Epstein-Barr Virus Associated Hemophagocytic Lymphohistiocytosis in a Rheumatic Patient Receiving Abatacept Therapy

RAHUL S. DALAL, BS, MD'15; MARK P. LEGOLVAN, DO; DARIUSZ R. STACHURSKI, MD; LAURA R. GOLDBERG, MD, PhD

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory disease that causes extensive organ damage. It is generally triggered by viral, fungal, or parasitic infections in the setting of hematologic disease-induced immune deficiency. Occurrences in rheumatologic disease are less frequent, with the syndrome developing most often in patients with systemic lupus erythematosus and adult-onset Still disease. It is believed that the immunosuppression induced by rheumatologic disease itself and exacerbation by immunomodulatory therapies predispose to infection and subsequently HLH. Abatacept is a relatively new disease-modifying agent for rheumatoid arthritis (RA) that has been associated with varicella zoster virus, cytomegalovirus, and Epstein-Barr virus (EBV) infections, but not previously in the setting of HLH. Here we report a unique case of EBV-associated HLH in a RA patient receiving abatacept therapy.

KEYWORDS: Hemophagocytic lymphohistiocytosis, Epstein-Barr virus, abatacept, rheumatoid arthritis.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often-fatal hyperinflammatory syndrome caused by impairment in the down-regulation of immune cells. Most patients exhibit dysfunction of natural killer (NK) cells and cytotoxic T-lymphocytes, with excessive macrophage activity. This results in hypercytokinemia with overproduction of interleukins (ILs) 6, 10, and 12, soluble IL-2 receptor, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), leading to extensive tissue damage and multi-organ failure.[1,2]

The predominant signs and symptoms of HLH include persistent high fever, cytopenias, and hepatosplenomegaly. Patients less commonly exhibit edema, rash, lymphadenopathy, and jaundice. Associated laboratory findings include elevated triglycerides, ferritin, bilirubin, transaminases, lactate dehydrogenase, soluble IL-2 receptor, and low fibrinogen with coagulopathy, and specific clinical diagnostic guidelines for HLH (Table) have been set forth by the HLH-2004 trial.[3] For critically-ill patients, prompt treatment with dexamethasone and etoposide, with intrathecal methotrexate and hydrocortisone for those with central nervous system involvement, is crucial after diagnosis, as untreated patients have a survival of only months.[3]

The syndrome has both familial and acquired forms, originally distinguished by age of presentation. However, genetic cases have been identified in both children and adults, and a recent study found familial HLH gene mutations in 14% of 175 adults presenting with this condition.[4] Acquired HLH can also occur at any age and is often secondary to illnesses that modulate the immune system, including systemic infection, autoimmune disorders, and malignancy.[5] In the last decade, there have been increasing reports of HLH in systemic lupus erythematosus (SLE), Still disease, rheumatoid arthritis (RA), and other autoimmune diseases.[6-8]

Both familial and acquired HLH are commonly triggered by infection, with Epstein-Barr virus (EBV) as the leading cause.[4] EBV-associated HLH has been reported in patients with chronic active EBV and infectious mononucleosis, among other manifestations of EBV infection.[9,10] Interestingly, EBV-associated HLH is associated with infections of NK cells and T–lymphocytes in addition to B-lymphocytes.[11,12] The viral infections thought to induce HLH occur commonly as reactivations, which occur relatively frequently in

Table. Diagnostic Guidelines for HLH (adapted from Henter et al.[3])

A diagnosis of HLH requires (1) or (2) to be satisfied

1) A molecular diagnosis consistent with HLH (mutations of BIRC4, Munc18-2, PRF1, Rab27a, SH2D1A, STX11, or UNC13D)
2) Fulfillment of five of the diagnostic criteria below
   - Fever ≥ 38.5 °C
   - Splenomegaly
   - Cytopenias affecting ≥2 of the 3 cell lineages below
     - Hemoglobin <90 g/L (for infants <4 weeks: hemoglobin <100 g/L)
     - Platelets <100 x 10^9/L
     - Neutrophils <1.0 x 10^9/L
   - Hypertriglyceridemia and/or hypofibrinogenemia
     - Fasting triglycerides ≥265 mg/dL
     - Fibrinogen ≤1.5 g/L
   - Hemophagocytosis in bone marrow, spleen, or lymph nodes
   - No evidence of malignancy
   - Low or absent NK-cell activity
   - Ferritin ≥500 ng/L
   - Soluble IL-2 receptor ≥2,400 U/mL

rheumatic patients receiving immunosuppressive therapy. Abatacept, a T-lymphocyte co-stimulatory molecule inhibitor, is a relatively new treatment for RA that has been associated with reactivation of varicella zoster virus, cytomegalovirus, and EBV, but not yet in the setting of HLH.[13] We report a unique case of EBV-associated HLH in a RA patient receiving abatacept therapy.

CASE REPORT

A 48-year-old man with a history of RA, on methotrexate and abatacept, presented with several weeks of malaise, fever, and upper respiratory symptoms. He was treated with azithromycin as an outpatient but his symptoms worsened. He subsequently developed jaundice and confusion and was admitted to the hospital, where he was found to have ALT 161 U/L, AST 153 U/L, alkaline phosphatase 404 U/L, total bilirubin 13.4 mg/dL, direct bilirubin 8.6 mg/dL, hemoglobin 8.3 g/dL, platelets 122 x 109/L, creatinine 1.5 from a baseline of 0.9 mg/dL, international normalized ratio 1.5, ferritin 19,278 µg/L, fibrinogen 71 mg/dL, triglycerides 207 mg/dL, sIL-2R 7304 U/mL, melena, and ongoing fevers of 102-103°F despite broad-spectrum antimicrobials. CT scans revealed diffuse axillary, mediastinal, right hilar, and mesenteric lymphadenopathy in addition to splenomegaly; there was no evidence of liver or bile duct abnormalities.

Liver biopsy showed lymphohistiocytic granulomatous inflammation and hypertrophy of Kupffer cells, with frequent phagocytosed red blood cells, consistent with HLH (Figure 1). A bone marrow biopsy revealed a histiocytic infiltrate with erythrophagocytosis and emperipolesis (Figure 2). Both bone-marrow biopsy and a lymph-node biopsy were negative for malignancy. EBV IgM was positive and PCR for EBV DNA returned with 127,000 IU/mL. Serologies for anaplasma, babesia, lyme, herpes simplex virus, and parvovirus were negative. Cerebral spinal fluid gram stain and culture were both negative with no evidence of pleocytosis, phagocytosed erythrocytes, or elevated protein to suggest HLH involvement of the central nervous system.

Given the patient's clinical presentation, laboratory, and histological data, he was diagnosed with EBV-associated HLH and started on a regimen of daily dexamethasone and twice weekly etoposide.[3] In addition, given his EBV-positivity, he was given weekly rituxan over four weeks. His course was complicated by liver failure, renal failure requiring hemodialysis, respiratory failure requiring a brief period of intubation, pancytopenia, and disseminated intravascular coagulation requiring multiple cryoprecipitate, packed red blood cell, and plasma transfusions. Over the remainder of his seven-week hospitalization, his international normalized ratio (INR) slowly improved but he remained transfusion-dependent. Persistent melena prompted an upper endoscopy that found diffusely friable gastric and duodenal mucosa but no overt gastrointestinal hemorrhage. He became progressively leukopenic, reaching an absolute neutrophil count

Figure 1. Liver parenchyma highlighting histiocytes packed in the sinusoids, many with erythrophagocytosis (arrows) (Hematoxylin-Eosin stain, magnification x 400).

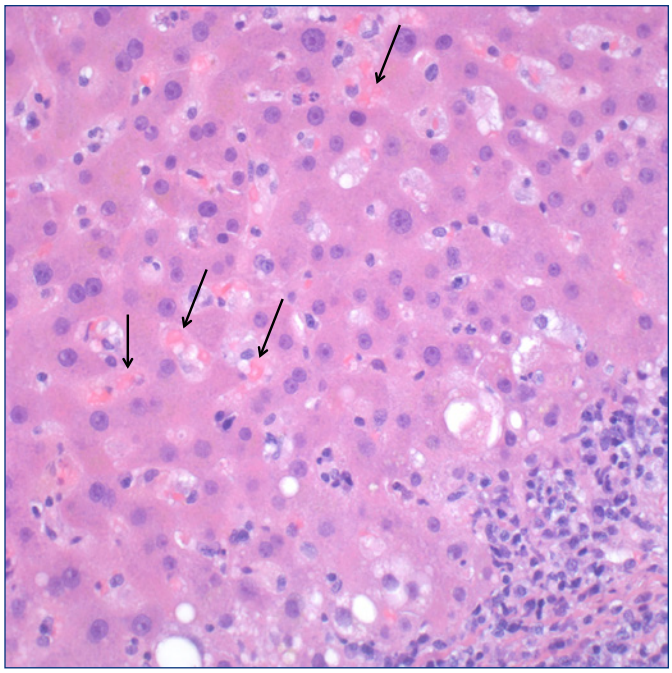
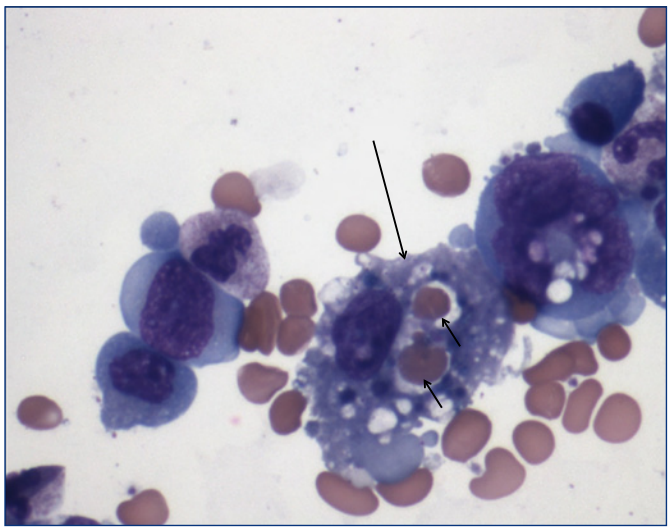


Figure 2. Characteristic bone marrow aspirate demonstrating phagocytosis of non-nucleated erythrocytes (short arrows) by macrophages (long arrow) (Wright-Giemsa stain, magnification x 600).



<100/µL requiring atovaquone and acyclovir prophylaxis. He was also treated with vancomycin and cefepime for hospital-acquired pneumonia and voriconazole for thrush. The patient began to demonstrate improvement in his liver enzymes, renal function, inflammatory parameters, and mental status. However, despite continued treatment, he suffered from ongoing pancytopenia and subsequently developed daptomycin-resistant VRE bacteremia. He ultimately succumbed to sepsis and respiratory failure.

DISCUSSION

RA is a systemic autoimmune condition characterized by polyarticular synovial inflammation that leads to chronic, irreversible joint damage and disability. The joint damage and deformity result from excess inflammatory cytokines, including IL-1, IL-6, and TNF-α, produced by activated T-lymphocytes. Treatment of RA typically consists of corticosteroids and disease-modifying agents such as methotrexate. In some cases, RA may persist despite these treatments, and biologic therapies targeting pro-inflammatory cytokines,[15,16] IL-1 receptor,[17] T-cell activation,[18] or B-cells are necessary.

Prior to the introduction of biologic agents, the incidence of infection in RA was twice that of healthy matched controls.[20] This is believed to be secondary to the immunologic alterations caused by the disease itself in addition to the disability, skin damage, and immunosuppressive drugs associated with the illness. Since the start of the biotherapy era, studies have identified even greater risks of infection associated with biologic agents.[21] A meta-analysis of seven randomized controlled trials comparing abatacept to placebo or other disease modifying agents in RA found that at 12 months, serious infections were more common in the abatacept group compared to controls (Peto odds ratio 1.91, 95% CI 1.07-3.42).[22] Furthermore, the risk of serious adverse events increased further when abatacept was combined with other disease-modifying agents (RR 2.3, 95% CI 1.2–4.6). Thus, our patient receiving abatacept therapy concurrently with methotrexate and prednisone may have been extraordinarily susceptible to an EBV infection capable of triggering HLH.

In addition to predisposition to infection, it is important to consider immunosuppressive therapy as an independent trigger or cofactor for HLH. A recent systematic review of hemophagocytic syndrome in rheumatic patients reports that 20 HLH cases may have been triggered by immunosuppressive treatments including adalimumab, azathioprine, etanercept, infliximab, leflunomide, methotrexate, and sulfasalazine.[23] Abatacept, which has not yet been associated with HLH, is a fully humanized fusion protein consisting of the Fc portion of IgG1 and the extracellular domain of CTLA-4, modified to prevent complement activation.[24] The drug binds to CD80 and CD86 on antigen presenting cells, blocking the CD28 interaction with T cells. Abatacept was the first drug to selectively target the co-stimulatory signal necessary for T-cell activation, a function that may exacerbate the underlying T-cell dysfunction found in most patients with HLH.

While the mechanism of HLH induction remains unclear and further experience will be necessary to elucidate the potential association of this syndrome with this relatively new drug, HLH should be considered in rheumatic patients receiving abatacept therapy who develop a sepsis-like presentation with acute multi-organ injury. Prompt recognition and treatment of this rare condition is crucial to maximize opportunity for a favorable outcome.

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Authors

Rahul S. Dalal, BS, is a Medical Student, Class of 2015, at The Warren Alpert Medical School of Brown University.

Mark P. LeGolvan, DO, is an Assistant Professor of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University.

Dariusz R. Stachurski, MD, is an Assistant Professor of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University.

Laura R. Goldberg, MD, PhD, is an Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University.

Conflicts of interest

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Correspondence

Rahul S. Dalal, BS, MD'15
The Warren Alpert Medical School of Brown University
222 Richmond Street, Box G-9230,
Providence, RI 02912
269-377-2711
rahul_dalal@brown.edu