

# Hemophagocytic Syndrome in a Patient With Human Immunodeficiency Virus, Epstein-Barr Viremia, and Newly Diagnosed Hodgkin Lymphoma

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## Introduction

Hemophagocytic syndrome (HPS) is a rare disorder of lymphocyte and histiocyte activation through cytokine dysfunction leading to widespread organ compromise. With widespread lymphocytic and histiocytic activation, it is known to cause considerable end-organ dysfunction quickly and with relatively few options for treatment.<sup>1</sup> HPS has been associated with Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and the initiation of highly active antiretroviral therapy (HAART).<sup>2-4</sup> We report a case of HPS from our institution, describing the complexity of diagnosis and an attempt at treatment.

## Case Report

A 58-year-old man with longstanding HIV and newly diagnosed, untreated, stage IIB Hodgkin lymphoma (HL) presented to an outside hospital with a 4-week history of pancytopenia, intermittent fevers, chills, progressive weakness, and persistent diarrhea. Broad-spectrum antibiotics were started for neutropenic fever, and the patient was transferred to a tertiary care facility for continued management. On physical examination, he was somnolent, febrile, tachycardic, and hypoxic. His skin was markedly jaundiced, and he had mild abdominal distention without hepatomegaly. His complete blood count was notable for an absolute neutrophil count of 0, platelets of  $41 \times 10^3/\mu\text{L}$ , and hemoglobin of 11.1 g/dL. Although the patient was receiving long-term HAART and had an undetectable HIV viral load, his CD4 count

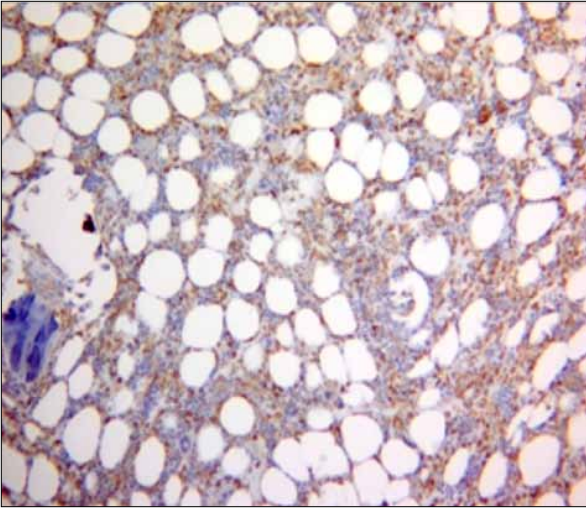
was 40 cells/ $\mu\text{L}$ . The patient's electrolytes were significant for a sodium of 121 mmol/L and a potassium of 3.2 mmol/L. His liver enzymes were notable for an aspartate aminotransferase (AST) of 380 units/L and an alanine transaminase (ALT) of 232 units/L. His total bilirubin and direct bilirubin were 6.7 mg/dL and 5.7 mg/dL, respectively. The patient had elevated triglycerides at 572 mg/dL. Blood, urine, and stool cultures were negative. Quantitative EBV titers, however, were markedly elevated at 54,954 copies/mL. A bone marrow biopsy showed atypical megakaryocytes and increased histiocytic infiltration (Figure 1) demonstrating erythrophagocytosis (Figure 2). A computed tomography (CT) scan of the chest, abdomen, and pelvis was significant for diffuse lymphadenopathy (Figure 3) and splenomegaly (Figure 4). A liver biopsy showed virus-induced hepatic damage without evidence of an obstructive process. He was initially treated with prednisone and rituximab (Rituxan, Genentech), and then received dexamethasone, cytarabine, and cisplatin (DHAP) as therapy for HL, as well as for the underlying HPS. Unfortunately, the patient became hemodynamically unstable and died shortly after the initiation of chemotherapy.

## Discussion

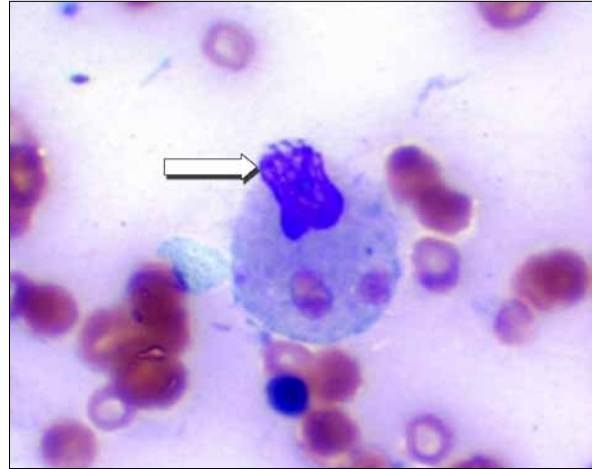
Due to the rarity of HPS and its aggressive, rapidly progressive course, most cases are diagnosed at autopsy. Our case highlights the difficulty in diagnosing and treating HPS, even in a patient with known risk factors (HIV, HL, and EBV). The major clinical criteria for diagnosis are fever, splenomegaly, cytopenia in at least 2 cell lines, hypertriglyceridemia, and tissue sampling demonstrating hemophagocytosis.<sup>5</sup> Additionally, hypofibrinogenemia can be substituted for hypertriglyceridemia in the major criteria. Patients with the familial form of hemophago-

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**Figure 1.** CD18 staining for histiocytes (brown).



**Figure 2.** Erythrocyte (arrow) undergoing erythrophagocytosis.



**Figure 3.** Pelvic lymphadenopathy (arrow).



**Figure 4.** Splenomegaly (arrow).

cytosis have additional criteria that occasionally may be present in sporadic cases. These criteria are absent natural killer cell activity, serum ferritin greater than 500  $\mu\text{g/L}$ , and a soluble CD25 level greater than 2,500 U/mL.<sup>6-9</sup> However, the rapidly progressive nature of HPS makes it difficult to find all the necessary factors to make the appropriate diagnosis. A high level of suspicion of HPS is needed in patients presenting with these symptoms and signs in order to facilitate rapid diagnosis and treatment.

### **Chemotherapy**

The role of chemotherapy has not been clearly defined, especially in the presence of multiorgan system compromise, as in our patient. Dexamethasone plays a significant role in a number of therapeutic regimens used in the pediatric form of HPS, namely the HLH-2004 protocol.<sup>10</sup>

However, the roles of cytarabine and cisplatin have not been elucidated in the literature. Our treatment regimen was initiated due to the patient's declining clinical status and concurrent hepatic dysfunction.

### **Immunotherapy**

Rituximab has been used with varying degrees of success in treating HPS; however, most case reports describe its use in pediatric patients. Recently, several case reports have lauded the use of rituximab as a single agent in adult patients with HPS. In 2009, a case report by Bosman and associates<sup>11</sup> noted significant decreases in EBV viral load, overall decline in hemophagocytosis, and improvement in patient outcomes. In regard to lymphoma-associated HPS, 8 doses of rituximab were efficacious, as described in a 2006 case report by Sano and colleagues.<sup>12</sup>

## Conclusion

The diagnosis of HPS can be established via the criteria set forth by Henter and colleagues.<sup>5</sup> With early diagnosis and goal-directed therapy, it may be possible to stem the tide of progression to multisystem organ failure. At this point, most chemotherapeutic and immunotherapeutic agents have shown only modest improvement in survival, with most trials focusing on the hereditary form in pediatric patients. Our experience suggests that it is possible to initiate therapy at the onset of symptoms, provide early goal-directed therapy to blunt the systemic inflammatory response, and focus on known causative agents for HPS, such as CD20 cell types that contribute to unchecked erythrophagocytosis.

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# Review

## Hemophagocytic Lymphohistiocytosis: A Syndrome With Diverse Etiologies and Treatment Options

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## Introduction

Khagi and colleagues describe an interesting case of a patient with human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and Hodgkin lymphoma, who

developed hemophagocytic syndrome, or hemophagocytic lymphohistiocytosis (HLH).<sup>1</sup> HLH is a clinicopathologic syndrome characterized by uncontrolled hemophagocytosis by nonmalignant macrophages and defects in cytotoxic lymphocyte function. HLH is associated with a variety of inherited or acquired immune deficiencies.<sup>2</sup> It is commonly fatal, but early treatment can result in cure.

Corticosteroids and immunotherapy were initiated, along with chemotherapy for the Hodgkin lymphoma. However, the patient had a fulminant course and succumbed to the disease during the initiation of treatment. This case illustrates the challenges in the diagnosis and management of this rare and aggressive syndrome.

## Background

Initially thought to be a familial immune dysregulatory disorder of childhood,<sup>3</sup> HLH was later discovered to occur as either an inherited (primary) or acquired (secondary) syndrome. In primary HLH, inheritance follows an autosomal recessive pattern in association with immune deficiencies, such as Chediak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome.<sup>4</sup> HLH has been associated with a growing spectrum of autosomal recessive gene defects that share the common

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feature of impaired cytotoxic function of natural killer (NK) cells and cytotoxic T cells through ineffective delivery of perforin and granzyme B in cell killing.<sup>5</sup> Patients are usually infants or young children with a high risk of recurrence. In these patients, HLH can also be associated with infections, such as cytomegalovirus (CMV) or EBV.

In secondary HLH, the syndrome is associated with another condition, such as a viral illness, autoimmune disease, or lymphoma, without the presence of a genetic mutation or inherited immune deficiency.<sup>4,6</sup> Secondary HLH is generally observed in adults, and the concurrent conditions are thought to trigger the syndrome. In some cases of secondary HLH, hypomorphic mutations have been found in genes that are altered in primary HLH and affect the perforin1-dependent cytotoxic pathway. This suggests that some secondary HLH patients may have a genetic predisposition.<sup>7</sup> NK-cell and cytotoxic T-cell dysfunction are also characteristic of secondary HLH.

## Pathophysiology

In inherited forms of HLH, the underlying immune deficiency condition is associated with defects in perforin function and other intracellular pathways required for the release of cytolytic granules by NK cells and cytotoxic T lymphocytes.<sup>2</sup> In the presence of a trigger (eg, infection, vaccination), these individuals are predisposed to develop HLH.

Many diverse infectious and malignant diseases have been associated with secondary HLH, and the mechanisms inducing the cytotoxic defects in patients with secondary HLH are only partially understood.<sup>8</sup> EBV is the most frequent infection associated with HLH.<sup>9</sup> In EBV-associated HLH, EBV may infect B cells, T cells, and NK cells.<sup>10-12</sup> Other viral, bacterial, parasitic, mycobacterial, and fungal infections have also been linked to HLH.<sup>6</sup> The most common malignancies associated with HLH are lymphomas or leukemias of the T-cell and NK-cell lineages.<sup>4</sup> Associations with anaplastic large cell lymphoma, early B lineage lymphoblastic leukemia, myeloid leukemias, mediastinal germ cell tumors, Hodgkin lymphoma, and other solid tumors have also been identified. Malignant cells may induce immune system dysfunction by the production of cytokines. Chemotherapy or concurrent bacterial, viral, or fungal infection may induce HLH in the setting of malignancy.

The increased inflammatory response seen in HLH is characterized by infiltration of tissues by activated T-lymphocytes and histiocytes. These cells secrete proinflammatory cytokines, such as interferon  $\gamma$ , tumor necrosis factor  $\alpha$ , interleukin (IL)-6, IL-10, and macrophage colony-stimulating factor, which lead to defects in perforin function and NK-cell dysfunction resulting in tissue necrosis and organ failure.<sup>4,8</sup> Viral infections, such as EBV, CMV,

and HIV, may interfere with cytolytic function through the induction of cytokine secretion and the activation of macrophages and T cells.

## Diagnosis

In 1994, the Histiocyte Society proposed a standard definition of HLH in their prospective international collaborative therapeutic study (HLH-94), which was later revised for the HLH-2004 study.<sup>13</sup> A diagnosis of primary HLH can be made by molecular diagnostic criteria for inherited conditions or by the presence of specific clinical features for secondary HLH. Inherited criteria include mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4* genes. A diagnosis of secondary HLH requires the presence of 5 out of the 8 criteria: fever of 38.5°C or higher; splenomegaly; cytopenias affecting at least 2 of 3 lineages in the peripheral blood (hemoglobin <9 g/dL, platelets <100 × 10<sup>3</sup>/mL, neutrophils <1 × 10<sup>3</sup>/mL); hypertriglyceridemia (fasting >265 mg/dL and/or hypofibrinogenemia <150 mg/dL); hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver; low or absent NK-cell activity; ferritin greater than 500 ng/mL; and elevated soluble CD25 (sCD25; alpha chain of soluble IL-2 receptor).

Making a timely diagnosis of this condition for institution of appropriate treatment is critical but challenging, due to its variable presentation and broad differential diagnosis. When a patient presents with prolonged fever, hepatosplenomegaly, and cytopenias, there needs to be a high degree of suspicion for HLH.<sup>4</sup> Otherwise, a delay in diagnosis may allow the syndrome to progress to the point where multisystem organ failure makes administration of definitive therapy impossible. In addition to assessment of complete blood count, liver enzymes, bilirubin, triglycerides, ferritin, and a coagulation profile including fibrinogen, all patients should have a bone marrow aspirate.<sup>4</sup> Hemophagocytosis may not be seen in all cases on the initial bone marrow aspirate, so the test may need to be repeated to make a diagnosis. Two highly diagnostic disease parameters are an increased plasma concentration of the  $\alpha$  chain of the soluble IL-2 receptor (sCD25) and impaired NK-cell activity. In institutions where sCD25 assays are not readily available, ferritin can be reliably used as a marker of disease activity. High levels of ferritin (>10,000 ng/mL) can be notably sensitive and specific for the diagnosis of HLH.<sup>14</sup>

It is essential to make a careful search for infectious, inflammatory, and malignant disease in all HLH patients, as these associated conditions will need to be treated in order to effectively manage the HLH. Autoimmune diseases, malignancy, and treatable infections (EBV, herpes simplex viruses [HSV], CMV, and varicella-zoster virus [VZV]) should be

sought at the outset of the work-up.<sup>4</sup> In younger patients, a work-up for inherited conditions should be undertaken.

The detection of hemophagocytic cells in the initial bone marrow aspirate is an insensitive test for HLH. Therefore, if other criteria sufficient for a diagnosis can be met, therapy should not be delayed because of a negative bone marrow examination.<sup>15,16</sup>

## Treatment

The aim in the treatment of HLH is to suppress the severe hyperinflammation and to remove the trigger for the ongoing T-cell activation.<sup>4,15</sup> The current standard of care is the HLH-94 protocol, an 8-week induction regimen with dexamethasone and etoposide, with or without intrathecal methotrexate. Patients with secondary HLH who respond well to this therapy do not require maintenance therapy if they show no signs of recurrence and recover normal immune function. Allogeneic hematopoietic stem cell transplantation can be curative for patients with inherited disease and is indicated in the setting of treatment-refractory disease, persistent NK-cell dysfunction, or central nervous system involvement. A recent update of results from the HLH-94 protocol has shown a 5-year survival of 54%, with a median follow-up of 6.2 years.<sup>13</sup>

Etoposide has high activity in HLH, and it inhibits EBV-determined nuclear antigen synthesis in EBV-infected cells.<sup>4</sup> It is most effective in EBV-associated HLH when administered within 4 weeks of the time of diagnosis.<sup>9</sup> Corticosteroids help control hyperinflammation by their inhibitory action on lymphocytes and release of cytokines. It is also essential in patients with secondary HLH to treat the associated infection and/or malignancy.

Salvage therapy should be considered in patients who do not display at least a partial response within 2–3 weeks of therapy initiation. Case reports have described a diverse array of immune modulators that may be helpful in the salvage setting or for patients who are unable to receive standard HLH-94 therapy. These include therapies that target B-cell (rituximab [Rituxan, Genentech]) or other lymphocyte functions (infliximab [Remicade, Janssen Biotech], etanercept [Enbrel, Immunex], anakinra [Kineret, Amgen], tacrolimus, and alemtuzumab).<sup>17–22</sup> Excellent comprehensive articles on the treatment of HLH have recently been published.<sup>9,13,15</sup>

## Case Commentary

This case demonstrates many of the curious and troubling characteristics of secondary HLH.<sup>1</sup> Because the patient had a history of HIV and a new diagnosis of Hodgkin lymphoma, the differential diagnosis for his presentation was very broad. By the time the patient had reached the

tertiary care center, he had evolved into a fulminant case of HLH. All of the features required for diagnosis of secondary HLH were present, as well as the identification of hemophagocytic cells in the bone marrow. Each of the patient's conditions (Hodgkin lymphoma, HIV, and EBV) has been independently associated with HLH, although they can be seen together. EBV viremia HLH in the setting of well-controlled HIV has been reported.<sup>23</sup> The Hodgkin lymphoma in this patient may have been EBV-related, as the EBV genome has been found in approximately 90% of Hodgkin lymphomas in HIV patients.<sup>24</sup> Because of these associations, and due to the fact that the incidence of Hodgkin lymphoma is increased in those with HIV, this patient's syndrome may have been, essentially, a multifactorial complication of his HIV disease.

Upon presentation, the patient was too ill to receive many therapies that have been shown to be effective in the disease.<sup>1</sup> It is not uncommon for HLH to present with multiorgan system dysfunction and cytopenias that lead to concerns about the potential toxicity of therapy. This patient had significant hepatic dysfunction, which is a contraindication for the highly effective HLH drug etoposide, as well as for doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), a standard induction regimen for Hodgkin lymphoma. In this case, the authors chose a strategy that included prednisone and rituximab for the HLH. Rituximab may directly inhibit EBV replication by killing EBV-infected B cells.<sup>9,25</sup> They also administered a standard salvage regimen for Hodgkin lymphoma, cisplatin, cytarabine, and prednisone (DHAP), which can be safely dose-reduced for administration in patients with elevated serum bilirubin.

As early diagnosis is essential to successful HLH treatment, it is worthy to consider when the initial symptoms of HLH may have first occurred in this patient. HLH typically follows a rapid course, with the first symptoms preceding death by only 1–2 months. However, we recently described a 57-year-old patient who was similar to the present case in that she had Hodgkin lymphoma and EBV viremia, but she also had a CMV infection.<sup>26</sup> Her course was unusual in that her fulminant disease was preceded by a 3-year period of unexplained cytopenias and fevers, suggesting that secondary HLH may also exist in a prodromal, chronic form. In EBV-associated HLH, this type of presentation may be similar to diseases clinically staged as mild or intermediate.<sup>9</sup>

## Conclusion

HLH is a rare syndrome, characterized by an activated, ineffective immune response leading to hyperinflammation and multiorgan failure. It can be familial or acquired in the setting of infection, cancer, or rheumatologic disorders. It has variable presentation, with many nonspecific

findings that generate a broad differential diagnosis. A high degree of suspicion plays a key role in early diagnosis and institution of treatment. Treatment of HLH requires treatment of both the syndrome itself and any inciting or associated diseases. HLH is often fatal, and optimal treatment may be contraindicated due to the health status of the patient. The patient described by Khagi and colleagues<sup>1</sup> demonstrates a fulminant case of HLH in which critical illness and organ dysfunction prevented the institution of curative therapy.

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