Babesiosis

Two Atypical Cases From Minnesota and a Review

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Abstract

We present 2 atypical cases of babesiosis and a review of babesiosis. The first patient was a 72-year-old man with an intact spleen, who had marked intravascular hemolysis. His RBCs were parasitized heavily with trophozoites of Babesia, and he had a large number of extracellular aggregates of Babesia. The infection did not respond to oral antibiotic therapy, and he required an RBC exchange transfusion. The second patient was a 29-year-old man who had undergone splenectomy and who had multiple episodes of fever and gastrointestinal symptoms for 4 months, with partial response to antibiotics. Thin smears revealed both intraerythrocytic and extraerythrocytic forms in very low numbers. The infection responded promptly to clindamycin and quinine therapy.

The varying clinical manifestations, from acute to chronic, at a wide range of ages and often the difficulty of detection by routine blood smears make it necessary that a high index of clinical suspicion be present for prompt diagnosis. With increasing numbers of cases of transfusion-transmitted babesiosis being reported, protection of the blood supply is essential.

Babesia species are tick-borne, intraerythrocytic protozoa that are well-known pathogens in animals. During the past 3 decades, they have been recognized as occasional pathogens in humans. Most infection passes undetected, especially in healthy adults with an intact spleen. However, occasionally in people who have undergone splenectomy and in immunocompromised people, Babesia infection may be severe and life-threatening. We report 2 contrasting cases of babesiosis, one in a 72-year-old man with an intact spleen who did not respond to oral therapy and the other in a 29-year-old man who had undergone splenectomy. They both had numerous extracellular organisms. We also review the literature on babesial infection.

Case 1

A 72-year-old man was admitted to the Veterans Affairs Medical Center, Minneapolis, MN, in mid-August, with fever and shaking chills for a week. He had been camping several times during the previous month in the area of Hinckley, MN. He had no history of insect bite. His hemoglobin concentration dropped 3 g/dL (30 g/L) during the 3 days after admission. His lactate dehydrogenase level was elevated markedly, and his laboratory test results were consistent with intravascular hemolysis. The patient’s medical history included colon cancer and subsequent surgery. Physical examination revealed no hepatomegaly or splenomegaly. The patient was not taking any medication at the time of admission.

Microscopic examination of a blood smear obtained 3 days after admission revealed intraerythrocytic images of Babesia. Numerous classic “Maltese
“cross” forms (tetrads) were identified. Heavy parasitization of erythrocytes and large extracellular clusters of trophozoites were present. Pleomorphism of the ring forms, lack of synchronous stages, absence of hemozoin, and a history of exposure to the wooded areas in an endemic region during the feeding time of the *Ixodes scapularis* nymph were consistent with *Babesia* infection. A search for a simultaneous infection with *Ehrlichia* was negative on buffy coat smear. The buffy coat preparation seemed to have numerous *Babesia* inclusions in the WBCs, which gave a false impression of intracellular infection. The findings on the buffy coat were assumed to be due to the numerous extracellular forms overlying the WBCs. Therapy with oral clindamycin and quinidine were initiated. The patient’s RBCs continued to hemolyze, and he received a 1-volume exchange transfusion with packed, washed RBCs. His hemoglobin rose by 3 g/dL (30 g/L) after the procedure and remained stable thereafter.

**Case 2**

A 29-year-old man was admitted to the University of Minnesota Hospitals, Minneapolis, in July, with fever (temperature up to 103°F [39.5°C]), chills, headache, neck stiffness, and photophobia for 4 days. This was the third episode during the last 4 months. The previous episode had been similar, with associated arthralgia, diarrhea, and cough. He had an intermittent, blotchy, red rash on the epigastrium. He received an amoxicillin-clavulanate potassium combination drug for the first 2 episodes, which resulted in partial relief of symptoms. The intervals between acute episodes were associated with fatigue, night sweats, and loss of appetite. He had no history of insect bite. His hemoglobin concentration at the last admission was 9.2 g/dL (92 g/L), with slightly elevated total bilirubin and liver enzyme levels. His medical history included a splenectomy 15 years earlier.
for a posttraumatic rupture of the spleen. The physical examination revealed no hepatomegaly. The patient was not taking any medication at the time of admission.

Microscopic examination of a Giemsa-stained blood smear obtained at admission revealed a low number of intraerythrocytic and extracellular trophozoites of *Babesia*. A rare classic “Maltese cross” (tetrads) was identified. Small extracellular clusters of trophozoites were present. A search for a simultaneous infection with *Ehrlichia* was negative on thin- and thick-smear preparations. The Lyme antibody titer was negative. Therapy with oral clindamycin and quinine was initiated. His condition improved within 8 days, and he was discharged from the hospital.

**Epidemiology and Life Cycle**

*Babesiosis* is a zoonotic disease caused by protozoa in the phylum Apicomplexa, order Piroplasmorida that parasitize erythrocytes of wild and domestic animals. The first epidemic of *Babesia* probably occurred in biblical times when it resulted in infection of the cattle of Pharaoh Ramses II. In 1888, Babes described “intraerythrocytic bacteria” as responsible for the death of 30,000 to 50,000 head of Romanian cattle with febrile hemoglobinuria. In 1893, Smith and Kilborne recognized *Babesia* as a protozoan transmitted by a blood-sucking tick. The first human case of babesiosis, believed to be caused by *Babesia bovis*, was reported in 1957 in a 33-year-old asplenic farmer from the former Yugoslavia. In 1969, the first case of babesiosis in a patient with an intact spleen was reported from Nantucket Island, MA, and was caused by *Babesia microti*.4

Babesiosis is endemic to Europe and the northeastern islands, mainland, upper Midwest, and the West Coast of the United States. Of the approximately 99 species of *Babesia*, few are known to infect humans. In Europe, *Babesia divergens* and *B bovis* are cattle strains that cause a severe and often fatal disease, particularly in people who have undergone splenectomy, whereas *B microti*, in North America, infects patients with intact spleens and produces a milder and often asymptomatic disease. Two newly described strains of *Babesia* affect immunocompetent patients in the United States: WA1 described in Washington State and *Babesia MOI* in Missouri.5-7

*Ixodes dammini* is the vector for transmission of babesiosis in the northeastern areas of the United States. In the southern United States, the name *I scapularis* has been used for the same vector. The vector in the western United States is *Ixodes pacificus*. The sexual stage occurs in the tick where transmission from larva to nymph (transstadial transmission) occurs. The larval and nymph stages of the tick feed on the naturally infected white-footed mouse (*Peromyscus leucopus*, the reservoir host), which remains parasitemic for life, while the adult tick favors the white-tailed deer, *Odocoileus virginianus*.

**Transmission, Clinical Findings, and Pathogenesis**

*Babesia* sporozoites are transmitted to humans mostly by the bite of the *Ixodes* nymph and occasionally by the adult tick. In the infected nymph, the organism migrates to the salivary gland. The nymph then seeks a blood meal and infects another rodent or human by injecting sporozoites into the bloodstream. The sporozoites enter the erythrocytes, possibly by binding to the C3 in the circulation and attaching to the erythrocytic C3b receptors, as observed in *Babesia rodhainii*.8 The sporozoites undergo asexual budding into 4 merozoites, followed by perforation of the RBC membrane, leading to hemolysis. The merozoites then infect other RBCs; the parasites become trophozoites and can divide by binary fission, creating the ring forms and tetrads seen in erythrocytes on stained blood smears. Usually, 1% to 10% of the RBCs are parasitized. However, up to 85% parasitemia has been noted.9 The disease is mild to asymptomatic in healthy people. However, overwhelming infection is seen in immunocompromised and asplenic patients in the United States and in most cases in Europe.

Another mode of transmission to humans is via blood transmission, with longer incubation periods (6-9 weeks) than after a bite (1-3 weeks).10 Transmission of more than 20 cases of babesiosis by RBC and blood component transfusion has been reported.11-13 In addition, the variant WA1 also has been associated with transfusion-associated babesiosis.12 Parasitemia in humans is transient and episodic. For this reason, there is a risk of asymptomatic donors transmitting the disease to recipients. These parasites can remain viable under blood bank conditions, at a temperature of 4°C for up to 35 days in packed RBCs and platelet concentrates that contain residual erythrocytes. Because *Babesia* has been described as an intraerythrocytic parasite, plasma transfusion has not usually been believed to be associated with a risk of transmission.

When symptoms occur, they are nonspecific and include fatigue, anorexia, myalgia, nausea, headache, sweating rigors, abdominal pain, emotional lability, depression, and dark urine.14 Acute respiratory symptoms, including edema, may appear during the course of the disease.15 Renal function also is affected occasionally. Reduced platelet counts are observed, with a direct Coombs test result occasionally being positive. The mechanism for this is not known.

Pathogenesis has not been defined clearly. Abnormal erythrocytes are retained by the spleen and ingested by
macrophages; therefore, disease is more severe in asplenic patients. Complement activation by *Babesia* may lead to generation of tumor necrosis factor and interleukin-1 release, causing fulminant symptoms. Decreased complement levels of C3, C4, and CH50 are seen in *Babesia* infection. Also, increased C1q binding activity owing to immune complexes is present.

**Prevalence**

The prevalence of human babesiosis is difficult to measure, owing to the asymptomatic nature of the infection. Several surveys have shown the presence of *Babesia* antibodies in asymptomatic individuals. Krause et al demonstrated that the prevalence of *Babesia* increased in Connecticut during a 30-year period (1959-1989). In their study, there was no evidence of babesial infection in residential college students between 1959 and 1963, whereas 2.9% were positive for *Babesia* antibodies between 1986 and 1989, and the prevalence remained constant during the following 5 years. A serosurvey in Block Island, RI, where *Babesia* is endemic, showed that 9% of the population (12% of children and 8% of adults) was seropositive; in Connecticut, 21% of the population (16% of children and 22% of adults) was seropositive.

The parasite that once was confined to a circumscribed area in New England has been now reported in Maryland, Virginia, Wisconsin, Minnesota, Washington State (WA1), and Missouri (MO1). The reason for this geographic spread seems, in part, to be linked to the expanding population of white-tailed deer in the eastern half of the United States. As the deer population has increased, so has the habitat range of *I. dammini*. As a consequence, more people will be exposed to infection with *Babesia* in the coming years. More cases of transfusion-associated transmission also are likely, given the increase in the range of the tick, the increase in the deer population, and the general increase in travel by North Americans. Since the same tick and primary host also harbor the organisms for Lyme disease and ehrlichiosis, many donors may have dual or triple infections.

Krause et al reported that 24 of 46 *Babesia*-infected subjects, who received no specific treatment, had *Babesia* DNA detectable in their blood for an average of 82 days. One subject in that study had recrudescent disease after 2 years, at a time when the risk of reinfection was nil. The recrudescence occurred when the patient became immunocompromised after developing cancer. It, therefore, seems that when left untreated, silent babesial infection may persist for months or even years. Parasitemia has been observed to wax and wane in infected asymptomatic donors, even without treatment. For example, a donor with WA1 infection was parasitemic more than 7 months after donation and was found, in retrospect, to have been parasitemic more than 6 months before donation.

**Diagnosis**

Diagnosis is based on clinical suspicion and history of exposure. Thin and thick smears stained with Giemsa will demonstrate the presence of trophozoites in the RBCs. It is necessary to examine 200 to 300 oil immersion fields before declaring a specimen negative. Also, a single negative set of blood smears does not rule out a *Babesia* infection. As in the examination of smears for the presence of malarial parasites, multiple sets of blood films must be examined before concluding that a patient does not have babesiosis. The parasite often is undetectable in the thin-smear preparation, which makes careful examination of the thick-smear preparation imperative. Automated instruments have been reported to fail to detect *Babesia*. The organism may be misdiagnosed as *Plasmodium* species owing to its ring conformation, the presence of a single chromatin dot, and a peripheral location in the erythrocytes. However, it can be distinguished from *Plasmodium* species by the absence of travel history outside the United States, pleomorphism of the ring forms, Maltese cross formation, lack of hemozoin, and lack of stages other than the ring form. Additionally, the presence of smaller rings without central pigment can help distinguish *Babesia* species from *Plasmodium* species. Although the presence of tetrad formations often is mentioned as a diagnostic aid, the forms often are not found, and, therefore, diagnosis must be based on the pleomorphic appearance of the ring forms. Occasionally, trophozoites may be seen outside erythrocytes with *Babesia* infection.

Indirect fluorescent antibody titers of more than 1:1,024 indicate active infection; a titer of 1:256 or more is diagnostic, and a titer of 1:32 or more indicates previous infection. Various polymerase chain reaction detection assays are available for detection of *B. microti* and other species. A study by Homer and coworkers has demonstrated that species-specific primers can be designed for *B. microti*. Confirmation can be obtained by intraperitoneal inoculation of 1.0 mL of EDTA-anticoagulated whole blood into the peritoneum of golden hamsters followed by smear positivity in 2 to 4 weeks.

**Prevention**

Prevention consists of avoiding tick habitats during the tick-biting season, protective clothing, and use of diethyltoluamide insect repellent or permethrin spray. Inspection of pets for ticks and removal of ticks with tweezers are appropriate.
Effective measures for prevention of transfusion-transmitted babesiosis are needed. Babesia is the most commonly reported cause of transfusion-transmitted parasitic infection in the United States. Microscopic methods are not very sensitive, since the level of parasitemia may be low. Clinically overt cases of babesiosis should not pose a risk of transmitting the disease via blood transfusion since the affected patients are unlikely to be blood donors. It is the asymptomatic infected would-be donor who is important to identify. No test is in routine use for mass screening of blood donors for Babesia infection. Donor-screening methods include a subjective evaluation of the donor’s health and objective methods such as the measurement of temperature and hemoglobin concentration, each of which would exclude some individuals with a Babesia infection. The results of some studies indicate that additional medical history would not be useful.\(^3\)

Another approach would be to avoid collecting blood in endemic areas, particularly during the spring and summer. Studies have shown this approach to have limited value,\(^3\) based on a statistically insignificant difference in seropositivity in endemic and nonendemic areas. In addition, the loss of healthy donors would adversely affect the blood supply.

Finally, donors who have a history of babesiosis are currently deferred indefinitely because of the possibility of ongoing infection.\(^3\) More data are needed to determine the efficacy of antimicrobials in eradicating the parasite. In areas where babesiosis is endemic, blood-donor screening for \(B\) microti and other species by means of polymerase chain reaction–based methods is being studied. A higher degree of safety of blood transfusion would be reached if new methods were available for inactivating these parasites. Inactivation of Babesia in RBC and platelet preparations, by photosensitization using lipophilic phophorbide derivatives, seems to be a promising approach.\(^3\)\(^,\)\(^3\)\(^4\)

**Discussion**

The spread of Babesia infection and blood transmission of the organism have renewed our interest in studying this organism. Fevers of unknown origin in patients with a history of travel to areas endemic for the \(Ixodes\) tick should result in a high index of suspicion, and a search for Babesia, Borrelia, and Ehrlichia infections should be instituted, since they might occur simultaneously, particularly with the latter 2 genera.

Historically, Babesia has been described predominantly as an intracellular parasite. An earlier abstract and a subsequent report from Massachusetts described the presence of extracellular forms detected by blood smears.\(^3\)\(^,\)\(^8\) Both of our cases, with low and high parasite numbers, had extracellular forms, which suggests the possibility of transmission by plasma and platelet products. There is a risk of asymptomatic blood donors transmitting the parasite to recipients of their blood products. This is important to note since Babesia infection reportedly can recur for up to 2 years without a new exposure. The first line of treatment is oral therapy with both clindamycin and quinine. In case of a high level of parasitemia (above 10%), an RBC exchange transfusion may be lifesaving.

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**References**


