Transfusion-associated transmission of babesiosis in New York State

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BACKGROUND: Babesiosis can be life-threatening in immunocompromised individuals. Although the disease is usually transmitted by tick bite, more than 20 cases have been reported of infection transmitted by transfusion of blood or blood components obtained from apparently healthy donors from endemic areas in the United States. This report describes several recent cases of transfusion-transmitted babesiosis in New York State.

STUDY DESIGN AND METHODS: Transfusion-associated incidents of babesiosis infection were identified and investigated. Seroprevalence of babesiosis in healthy blood donors in a highly endemic area was ascertained.

RESULTS: In three incidents, babesiosis was diagnosed in five of eight patients given infected blood: two premature infants, an elderly patient with gastrointestinal bleeding, and two patients with thalassemia. Seroprevalence in blood donors on Shelter Island (Suffolk County, eastern Long Island), a highly endemic area, was 4.3 percent in May 1998.

CONCLUSIONS: Infected donors lived in endemic areas and were asymptomatic with no history of tick bite. Blood collected in January 1997 from one donor was infectious. Those transfusion recipients who were infected were neonatal, elderly, or chronically transfused patients. Babesiosis should be included in the differential diagnosis of febrile illness in immunocompromised recipients of blood transfusion, particularly in the Northeastern United States.

Babesiosis is a tickborne disease characterized by fever and hemolytic anemia, caused by *Babesia microti*, a protozoan that parasitizes RBCs.[1,2] Rodents are reservoirs for the parasite. Humans usually acquire babesiosis through the bite of a vector tick that has fed on an infected mouse. Babesia are parasites of many mammals and are major pathogens of cattle. Deer are the primary host for the ticks.[3] They nourish and transport the ticks, spreading them from place to place, but do not exhibit symptoms of infection.

Most cases of babesiosis in the United States occur in the Northeast, particularly on eastern Long Island, Shelter Island, and Fire Island in New York; on Cape Cod, Nantucket, and Martha's Vineyard in Massachusetts; and in mainland Connecticut.[4] Cases have also been reported from the Midwest and Northwest.[5] Some cases from the Northwest are due to a different species of babesia.[6] Cases in New York State have been reported in at least 16 counties, including some in the central and western regions, but are concentrated downstate and on Long Island, particularly in Suffolk County. It is suspected that cases result largely from exposure during travel to highly endemic areas in eastern Suffolk County. In New York, babesiosis is caused by *B. microti*, which is transmitted to humans by infected nymphal and adult *Ixodes scapularis* (also known as *I. dammini*), the deer tick.[2,7]

ABBREVIATIONS: IFA = indirect immunofluorescence antibody (assay).

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Serologic surveys in endemic areas have shown fairly high prevalence rates, ranging from 3.7 percent to 6.9 percent,[4,8] which suggests that many infections are subclinical and/or that patients do not seek treatment. However, in some individuals, especially the elderly, those who have undergone a splenectomy, and others who are immunocompromised, including patients with AIDS, babesiosis can be severe or even fatal.[9] Symptoms of babesiosis are nonspecific and include malaise, fever, chills, myalgias, anorexia, abdominal pain, nausea, vomiting, and emotional lability and depression.[1] Reported incubation periods range from 1 to 6 weeks after tick exposure. Most infections are contracted from the tiny nymphal form,[1] and the majority of persons with babesiosis do not recall being bitten by a tick.[7] Because *Ixodes* sp. ticks also may carry the agents of Lyme disease and granulocytic ehrlichiosis, these diagnoses should be considered in patients in whom babesiosis is suspected.[3,10-13] Coinfection complicates the course of the disease.[10]

More than 20 cases have been reported of babesia infection transmitted by the transfusion of blood or blood components obtained from apparently healthy donors from endemic areas in the United States.[4,14-25] Reported incubation periods range from 2.5 to 8 weeks among transfusion recipients.[16,25]

Prompt diagnosis is especially important, because babesiosis is amenable to antibiotic therapy and can be fatal in certain risk groups if untreated. Treatment includes antibiotics; failing an adequate response, apheresis has proved successful.[14,25] This report presents three recent incidents of transfusion-associated babesiosis infection in New York State and describes a small study of the seroprevalence of babesiosis.

MATERIALS AND METHODS

Incident reports

In New York State, blood bank and transfusion-related errors and incidents (including transfusion-transmitted infection) must be reported to the state's Department of Health by facilities holding state permits to provide blood services. Department guidelines recommend that, if transfusion is implicated as a likely or possible means of transmission, infection be reported also to the facility that collected the blood in question. In addition, babesiosis must be reported to the local health department.

Investigation of incidents reported in 1997 included laboratory testing of blood from all possible implicated donors. Once a donor was implicated, any remaining frozen components from that donor were removed from inventory and sent for testing. Implicated donors were re-interviewed for risk factors. All blood or blood components prepared from the implicated blood were traced, and physicians who had administered the blood were notified. Previous donations were identified. The incidents were discussed with epidemiologists, attending physicians, and laboratorians. The investigations were coordinated with the surveillance staff.

Seroprevalence study in New York

Unlinked blood samples were collected by a regional blood center in late May 1998 on Shelter Island (Fig. 1) in Suffolk County at the eastern extremity of Long Island, an area that is highly endemic for babesia. One hundred fifteen consecutive samples from donors who passed the health history screening were tested for evidence of current or past infection with *B. microti*.

Specimens were tested by the Wadsworth Center of the New York State Department of Health by an indirect immunofluorescence antibody (IFA) assay as used at the CDC[26] and by PCR with primer sets Bab2/Bab3 or Bab1/Bab4.[27] Antigen slides were prepared from *B. microti*-infected mouse RBCs, 80 percent of which were infected. Serum was tested at dilutions of 1-in-16, 1-in-64, and 1-in-256 with goat anti-human IgG, IgA, and IgM (Kirkegaard and Perry Laboratories, Gaithersburg, MD). Specimens positive for babesia-specific immunoglobulins were retested as above for IgM after the removal of IgG by the preparation of an IgM fraction by separation on affinity chromatography columns (Quick-Sep, ISOLAB, Akron, OH).

RESULTS

As a result of New York State Department of Health requirements for reporting babesiosis and transfusion-related errors and incidents, attention was drawn to three incidents of transfusion-transmitted babesiosis reported in downstate New York in 1997.

Cases

Case 1. Blood donated in January 1997 resulted in transfusion-transmitted babesiosis in a neonate at a downstate hospital; this case has been described in more detail elsewhere.[16] The index patient was a 44-day-old term infant with achondroplastic dwarfism and pulmonary hypoplasia. The patient was febrile 22 days after the transfusion of 60 mL of 16-day-old packed RBCs. Parasites were evident on a blood smear from the patient, with 1 percent of cells initially infected and with the proportion subsequently rising to as high as 8 percent. Serologic testing revealed an increase in IgG antibody titer to 1024 on IFA assay for babesia. A PCR assay for babesia was positive. Epidemiologic investigation revealed that the mother was not at risk for babesiosis. On examination of a blood smear, a segment from the RBC unit revealed parasites. Cryoprecipitate from the blood donation had not been transfused; it had an antibody titer of 1024. The patient was treated with quinine and clindamycin but continued to be parasitemic. Recovery followed the administration of atovaquone.

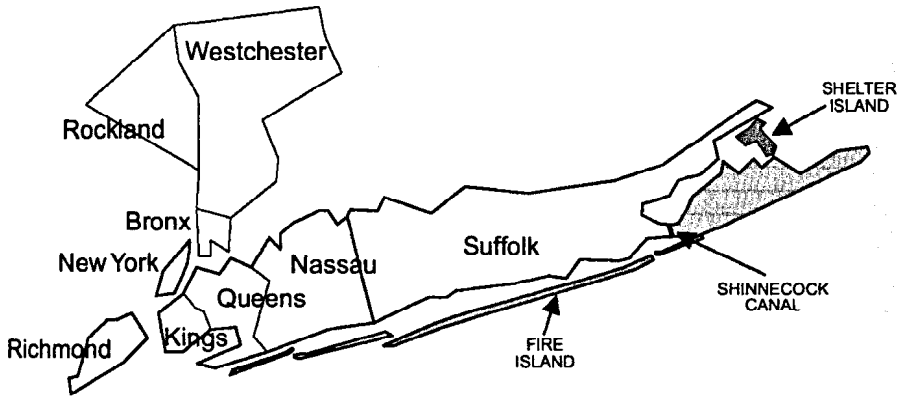

Fig. 1.: Highly endemic areas, Long Island, NY. Suffolk County, on eastern Long Island, is an area endemic for *B. microti*. Shelter Island, the South Fork (east of the Shinnecock Canal), and Fire Island are highly endemic areas.

The implicated donor was a 40-year-old male resident of an area endemic for babesia (Suffolk County), who engaged in outdoor activities during the previous summer and fall in highly endemic areas (Shinnecock Bay, Shelter Island). At the time of donation, there was no evidence that he should not have been accepted as a donor: he had no history of tick bite and was asymptomatic, with a Hb of 15.9 g per dL. The donor was recalled; the negative history was confirmed and a blood specimen drawn 45 days after the implicated donation. Testing of the specimen revealed an IgG antibody titer of 1024, and the specimen was positive on PCR testing for babesia. A blood smear was negative for parasites, as were blood smears, examined weekly for 8 weeks, from a hamster inoculated with the specimen. The specimen was negative on tests for markers of Lyme disease and ehrlichiosis. A search was made for previous donations to test, but the sample from the previous donation (March 1996) was insufficient for testing.

Two other recipients were infected by the January 1997 donation. One was a 31-day-old, premature infant (29 weeks' gestation). Blood drawn 42 days after the transfusion of 40 mL of a 13-day-old unit of RBCs was positive for parasites by smear and positive for *B. microti* on IFA assay and PCR. Blood from a hamster inoculated with the patient's blood tested positive. The patient had no signs or symptoms of infection, was treated, and cleared the infection. The second infected recipient was a 70-year-old patient with gastrointestinal bleeding. Blood drawn 28 days after the transfusion of a half-unit of RBCs from the implicated donation, near expiration of the unit, was positive by smear, IFA assay, PCR, and hamster inoculation. The patient had no signs or symptoms of infection, was treated, and cleared the infection.

Three recipients of the implicated donation (January 1997), two of whom received RBCs, were not infected. These were an 11-day-old, (25 weeks' gestation) premature infant with necrotizing enterocolitis, a 57-day-old, (26 weeks' gestation) premature infant, and an 11-year-old with a brain tumor, who had been given 16 mL of RBCs, 34 mL of RBCs, and platelets, respectively. Lookback on recipients of a previous donation was noncontributory. The implicated donation had resulted in infection in three of the six recipients.

Case 2. A 20-year-old, male, chronically transfused patient with thalassemia developed a febrile illness in September 1997. A blood smear was positive for parasites, and a blood specimen was antibody positive (IgG titer, 4096) and PCR positive for *B. microti*. The patient was not a resident of an area endemic for babesia and had no outdoor exposure, but was receiving 2 units of WBC-reduced RBCs per month in a downstate hospital.

The six donors of blood received by the patient in the previous 3 months were recalled. A specimen from one was antibody positive, with a titer of 1024. The implicated donation was made 17 days before the transfusion to the index patient. The incubation period for the transfusion-associated infection was 15 days. The implicated donor lived in an endemic area but had no history of tick bite. Two other donors were babesia antibody-positive, at lower titers, for IgG only, which was consistent with past infection. Lookback was not performed, because there were no donations by the implicated donor in the previous year.

Blood from the patient tested falsely positive for markers for Lyme disease, falsely positive for *Ehrlichia chaffeensis*, and strongly positive for antinuclear antibodies (titer, 640). Three weeks into the febrile illness, the patient was noted to have developed anti-I. Anti-E and anti-K could not be ruled out, but were not confirmed. It was also noted that his transfusion requirements increased. After treatment, the patient recovered and cleared the infection. Four months after the initial illness, antibody screens were again negative, and his transfusion requirements returned to baseline.

Case 3. A 27-year-old man with thalassemia receiving 4 units of frozen deglycerolized RBCs per month developed fever and monocytosis (up to 24%). Parasites were noted on a blood smear in November 1997. The patient was active in the outdoors in endemic areas, which raised the possibility that the disease was community-acquired. His blood specimen was antibody positive by IFA assay, with a titer of 1024. The patient was treated and cleared the infection.

Of the donors of 8 recently transfused units, one implicated donor was found to be IFA assay positive, with a titer of 256. A sample drawn 4 months later had a titer of 64, which is consistent with convalescence. The donor had a second home in a highly endemic area, but no history of a

tick bite. The caretaker for the second home had a history of being positive for *B. microti*. The donation was made in July 1997. The incubation period after transfusion was 46 days. No adverse effects were reported in recipients of a donation 8 months earlier.

Seroprevalence studies

One hundred fifteen blood samples collected from donors from a highly babesiosis-endemic area (Shelter Island; Fig. 1) in late May 1998 were tested by IFA assay. Five samples were positive for *B. microti*, all at a titer of at least 64 but less than 256, for a seroprevalence in donors of 4.3 percent. None was positive for IgM alone, and none was positive by PCR.

DISCUSSION

We report infection with *B. microti* in five recipients of 3 units of blood collected in downstate New York in 1997. In these incidents, none of the infected donors had a history of tick bite, and all were asymptomatic at the time of donation. The three donors lived in endemic areas: two were linked to a highly endemic area, and such a linkage cannot be ruled out in the third. The implicated donation in the first case was infectious despite collection in the winter (January 1997), which supports previous reports that infection may persist for months.[7,20,28] The incubation period after transfusion was 2, 3, and 6.5 weeks. The one infectious donation transfused to multiple recipients infected three of the six recipients; two of the three exhibited subclinical infections only. All infections were in very young, elderly, or chronically transfused individuals with thalassemia.

The seroprevalence study in late May 1998 revealed a higher rate of chronic infection with no evidence of current infection or primary response. Published reports indicate a seroprevalence of 2 percent in nonendemic areas and 6 to 16 percent in highly endemic areas of the state. Filstein et al.[8] reported rates of approximately 6 percent on Shelter Island in 1980, and, in the fall of 1984 in potential blood donors, Bianco et al.[29] reported rates of 2 percent (1/50 donors) in a nonendemic area (New York City), 2 percent (2/83) in an area adjacent (immediately west) to a highly endemic area (the South Fork area of eastern Long Island that is east of the Shinnecock Canal), and 16 percent (6/38) in a highly endemic area (the South Fork). In the latter report, samples were defined as positive for IgG with a titer higher than 64 and positive for IgM with a titer higher than 16, and all potential donors who were seropositive for IgM (i.e., those with current infection) were from the highly endemic area.

The most highly endemic areas in New York State are Shelter Island, Fire Island, and the South Fork, and it is thought that most cases in the New York City area relate to travel to this area. However, more cases have recently been linked only to residence in or travel to the North Fork. There was an increase in the number of babesiosis infections in the state in 1998 (unpublished New York State Department of Health data), although no transfusion-associated cases were reported. As the tick and its host expand their range, the endemic areas are expected to expand proportionally.

Despite the fact that donors in New York State are screened for history of babesiosis or current infections, babesiosis has been transmitted by the transfusion of infected blood or blood components. Thus, the department asked its Council on Human Blood and Transfusion Services to consider the issue. The council recommended the development of educational materials for physicians to alert them to transfusion-transmitted babesiosis. In response, the department developed *Babesiosis and ehrlichiosis: potential transfusion complications*[2] for distribution to physicians in New York State. The document is available on the department's website, at www.wadsworth.org/labcert/blood_tissue.

Transmission of babesiosis by a unit of blood in New York State is relatively rare. Approximately half a million units of blood are collected annually in the New York City area (unpublished New York State Department of Health data). Thus, the 3 units of babesia-infected blood identified in 1997 represent an incidence of 6 per 1 million units collected in that area. But because infection in immunocompromised recipients can be life-threatening, physicians who transfuse blood that may have been collected in highly endemic areas are advised to consider babesiosis in the differential diagnosis of febrile illness if the recipient is elderly, has undergone splenectomy, or is immunocompromised.

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