CASE REPORT

A 64-year-old female resident of Rockland County, New York, with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) awaiting hematopoietic cell transplantation (HCT) presented to the emergency department on 7/16/19 with fever and malaise for 1 day.

She had been previously diagnosed with CD20-positive Philadelphia chromosome-negative B-cell ALL in July 2018 and initiated treatment according to the dose-adjusted CALGB 10403 protocol [1]. Rituximab was incorporated into her regimen in the setting of CD20 positivity. Due to persistent minimal residual disease, she was transitioned to blinatumomab on 12/12/18 [2], then to salvage chemoimmunotherapy with inotuzumab plus mini–cyclophosphamide, vincristine, and dexamethasone (mini-CVD) on 4/9/19 [3]. She had been taking atovaquone 1500 mg daily for Pneumocystis prophylaxis since September 2018.

On hospital day 3, she was diagnosed with babesiosis after a Giemsa-stained thin blood smear revealed intra-erythrocytic and extracellular ring forms consistent with Babesia microti (2.5% parasitemia). The whole-blood B. microti polymerase chain reaction (PCR) and serum B. microti immunoglobulin M/immunoglobulin G (IgM/IgG; LabCorp Laboratories, Burlington, NC, USA) were positive and negative, respectively. The buffy coat smear was negative for Anasplasma/Ehrlichia. The source of infection was presumed tick-borne given the season and geography. Transfusion-transmitted infection was considered because the patient had received 2 red blood cell (RBC) transfusions in the preceding 5 weeks, but thought unlikely since the New York State blood supply is screened year-round for Babesia by nucleic acid amplification [4]. Figure 1 illustrates pertinent clinical and laboratory data (haptoglobin, percent parasitemia, and B. microti PCR positivity), as well as treatment regimens at the time of initial diagnosis and throughout the course of infection.

Because of her overall clinical stability, she was started on first-line therapy for babesiosis with azithromycin 1 g per os (PO) daily and atovaquone 750 mg twice daily on 7/18/19. Had she presented with more severe illness, alternative therapy might have been considered upfront given that she had previously been on atovaquone. Due to persistent fevers, clindamycin 600 mg IV every 8 hours was added on 7/21/19. She was transfused 1 unit of packed RBCs on hospital days 5 and 9. Her fevers eventually resolved, and the markers of hemolysis began to improve.
She was discharged on 7/25/19 with atovaquone 750 mg twice daily, azithromycin 1 g PO daily, and atovaquone-proguanil 1 tablet daily with continued weekly monitoring of the parasite blood smear, \textit{B. microti} PCR, and hemolysis labs [5–8, 13]. Although the haptoglobin normalized and the blood smear turned negative on 8/2/19, the \textit{B. microti} PCR and IgM/IgG remained positive and negative, respectively. Atovaquone and azithromycin were continued, but atovaquone-proguanil was stopped. Allogeneic HCT, initially scheduled for mid-August, was delayed until the following month.

She was admitted on 9/20/19 for HCT. The reduced intensity conditioning regimen consisted of cyclophosphamide, fludarabine, and total body irradiation (200 cGy). She underwent haploidentical allogeneic HCT on 9/27/19 (71 days from diagnosis of babesiosis). Tacrolimus and mycophenolate mofetil were administered for prevention of graft-vs-host disease (GvHD). The immediate post-transplant course was complicated by delayed engraftment and neutropenic fever due to central line–associated \textit{Staphylococcus epidermidis} and \textit{Escherichia coli} bloodstream infection.

**Figure 1.** Illustration of case patient’s clinical course, laboratory findings, and antibabesial therapies received from initial diagnosis to death. Abbreviations: aHUS, atypical hemolytic uremic syndrome; CMO, comfort measures only; HCT, hematopoietic cell transplantation; PCR, polymerase chain reaction.
While admitted for HCT, the *B. microti* PCR became undetectable on 10/5/19 (79 days from diagnosis). Atovaquone and azithromycin were discontinued on 10/13/19 following 2 consecutive negative PCRs and in the setting of elevated liver function tests that were thought to be medication-related. She continued weekly *B. microti* PCR surveillance. Neutrophil engraftment occurred on 10/28/19, and she was discharged on 11/4/19 on tacrolimus for GvHD prophylaxis and acyclovir, trimethoprim-sulfamethoxazole (TMP-SMX), and voriconazole for antimicrobial prophylaxis.

She was readmitted on 11/11/19 with acute kidney injury, ultimately determined to be prerenal in etiology, but TMP-SMX was changed back to atovaquone 1500 mg daily for possible drug-induced renal toxicity. The hospital course was further complicated by recurrent hemolysis. The blood parasite smear and *B. microti* PCR remained negative, so she was administered the first of 4 weekly doses of eculizumab 900 mg for presumed tacrolimus-associated thrombotic microangiopathy on 11/25/19. Due to difficulty achieving therapeutic levels of sirolimus, she was changed to ruxolitinib 10 mg twice daily and prednisone 35 mg (0.5 mg/kg) daily for GvHD prophylaxis. She was discharged home on 11/27/19.

She was readmitted 8 days later on 12/5/19 with sepsis secondary to *E. coli* bacteremia from spontaneous bacterial peritonitis in the setting of noncirrhotic portal hypertension and worsening cholestasis. She was diagnosed with severe sinusoidal obstruction syndrome, formerly known as hepatic veno-occlusive disease, via liver biopsy and started on defibrotide on 12/11/19 with rapid, albeit partial, improvement in her hyperbilirubinemia.

During this hospitalization, the *B. microti* PCR turned positive on 12/6/19 (141 days from diagnosis), although no parasite forms were initially detected on blood smear. The *B. microti* IgM/IgG remained negative. She was continued on atovaquone, restarted on azithromycin 500 mg PO daily on 12/13/19, and later initiated on clindamycin 600 mg IV every 8 hours on 12/17/19 in the setting of fevers. While on this regimen, she developed high-grade parasitemia (10%–12%) on 12/31/19 2 months of *B. microti* PCR negativity. In our review of 3

**DISCUSSION**

A history of B-cell lymphoid malignancy with either asplenia and/or treatment with immunosuppressive medications (rituximab, an anti-CD20 monoclonal antibody, in particular) is associated with more severe acute *Babesia* infection and poorer outcomes following standard treatment regimens [10]. The 2020 Infectious Diseases Society of America clinical practice guidelines recommend treating these patients for a longer duration—at least 6 weeks, including 2 weeks after parasites are no longer seen on blood smear [11].

Despite what is known about the clinical course and management of babesiosis in immunocompromised hosts, to our knowledge, there are only 3 other published case reports of babesial infections in HCT recipients (Table 1). These reports include a patient with refractory sickle cell anemia with transfusion-transmitted babesiosis in the immediate pretransplant period [12], a patient with chronic myelogenous leukemia who developed babesiosis 3 years post-transplant following treatment with rituximab and while on corticosteroids for chronic GvHD [13], and a patient with myelofibrosis who was diagnosed with babesiosis 14 months post-transplant after receiving tacrolimus, rituximab, and corticosteroids for GvHD [14]. Whereas the first patient responded to a 10-day course of therapy with atovaquone and azithromycin, the second patient had persistent parasitemia after 8 weeks on this regimen.

It was not until he was transitioned to clindamycin and quinine, started on atovaquone-proguanil, and had azithromycin increased to 1000 mg daily that the parasitemia cleared. The third patient, meanwhile, was treated with doxycycline, clindamycin, and atovaquone for 6 weeks with rapid improvement in his hematolytic anemia.

Herein we report the fourth such case of babesiosis in a patient following HCT and, to our knowledge, the first and only case of a patient who underwent HCT while on antibabesial therapy with a positive *B. microti* PCR and a negative *B. microti* IgG, with a post-transplant course complicated by relapsed babesiosis. Of note, none of the previous case reports in HCT recipients comment on the *B. microti* IgG status at the time of initial diagnosis or following treatment. Adding to the uniqueness of this particular case, our patient suffered a relapse following 2 months of *B. microti* PCR negativity. In our review of the literature, only 1 other case of relapsed babesiosis following a negative *Babesia* PCR result has been described [6]. The patient, who had a remote history of Hodgkin’s disease treated with splenectomy and chemoradiation, received 10 weeks of atovaquone and azithromycin until the *Babesia* PCR turned negative, but unfortunately developed relapsing infection decreasing to 0.4%, she developed worsening shock with multiorgan failure. After she and her family chose to pursue comfort care measures, she died on 1/12/20.
2 months later and ultimately died. Similar to our patient, she never had documented seroconversion during follow-up.

Our patient had several risk factors for relapsing/persistent infection, the most important of which was likely her net state of immunosuppression. Before infection, she had been treated with rituximab for her leukemia. Although the last dose had been administered ~9 months before her initial diagnosis, the immunomodulatory effects of rituximab have the potential to last >18 months [7]. Even after clearing her blood smear, she was unable to mount an antibody response to the parasite, as evidenced by persistently negative B. microti serologies, suggesting ongoing humoral deficiency.

Although the specific role of humoral immunity in achieving clinical cure remains unclear, it would appear that B cells, whether by producing antibodies and/or serving as antigen-presenting cells for T cells, are highly important, if not necessary, for sustained remission of babesiosis [7, 10]. Following a prolonged treatment course, our patient never seroconverted, possibly signifying incomplete parasite clearance despite a negative blood parasite smear and B. microti PCR.

Aside from chemotherapy for her ALL, our patient received multiple other immunosuppressive medications, including fludarabine (associated with profound and prolonged T lymphopenia) [15], eculizumab (associated with terminal complement deficiency) [16], and ruxolitinib (associated with impaired dendritic cell function and T-cell priming) [17]. Although none of these drugs have been implicated in relapsing/persistent babesiosis, their precise contribution (alone or in combination) remains unknown.

Our patient also received an extended course of corticosteroids, which only further contributed to her degree of immunosuppression.

Based on prior reports, we also considered whether atovaquone or azithromycin drug resistance contributed to our patient’s poor outcome. She was on atovaquone monotherapy during the initial incubation period and received nearly...
In summary, the management of babesiosis in HCT patients in the peri-transplant period remains a significant challenge. These patients are at significantly increased risk of persistent/relapsing infection due to profound and prolonged immunosuppression. Complicating matters are that reduction of immunosuppression increases the risk of GvHD, extended antibabesial therapy carries a risk of acquired drug resistance, and no standardized approach to monitoring these patients has been established.

Taking all this into account, it may be most prudent to consider continuation of antibabesial therapy in highly immunocompromised hosts until it is possible to achieve some degree of immune reconstitution, either through reduction of iatrogenic immunosuppression or remission of the underlying immunosuppressive condition. Further studies are needed in this population to help define the most appropriate combination of medications, the optimal duration of therapy, and the best approach to monitoring. Given the rapidly expanding population of immunosuppressed hosts, in part due to novel therapeutics compromising humoral and cell-mediated immunity, this research would be especially timely.

### Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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#### Potential conflicts of interest
All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

#### Patient consent
Consent was unable to be obtained from the patient before death. Ethical board approval was not believed to be indicated because this case report did not involve human subjects research.

### References

1. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood 2019; 133:1548–59.

2. Gökbüget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018; 131:1522–31.

3. Jabbour E, Ravandi F, Kebriaei P, et al. Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini–hyper-CVD for patients with relapsed or refractory philadelphia chromosome–negative acute lymphoblastic leukemia. JAMA Oncol 2018; 4:230–234.

4. US Food and Drug Administration, Center for Biologics Evaluation and Research. Recommendations for reducing the risk of transfusion-transmitted babesia. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-reducing-risk-transfusion-transmitted-babesia. Accessed 28 May 2021.

5. Vyas JM, Telford SR, Robbins GK. Treatment of refractory Babesia microti infection with atovaquone-proguanil in an HIV-infected patient: case report. Clin Infect Dis 2007; 45:1588–90.

6. Wormser G, Prasad A, Neuhaus E, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with Babesia microti infection. Clin Infect Dis 2010; 50:381–6.
7. Raffalli J, Wormser GP. Persistence of babesiosis for >2 years in a patient on rituximab for rheumatoid arthritis. Diagn Microbiol Infect Dis 2016; 85:231–2.
8. Simon MS, Westblade LF, Dziedziech A, et al. Clinical and molecular evidence of atovaquone and azithromycin resistance in relapsed Babesia microti infection associated with rituximab and chronic lymphocytic leukemia. Clin Infect Dis 2017; 65:1222–5.
9. Centers for Disease Control and Prevention. Babesiosis surveillance - United States, 2011–2015. 2019. Available at: https://www.cdc.gov/mmwr/volumes/68/ss/ss6806a1.htm. Accessed 26 May 2021.
10. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis 2008; 46:370–6.
11. Krause PJ, Auwaerter PG, Bannuru RR, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA): 2020 guideline on diagnosis and management of babesiosis. Clin Infect Dis 2021; 72:e49–64.
12. Cirino CM, Leitman SF, Williams E, et al. Transfusion-associated babesiosis with an atypical time course after nonmyeloablative transplantation for sickle cell disease. Ann Intern Med 2008; 148:794–5.
13. Lubin AS, Snydman DR, Miller KB. Persistent babesiosis in a stem cell transplant recipient. Leuk Res 2011; 35:e77–8.
14. Bade NA, Yared JA. Unexpected babesiosis in a patient with worsening anemia after allogeneic hematopoietic stem cell transplantation. Blood 2016; 128:1019.
15. Gamberale R, Galmarini CM, Fernández-Calotti P, et al. In vitro susceptibility of CD4+ and CD8+ T cell subsets to ß-hydroxybutyrate. Biochem Pharmacol 2003; 66:2185–91.
16. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. Curr Opin Infect Dis 2016; 29:319–29.
17. Lussana F, Cattaneo M, Rambaldi A, Squizzato A. Ruxolitinib-associated infections: a systematic review and meta-analysis. Am J Hematol 2018; 93:339–47.
18. Wittner M, Lederman J, Tanowitz HB, et al. Atovaquone in the treatment of Babesia microti infections in hamsters. Am J Trop Med Hyg 1996; 55:219–22.
19. Lemieux JE, Tran AD, Freimark L, et al. A global map of genetic diversity in Babesia microti reveals strong population structure and identifies variants associated with clinical relapse. Nat Microbiol 2016; 1:16079.
20. Korsicszky M, Chen N, Kotecka B, et al. Mutations in Plasmodium falciparum cytochrome b that are associated with atovaquone resistance are located at a putative drug-binding site. Antimicrob Agents Chemother 2000; 44:2100–8.
21. Lawres LA, Garg A, Kumar V, et al. Radical cure of experimental babesiosis in immunodeficient mice using a combination of an endothclin-like quinolone and atovaquone. J Exp Med 2016; 213:1307–18.