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CASE REPORT PEER REVIEWED | OPEN ACCESS

Refractory autoimmune hemolytic anemia secondary to *Babesia*

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ABSTRACT

Introduction: *Babesia* is endemic in the northeast and upper midwestern United States. Two species that cause human infections are *Babesia microti* and *Babesia divergens*. The parasite is transmitted by the bite of the tick *Ixodes scapularis*. Another mode of transmission is blood transfusion producing either an asymptomatic to mild flu-like illness or hemolytic anemia in immunocompromised and asplenic individuals. Hemolysis is usually non-immune and attributed to lysis of infected erythrocytes. Rarely the infection may cause immune dysregulation and lead to the formation of autoantibodies that cause immune mediated hemolytic anemia.

Case Report: A previously healthy young adult male with a recent history of multiple blood transfusions, presented with refractory autoimmune hemolytic anemia within two months of transfusion. The anemia was unresponsive to various immunosuppressive medications and blood transfusions. On follow-up, his peripheral smears showed heavy parasitemia consistent with *Babesia* species. The organism was speciated to *Babesia microti* by polymerase chain reaction at the Center for Disease Control. The patient was treated with intravenous quinidine and oral clindamycin. Immune hemolytic anemia resolved following the treatment of Babesiosis.

Conclusion: In conclusion, Babesiosis should be in the differential diagnosis of autoimmune hemolytic anemia in a patient with a history of blood transfusion and poor response to steroids or immunosuppressive drugs.

Keywords: Autoimmune hemolytic anemia, *Babesia*, Refractory, Transfusion

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INTRODUCTION

Babesia is endemic in the northeast and upper midwestern United States. Two species that cause human infections are *Babesia microti* and *Babesia divergens*. The parasite is transmitted by the bite of *Ixodes scapularis*. Another mode of transmission is blood transfusion [1]. *Babesia microti* produces either an asymptomatic to mild flu-like illness or hemolytic anemia in immunocompromised and asplenic individuals [1, 2]. Hemolysis is often non-immune and attributed to lysis of infected erythrocytes. Rarely the infection may cause immune dysregulation and lead to the formation of autoantibodies that cause immune-mediated hemolytic anemia [2].

CASE REPORT

A previously healthy adult male presented with injuries following a motor vehicle accident. He underwent

multiple surgeries and required massive transfusion of greater than 40 units of blood components on admission. He was discharged in stable condition after 1.5 months of hospital stay. On his initial follow-up visit, he presented with new onset fatigue, dark colored urine, decreased urinary output, and jaundice. Laboratory results suggested anemia with transaminitis, and the patient was readmitted. His hemoglobin was 7.5 g/dL (12.5–16.3 g/dL); compared to 12.5 g/dL at discharge, haptoglobin was less than 8 (30–200 mg/dL), lactate dehydrogenase (LDH) was 693 U/L (84–246 U/L) and was transfused with 2 units of red blood cells. Testing for cytomegalovirus (CMV) was negative. His liver function tests trended down without any intervention. The direct antiglobulin test (DAT) was negative. At the time of discharge, his hemoglobin was 10 g/dL.

On a return follow-up, laboratory results confirmed continuing hemolysis [hemoglobin of 5.5 g/dL, LDH of 653 U/L and reticulocyte count of 25% (0.5–2.2%)]. At this time, warm and cold autoantibodies were identified and direct antiglobulin test was positive for IgG and complement. He was started on prednisone, received his first dose of Rituximab and was transfused with packed red blood cells.

On his next follow-up visit, the patient was clinically doing well. However, the hemoglobin remained low at 9.3 g/dL. He received 3 additional doses of Rituximab.

Despite treatment with prednisone and Rituximab, anemia (hemoglobin 6.4 g/dL) and hemolysis persisted suggesting a poor response. At this time, a new antibody (anti-C) was identified. He was started on IVIg but no response was observed. He also started on cyclophosphamide and cyclosporine. During the same period, an additional red cell antibody (anti-E) was detected. At a subsequent follow-up visit five months after discharge from his initial admission, extra and intraerythrocytic parasites were observed in the peripheral blood smear (Figures 1 and 2), identified as *Babesia* species and later confirmed by RT-PCR at the CDC as *Babesia microti*. The parasite index was calculated at 27%. No eosinophilia was noted on the smears. Treatment started with intravenous Quinidine and oral Clindamycin. Immunosuppressants were stopped. After reduction of parasite index to less than 1%, the patient was switched to Atovaquone and Azithromycin. Therapy was completed after six weeks once peripheral smears confirmed the absence of parasites, and resolution of hemolysis. The patient is an urban resident of Louisiana. The patient denied any recent history of travel to endemic areas except to Texas and Oklahoma.

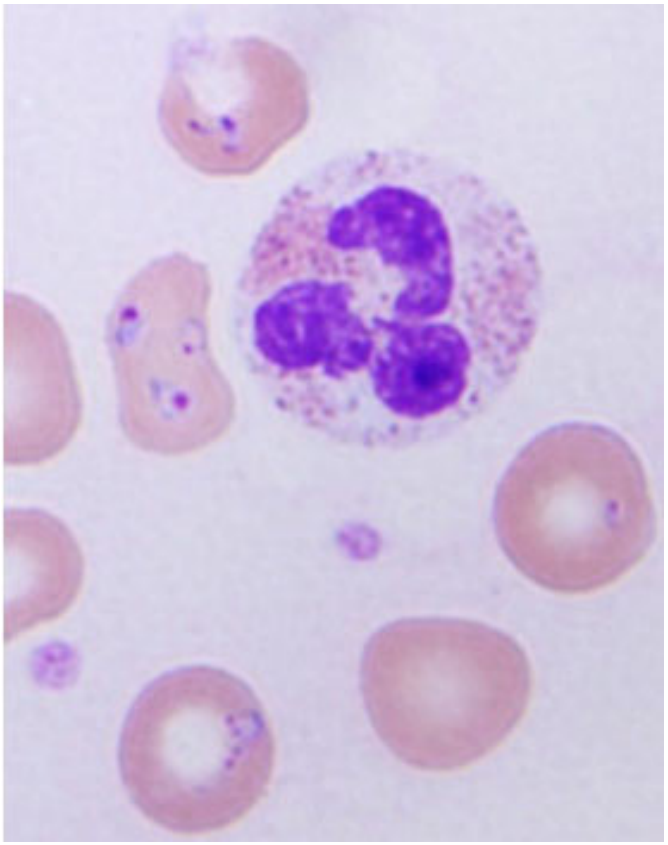

Figure 1: Multiple small parasite forms of *Babesia* in erythrocyte (Giemsa stain, oil immersion lens magnification).

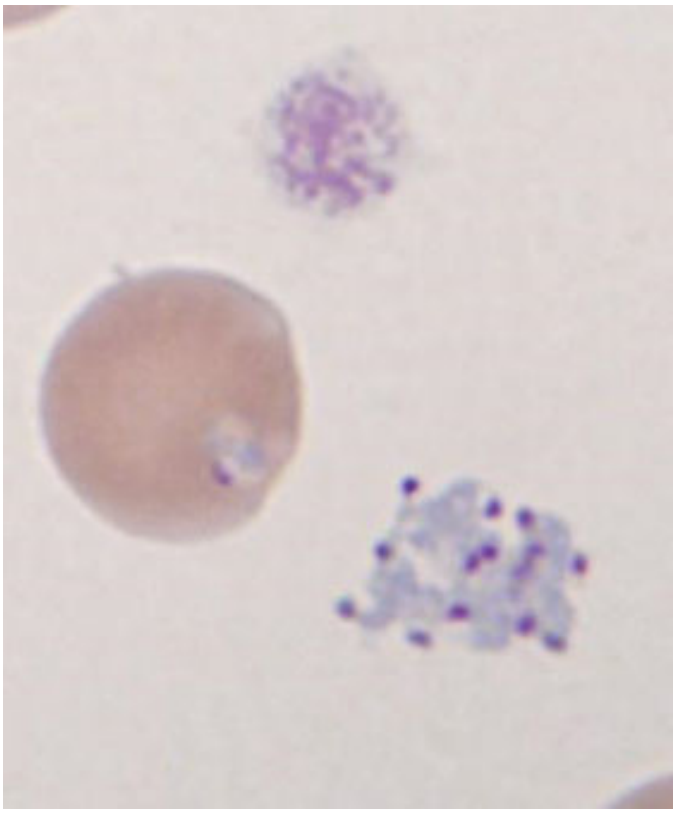

Figure 2: Intracellular and extracellular parasites (Giemsa stain, oil immersion lens magnification).

DISCUSSION

Babesiosis or piroplasmosis is caused by an Apicomplexan protozoa that infects erythrocytes. The first case of human babesiosis in the United States was identified in 1966 on Nantucket Island. *Babesia* is endemic in the

northeast and upper midwestern United States. There are 2 species of *Babesia* that cause infections in humans: *B. microti* and *B. divergens*. The former is endemic in the United States and Europe, while the latter is predominantly seen in Europe. Other *B. divergens*-like and *Babesia*-like organisms have also been identified in the United States. The vector for *B. microti* in the United States is *Ixodes scapularis*. For successful parasite transmission, feeding for more than 48 hours is necessary. The reservoirs of *B. microti* are the white-footed mouse and the white-tailed deer [1, 3, 4].

Another mode of transmission of *Babesia* is through blood transfusion. This risk is felt to be due to the absence of symptoms in blood donors and survival of organisms in refrigerated or frozen-thawed red cells. Prior to March 2018 there were no licensed tests for screening blood donors for *Babesia*, and potential donors were indefinitely deferred if they have a history of babesiosis [2, 5–7]. The severity of infection is influenced by the species of *Babesia*. After 48 hours of feeding, the tick deposits a significant quantity of sporozoites in the dermis of the human host, which infect erythrocytes and later become trophozoites. Replication of the trophozoites may lead to the formation of tetrad (Maltese cross forms). Rupture and lysis of red cells leads to the release of the merozoites, and infestation of additional red cells. Tetrad forms were not observed in this case. It is of interest that the latter are frequently observed in patients with *B. duncani* infection. *Babesia microti* usually produces asymptomatic to mild flu-like symptoms 1–6 weeks after exposure. In immunocompromised and asplenic individuals, complications of greater severity are often non-immune and attributed to the lysis of infected erythrocytes. Rarely, the organism may cause immune dysregulation and lead to formation of autoantibodies that cross react with similar antigens on blood red cells, as seen in this patient. Chronic infection with *B. microti* is believed to be due to the organism's ability to undergo antigenic variation enhancing survival in human tissues. In contrast, infection with *B. divergens* is more severe, with a mortality rate in asplenic patients up to 42%. Additionally, no chronic cases of *B. divergens* have been reported [3, 4]. Babesiosis can be treated effectively with antibiotics (clindamycin plus quinine). Severe cases, defined as 10% parasitemia with presence of severe symptoms, have been treated with red cell exchange. The goal of the exchange is to reduce the parasitic burden to less than 5% with improvement of clinical signs and symptoms [8, 9]. Our case responded well to medications and did not require red cell exchange.

Babesia can be diagnosed by serology and examination of thick and thin smears. By smear examination the trophozoites of *B. microti* usually appear as delicate ring forms, resembling that of *Plasmodium falciparum*. While the trophozoites of *P. falciparum* may lie on the surface of the red cells with double chromatin dots in ring forms, tetrad (Maltese cross) forms, and extracellular forms are absent. Additionally, gametocytes are absent in *Babesia* and infected cells lack hemozoin pigment, a feature observed in *Plasmodium* species. Another clue is the absence of fever despite the high degree of parasitemia. Polymerase chain reaction and arrayed fluorescence immunoassays have been previously used as investigational tools for screening and follow-up of donors in endemic areas [10]. On March 6, 2018, the US Food and Drug Administration approved the *B. microti* Arrayed Fluorescent Immunoassay (AFIA), for the detection of antibodies to *B. microti* and the *B. microti* Nuclei Acid Test (NAT), for the detection of *B. microti* DNA for screening of blood, tissue and organ donors. Speciation is achieved by RT-PCR on peripheral blood as in this case. This case reiterates Babesiosis as a cause of hemolytic anemia and should be included in the differential diagnosis of autoimmune hemolytic anemia in a patient with a history of blood transfusion and poor response to steroids or immunosuppressive drugs. Such hemolysis is curable by elimination of the *Babesia* infection.

CONCLUSION

In conclusion, Babesiosis should be in the differential diagnosis of autoimmune hemolytic anemia in a patient with a history of blood transfusion and poor response to steroids or immunosuppressive drugs.

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Author Contributions
Menchu Ong – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jennifer Lee – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Data Availability
All relevant data are within the paper and its Supporting Information files.