhibitors.[2-3, 7-8] While the patient did have a history of poorly controlled diabetes mellitus, diabetes has not previously been shown to be a significant risk factor for severe babesiosis.[3] Chronic medical conditions have been shown to be a significant risk factor for transfusion-associated babesiosis but are not associated with the tick-associated disease.[9]

Complications of severe babesiosis include hemodynamic instability, encephalopathy, renal failure, DIC, hepatic failure, ARDS, and MI. These complications most commonly occur in those with severe anemia (hemoglobin <10 g/dL) and in those with parasitemia ≥10%.[3] Our patient developed acute renal failure, septic shock, acute liver failure and ARDS during his hospitalization.

Treatment is not recommended for asymptomatic B. microti infections. For both mild/moderate and severe cases, current first-line treatment entails a dual antimicrobial regimen of azithromycin and atovaquone. Severe babesiosis requires hospitalization. Prior to the IDSA guideline change in 2020, clindamycin plus quinine was recommended for severe infections. The new guidelines recommend azithromycin plus atovaquone for both mild/moderate and severe infections, with clindamycin plus quinine as an alternative regimen in cases of treatment failure. While treatment is effective for the vast majority of B. microti infections, there remains a dearth of safe, proven adjunctive treatments for severe presentations. Currently, RCE is weakly recommended (low-quality evidence) by the IDSA for severe babesiosis presenting with parasitemia >10% or with mild/moderate parasitemia with severe hemolytic anemia (hemoglobin <10 g/dL), and/or severe renal, pulmonary, or hepatic impairment.[5] Although our patient presented with high-grade parasitemia with end-organ dysfunction, it was thought he presented too late in his illness for RCE to have an effect. Pigment nephropathy from hemolytic anemia was thought to be a large contributor to his severe renal failure, which would not be corrected with RCE. It should also be noted that our hospital system typically avoids RCEs. A previous paper that also studied hospitalized patients in Rhode Island had reported four deaths out of 19 patients who received an RCE as opposed to no deaths out of nine patients who received antimicrobials alone.[10] Conversely, a recent retrospective analysis, at another large tertiary northeastern hospital that used parasitemia >10% to determine need for RCE, showed that parasitemia levels are closely associated with disease severity, and the authors concluded the use of parasitemia >10% seemed to be a reasonable indicator for RCE. Their review found that increasing parasitemia was associated with an increased severity of the most common complications of babesiosis – hematologic, pulmonary, renal, and hepatic impairment. Nineteen patients received RCE, 17 of whom met AFSA/IDSA clinical indicator criteria of parasitemia >10%. The mortality rates were 10.5% (2/19) and 1.4% (1/72) in the RCE and non-RCE groups, respectively. However, given that the patients treated with RCEs were generally more ill, no definitive conclusions could be made regarding which treatment was more efficacious.[11] Based on the conflicting evidence of RCE in babesiosis compared to antimicrobials alone, it is possible that our patient would have expired even if one or multiple RCEs were performed.

CONCLUSION

In conclusion, we report a case of fatal babesiosis in a 48-year-old male without significant risk factors for a severe presentation. Despite recent treatment guideline changes, further research is needed for alternative treatment options who do not respond to the current first-line antimicrobials considering the lack of strong evidence supporting RCE. Given the rare nature of severe presentations, this could best be accomplished with a registry of patients with severe illness treated with and without RCE.

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