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Transient False-Reactive Fourth-Generation HIV Screening and Delayed Warm Autoimmune Hemolytic Anemia Following Acute Babesia microti Infection in an Asplenic Patient

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Abstract

Babesiosis is a tick-borne infection caused by intraerythrocytic *Babesia* species and may be associated with both direct hemolysis and uncommon immune-mediated complications. We describe a 47-year-old man with asplenia who presented with acute *Babesia microti* (*B. microti*) infection and 2.21% parasitemia. During the acute illness, a fourth-generation Elecsys HIV Duo HIV-1/2 antigen/antibody screening assay was reactive, while HIV-1/HIV-2 antibody differentiation testing was negative and HIV-1 RNA was not detected (<20 copies/mL). Repeat HIV testing after clinical recovery was negative, supporting a transient false-reactive screening result. Approximately two weeks after the initial hospitalization, the patient developed warm autoimmune hemolytic anemia (WAHA), with hemoglobin declining from 14.1 to 8.8 g/dL, reticulocytosis, markedly elevated lactate dehydrogenase, low haptoglobin, and a positive direct antiglobulin test with IgG 2+ and C3d negative. He improved with prednisone 60 mg daily without transfusion, rituximab, or intravenous immunoglobulin. This case highlights two unusual phenomena occurring in temporal association with acute *B. microti* infection and underscores the importance of confirmatory HIV testing and vigilance for delayed autoimmune hemolysis, particularly in asplenic patients.

Categories: Hematology, HIV/AIDS, Infectious Disease
Keywords: asplenia, babesia microti, babesiosis, false-reactive hiv test, fourth-generation hiv assay, warm autoimmune hemolytic anemia

Introduction

Babesiosis is a tick-borne infection caused by intraerythrocytic protozoa of the genus *Babesia*. In the United States, *Babesia microti* (*B. microti*) is the predominant cause, particularly in the Northeast. Hemolytic anemia is a well-recognized manifestation of babesiosis, but delayed warm autoimmune hemolytic anemia (WAHA) after clinical improvement is uncommon and has been reported particularly in asplenic patients [1,2]. False-reactive human immunodeficiency virus (HIV) serology has also been described during acute babesiosis [3-6]. We report an asplenic patient with acute *B. microti* infection in whom a transient reactive fourth-generation HIV screening assay was followed by delayed WAHA.

Case Presentation

A 47-year-old man with a significant history of asplenia following a motor vehicle accident presented with approximately 10 days of fever and headache. Initial laboratory testing demonstrated a white blood cell count of 10.5 K/µL, hemoglobin of 14.1 g/dL, platelet count of 149 K/µL, total bilirubin of 0.8 mg/dL, aspartate aminotransferase (AST) of 52 U/L, alanine aminotransferase (ALT) of 152 U/L, and creatinine of 0.8 mg/dL (Table *1*).

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Laboratory parameter	Day 1/presentation	Week 1/discharged	Week 2/readmission	Week 3/early recovery	1 month/recovery
Hgb (g/dL)	14.1	11.8	8.8	9.3-10.5	14
Platelets (x10^3/uL)	149	241	262	400-444	423
WBC (x10^3/uL)	10.5	8.6	11.9	10.9-16.7	15.8
Corrected retic (%)			5.4	11.7 -> 9.3	5.5
LDH (IU/L)			1,966	867 -> 520	
AST (IU/L)	52	37	83	22-23	
ALT (IU/L)	152	107	70	40-39	
Total bilirubin (mg/dL)	0.8	0.6	1.6	0.6 -> 0.4	0.6

TABLE 1: Evolution of hematologic and biochemical parameters during babesiosis and subsequent warm autoimmune hemolytic anemia

Hgb, hemoglobin; WBC, white blood cell count; retic, reticulocyte count; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; g/dL, grams per deciliter; mg/dL, milligrams per deciliter; IU/L, international units per liter; µL, microliter; ×10^3/µL, thousands per microliter

Reference ranges: Hgb, 13.0-17.7 g/dL; platelets, 150-450 ×10^3/µL; WBC, 3.4-10.8 ×10^3/µL; corrected reticulocyte count, 0.6-2.6%; LDH, 121-224 IU/L; AST, 0-40 IU/L; ALT, 0-44 IU/L; total bilirubin, 0.0-1.2 mg/dL

As part of his initial evaluation, HIV testing was performed using the Elecsys HIV Duo fourth-generation HIV-1/2 antigen/antibody immunoassay on a Roche Diagnostics platform. The screening assay was reactive. Subsequent HIV-1/HIV-2 antibody differentiation testing was negative. HIV-1 RNA testing using an ultrasensitive assay reported: “not detected” (<20 copies/mL). The patient had also undergone HIV testing in 2025, which was negative. The signal-to-cutoff ratio from the initial reactive HIV screening assay was not available. The Elecsys HIV Duo assay detects HIV-1 p24 antigen and antibodies to HIV-1 and HIV-2, and a reactive result requires confirmatory evaluation according to the HIV diagnostic testing algorithm [7,8].

On the day of presentation, peripheral blood smear demonstrated red blood cell inclusion bodies consistent with parasitic infection. The patient belonged to the New England area, lived in the woods, and reportedly had removed a tick from the scrotum about 37 days prior to this presentation. He was empirically started on treatment for suspected babesiosis with atovaquone and azithromycin on hospital day 2. Four days later, a positive polymerase chain reaction (PCR) test along with a parasite smear showing parasitemia confirmed acute *B. microti* infection. The peripheral blood examination demonstrated 2.21% parasitemia. The patient showed rapid clinical improvement following antimicrobial therapy and was discharged on hospital day 6. He was discharged with a planned four-week course of antimicrobial therapy with atovaquone and azithromycin and close follow-up, including repeat peripheral blood smears to document clearance of parasitemia before discontinuation of therapy.

Approximately two weeks after the initial hospitalization, the patient was readmitted with new-onset significant hemolytic anemia. At the time of readmission, his hemoglobin had decreased to 8.8 g/dL from an initial value of 14.1 g/dL. Laboratory evaluation demonstrated a reticulocyte count of 7.1%, an LDH of 1,966 U/L, haptoglobin <10 mg/dL, and total bilirubin of 1.7 mg/dL. AST was 67 U/L, and ALT was 62 U/L. The platelet count had increased to 262 K/µL (Table *1*). The patient was discharged on prednisone 60 mg with a plan for taper under close follow-up with the hematology team. Antibiotics, atovaquone, and azithromycin were continued.

The direct antiglobulin test (DAT) was positive, with IgG 2+ and C3d-negative. Blood-bank evaluation demonstrated warm-reactive autoantibodies of undetermined specificity coating the patient's red blood cells and present in plasma. Additional cold-reactive autoantibodies were detected in plasma. In the context of a marked decline in hemoglobin, reticulocytosis, markedly elevated LDH, low haptoglobin, and a positive IgG DAT, the findings were consistent with WAHA.

No blood transfusion was required. The patient was treated with prednisone 60 mg daily. Rituximab and intravenous immunoglobulin were not administered. His hemoglobin subsequently began to improve, increasing from 8.8 g/dL to 9.3 g/dL to 10.5 g/dL and subsequently to 14 g/dl (Table *1*).

A peripheral blood smear obtained near the end of the second admission showed no detectable *Babesia* organisms. However, *B. microti* PCR remained positive at that presentation and again approximately one month later. Repeat HIV testing obtained during the subsequent evaluation about 3-4 weeks later was negative. The overall clinical course is summarized in Figure *1*.

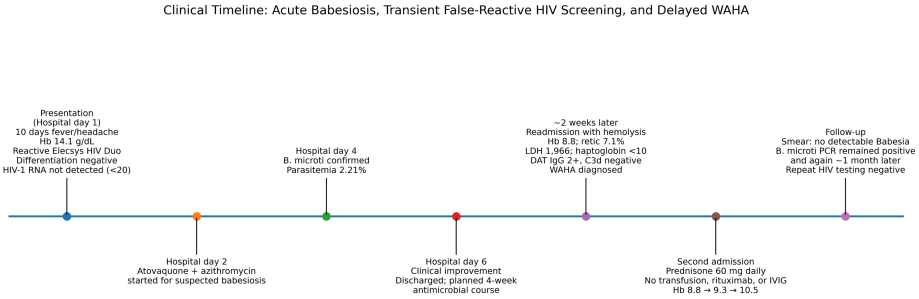


FIGURE 1: Clinical timeline of acute Babesia microti infection, transient false-reactive fourth-generation HIV screening, and delayed WAHA

DAT, direct antiglobulin test; Hb, hemoglobin; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; WAHA, warm autoimmune hemolytic anemia

Discussion

This case illustrates two unusual phenomena occurring in temporal association with acute *B. microti* infection: a transient reactive fourth-generation HIV screening assay and delayed WAHA.

Transient reactive HIV screening assay

Fourth-generation HIV antigen/antibody assays are designed to detect both HIV-1 p24 antigen and antibodies to HIV-1 and HIV-2 and are highly sensitive for early HIV infection. However, a reactive screening assay does not by itself establish an HIV diagnosis. The recommended diagnostic algorithm requires supplemental HIV-1/HIV-2 antibody differentiation testing, followed by HIV-1 nucleic acid testing when the differentiation assay is negative or indeterminate [7,8].

In this patient, the initial fourth-generation screening assay was reactive, whereas the HIV-1/HIV-2 antibody differentiation assay was negative and HIV-1 RNA was not detected (<20 copies/mL). The patient had also had a negative HIV test in 2025. Repeat HIV testing after treatment of the acute illness was negative, further supporting a transient false-reactive screening result rather than true HIV infection.

False-reactive HIV screening in the setting of babesiosis has been reported previously, although it appears to be uncommon. Mesiha et al. reported a false-positive HIV result in a patient with babesiosis, while Smotrys et al. described babesiosis as a potential cause of false-positive HIV serology [3,4]. More recently, He et al. described a patient with acute babesiosis who had an initially positive fourth-generation HIV test followed by negative HIV testing after treatment of babesiosis [5]. Hindosh et al. similarly reported a false-positive HIV result in the setting of acute babesiosis [6].

The mechanism underlying this apparent association remains uncertain. One proposed explanation is immunologic cross-reactivity between antibodies or other immune mediators generated during acute babesiosis and components of HIV serologic assays. Similar false-reactive HIV results have been reported in association with other infectious and inflammatory conditions [4-6]. Importantly, the signal-to-cutoff ratio of the initial reactive assay was unavailable in this case, limiting further assessment of the magnitude of the initial reactivity.

The temporal relationship in this patient is notable: the reactive fourth-generation HIV assay occurred during acute babesiosis, confirmatory HIV-1 RNA testing was not detected, and subsequent HIV testing after clinical recovery was negative. This clinical course is consistent with a transient false-reactive HIV screening result associated with acute babesiosis.

Delayed warm autoimmune hemolytic anemia

The second unusual feature of this case was the development of WAHA approximately two weeks after the initial diagnosis and treatment of babesiosis. Babesiosis itself commonly causes hemolytic anemia through direct destruction of infected erythrocytes. However, the development of warm-antibody autoimmune hemolytic anemia after apparent clinical improvement from babesiosis is a distinct phenomenon.

Woolley et al. described six cases of post-babesiosis WAHA in a cohort of 86 patients with babesiosis. All six affected patients were asplenic, and WAHA developed 2-4 weeks after the diagnosis of babesiosis, after clinical and laboratory responses to antimicrobial therapy and clearance of detectable *B. microti* parasitemia. Warm autoantibodies were identified in all six patients [1]. Their findings suggest that asplenic patients may be particularly susceptible to this complication.

The clinical course of our patient closely parallels this previously described phenomenon. He was asplenic, initially had relatively preserved hemoglobin, developed documented *B. microti* parasitemia, and improved clinically following antimicrobial therapy. Approximately two weeks later, he developed a substantial decline in hemoglobin accompanied by reticulocytosis, markedly elevated LDH, low haptoglobin, mild hyperbilirubinemia, and a positive IgG DAT. Blood-bank testing demonstrated warm-reactive autoantibodies, supporting a diagnosis of WAHA rather than ongoing nonimmune hemolysis alone.

The persistence of *B. microti* PCR positivity despite the absence of detectable organisms on peripheral smear is also noteworthy. PCR can remain positive after parasites are no longer detectable by smear, and persistent or relapsing babesiosis is particularly recognized in immunocompromised individuals, including those who are asplenic [9]. Therefore, the positive PCR results in this patient should not by themselves be interpreted as evidence of active high-level parasitemia or as the sole explanation for the subsequent hemolysis.

Treatment of WAHA generally begins with corticosteroids. International consensus recommendations identify corticosteroids as first-line therapy for WAHA, with rituximab generally considered in severe disease or when there is inadequate response to corticosteroids [10]. In this patient, prednisone 60 mg daily was associated with progressive improvement in hemoglobin, from 8.8 g/dL to 9.3 g/dL and subsequently to 10.5 g/dL, without the need for transfusion, rituximab, or intravenous immunoglobulin.

Relationship between the two phenomena

The coexistence of transient false-reactive HIV screening and delayed WAHA in the same patient raises the possibility of a broader immune dysregulation associated with acute B. microti infection. Although a direct mechanistic relationship cannot be established from a single case, both phenomena occurred within a relatively narrow temporal window surrounding the patient's acute babesiosis.

The case is particularly notable because the patient was asplenic, a recognized risk factor for severe and persistent babesiosis and a population in which post-babesiosis WAHA has been described [1,9]. The transient HIV reactivity adds another potential immunologic manifestation of acute babesiosis and reinforces the importance of confirmatory HIV testing before establishing a diagnosis of HIV infection.

Conclusions

Acute *B. microti* infection may be associated with uncommon immune-mediated complications, including transient false-reactive HIV screening and delayed WAHA. In patients with babesiosis and a reactive fourth-generation HIV screening assay, confirmatory HIV-1/HIV-2 differentiation testing and HIV-1 RNA testing are essential before diagnosing HIV infection. Clinicians should also remain vigilant for delayed autoimmune hemolysis after apparent clinical improvement from babesiosis, particularly in asplenic patients. Recognition of these complications can prevent misdiagnosis of HIV infection and facilitate timely treatment of potentially significant autoimmune hemolytic anemia.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Sanjay Timilsina, Sambida Timilsina, Kashif Mukhtar

Drafting of the manuscript: Sanjay Timilsina, Sambida Timilsina

Critical review of the manuscript for important intellectual content: Sanjay Timilsina, Sambida Timilsina, Kashif Mukhtar

Acquisition, analysis, or interpretation of data: Sambida Timilsina

Supervision: Sambida Timilsina

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