

# Classical hodgkin's lymphoma presenting with hemophagocytosis

## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare, hyper inflammatory disorder which may be associated with hematologic malignancy. This is a case of fulminant HLH associated with classical Hodgkin's lymphoma. A 42-year-old Malian woman presented with constitutional symptoms and was eventually diagnosed with lymphoma and HLH. Her initial work-up was unrevealing for malignancy and infectious etiology. Hematologic malignancy may be complicated by severe forms of HLH. To ensure better clinical outcomes, physicians should consider initiation of treatment for HLH prior to treatment of lymphoma. This case demonstrates the importance of considering rare conditions in a critically ill, febrile patient while also evaluating for other more common etiologies.

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## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyper inflammatory disorder which results from immune dysfunction, either from primary immune deficiency or acquired failure of normal immune homeostasis. There is often phagocytosis by macrophages of blood cells, hence the name "hemophagocytosis".<sup>1</sup> HLH may be inherited (known as familial hemophagocytic lymphohistiocytosis), or

it may occur secondary to another disease process, most commonly infection with various pathogens or hematologic malignancy (Table 1).<sup>2</sup> In 1991, diagnostic guidelines for HLH were first presented (Table 2).<sup>3</sup> In January 2004, the diagnostic criteria for HLH were revised.<sup>4</sup> HLH is a rare condition, and the diagnostic guidelines have important implications for the medical management of patients. Without recognition, HLH is a deadly syndrome with an estimated mortality of 90% without appropriate treatment.<sup>5</sup>

**Table 1** Causes of HLH

Etiology	Examples
Genetic mutation	Perforin, Munc13-4, Syntaxin 11, Rab 27a, Lyst
Acquired immune dysregulation	Immune-modulating drugs, cytokine-antagonists
Malignancy	Leukemia, lymphoma
Autoimmune/autoinflammatory disorders	Systemic lupus erythematosus, Kawasaki disease, inflammatory bowel disease
Infection	Viral, bacterial, fungal, parasitic

**Table 2** Criteria for diagnosing HLH

HLH is diagnosed with at least five of the following:

Fever

Splenomegaly

Cytopenias in at least two cell lines: hemoglobin <9.0g/L, platelets <100 x10<sup>9</sup>/L, neutrophils <1x10<sup>9</sup>/L, fibrinogen <1.5g/L, fasting triglycerides >265mg/dL

Hemophagocytosis in marrow or spleen or lymph nodes

Low or absent activity of NK cells

Ferritin >500mcg/L

Soluble CD25 >2400units/mL

## Case report

The patient is a 42-year-old woman from Mali, with AIDS (diagnosed in 1997), who presented with seven months of intermittent fevers, night sweats, unintentional weight loss, and a cough productive of white sputum. During the initially negative infectious and malignancy work-up, she was noted to have cholestatic liver

failure. She underwent a liver biopsy, which showed aggregates of plasma cells. Due to an unexplained increase in liver function tests, her anti-retroviral therapy was temporarily held during the admission.

One month later, the patient was transferred to a large academic medical center for further evaluation. At that time, her CD4 count was 28 and viral load was 334,495. She continued to spike fevers with an

unrevealing infectious work-up. She was noted to have an elevated ferritin level to 18,810. Triglycerides were elevated to 352 and she had normocytic anemia with lowest hemoglobin 7.3.

A computed tomography (CT) chest without contrast showed scattered pneumatoceles and micro nodules in the lungs, some of which have a tree-in-bud configuration. There were also ground glass and reticular opacities. This was concerning for disseminated tuberculosis, disseminated mycobacterium avium complex infection, an opportunistic fungal infection (such as histoplasmosis), vs neoplastic etiology (such as a lymphoproliferative malignancy). After ruling out pneumocystis jiroveci pneumonia, the patient was started on prophylaxis with Atovaquone. A peripheral smear showed normocytic red cells, polychromasia, a few target cells, toxic granules, a few atypical lymphocytes, and normal platelets without clumping. She had a bronchoscopy with transbronchial right middle lobe lung biopsy with no significant histopathologic findings.

Given continuous high fevers, the patient had a bone marrow biopsy which did not show evidence of infection with negative special stains for acid-fast bacilli and fungi microorganisms. Immunostains for cytomegalovirus, herpes simplex virus, and parvovirus were negative. Immunohistochemistry of the bone marrow aspirate and biopsy confirmed a diagnosis of classical Hodgkin's lymphoma. Soluble IL-2 receptor alpha resulted at 16,707. This confirmed the diagnosis of lymphoma-associated HLH. The patient was initiated on the modified BEACOPP protocol (bleomycin, etoposide, cyclophosphamide, and prednisone) with subsequent resolution of fevers and normalization of hepatic function.

## Discussion

Hemophagocytic lymphohistiocytosis is an aggressive and often fatal condition that typically affects individuals from birth to 18 months of age. However, cases have been reported in older children and adults.<sup>5</sup> A review of HLH cases in Texas revealed an incidence of 1 in 100,000 children.<sup>6</sup> There has been no epidemiologic study of adults with HLH, so the incidence is unknown.

HLH cases may be familial or associated with a wide spectrum of illnesses. Infections associated with HLH include Epstein-Barr virus, cytomegalovirus, herpes simplex, HIV, tuberculosis, Leishmaniasis and fungal infections.<sup>7,8</sup> HLH is also associated with immune deficiencies associated with lysosomal trafficking defects, such as Chédiak-Higashi syndrome.<sup>9</sup> One possible mechanism for disease progression in this patient may have been a more immunocompromised state from advanced AIDS. An autopsy study of 56 patients with AIDS found the prevalence of hemophagocytosis to be approximately 20%.<sup>10</sup>

The pathogenesis of HLH involves defects in the function of cytotoxic T cells and natural killer (NK) cells. This causes the inappropriate activation of macrophages and T cells, which produce pro-inflammatory cytokines that lead to multi-organ dysfunction and possibly death.<sup>11</sup> Studies have shown poor expression of perforin in NK cells and cytotoxic T lymphocytes of HLH patients.<sup>12</sup> One study showed early clinical signs of HLH to be fever (91%), hepatomegaly (90%), splenomegaly (84%), neurologic signs (47%), rash (43%) and lymphadenopathy (42%).<sup>13</sup> Another study revealed that 75% of patients with HLH had CNS symptoms that resembled encephalitis.<sup>14</sup> A study looking at the autopsy evaluation of the liver has shown chronic persistent hepatitis with periportal lymphocytic infiltration in 22 of 27 patients with HLH.<sup>15</sup>

A 2004 study examined perforin-deficient mice as a model of HLH. Following lymphocytic choriomeningitic virus (LCMV infection), perforin-deficient mice develop fever, splenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevation of multiple serum cytokine levels, and hemophagocytosis is evident in many tissues. The study revealed that CD8+ T cells, but not natural killer (NK) cells, are necessary for the development of this disorder.<sup>16</sup>

The Histiocyte Society HLH-2004 includes diagnostic guidelines for HLH. The following gene mutations are diagnostic for the condition: PRF1 (encodes perforin), UNC13D (encodes MUNC13-4), or syntaxin 11 genes. In the absence of a known gene mutation, HLH can be diagnosed with at least five of eight criteria (Table 1).<sup>14</sup> When evaluating a patient for HLH, it is crucial to follow serial measurements of ferritin, complete blood count, and NK cell activity level, and soluble CD25 levels. In addition, tissue biopsy of bone marrow, spleen and lymph nodes should be attempted. However it is important to note that in about one-third of HLH patients, bone marrow biopsies do not reveal hemophagocytosis. It is crucial to obtain coagulation and liver function tests because patients with HLH may develop liver failure with markedly elevated bilirubin levels and coagulopathy.<sup>17</sup>

Prior to the use of immune-modulating therapy, less than 10% of HLH patients survived.<sup>13</sup> The current treatment protocol for HLH patients involves induction therapy with etoposide and dexamethasone followed by continuous treatment with cyclosporine and pulses of etoposide and dexamethasone.<sup>17</sup> Patients with central nervous system symptoms should have a lumbar puncture. If pleocytosis, lymphocytosis or hyperproteinemia are detected in cerebrospinal fluid, patients should also be treated with intrathecal methotrexate.<sup>3</sup> Patients with resistant or recurrent disease, or with familial HLH, are treated with a hematopoietic stem cell transplant. The overall 3-year survival with the above treatment plan (deemed the HLH-94 protocol) is estimated to be 55%.<sup>18</sup>

Our patient presented with fever of unknown origin and hepatic dysfunction for months. She initially had a negative infectious and malignant work-up. Given the patient's young age and critical clinical status, broader differential diagnoses were considered. This led to a diagnosis of HLH (based on the presence of fevers, anemia, and elevation of triglycerides, ferritin and soluble CD-25 levels) and Hodgkin's lymphoma. Initiation of treatment for HLH prior to treatment of lymphoma, as was done for our patient, is associated with better outcomes. This case highlights the importance of considering rare conditions in a critically ill patient while pursuing work-up for more commonly seen etiologies of febrile illness.

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## Conflicts of interest

Author declares that there is no conflicts of interest.

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