Transfusion-Transmitted Babesiosis During Total Hip Arthroplasty

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abstract

Babesiosis is a potentially life-threatening zoonotic disease that is endemic to the northeastern United States and increasing in prevalence worldwide. Transmitted by the same *Ixodes* tick responsible for Lyme disease, the intraerythrocytic parasite *Babesia* causes a wide range of clinical presentations—from asymptomatic carriage to a fulminant course with rapid deterioration. Symptoms typically present 1 to 6 weeks after inoculation, with the gradual onset of fatigue, malaise, weakness, and intermittent or sustained fever as high as 40.9°C. Severe cases are associated with parasitemia greater than 4%, alkaline phosphatase greater than 125 U/L, and white blood cell counts greater than 5×10⁹/L. Definitive diagnosis is made by microscopic examination of thin blood smears, polymerase chain reaction, and indirect immunofluorescent antibody testing. The increasing frequency of babesiosis paired with a lack of blood-donor screening assays poses a serious threat to the safety of the US blood supply. Although babesiosis is responsible for 3.6% of transfusion-related deaths, the Food and Drug Administration has yet to approve mandatory screening for the parasite in donated blood. Historically, transfusion-transmitted babesiosis has been thought to be isolated to the immunocompromised patient population. However, a recent case of transfusion-transmitted babesiosis in an immunocompetent patient following total hip arthroplasty is the first reported in the literature and may represent a growing risk to a far greater segment of the population than previously thought. This article summarizes the current state of transfusion-transmitted babesiosis and the detrimental impact of this infection on blood transfusion safety. [Orthopedics. 2015; 38(9):e852-e855.]
Human babesiosis presents with wide ranging clinical symptoms. Whether transmitted via tick, transfusion, or placenta, the *Babesia* parasite invades erythrocytes and rapidly reproduces, resulting in cellular damage, lysis, and further spread.\(^1\)\(^2\) The clinical severity of human babesiosis varies widely from asymptomatic infection to fulminating and potentially lethal disease.\(^3\) In asymptomatic individuals, the *Babesia* infection can persist for sustained periods, with parasites circulating up to 27 months.\(^4\) This often unnoticed, chronic low-grade parasitemia is now known to be a significant cause of transfusion-transmitted babesiosis (TTB).\(^4\)

*Babesia* is a serious threat to the blood supply simply because many people experience a clinically silent infection and donate blood, which is then used for transfusions, causing serious, often life-threatening, infections.\(^5\) Once the *Babesia* parasite has been introduced, the incubation period varies slightly depending on the mode of transmission. The incubation period of an infecting tick bite is 1 to 3 weeks, whereas the incubation period of TTB ranges from 2 to 8 weeks.\(^3\)\(^5\) In symptomatic individuals, babesiosis pathology results in fever and hemolysis leading to anemia, hyperbilirubinuria, hemoglobinuria, and possible organ failure.\(^4\)

**Case Report**

A 75-year-old woman with long-standing left hip osteoarthritis underwent total hip arthroplasty after failure of conservative management. Her medical history was negative for significant immunosuppression or splenectomy. Her perioperative course was complicated by acute anemia requiring several blood transfusions. On postoperative day 3, she was discharged in good condition to a rehabilitation facility.

Four weeks postoperatively, the patient presented to the local emergency department with a 1-week history of weakness, dizziness, fatigue, abdominal pain, and night sweats. Her work-up revealed pancytopenia with an inappropriate reticulocyte response, elevated lactate dehydrogenase, and intraerythrocytic parasites on a peripheral blood smear consistent with babesiosis (Figure). The patient was started on treatment with oral azithromycin and atovaquone, with a gradual improvement in her symptoms and resolution of parasitemia after 5 days of treatment. The epidemiological data and case studies concerning babesiosis, as well as the increasing incidence of TTB over the past decade, clearly demonstrate the need for developing and expanding prevention techniques.

**Growing Concern of Transfusion-Transmitted Babesiosis**

Babesiosis is caused by the intraerythrocytic parasite *Babesia*.\(^6\) In the United States, the parasite *B microti* is the main species of the protozoan identified; however, occasional babesiosis cases have been caused by other *Babesia* species.\(^7\) Babesiosis is a tick-borne zoonotic disease endemic in the Northeast and Midwest United States, yet the geographic spread of *Babesia* is far greater than originally predicted.\(^1\)\(^8\)\(^9\)

The transmission of the parasite is also known to occur through blood transfusion and transplacentally.\(^1\) Transfusion-related cases of babesiosis are increasing, especially among older asplenic and immunocompromised patients who receive large amounts of blood. Due to the lack of licensed blood screening tests, preventing the transmission of *Babesia* remains problematic because manufacturers of screening assays view it as a limited market.\(^5\) However, as of 2013, *B microti* is the leading reported cause of red blood cell transfusion-transmitted infection in the United States.\(^10\) That said, the “geographic expansion and increasing incidence of human babesiosis” emphasize the necessity for sensitive and specific assays to detect *Babesia* not only to diagnose acute infections, but also to screen the blood supply.\(^1\)

In endemic areas, TTB is increasing in frequency and represents a serious concern for the safety of the United States’ blood supply.\(^2\) From 2005 to 2010, 3.6% (11 of 307) of transfusion-related deaths reported to the Food and Drug Administration (FDA) were attributed to TTB.\(^6\) States such as Rhode Island are highly endemic for babesiosis, with reports exceeding 90 cases per 100,000.\(^11\) At the Rhode Island Blood Center, serological and molecular screening methods were used under an investigational new drug protocol to test transfusion blood destined for high-risk groups, including newborns, sickle cell patients, and thalassemia patients. Of the 2113 units of blood tested by immunofluorescence assay and polymerase chain reaction, 26 (1.26%) were positive for *B microti*.\(^11\) The year after implementation of this laboratory screening, there were no cases of TTB.\(^11\) This unique investigational new drug protocol suggests that blood screening could be an effective approach to preventing TTB.\(^11\) This is especially true in endemic states such as Rhode Island, where 10% of babesiosis infections occur due to a blood transfusion.\(^12\) Despite numerous studies calling for appropriate intervention to reduce the

**Figure:** Photomicrograph of *Babesia* parasites (black arrows) on Giesma-stained peripheral blood smears showing characteristic ring forms of *B microti*. Parasites are approximately 1.5 to 2.5 µm in diameter. (Reprinted from *International Journal of Medical Microbiology*, 298, Hildebrandt A, Tenter AM, Straube E, Hunfeld KP, Human babesiosis in Germany: Just overlooked or truly new?, 336-346, Copyright 2008, with permission from Elsevier.)
risks posed by TTB, the FDA, the regulatory authority over all blood transfusion products related to the blood supply in the United States, offers no licensed testing modality for *B. microti.*

**Prevention Techniques**

Current TTB preventive practice includes the refrigeration of blood donations to 4°C, thereby altering parasite morphology and lowering parasite numbers. However, review of this practice has shown that *Babesia* is capable of surviving this refrigeration process for several weeks and still cause infection.

With no FDA-licensed test for screening, blood centers must rely on personal tick prevention techniques and blood donor questionnaires to reduce the risk of TTB. Similar to Lyme disease, babesiosis is most effectively prevented by avoiding outdoor activity in known endemic areas or using personal protection practices, including appropriate clothes and tick repellents. Nevertheless, avoiding tick habitats may be impractical, especially in endemic regions. Besides these individual measures, blood banks use standardized donor screening questionnaires in an attempt to alleviate TTB risk. However, this effort has proved to be largely ineffective not only in the United States, but also in Europe.

**Transfusion-Related Immunomodulation**

At first glance, perioperative autologous blood transfusion would seem like an appropriate solution toward eliminating the transfusion risks. However, review of this procedure shows no risk reduction and substantially increases cost of treatment. Moreover, perioperative autologous blood transfusion in patients who undergo arthroplasty can result in iatrogenic anemia, thus requiring further allogeneic blood transfusions. This carries not only an infectious risk, as seen in this case, but also an immune-modulatory effect.

For many years, researchers and clinicians have become increasingly aware of the transient shift in immune function following allogeneic blood transfusion. Experimental and epidemiological observations report a posttransfusion down-regulation of cytokine production, natural killer cells, lymphocyte numbers, and overall cell-mediated cytotoxicity, thereby resulting in increased prevalence of postoperative bacterial and viral infections. The deleterious effect on cell-mediated immunity is due to a shift in white blood cell cytokine production to the Th2 phenotype, which down regulates the Th1 phenotype responsible for antigen processing, macrophage activation, lymphocyte cytotoxic function, and neutrophil cytoidal activity.

In *Transfusion Medicine,* Blajchman et al stated that perioperative transfused patients, when compared with un-transfused patients, experience a 2- to 5-fold increased risk of postoperative infection. Moreover, multiple allogeneic transfusions result in more pronounced and longer lasting immune-modulatory effects. European and American randomized controlled trials have since demonstrated that white blood cell–depleted allogeneic transfusions not only reduce hospitalization cost by $2,000 per unit transfused, but also substantially decrease postoperative risk of infection. Therefore, the Blood Products Advisory Committee of the FDA currently recommends leukocyte reduction of all transfused blood products to avoid recipient immunosuppression.

**Conclusion**

Along with growing literature on the subject, this article should be considered a wake-up call to researchers and clinicians concerning the real threat of TTB. This case report highlights the wide geographic distribution of the *Babesia* parasite and its increasing prevalence in clinical practice. According to the Transfusion-Transmitted Diseases Committee, babesiosis, along with Creutzfeldt-Jakob disease and dengue virus, is the highest risk level for blood safety and should be prioritized for intervention. Further studies, both epidemiological and preventive, are urgently needed to raise public and clinical awareness of babesiosis. With more arthroplastic procedures, immunocompromised patients, and no effective screening method, the number of *Babesia* infections will continue to increase. To successfully counteract the growing risk of TTB, transmission can be mitigated by increasing public consciousness, clinical awareness, and transfusion screening techniques.

**References**


