

Rare Cause of Fever in a Patient with Ulcerative Colitis

To the Editor:

A 19-year-old boy with a 7-year history of extensive ulcerative colitis (UC), in remission for 4 years with azathioprine 2.5 mg/kg/d, was admitted reporting a 3-day history of fever (39–40°C), headache, and abdominal discomfort. He denied other symptoms. Physical examination showed fever (40°C), jaundice, generalized lymphadenopathies (cervical, submandibular, occipital, pre-auricular, axillary, and inguinal, up to 3 cm in diameter), painless hepatosplenomegaly, and peripheral edema. Laboratory data on admission revealed pancytopenia (hemoglobin 8.1 g/dL, leukocytes 0.6×10^3 U/L, platelets 45×10^3 μ L) decreased prothrombinemia (37%), hypofibrinogenemia (1.4 g/L), hypoalbuminemia (2.8 g/dL), positive C-reactive protein (12.4 mg/dL), increased ferritin (10,080 ng/dL), and liver enzymes (AST 342 U/L, ALT 165 U/L, AF 802 U/L, GGT 715 U/L, bilirubin 21 U/L), increased triglyceride values (633 mg/dL), decreased NK cells (<1%), and increased proteins in urine (3237 mg).

Thoracoabdominal computed tomography (CT) showed small bilateral pleural effusion, multiple and bilateral lymphadenopathies, homogenous hepatomegaly, splenomegaly with pericentrimetric hypodense nodular lesions, and peri-hepatic, peri-splenic ascitic fluid. Several blood, urine, sputum, and stool cultures were negative. Tuberculin skin test was nonreactive. Serum immunoglobulin G and M antibodies against Epstein–Barr virus

(EBV) viral capsid antigen were present, but EBNA was negative. It became positive in 11 days. Serologies for other common viruses were negative, as well as autoantibodies. At this point infectious mononucleosis alone did not seem to explain this exuberant clinical picture. Therefore, a lymphoproliferative disorder was investigated. Bone marrow aspirate revealed an increased number of histiocytes with hemophagocytosis (Fig. 1). Histopathologic study of a cervical lymph node showed expansion of T area with EBV-positive cells.

A diagnosis of hemophagocytic lymphohistiocytosis secondary to recent EBV infection was established. He was first treated with prednisolone (maximum dose 2 mg/kg) and 8 days later, intravenous immunoglobulin (0.5 g/day for 3 consecutive days) with clinical improvement. Broad-spectrum antibiotics, blood transfusions of erythrocytes and platelets, fibrinogen, and granulocyte-colony-stimulating factor were also used.

The patient was discharged at day 33 after admission. One year later he is asymptomatic and relapse-free, maintaining 5-aminosalicylate (5-ASA) 3 g/day therapy.

Hemophagocytic syndrome, more properly referred to as hemophagocytic lymphohistiocytosis (HLH), is a clinical pathological entity characterized by fever, pancytopenia, splenomegaly, and the pathological finding of hemophagocytosis in bone marrow and other tissues.¹ First described by Scott and Robb-Smith in 1939, is characterized by a deficiency in cytolytic activity (impaired or absent function of NK cells and cytotoxic T cells), resulting in persistent activation of lymphocytes and histiocytes. This uncontrolled and inappropriate immune response leads to hypersecretion of proinflammatory cytokines and uncontrolled hemophagocytosis throughout the reticuloendothelial system.²

Diagnosis of HLH relies on specific clinical, laboratory, and histopath-

ological findings, proposed by the Histiocyte Society in 1991 and updated in 2004.³ The diagnosis can be established if five of the eight criteria are fulfilled, namely, clinical criteria (fever for more than 7 days and splenomegaly), laboratory criteria (bicytopenia without marrow hypoplasia, hypertriglyceridemia, and/or hypofibrinemia, hyperferritinemia, low/absent NK cell activity, increased soluble CD25 levels), and histological criteria (hemophagocytosis which can be seen in any organ, but is particularly common in bone marrow, lymph nodes, liver, and spleen). Jaundice, hepatomegaly, lymphadenopathy, rash, and neurological signs are also common. Common laboratory findings are high bilirubin levels, elevated serum transaminases, elevated prothrombin, and partial thromboplastin times.⁴

The main diagnostic problem is that initially HLH masquerades as a normal infection and too little attention is paid to the severity of symptoms. When a patient presents with prolonged fever unresponsive to antibiotics, hepatosplenomegaly, and cytopenias, HLH as a differential diagnosis should be considered. Unfortunately, hemophagocytosis is often absent initially, but can be more easily detected as the syndrome progresses. The absence of hemophagocytosis is often the reason why the diagnosis of HLH is ruled out as unwarranted. Therefore, if hemophagocytosis is absent in initial biopsy specimens, the biopsy may be need to be repeated in cases with high suspicion.⁵

This clinical syndrome occurs in all age groups and may be encountered with a variety of underlying conditions, namely, genetic (autosomal or x-linked) or acquired (more commonly associated with viral infections, although bacterial and parasites may be involved; malignancies and autoimmune diseases). This distinction is not categorical, as primary HLH can occur late in life and may be triggered by infections.⁴

Without treatment, the uncontrolled hyperinflammation leads to

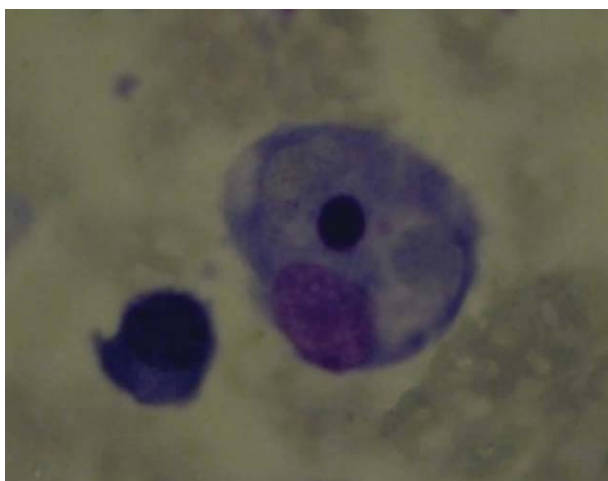


FIGURE 1. Hemophagocytosis in bone marrow aspirate. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

sustained neutropenia with opportunistic infections or even to cerebral dysfunction. It is a life-threatening condition which may be difficult to distinguish from severe sepsis. Poor prognosis appears to be determined by the presence of disseminated intravascular coagulation, coexisting significant hepatic, renal or respiratory dysfunction, and sustained hyperferritinemia.⁶

The overall mortality rate ranges across studies from 22%–59%. HLH related to hematological malignancies or EBV infection carries a higher mortality rate than cases related to viruses or intracellular bacteria.^{1,7,8}

Treatment is based on control of the cytokine storm and cellular proliferation. Immunochemotherapy as proposed by the Study Group of the Histocyte Society (first international protocol in 1994, updated in 2004) consists of combination therapy with etoposide, dexamethasone, and cyclosporine A, as well as, in selected patients with central nervous system involvement, intrathecal therapy with methotrexate and corticosteroids.³ Subsequent hematopoietic stem cell transplantation is recommended for patients with familial disease or molecular diagnosis, and patients with severe and persistent, or reactivated, disease. In order to further improve diagnosis, therapy, and biological

understanding, participation in HLH studies is encouraged.⁷ The administration of IvIG has also been established.⁶

EBV-specific therapy in treating EBV-associated hemophagocytic syndrome remains uncertain, although larger trials are needed to assess the effectiveness of specific anti-EBV therapy in EBV-associated HLH.⁹ Antiviral therapy with acyclovir, ganciclovir, or cidofovir are generally ineffective in EBV-HLH. Acyclovir and ganciclovir (alone, with IvIG or steroids plus IvIG) have achieved a reduction in EBV DNA levels and clinical improvement in isolated case reports.⁶ In HLH 2004, it is recommended that antiviral agents are considered when ongoing viral infection is apparent.³

As highlights, we emphasize an unusual successful HLH secondary to viral infection in an immunosuppressed 19-year-old boy. This diagnosis should always be considered in young patients with marked bone marrow dysfunction and multiple organ failure. Management of this syndrome relies on early diagnosis, identification of a triggering pathogen or an underlying disease, and control of the lymphocyte/macrophage proliferation and activation. The widespread use of immunosuppressive therapy in the treatment of inflammatory bowel disease (IBD) places patients at

risk of infection and so at risk of HLH. Patients who present with fever and cytopenia should be evaluated for HLH.

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