**The unusual case of babesiosis causing disseminated intravascular coagulation with hemophagocytic lymphohistiocytosis**

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**Abstract**

Babesiosis is increasing in the elderly due to an age-related decline in immunity. Prompt diagnosis with blood smear and PCR prevent life-threatening complications, like DIC and HLH. Studies focusing on pathophysiology and risk factors are needed.

**KEYWORDS**
age-related immunity, apheresis, Babesiosis, disseminated intravascular coagulation (DIC), hemophagocytic lymphohistiocytosis (HLH)

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**Funding information**
The authors have no financial disclosures or funding to declare

**INTRODUCTION**

Babesiosis is a tick-borne illness with life-threatening complications. The deleterious combination of DIC and HLH as a complication of Babesiosis is rare. We present a case of DIC and HLH, caused by babesiosis, with a favorable outcome due to prompt clinical diagnosis with blood smear, PCR, and treatment with apheresis.

Babesiosis is an intra-erythrocytic Protozoan infection, transmitted through the *Ixodes scapularis* ticks (also called black-legged or deer ticks), most commonly found in the Northeastern and upper Midwestern regions of the United States (US).¹ *Babesia microti* is most frequently found in humans, and the CDC has reported approximately 2000 cases each year.²³ It is common for infected people not to recall a tick bite, as they can be as small as a poppy seed when sporozoites become transmissible. Sporozoites subsequently enter erythrocytes and undergo asexual replication leading to red blood cell (RBC) lysis.¹³ Clinical manifestations range from asymptomatic to severe fulminating disease, leading to hemolytic anemia, thrombocytopenia, hemophagocytic lymphohistiocytosis (HLH), splenic rupture, or even disseminated intravascular coagulation (DIC).⁴ The major risk factors for these life-threatening
complications primarily include immunocompromised status, asplenic patients, and those 60 years of age or older. 

This case emphasizes the significance of maintaining a high clinical suspicion, particularly in the elderly from endemic regions. These patients are at increased risk of rapid decompensation from severe Babesiosis. Thus, early diagnosis with a blood smear or polymerase chain reaction (PCR) analysis is vital to determine whether apheresis is required. Babesiosis is an easily treatable and preventable cause of death that should urge clinicians to make a prompt diagnosis. We present a unique case of an elderly male, without any underlying chronic medical illnesses, who was diagnosed with severe babesiosis, complicated by multi-organ failure with a notable presence of both DIC and HLH. This case aims to bring attention to this exceedingly rare phenomenon where DIC can occur in conjunction with HLH, thus prompting early diagnosis and treatment in high-risk patients.

2 | CASE PRESENTATION

An 81-year-old Korean male with no significant medical or surgical history, not on any chronic medications, presented with fevers, rigors, confusion, and non-specific abdominal pain for five days in the month of June. The family reported that the patient had lived in the United States since he was a child. His only recent travel was to the Bahamas five months before admission. He is an avid golfer and had recently spent significant time outdoors. They did not recall any tick bites or rashes.

On physical examination, vital signs were within normal limits. However, the patient was altered, diaphoretic, and jaundiced with scleral icterus. He exhibited abdominal distention but with intact bowel sounds and without fluid shift, rigidity, or guarding. He had hematuria and a lower extremity petechial rash. The patient's initial laboratory findings are summarized in Table 1. The key findings to note are normocytic anemia, thrombocytopenia, elevated blood urea nitrogen (BUN) and creatinine, and a mixed liver injury pattern with conjugated hyperbilirubinemia. An acute and chronic liver injury workup including autoimmune and viral panels, including HIV, along with a metabolic workup was unrevealing. Computed tomography (CT) of the abdomen and pelvis did not reveal any signs of acute cholecystitis or biliary ductal obstruction. Abdominal ultrasound demonstrated splenomegaly of 13.4 cm. Blood smear demonstrated intra-erythrocytic blood parasite structures. Wright stain showed Trophozoites in ring form, some with four parasites per cell (Figure 1). The blood smear was positive for Babesia species, and PCR confirmed Babesia microti. 

The patient was diagnosed with severe Babesiosis: There were signs of both renal and hepatic dysfunction, as evidenced by a significantly elevated BUN, creatinine, and mixed liver injury with marked direct hyperbilirubinemia. The patients’ labs suggested a non-immune mediated, acquired hemolytic anemia as evidenced by normocytic anemia, thrombocytopenia, elevated lactate dehydrogenase, and indirect bilirubin along with a low haptoglobin, and a negative Coomb's test (Table 1). He was empirically started on IV azithromycin, atovaquone, and clindamycin. Within twelve hours of admission, the patient rapidly decompensated with evidence of septic shock complicated by multi-organ dysfunction (encephalopathy, acute hypoxic respiratory failure, oliguric acute renal failure, and worsening liver dysfunction) along with acute hematemia and hemoptysis. The patient developed signs indicative of DIC with prolonged prothrombin time (PT) of 21.4 s (normal: 12.5–14.9 s) and partial thromboplastin time (PTT) of 42.1 s (normal: 24.0–34.0 s), elevated D-dimer to 1.36 ug/ml (normal: <0.50 μg/ml), thrombocytopenia 34,000/μl, hypofibrinogenemia of 189 mg/dl, excessive bleeding, and a diffuse petechial rash. Additionally, the patient met criteria for secondary HLH as defined by the HLH-2004 Criteria as evidenced by the following: immunocompetency, fever, organomegaly, cytopenias (hemoglobin <9 g/dl and platelets <50,000/μl), elevated ferritin, hypofibrinogenemia, and hepatitis.

The patient was subsequently transferred to the medical intensive care unit (ICU), intubated, and sedated for airway protection. The Hematology department recommended apheresis as the parasitemia load was high at 25.6%. Nephrology initiated continuous veno-venous hemofiltration. He required maximal IV pressor support medications to maintain his mean arterial pressure >65 mmHg. Gastroenterology was consulted for continued gastrointestinal bleeding (GIB). The patient was started on a continuous IV pantoprazole drip but was evaluated to be too high risk for endoscopic intervention. He required repeated red blood cell transfusions, cryoprecipitate, plasma, and one unit of plateletppheresis to maintain hemoglobin >8 g/dl and platelets >50,000/μl. However, with adequate resuscitation and IV pantoprazole, the patient’s GIB spontaneously resolved without any further intervention. The antibiotic regimen was escalated to piperacillin and tazobactam to mitigate gut bacterial translocation. The challenge faced was the lack of an IV equivalent for atovaquone, which was given via the OG tube. IV clindamycin, azithromycin, and doxycycline were also used due to the concern of co-infection with acute Lyme disease, despite negative Lyme serology test (possible false-negative). Apheresis was continued until parasite load was <10%.
Over time, the treatment reduced parasitic load, and apheresis was no longer indicated. The requirement for blood products, pressor support, and coagulopathy reversal agents became less. With continued antibiotics and supportive treatment, the patient gradually improved, and the parasitemia level trended down to <1%. His encephalopathy improved and he was successfully extubated. The patient's kidney and liver function, hemolytic and fibrinolytic laboratories all normalized. After 16 days of hospitalization, he was discharged home. At a one-month follow-up, the patient had fully recovered without any further complications.

### Table 1: Laboratory parameters on admission

| Laboratory Parameter | Value (Normal Range) | Laboratory Parameter | Value (Normal Range) |
|----------------------|----------------------|----------------------|----------------------|
| **Chemistry Profile** |                      | **Complete Blood Count** |                      |
| Sodium               | 133 mmol/L (135–145 mmol/L) | White Blood Cell | 4.2 x 10^3/μl (4–10 x 10^3/μl) |
| Potassium            | 4.9 mmol/L (3.4–5.1 mmol/L) | Red Blood Cell | 3.13 x 10^6/μl (4.6–6.1 x 10^5/μl) |
| Chloride             | 104 mmol/L (98–107 mmol/L) | Hemoglobin | 10.7 g/dl (13.5–18.0 g/dl) |
| Bicarbonate          | 27 mmol/L (22–29 mmol/L) | Hematocrit | 31.2% (41–53%) |
| BUN                  | 64 mg/dl (8–23 mg/dl) | Mean Cell Volume | 99.5 fl (80–96 fl) |
| Creatinine           | 2.21 mg/dl (0.7–1.2 mg/dl) | Mean Cell Hgb | 34.1 pg (27–33 pg) |
| Glucose              | 136 mg/dl (70–140 mg/dl) | Mean Cell Hgb Conc | 34.3 g/dl (32.0–36.0 g/dl) |
| Anion Gap            | 10 mmol/L (8–15 mmol/L) | Red Cell Dist Width | 16.1% (11.5–14.5%) |
| Albumin              | 2.9 g/dl (3.5–5.2 g/dl) | Platelet Count | 34 x 10^3/μl (150–400 x 10^3/μl) |
| ALT                  | 50 U/L (<41 U/L) | % Reticulocyte | 1.4% (0.6–2.8%) |
| AST                  | 125 U/L (<40 U/L) | Absolute Retic | 44.4 x 10^3/μl (26–122 x 10^3/μl) |
| Alkaline Phosphatase | 134 U/L (40–129 U/L) | Immature Retic | 0.37% (0.26–0.5%) |
| Direct Bilirubin     | 4.4 mg/dl (<0.3 mg/dl) | LDH | 1,274 U/L (122–225 U/L) |
| Total Bilirubin      | 7.5 mg/dl (<1.2 mg/dl) | Haptoglobin | <15 mg/dl (30–200 mg/dl) |

### Coagulation Studies

| INR | 1.79 (1-1.1) |
| PT  | 21.4 s (12.5–14.9 s) |
| PTT | 42.1 s (24.0–34.0 s) |
| D-Dimer | 1.36 μg/ml (0.5 μg/ml) |
| Fibrinogen<sup>a</sup> | 730 mg/dl (190–450 mg/dl) |

### Inflammatory Markers

| Ferritin | 1393 ng/ml (30–400 ng/ml) |

**Note:** Values listed as high, low, or if not indicated are within normal limits, according to ranges set by SUNY Upstate Medical University Laboratory.

<sup>a</sup>Fibrinogen significantly decreased throughout admission to 166 mg/dl.

<sup>b</sup>Hemoglobin significantly decreased throughout admission to 4.7 g/dl.
DISCUSSION

Babesia is the second most common blood-borne parasite affecting mammals after trypanosomes.5,6 Babesiosis is mostly self-limiting. However, a fulminant disease causing DIC and HLH has rarely been reported. With an increasing number of cases, it is paramount to promptly diagnose, treat, and perform RBC exchange apheresis if clinically indicated.

In a rural setting, it is imperative that clinicians obtain a blood smear sample for patients demonstrating hemolytic anemia. This is a quick and low-cost method to diagnose the disease and will prevent delays in treatment, where apheresis may not be readily available.

According to the 2011–2015 Babesiosis Surveillance report, created by the CDC, there were 2,074 cases reported in 2015, with 57.9% occurring in individuals ≥60 years of age.7 Over 70% of the cases reported symptom onset to be during the months of June through August, with deaths occurring in about a tenth of hospitalized patients with B. microti.7,8 Severe cases occur in the elderly patients who are splenectomized or immunocompromised. Our patient was 81 years old and had a severe case of babesiosis. One explanation for this may be that as one ages, there is an associated loss of immunity against B. microti.9 Vannier et al. (2005) and Igarashi et al. (1999) performed studies in murine models that demonstrated the importance of CD4+ helper T cells and gamma-interferon as protection and that resistance to Babesiosis might be genetically determined.10,11 With most clinically ill patients over the age of 60, they postulated there to be an age-related difference in gene expression related to Babesia microti immunity.10

Complications of severe Babesiosis include acute respiratory failure, congestive heart failure, liver, and renal failure, yet few cases of DIC and HLH in humans, have been reported.12 One review reported that 6 of the 34 patients with Babesiosis, hospitalized in Long Island, acquired DIC.13 However, this study did not report any patient with concomitant HLH. To our knowledge, our case is one of the few to be reported in the literature where severe Babesiosis led to both DIC and HLH. The mechanism of Babesia microti causing DIC or HLH is not known, and there is little information to suggest that current studies are underway.

Babesiosis causing DIC is frequently discussed within veterinary medicine. Moore et al. studied the pathophysiology by examining the autopsies of canine species, with severe babesiosis, and microscopically identified fibrin microthrombi, which is often seen in DIC.14 The article discusses five different mechanisms by which DIC occurs: The first is that Babesia species enter and shear cells, which causes sludging of erythrocytes, leading to hypoxic injury and damage to the vascular endothelium, which stimulates the intrinsic clotting pathway.14 Secondly, mechanical destruction of invaded erythrocytes causes intravascular hemolysis leading to the release of thromboplastin and activation of the extrinsic clotting pathway.14 Platelet lysis and
ongoing tissue injury are also mechanisms by which thromboplastin is released to cause DIC. Lastly, Moore et al. proposed that the blockade of the reticuloendothelial system is another explanation as to how Babesia leads to DIC in dogs. It can be inferred that these mechanisms play a role in Babesia’s induction of DIC in humans.

HLH is a rare hematologic complication of Babesiosis, which is often underdiagnosed. HLH is disorder of excessive inflammation, abnormal immune activation, tissue destruction, and an abnormal downregulation by activated macrophages and lymphocytes. Our patient met the criteria set forth by the HLH-2004 trial, with fever, splenomegaly, cytopenia affecting two lineages, hypofibrinogenemia, a high ferritin level, and hepatitis. His trend of abnormal RDW, as well as nucleated RBCs, is suggestive of dyserythropoiesis, which is often associated with HLH. The mechanism by which Babesiosis causes HLH is poorly understood. However, it can be hypothesized that Babesiosis shears erythrocytes, setting off a cascade of events, which disrupt immune hemostasis, leading to a hyperinflammatory response and HLH.

4 | CONCLUSION

The incidence of Babesiosis is increasing in the United States and is expected to rise with our aging population. Recognizing that there is an age-related decline in immunity against Babesiosis becomes particularly pertinent. The case described, illustrates the importance of considering a blood-borne infection in a patient presenting with febrile hemolytic anemia and promptly obtaining a peripheral blood smear or PCR analysis to determine whether emergent apheresis is needed. The novelty of babesiosis causing DIC with concomitant HLH in severe Babesiosis requires further studies to explore the possible underlying mechanisms and risk factors. Particularly in the setting of high parasitemia and multi-organ dysfunction, early diagnosis and initiation of apheresis are essential to prevent life-threatening complications, such as DIC and HLH.

ACKNOWLEDGMENTS

Published with written consent of the patient.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Alexandra Goodman performed the literature research, responsible for conception, design, and production of the manuscript. Musa Bilal, Zachary Shepherd, and Teresa Gentile edited and reviewed the manuscript. Shivantha Amarnath contributed to conception, design, and editing manuscript.

ETHICAL APPROVAL

There is no information revealing the subject’s identity, and this manuscript complies with guidelines set forth by our institution and hereby confirms that informed consent was obtained from the patient for publication of the case details.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Goodman A, Bilal M, Amarnath S, Gentile T, Shepherd Z. The unusual case of babesiosis causing disseminated intravascular coagulation with hemophagocytic lymphohistiocytosis. *Clin Case Rep*. 2021;9:e04744. [https://doi.org/10.1002/ccr3.4744](https://doi.org/10.1002/ccr3.4744)