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Rapidly Progressive and Severe Hemolytic Anemia Associated With Epstein-Barr Virus: A Case Report

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Abstract

Epstein-Barr virus (EBV) infection is rarely associated with severe hemolytic anemia. We report a case of a 41-year-old woman with sickle cell trait who developed rapidly progressive hemolytic anemia following travel to Guinea. She presented with fever, jaundice, abdominal pain, and splenomegaly. Laboratory evaluation revealed severe hemolysis, with hemoglobin declining from 11.4 g/dL to 4.6 g/dL, complicated by hemodynamic instability and acute kidney and liver injury. Despite a reported history of malaria, repeated blood smears and *Plasmodium* polymerase chain reaction (PCR) testing were negative. The initial direct antiglobulin test (DAT) was negative, but repeat testing became positive for complement C3d, while cold agglutinin testing remained negative. EBV serology and polymerase chain reaction findings raised suspicion for EBV-associated hemolysis, although a definitive causal relationship could not be established. The patient required multiple red blood cell transfusions, corticosteroids, and supportive care, with gradual clinical improvement. This case highlights the diagnostic challenges of severe hemolytic anemia with evolving immunohematologic findings. It emphasizes the importance of repeat DAT testing and the consideration of EBV as a potential associated infection.

Categories: Hematology, Internal Medicine, Infectious Disease
Keywords: complement c3d, epstein-barr virus, epstein-barr virus infections, immune hemolytic anemia, malaria drugs, severe hemolysis

Introduction

Epstein-Barr virus (EBV) is a ubiquitous human herpesvirus commonly associated with infectious mononucleosis and a generally self-limited clinical course. Although hematologic abnormalities may occur during EBV infection, severe hemolytic anemia is an uncommon complication [1].

EBV-associated hemolytic anemia is predominantly immune-mediated, with cold-antibody-mediated hemolysis being the most frequently reported mechanism, followed by warm-antibody-mediated hemolysis [1]. A systematic review identified 60 reported cases between 1973 and 2024, including severe presentations requiring blood transfusions and immunosuppressive therapy [1-3]. Although the direct antiglobulin test (DAT) is essential in evaluating autoimmune hemolytic anemia (AIHA), an initially negative result does not entirely exclude an immune-mediated process, particularly when clinical and laboratory evidence of hemolysis persists [4].

We report a case of rapidly progressive and severe hemolytic anemia potentially associated with EBV infection, characterized by profound anemia, hemodynamic instability, and an initially negative DAT that subsequently became positive for complement C3d. The diagnostic evaluation was further complicated by recent travel to a malaria-endemic region. This case emphasizes the importance of considering EBV in unexplained severe hemolysis and repeating immunohematologic testing when initial findings are inconclusive.

Case Presentation

A 41-year-old woman with a medical history of hypertension, hyperlipidemia, and sickle cell trait presented with persistent fever, chills, malaise, generalized body aches, and abdominal pain following recent travel to Guinea, West Africa. She had spent approximately four months in Guinea and reported having been diagnosed with malaria and hepatitis B infection while abroad; however, it was unclear whether she had received complete treatment. Her home medications included acetaminophen, ibuprofen, and amoxicillin/clavulanate.

On presentation, the patient was febrile with a temperature of 38.5°C. Her blood pressure was 128/64 mmHg, heart rate was 97 beats/minute, respiratory rate was 22 breaths/minute, and oxygen saturation was 100% on room air. Physical examination was notable for mild scleral icterus, abdominal distention, and generalized abdominal tenderness. There was no rash, synovitis, or dactylitis. Subsequent abdominal imaging demonstrated splenomegaly.

Initial laboratory evaluation demonstrated normocytic, normochromic anemia with biochemical evidence of active hemolysis. Her hemoglobin was initially 11.4 g/dL and subsequently declined to a nadir of 4.6 g/dL. Lactate dehydrogenase (LDH) increased from 1,328 U/L to a peak of 3,494 U/L. Total bilirubin was initially 3.1 mg/dL, with a direct bilirubin of 1.7 mg/dL, and total bilirubin subsequently peaked at 9.5 mg/dL. Haptoglobin was <10 mg/dL. The reticulocyte count increased from 4.42% to 15.21% during hospitalization. Inflammatory markers were elevated, with an erythrocyte sedimentation rate (ESR) of 51 mm/hour and C-reactive protein (CRP) of 31.9 mg/L. Liver enzymes also increased, with aspartate aminotransferase (AST) increasing from 50 U/L to a peak of 373 U/L and alanine aminotransferase (ALT) increasing from 31 U/L to 77 U/L. Alkaline phosphatase remained within the reference range. The evolution of key laboratory parameters is summarized in Table *1*.

Parameter	Initial value	Peak/nadir	Follow-up	Reference range
Hemoglobin (g/dL)	11.4	4.6	8.8	12.6-15.7 (g/dL)
LDH (U/L)	1,328	3,494	761	100-190 (U/L)
Total bilirubin (mg/dL)	3.1	9.5	0.6	0.1-1.2 (mg/dL)
Direct bilirubin (mg/dL)	1.7	-	-	<0.3 (mg/dL)
Haptoglobin (mg/dL)	<10	<10	-	42-296 (mg/dL)
Reticulocyte count (%)	4.42	15.21	-	0.50-1.7 (%)
AST (U/L)	50	373	11	8-33 (U/L)
ALT (U/L)	31	77	19	4-36 (U/L)
Alkaline phosphatase (U/L)	90	90	65	38-126 (U/L)
ESR (mm/hour)	51	-	-	0-20
CRP (mg/L)	31.9	-	-	<1

TABLE 1: Laboratory Parameters During Hospitalization.

Initial values represent the earliest available measurements, peak/nadir values represent the highest or lowest recorded measurements during hospitalization, and follow-up values reflect subsequent improvement.

LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

The initial direct antiglobulin test (DAT) was negative despite laboratory evidence of ongoing hemolysis. Cold agglutinin testing was also negative. Peripheral blood smear did not demonstrate spherocytes, schistocytes, or findings suggestive of sickle cell disease or microangiopathic hemolytic anemia.

Because of her recent prolonged stay in Guinea and reported history of malaria, recurrent or inadequately treated malaria was initially considered a possible cause of her febrile illness and hemolysis. Empiric therapy with artemether/lumefantrine was initiated while additional testing was pending. Broad-spectrum antimicrobial therapy with cefepime and vancomycin was also administered because of concern for sepsis, and azithromycin was subsequently added during the infectious evaluation.

Despite empiric treatment, the patient continued to experience persistent fevers and rapidly progressive anemia. Her hemoglobin decreased to 4.6 g/dL, accompanied by hypotension and ongoing laboratory evidence of hemolysis. The severity of the anemia required extensive transfusion support, and she ultimately received 14 units of packed red blood cells during hospitalization. Her clinical course was further complicated by acute kidney injury and acute liver injury.

An extensive infectious evaluation was performed. Serial thick and thin peripheral blood smears and polymerase chain reaction (PCR) testing for *Plasmodium* species were negative, making active malaria less likely. Testing for *Babesia* and *Mycoplasma* was also negative. Consequently, artemether/lumefantrine was discontinued. Blood and urine cultures remained negative, and broad-spectrum antibiotics were subsequently discontinued after no bacterial source of infection was identified. Glucose-6-phosphate dehydrogenase deficiency and alternative autoimmune causes of hemolysis were also investigated without identifying another explanation for the rapidly progressive anemia.

Because of persistent severe hemolysis and concern for an immune-mediated process, intravenous

methylprednisolone 80 mg was administered before the repeat DAT became positive. Subsequent testing demonstrated complement C3d positivity with negative IgG, suggesting possible complement involvement. However, negative cold agglutinin testing prevented definitive classification as cold agglutinin disease or syndrome.

Further infectious evaluation demonstrated evidence of Epstein-Barr virus (EBV) infection. EBV viral capsid antigen (VCA) IgM was 56.1, VCA IgG was 333, and EBV real-time PCR was positive. These findings, together with the compatible febrile illness, ongoing hemolysis, and unrevealing evaluation for several alternative causes, supported a possible EBV-associated hemolytic process. However, the available testing did not definitively establish primary acute EBV infection or prove causation.

Computed tomography (CT) of the abdomen demonstrated moderate splenomegaly, with the spleen measuring 14.5 cm in length. The splenic vasculature and enhancement pattern were unremarkable. The liver was normal in size, contour, and parenchymal attenuation, without focal hepatic lesions (Figures *1*, *2*).

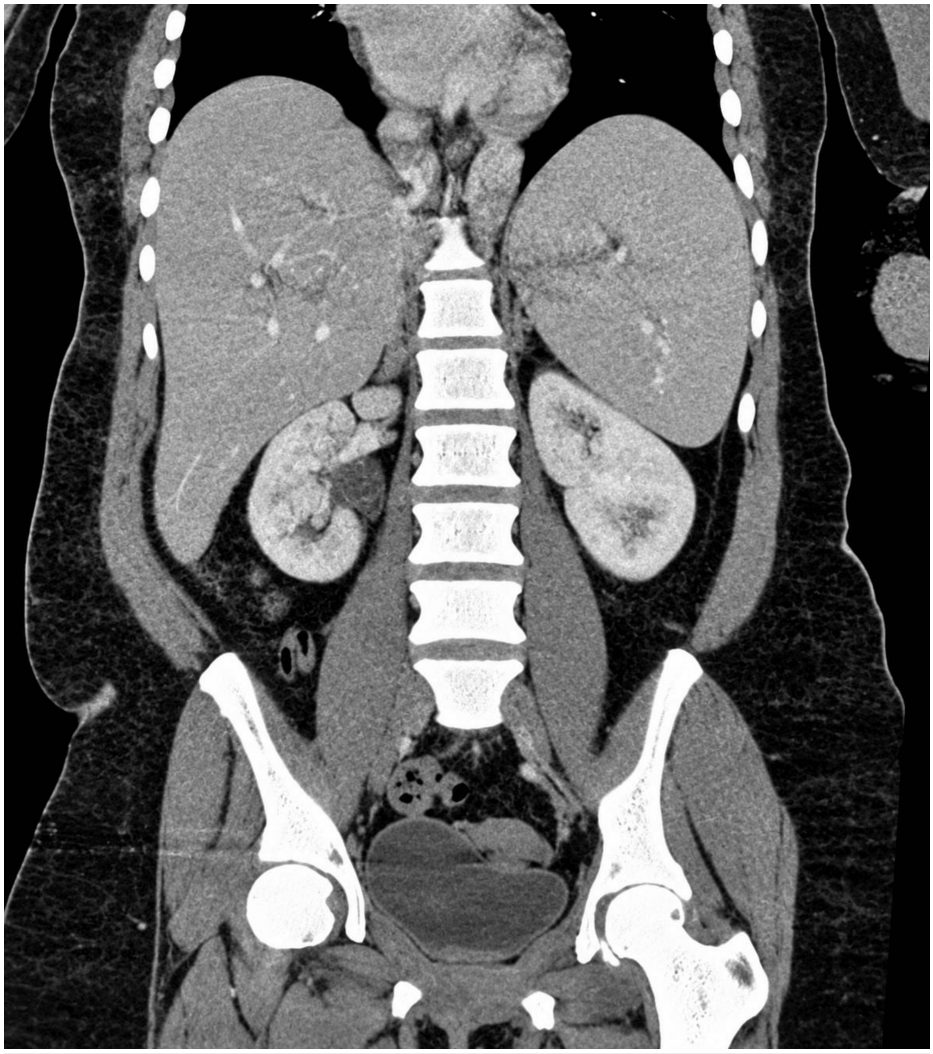


FIGURE 1: Coronal Contrast-Enhanced CT Image Demonstrating Splenomegaly.

Coronal contrast-enhanced CT image of the abdomen demonstrating moderate splenomegaly. The spleen measured approximately 14.5 cm in length on radiologic assessment.

CT: computed tomography

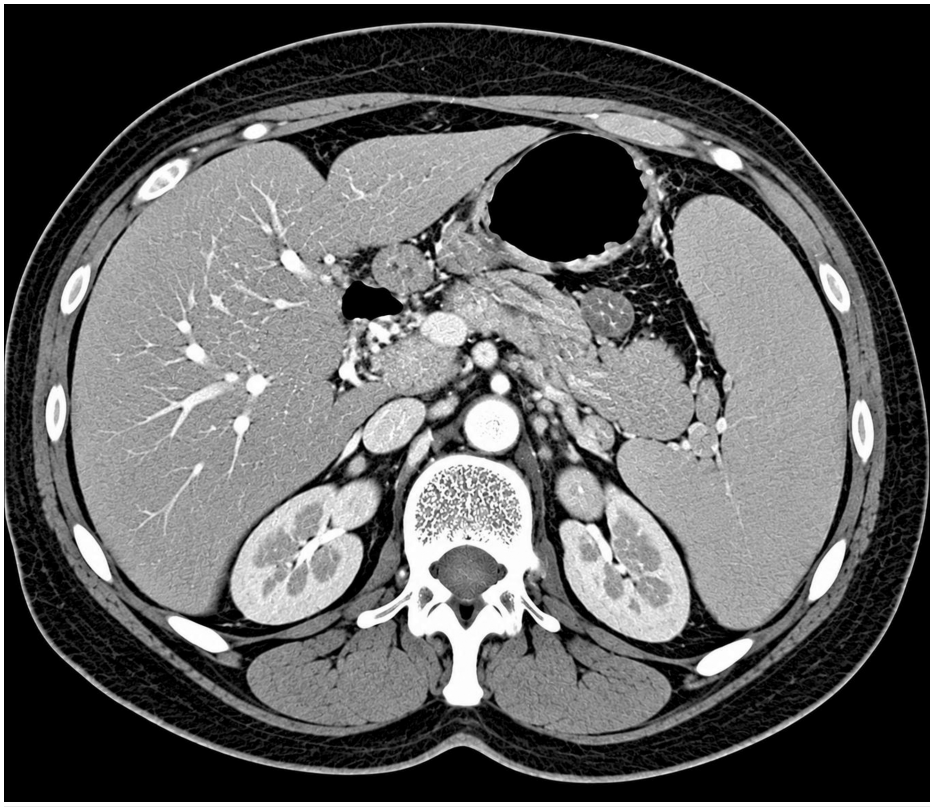


FIGURE 2: Axial Contrast-Enhanced CT Image Demonstrating Splenomegaly.

Axial contrast-enhanced CT image of the abdomen demonstrating splenic enlargement.

CT: computed tomography

The patient was managed with extensive transfusion support, corticosteroid therapy, and supportive care. Hemolysis gradually improved, and her hemoglobin subsequently increased to 8.8 g/dL, while LDH decreased to 761 U/L. AST and ALT also improved to 11 U/L and 19 U/L, respectively. The hemolytic process ultimately resolved over approximately one month. The overall clinical presentation was considered consistent with severe EBV-associated hemolytic anemia, although the precise mechanism could not be definitively established.

Discussion

Epstein-Barr virus (EBV)-associated hemolytic anemia is an uncommon hematologic complication of EBV infection. Although mild hematologic abnormalities may accompany infectious mononucleosis, clinically significant hemolysis is rarely reported. A recent systematic review identified 60 patients with hemolytic anemia associated with EBV infectious mononucleosis between 1973 and 2024 [1]. Cold-reactive antibodies were the most frequently reported mechanism, followed by warm antibodies and mixed antibody patterns. These findings reflect the heterogeneous immunologic manifestations of autoimmune hemolytic anemia (AIHA) [2-6].

The present case is notable for the severity and rapid progression of hemolysis. The patient's hemoglobin decreased from 11.4 g/dL to 4.6 g/dL, accompanied by markedly elevated LDH, hyperbilirubinemia, decreased haptoglobin, jaundice, and hemodynamic instability. She required 14 units of packed red blood cells, and her course was complicated by acute kidney and liver injury. In the systematic review by Meloni et al., blood transfusion was required in 38% of reported cases, emphasizing the unusual severity of our patient's presentation [1].

Another important feature was the evolution of the direct antiglobulin test (DAT). Initial testing was negative despite convincing biochemical evidence of hemolysis, whereas subsequent testing became positive for complement C3d and negative for IgG. A negative conventional DAT does not completely exclude immune-mediated hemolysis because antibody levels may fall below the detection threshold or antibodies may not be adequately detected by standard methods [4,7]. Repeat immunohematologic testing is therefore important when hemolysis persists or progresses despite initially negative findings.

Complement C3d positivity may suggest complement involvement, which is particularly relevant because cold-reactive antibodies are frequently described in EBV-associated hemolysis [1,5,8,9]. However, cold agglutinin testing was negative in this patient. Therefore, the available findings do not establish classic cold agglutinin disease or secondary cold agglutinin syndrome [9,10]. The changing DAT results may reflect an evolving immune response, but the precise mechanism remains uncertain.

The diagnostic evaluation was further complicated by the patient's prolonged stay in Guinea and reported history of malaria. Empiric antimalarial therapy was initially appropriate while diagnostic studies were pending, but serial blood smears and *Plasmodium* PCR testing were negative. Additional investigations for *Babesia*, *Mycoplasma*, microangiopathic hemolysis, and other potential causes were unrevealing. Positive EBV serologic findings and PCR supported an association with EBV infection. Nevertheless, positive EBV testing does not independently establish causation, particularly in adults with potentially preexisting EBV immunity. The diagnosis was therefore based on the overall clinical presentation and the exclusion of several competing explanations.

The management of severe hemolytic anemia depends on the clinical condition and suspected underlying mechanism. Transfusion support is essential when profound anemia results in hemodynamic instability or inadequate oxygen delivery [7]. Corticosteroids are commonly used in warm AIHA but have limited efficacy in classic cold agglutinin disease [2,5,7-10]. In our patient, corticosteroids were administered during clinical deterioration before the later C3d-positive DAT result. Hemolysis subsequently improved, with hemoglobin increasing to 8.8 g/dL and LDH decreasing to 761 U/L. However, improvement cannot be attributed definitively to corticosteroids because supportive care and spontaneous resolution may also have contributed. A systematic review reported a median recovery time of approximately 28 days in EBV-associated hemolytic anemia, similar to the course observed in this patient [1].

This case highlights the importance of considering EBV among the potential infectious associations of otherwise unexplained severe hemolytic anemia. An initially negative DAT should not exclude an evolving immune-mediated process when clinical and biochemical evidence strongly supports hemolysis. Repeat testing may provide additional diagnostic information, while isolated C3d positivity should be interpreted cautiously when cold agglutinin testing is negative. Early recognition, close monitoring, and appropriate supportive management remain essential in patients with rapidly progressive anemia and multiorgan complications.

Conclusions

EBV-associated hemolytic anemia is an uncommon but potentially life-threatening clinical manifestation reported in association with EBV infection. This case illustrates an unusually severe and rapidly progressive presentation, with profound anemia, hemodynamic instability, multiorgan dysfunction, and the need for extensive transfusion support. Although the initial direct antiglobulin test (DAT) was negative, subsequent C3d positivity suggested possible complement involvement in the hemolytic process.

This case emphasizes that an initially negative DAT does not completely exclude an immune-mediated mechanism in a patient with convincing clinical and laboratory evidence of ongoing hemolysis. Repeat immunohematologic testing should be considered when hemolysis persists or progresses despite an initially unrevealing evaluation. EBV should also be considered among the potential infectious associations of otherwise unexplained hemolytic anemia after alternative infectious, hematologic, and autoimmune causes have been appropriately investigated. Early recognition, close monitoring, and supportive management are particularly important in severe presentations.

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.

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Disclosures

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