A Cluster of Transfusion-Associated Babesiosis Cases Traced to a Single Asymptomatic Donor

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ABSTRACT

Babesiosis is a tick-borne disease of animals that occasionally occurs in humans. In the United States, most cases of babesiosis occur in the Northeast and are caused by the rodent parasite Babesia microti, an intraerythrocytic protozoan transmitted by the northern deer tick, Ixodes dammini. Babesiosis is prevalent in the coastal areas and islands of New England and New York. More recently, cases of babesiosis caused by various Babesia species have been reported from California, Washington, Missouri, Wisconsin, and Minnesota. Evidence suggests that because most B microti infections are asymptomatic or are not diagnosed for other reasons, Babesia infection is more common than the several hundred reported tick-borne cases would suggest. The clinical manifestations of babesiosis vary from asymptomatic infection to severe and sometimes fatal disease characterized by fever, hemolytic anemia, hemoglobinuria, and renal failure. Asplenic individuals and patients with underlying immunodeficiency, eg, elderly patients or patients with acquired immunodeficiency syndrome, are particularly susceptible to severe manifestations.

Because asymptomatic parasitemia can be prolonged for months to years, and the parasite can remain infective under blood-banking conditions, transmission of Babesia is a risk of blood transfusion. The blood components that have been implicated in transfusion babesiosis are plasma, platelets, and red cells. All blood components are free of Babesia-infected organisms if they are banked and processed to sterility. Babesiosis is responsive to antibiotic therapy and, untreated, can be a fatal disease in certain risk groups.

Context The risk of acquiring babesiosis by blood transfusion is largely unknown since in areas where it is endemic it is often an asymptomatic infection.

Objective To investigate and treat a cluster of blood transfusion–associated babesiosis cases.

Design Case series and epidemiologic investigation.

Setting Urban inner-city hospital.

Patients Six persons who received Babesia microti–infected blood components from a donor.

Main Outcome Measure Diagnosis and successful therapy of babesiosis following transfusion.

Results Six individuals (1 adult, 1 child, and 4 neonates) were exposed to products from a single blood donation by an asymptomatic Babesia-infected donor. Three of the 6 exposed patients became parasitemic. Polymerase chain reaction testing, animal inoculation studies, and indirect immunofluorescent antibody testing were used to confirm the presence of Babesia microti in the donor’s blood and to establish the presence of infection in 3 of the 6 recipients. The 3 infected recipients and 1 additional recipient were treated without incident.

Conclusion Physicians should consider babesiosis in the differential diagnosis of a febrile hemolytic disorder after blood transfusion. Prompt diagnosis is important since babesiosis is responsive to antibiotic therapy and, untreated, can be a fatal disease in certain risk groups.

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sis include liquid-stored erythrocytes, frozen-deglycerolized red cells, and platelet concentrates, which usually contain residual erythrocytes. 8 With the substantial increase in the white-tailed deer population (the preferred host for the adult tick) and the widening range of the tick vector, an increase in the incidence of babesiosis and transfusion-transmitted infections is possible.

We describe a cluster of cases of transfusion-transmitted babesiosis. Six persons were exposed to components from a single blood donation by an asymptomatic Babesia-infected donor and 3 became demonstrably parasitemic.

METHODS

At least 300 thin-smear fields were examined at a magnification of 1000. If no parasites were identified, at least 300 thick-smear fields were examined weekly for 8 weeks for parasitemia.

Blood from the donor and recipients was examined using polymerase chain reaction (PCR) for parasite DNA. The primers used were Bab1 (5' - TTAAGCTTTTATACAGC-3') and Bab4 (5' - ATAGTGCAAACTGTAATGATA-3'). 9 Parasite DNA was extracted from blood using the XTRAX Kit (Gull Laboratories, Salt Lake City, Utah).

CASE REPORTS

The index case (patient 1) was a 44-day-old, full-term male infant who was ventilator dependent and had been hospitalized for his entire life. On the 22nd day of life, he was transfused with 20 mL/kg (60 mL) of packed red blood cells because his hematocrit was 0.27. He had received no other transfusions. Twenty-two days later he became febrile (temperature, 39°C). Total white blood cell count was 24.0 × 10^9/L with 13.2 × 10^9/L neutrophils, 0.24 × 10^9/L band forms, 7.7 × 10^9/L lymphocytes, and 2.9 × 10^9/L monocytes; hematocrit was 0.35 and platelet count was 8.8 × 10^9/L. Examination of the peripheral smear revealed intraerythrocytic ring forms, consistent with either Plasmodium or B microti with an estimated 1% parasitemia. The diagnosis of babesiosis was confirmed by the presence of pathognomonic intraerythrocytic tetrad forms and by PCR results that were positive for B microti DNA.

Therapy with oral quinine sulfate (25 mg/kg per day) and intravenous clindamycin phosphate (20 mg/kg per day) was initiated. He remained febrile for the first 4 days of therapy, the parasitemia increased to 8%, and the hematocrit fell to

| Table. Summary of the Diagnosis, Treatment, and Outcome of the Patients Transfused With Babesia microti–Infected Blood* |
|---|---|---|---|---|---|---|---|
| Patient No./ Age at Transfusion | Diagnosis | PRBCs Transfused, mL | Blood Smear† | Signs and Symptoms | Incubation Period, d‡ | Confirmatory Tests | Treatment | Duration of Therapy, d | Outcome |
| 1 (Index)/ 22 d | Hypoplastic lung | 60 | + | Fever | 22 | Rise in IFA titer, PCR (+), hamster inoculation (–) | Quinine and clindamycin | 1–4 | Rising parasitemia and fever |
| | | | | | | Atovaquone added | 5–12 | Parasitemia resolved on day 8; PCR (–) on day 12 |
| 2/31 d | Prematurity (29 wk) | 40 | + | None | 42 | Rise in IFA titer, PCR (+), hamster inoculation (+) | Atovaquone and azithromycin | 7 | Parasitemia resolved on day 4 |
| 3/57 d | Prematurity (26 wk) | 34 | – | None | NA | IFA titer (–), PCR (–), hamster inoculation (–) | Atovaquone and azithromycin | 7 | Remained aparasitemic |
| 4/11 d | Prematurity (25 wk), necrotizing enterocolitis | 16 | – | None | NA | IFA titer (–), PCR (–), hamster inoculation (–) | Observation§ | NA | Remained aparasitemic |
| 5/70 y | Thalassemia, minor Gl bleeding | 220 | + | None | 28 | Elevated IFA titer, PCR (+), hamster inoculation (+) | Quinine and clindamycin | 7 | Parasitemia resolved |
| 6/11 y | Brain tumor (undergoing chemotherapy) Platelets only | – | None | NA | IFA titer (–), PCR (not done), hamster inoculation (–) | Observation | NA | Remained aparasitemic |

*GI indicates gastrointestinal; PRBCs, packed red blood cells; NA, not applicable; IFA, immunofluorescent antibody; and PCR, polymerase chain reaction.
†A plus sign indicates positive test results; minus sign, negative test results.
‡Period from the time of the transfusion to the time parasitemia was detected.
§Patient was not treated because of necrotizing enterocolitis.

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0.31. On day 5, the quinine dosage was increased to 30 mg/kg per day, clindamycin therapy was continued, and atovaquone therapy was added. The following day, the parasitemia fell to less than 3% and the fever subsided. By the fourth day following the addition of atovaquone therapy, no parasites were seen on blood smears. The findings of daily smears for the next 2 weeks were consistently negative for parasites; PCR done 3 weeks following treatment was also negative for Babesia DNA. The infant’s pretreatment serum had no antibody to malaria but showed a rising titer to B microti antigen (TABLE). The infant’s mother had not traveled outside the New York City metropolitan area, and had never received a blood transfusion. No parasites were seen in her blood smear, and her IFA titer to B microti antigen was 1:8 or lower.

The donor was a resident of Suffolk County (Long Island), New York, an area where babesiosis is endemic. During the fall of 1996, he had taken 3 hunting trips near his home. He did not recall finding ticks on his body. An interview with the donor when he donated blood (January 1997) was unremarkable; he had remained well thereafter. No parasites were seen when his blood smear was examined on postdonation day 45, but his IFA titer to B microti antigen was 1:1024. Untransfused cryoprecipitate from the implicated donation had an IFA titer of 1:1024. In addition, a smear of blood obtained from the remnant (tubing) sample of the implicated packed red blood cell unit showed a single ring form consistent with B microti, and the PCR results were positive for B microti DNA. A hamster inoculated with blood from the donor (postdonation day 45) did not become parasitemic. The donor’s antibody titer as measured by enzyme-linked immunosorbent assay to Borrelia burgdorferi antigen was negative.

Five additional individuals were identified as having received portions of the implicated blood donation and were evaluated for babesiosis. Three premature neonates received packed red blood cells (20 mL/kg; volume ranged from 16 to 40 mL); a 70-year-old woman with a history of thalassemia and gastrointestinal bleeding was transfused with 220 mL of packed red blood cells; and an 11-year-old boy receiving chemotherapy was transfused with platelets from the implicated donation. The evaluations and outcomes of these 5 patients are summarized in the Table.

Two additional recipients besides the index case became infected, but neither showed signs of clinical illness. All recipients were tested for antibody to B microti, had blood smears examined daily, and had blood inoculated into hamsters. On the 11th day of daily monitoring, (posttransfusion day 40), patient 2 was afebrile but had positive blood smear results with less than 1% parasitemia and positive PCR results. Treatment with oral atovaquone, 40 mg/kg per day, and oral azithromycin, 12 mg/kg per day, was given for 7 days. The regimen was well tolerated and results of smears became negative on the fourth treatment day. Hamsters inoculated with blood drawn on the fifth treatment day became parasitemic; inoculation of hamsters with blood obtained 8 weeks after completion of therapy failed to demonstrate parasitemia and the PCR results were negative. Serological test results showed a rise in B microti antibody titer. The infant was monitored after discharge and was healthy and thriving at age 1 year. All test results, including daily blood smears, remained negative for patients 3 and 4 (Table). Patient 3 was treated prophylactically with atovaquone and azithromycin.

The adult recipient, patient 5, had a blood smear with a 3% parasitemia (posttransfusion day 28). The results of serological testing, PCR analysis, and hamster inoculation were positive (Table). Although afebrile and asymptomatic, she was treated with a 7-day course of oral quinine (650 mg 3 times daily) and oral clindamycin (10 mg/kg 3 times daily). No parasites were seen in her blood smear on the fifth day of therapy. She has remained asymptomatic and blood smears and PCR results have remained negative. Patient 6, who received platelets, remained asymptomatic, and no parasites were ever detected in his blood smear; IFA titer and hamster inoculation were negative.

**COMMENT**

This is the first report of transmission of *B microti* to multiple recipients of a single contaminated blood unit and only the second of transfusion-acquired babesiosis in the neonatal host.10 The risk for transmission of *B microti* infection via contaminated blood components has been recognized since the late 1970s. However, direct measures of risk are not available and estimates of the likelihood of acquiring Babesia from a unit of blood are based on reported cases or seroepidemiologic studies. Including those in the present report, more than 20 cases of posttransfusion babesiosis have been reported. Since the number of blood units donated each year in the United States is approximately 12 million, the annual incidence of recognized posttransfusion babesiosis has been less than 1 per 1 million units of donated blood.11,12 However, the risk of transmission by blood components may vary by region. For example, in a study of surgical patients from Connecticut, a state in which 2% to 4% of some outpatient populations have been found to be seropositive,13 the risk of acquiring Babesia infection was 0.17% (1/601) per unit of packed cells.13

Although *B microti* is the second most commonly reported cause of transfusion-acquired parasitic infection,14 testing of all blood donors for evidence of past or present *B microti* infection has not been considered practical; neither is screening of high-risk donors based on residence or tick exposure.15,16 In the United States, blood banks do not routinely ask blood donors about recent tick bites, although donors who report a history of babesiosis are deferred.1 However, since most infections with *B microti* are subclinical and, therefore, undiagnosed, the question “Have you ever had babesiosis?” will not identify most donors with past or present infection.

Currently, the IFA test is the serologic test of choice for the detection of *B microti* antibody. This test is reliable, although time consuming, labor intensive, and sub-

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TRANSFUSION-ASSOCIATED BABESIOSIS

PROJECT TO QUALITATIVE INTERPRETATION, AND IT DOES NOT

LEND ITSELF TO MASS SCREENING. SIMILARLY, PCR TESTING IS NOT

GENERICALLY AVAILABLE, AND ITS UTILITY FOR LARGE-SCALE TESTING FOR

BABESIOSIS IS UNKNOWN. THUS, BETTER SCREENING TOOLS ARE NEEDED AS WELL AS BETTER ASSESSMENT OF THE RISK BABESIOSIS POSES TO THE BLOOD SUPPLY.

OF THE PREVIOUSLY REPORTED CASES OF TRANSFUSION-ACQUIRED BABESIOSIS WERE IN PATIENTS WHO BECAME MODERATELY TO SEVERELY ILL FROM THEIR INFECTIONS. IN ADULTS, THE MOST SEVERE AND OCCASIONALLY FATAL CASES OF BABESIOSIS (BOTH TICK- AND TRANSFUSION-ACQUIRED) HAVE OCCURRED IN SPLENECTOMIZED AND OTHER IMMUNOCOMPROMISED INDIVIDUALS.13,14 THE PRESENCE OF HOWELL-JOLLY AND HEINZ BODIES IN THE PERIPHERAL CIRCULATION OF NEWBORN S HAS RAISED QUESTIONS ABOUT THE PHAGOCYTIC CAPACITY OF THE SPLENS OF NEWBORN S.15,16 THE PHAGOCYTIC ACTIVITY OF THE SPLEEN HAS BEEN DEMONSTRATED TO HAVE A CRITICAL ROLE IN THE CLEARANCE OF B. microti IN THE GOLDEN HAMSTER MODEL.17 STUDIES OF PHAGOCYTIC FUNCTION IN THE NEWBORN RAT HAVE INDICATED THAT ALTHOUGH SPLENIC PHAGOCYTIC ACTIVITY WAS SIGNIFICANTLY IMPAIRED AT BIRTH, IT RAPIDLY INCREASED TO ADULT LEVELS DURING THE FIRST 2 WEEKS OF LIFE.18 RAPID MATURATION OF SPLENIC FUNCTION MAY EXPLAIN WHY INFECTED INFANTS DO NOT UNFORMLY SUCCEED TO OVERWHELMING BABESIA INFECTION. CELLULAR IMMUNITY ALSO SEEMS TO BE IMPORTANT FOR RESISTANCE TO AND RECOVERY FROM BABESIOSIS, AS INDICATED BY STUDIES IN NUCLEAR MICE.21 THE INCREASED SUSCEPTIBILITY OF NEWBORN S TO SEVERE INFECTION WITH OTHER INTRACELLULAR PATHOGENS SUGGESTS THAT NEONATES ALSO MIGHT HAVE IMPAIRED ABILITY TO CLEAR B. microti, EVEN WITH A FUNCTIONAL SPLEEN.22 THESE CONSIDERATIONS PROMPTED THE AGGRESSIVE THERAPEUTIC AS WELL AS PROPHYLACTIC APPROACH IN THE MANAGEMENT OF BABESIOSIS IN THE INFECTED AND EXPOSED NEWBORN.

QUININE AND CLINDAMYCIN, STANDARD THERAPY FOR BABESIOSIS, WERE INITIALLY USED FOR THE TREATMENT OF PATIENT 1. HOWEVER, BECAUSE OF THE PERSISTENT AND RISING PARASITEMIA, ATOVAQUONE THERAPY WAS ADDRESSED ON THE FOURTH DAY OF TREATMENT. THE PARASITEMIA RESOLVED AFTER 10 YEARS OF COMBINED QUININE, CLINDAMYCIN, AND ATOVAQUONE THERAPY. THE USE OF ATOVAQUONE WAS PROMPTED BY 2 RECENT STUDIES DEMONSTRATING THE EFFICACY OF ATOVAQUONE IN THE HAMSTER MODEL.23,24 WHEN USED AS MONOTHERAPY, ATOVAQUONE WAS FOUND TO BE EFFECTIVE FOR BOTH TREATMENT AND PROPHYLAXIS. HOWEVER, OTHER STUDIES HAVE SHOWN THAT WITH MONOTHERAPY, RECURRENCE AND DEVELOPMENT OF HIGH-GRAD RESISTANCE APPEARED, WHICH WERE NOT ENCOUNTERED WITH THE ATOVAQUONE-AZITHROMYCIN COMBINATION.25 ATOVAQUONE AND AZITHROMYCIN WERE SELECTED FOR THE THERAPY AND PROPHYLAXIS, RESPECTIVELY OF PATIENTS 2 AND 3 AND WERE WELL TOLERATED IN BOTH CASES. THIS ADDS TO THE GROWING ANECDOTAL EXPERIENCE FOR THE USE OF ATOVAQUONE AND AZITHROMYCIN IN HUMAN CASES OF B. microti INFECTIONS.26,27 PHYSICIANS, ESPECIALLY IN AREAS WHERE THE DISEASE IS ENDEMIC, SHOULD CONSIDER BABESIOSIS IN THE DIFFERENTIAL DIAGNOSIS OF A FEBRILE HEMOLYTIC DISORDER AFTER BLOOD TRANSFUSION. PROMPT DIAGNOSIS IS IMPORTANT BECAUSE BABESIOSIS IS AMENABLE TO ANTIBIOTIC THERAPY AND UNINTERRUPTED, IN CERTAIN RISK GROUPS, CAN BE A FATAL DISEASE.

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