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Transfusion-transmitted babesiosis in a patient with sickle cell disease undergoing chronic red cell exchange

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Abstract

Background: Prior to laboratory-based blood donor screening for *Babesia*, transfusion-transmitted babesiosis (TTB) was a leading infectious risk to the blood supply in the United States.

Case Report: A 30-year-old man with sickle cell disease (SCD) who had been on a chronic automated red cell exchange (RCE) regimen since childhood, presented approximately 2 months after an RCE, with fever, neck pain, and photophobia. Meningitis was excluded, and he was discharged. He presented again 2 days later with persistent fever, chills, headache, fatigue, and loss of appetite.

Results: On examination, the patient was febrile but hemodynamically stable. Intra-erythrocytic inclusions were identified on a peripheral blood smear (<0.5%). *B. microti* IgM and IgG titers were >1:320 (Reference <1:20) >1:1024 (Reference <1:64), respectively. *B. microti* was confirmed by nucleic acid testing. The patient lived in a *Babesia* endemic state but had no risk factors for tick-borne acquisition. Of the 65 units he received in the preceding 6 months, 58 had been screened for *Babesia*. One of the donors of the 7 untested units was *B. microti* seropositive (titer 1:128; Reference 1: 64). The donor was asymptomatic and resided in a state in which *Babesia* screening was not required. He reported traveling in the year before his donation.

Conclusion: Although rare, TTB is still possible despite regional screening, underscoring the need for provider vigilance and education, especially in non-endemic areas. Patients with SCD

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CONFLICT OF INTEREST

Dr. Bloch is a member of the U.S. Food and Drug Administration (FDA) Blood Products Advisory Committee. Any views or opinions expressed in this manuscript are Dr. Bloch's and are based on his own scientific expertise and professional judgment; they do not necessarily represent the views of the Blood Products Advisory Committee or the formal position of the FDA and also do not bind or otherwise obligate or commit either the Advisory Committee or the FDA to the views expressed.

are particularly vulnerable given their high frequency of transfusion and complex needs requiring blood procurement from states where *Babesia* screening is not mandatory.

Keywords

Babesia ; blood donor; blood transfusion; polymerase chain reaction; screening

1 | INTRODUCTION

Babesia is a genus of tick-borne, intraerythrocytic parasites responsible for the infectious disease known as babesiosis.[1] While *Babesia* infection in immunocompetent adults typically results in a mild, flu-like illness (e.g., with fever, headache, myalgia, fatigue), asymptomatic parasitemia is not uncommon. By contrast, the very young, those of advanced age, and/or the immunocompromised (e.g., notably those with asplenism) are at risk of severe disease with manifestations that include hemolytic anemia, renal-, and/or cardiorespiratory failure or even death in some individuals.[1,2] *Babesia microti*, which accounts for the overwhelming majority of cases of human babesiosis, is endemic in the northeastern and upper midwestern United States (US).[1] Although transmitted primarily by a bite from the deer tick, *Ixodes scapularis, B. microti* is readily transmissible through the transfusion of any blood product containing red blood cells (RBC).[3,4] *Babesia* was previously regarded as a leading infectious risk to the US blood supply: over 250 cases of transfusion-transmitted babesiosis (TTB) had been reported, almost all (98%) of which implicated *B. microti*. This led to the adoption of regional blood donor screening for *Babesia* in those states deemed to be at the highest risk of transmission.[5] The US Food and Drug Administration (FDA) recommendations pertaining to donor screening for *Babesia* have been successful in reducing the number of TTB in endemic areas.[6] We describe the clinical and laboratory investigation of TTB attributed to RBCs collected in a non-endemic state.

2 | CASE REPORT

The patient, a 30-year-old man with sickle cell disease (SCD) complicated by red cell alloimmunization and cerebrovascular disease, had been on a chronic automated red blood cell exchange (RCE) regimen since childhood, whereby he was transfused ~10 RBC units every 3–4 weeks. In October 2021, he presented to an outside emergency department with fever, neck pain, and photophobia. Vital signs included temperature of 38.3°C, heart rate 89 beats/min, respiratory rate 18 breaths/min, blood pressure 117/75 mm Hg and oxygen saturation 99% on room air. A complete blood count (CBC) revealed a white blood cell count 5.8 K/cu mm, hemoglobin 10.8 g/dl (baseline 11–12 g/dl), hematocrit 33.1%, and platelet count 241 K/cu mm. SARS-CoV-2 testing was negative. Cerebrospinal fluid testing and imaging of his head were unrevealing. In the setting of a negative evaluation for meningitis, the patient was discharged.

Two days later, the patient continued to feel unwell and presented with persistent fever, chills, headache, fatigue, and loss of appetite. The patient was febrile with a maximum temperature of 39.8 degrees Celsius, but was otherwise hemodynamically stable. A complete blood count revealed a white blood cell count 5.22 K/cu mm, hemoglobin 10.4

g/dl, hematocrit 32.6%, and a platelet count of 194 K/cu mm. Testing for a panel of respiratory viruses (including SARS-CoV-2), cytomegalovirus, human immunodeficiency virus, hepatitis A virus, hepatitis B virus, and hepatitis C virus was negative. Bacterial cultures of peripheral blood, urine, and stool showed no growth. Serologic testing was negative for *Borrelia burgdorferi,* West Nile virus, *Brucella,* and *Treponema pallidum.* Epstein–Barr virus serology was positive for IgG antibodies but not IgM antibodies. SARS CoV2 IgG antibodies were identified (the patient had been vaccinated). *Ehrlichia chaffeensis* IgG and IgM titers were 1:64 (reference <1:64) and <1:20 (reference <1:20), respectively. *Anaplasma phagocytophilum* IgG and IgM titers were <1:64 (reference <1:64) and 1:40 (reference <1:20), respectively. An immunochromatographic membrane assay for the detection of *Plasmodium* antigens was negative.

Intra-erythrocytic inclusions were identified on a peripheral blood smear (<0.5% parasitemia based on a representative 1000-cell count). *Babesia microti* IgM and IgG titers were positive to >1:320 (reference <1:20) and 1:1024 (reference <1:64), respectively. *B. microti* DNA was detected by nucleic acid testing (NAT). The patient was started on azithromycin and atovaquone therapy (1 dose of azithromycin 500 mg and then 250 mg azithromycin daily for 10 days and atovaquone 750 mg twice daily for 10 days), with resolution of symptoms. The recipient lived in Maryland, which is regarded as endemic for *B. microti,* but he had no risk factors for tick borne acquisition, such as travel or outdoor activities.

A donor lookback investigation was initiated with the blood supplier. RBCs transfused in the 6 months preceding the symptomatic infection were included in the investigation. Sixty-five extended antigen matched RBC units from 54 donors had been transfused to the index patient in the 6 months preceding his symptom onset; donors of 58 of the 65 units had been tested for *Babesia* by NAT prior to their distribution. The five donors of the remaining seven —untested— units (two donors contributed two units each) were contacted and brought back to be tested for *Babesia* (Table 1). One donor tested positive for *B. microti* antibodies by IFA (titer 1:128; cutoff off 1: 64) and negative by *Babesia* NAT (Procleix Babesia assay, Grifols Diagnostic Solutions, Inc.). The seropositive donor had not had any symptoms of babesiosis; he lived in Ohio and reported being very active over the past year, including hiking and camping in several states (Ohio, Tennessee, and North Carolina). He did not recall any tick exposure. The donor had donated both before as well as after the index donation. The implicated unit was collected in Ohio in July 2021 and transfused in August 2021. Approximately 3 months had elapsed between the implicated donation and diagnostic testing (July to October). No other cases of TTB were attributed to other donations from the implicated donor.

3 | DISCUSSION

Babesiosis, which was designated as a nationally-notifiable disease (as defined by the Centers for Disease Control and Prevention) in 2011,[7] has long been recognized as a major risk to the US blood supply. In 2019, after almost two decades of surveillance, the FDA recommended NAT testing of blood donors for *Babesia* or use of an FDA-approved pathogen reduction technology (PRT) to contend with the risk of TTB.[5] The policy was confined to 14 US states (Connecticut, Delaware, Maine, Maryland, Massachusetts,

Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin) and the District of Columbia, given that 99% of clinical- and 95% of TTB cases had been reported in those areas.[5] At the time of this writing, an FDA approved PRT remains only available for treatment of platelets and plasma products.

Our case highlights several points. First, there is still a risk of TTB outside of areas that are regarded as endemic for *Babesia.* This underscores the need for vigilance among transfusion recipients with unexplained symptoms that are not otherwise explained by their underlying disease alone. Prompt recognition is critical to prevent the progression of infection with the development of associated complications. Second, patients with SCD are disproportionately at risk of TTB— and specifically—of severe or even fatal sequelae.[8,9] There are both intrinsic and extrinsic factors that account for this vulnerability. Patients with SCD are typically functionally asplenic, anemic, and have a high burden of comorbid disease, collectively rendering them both likely to be transfused (conferring risk of TTB) and more likely to develop high parasitemia and complications when infection ensues. They are frequently multiply-transfused with RBCs, often in large volumes in the case of RCE procedures. Patients with SCD are also at high risk of transfusion-associated complications, such as hemolytic transfusion reactions (through prior alloimmunization) and hyperhemolysis, which may misdirect investigation of TTB, should it occur.[10] Alloimmunization—in turn—complicates procurement of compatible blood for transfusion, as was the case with our index patient.[11] While he was transfused in an endemic area (Maryland), his requirement for extended antigen matched RBC units necessitated broadening the search for RBC units in states where blood donor testing for *Babesia* is not routinely performed. Frequent transfusions may also obscure or delay presentation. The index patient underwent an RCE in September 2021, which could have reduced the level of parasitemia, thus delaying the onset of symptoms (i.e., to October 2021). Of note, the donor's NAT negative result was unsurprising. Almost 90% of blood donors have been observed to exhibit DNA clearance within a year following an index positive donation; by contrast, less than 10% of donors serorevert.[12] In a large study at American Red Cross, investigators detailed the first year's findings following implementation of *Babesia* NAT screening; most *Babesia* positive donors remained positive by NAT screening by transcription mediated amplification, up to 74 days following the index donation.[6]

Extant donor screening policy has reduced—but not obviated—the risk of TTB, given its regional mandate. However, blood is frequently transfused far from where it is collected (e.g., in non-endemic states). Further, blood donors who reside in non-endemic areas may still become infected during travel to endemic areas and unknowingly donate upon their return to a state that is not considered endemic. The states that were visited by the implicated donor are not known to be endemic for *Babesia. Babesia microti* can persist for months, or even years without noticeable effect on the donor.[13] Asymptomatic infection in donors confers a risk of delayed diagnosis and potentially severe infection in high-risk patients, notably the same population who may be undergoing frequent transfusions (e.g., SCD, oncological disorders).

While a regional screening policy for *Babesia* is rational, balancing epidemiological risk with operational and cost considerations appropriately, our case demonstrates the continued

vulnerability of the US blood supply to *Babesia*. Heightened awareness and health care provider education are imperative, especially in non-endemic areas where clinicians may not be accustomed to diagnosing community-acquired or TTB, placing transfusion recipients at risk of delayed diagnosis and severe disease.

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Abbreviations:

B. microti	Babesia microti
CBC	complete blood count
FDA	United States Food and Drug Administration
IFA	indirect fluorescent antibody testing
IgG	immunoglobulin G
IgM	immunoglobulin M
NAT	nucleic acid testing
PRT	pathogen reduction technology
RBCs	red blood cells
RCE	red blood cell exchange
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SCD	sickle cell disease
TTB	transfusion-transmitted babesiosis

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TABLE 1

Investigation of the five donors who had not undergone routine laboratory screening for *Babesia* during their donations

Donor	State where unit collected	Babesia IFA	Babesia NAT
Donor 1	Ohio	Positive	Negative
Donor 2, 3, 4, 5	Washington, Oklahoma, Indiana, Utah	Negative (n = 4)	Negative (n = 3), Unable to be performed (n = 1)

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