Secondary Hemophagocytic Lymphohistiocytosis in Adults: An Update on Diagnosis and Therapy

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Abstract: Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome (HPS), is a rare, life-threatening, hematologic disorder manifested by clinical findings of extreme inflammation and unregulated immune activation. In both its congenital (primary) and adult (secondary) forms, it is most often characterized by fevers, hepatomegaly or splenomegaly, and bi- or trilineage cytopenias. In addition, elevated liver enzymes, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia are commonly seen in HLH patients. A high index of suspicion is necessary for early diagnosis. Furthermore, a thorough diagnostic evaluation is necessary, and prompt treatment of the underlying causes is key in order to prevent irreversible tissue damage. Here we discuss the clinical signs, diagnosis, and treatments associated with this rare and potentially lethal disorder as manifested in adults.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) was first described in 1952 by the Scottish pediatricians James Farquhar and Albert Clarieaux, who encountered 2 infants with an unrecognized complex of cytopenias, hepatosplenomegaly, and unremitting fevers. Both infants died a few weeks after initial presentation. Upon autopsy, there was evidence of widespread infiltration in the lymph nodes, spleen, liver, and bone marrow with lymphocytes and benign-appearing histiocytes with hemophagocytosis. They identified this syndrome as familial hemophagocytic reticulosis,[1] which is now known as HLH. Its incidence is estimated to be approximately 1.2 cases per 1,000,000 individuals per year.[2] It is useful to think of HLH as the severe end of a spectrum of hyperinflammatory diseases in which the immune system causes damage to host tissues.

Classification: Primary Versus Secondary HLH

HLH can be classified according to the underlying etiology into either primary (genetic) or secondary (acquired) HLH, both of which are clinically characterized by hepatosplenomegaly, cytopenias, and prolonged fevers (often hectic and persistent). Primary

Table 1. Classification of Hemophagocytic Lymphohistiocytosis

Genetic HLH	Gene	Protein	Chromosome Location
Familial HLH			
FHL-1	*HPLH1*	Unknown	9q21.3–q22
FHL-2	*PRF-1*	Perforin	10q22
FHL-3	*UNC13D*	Munc13–4	17q25.3
FHL-4	*STX11*	Syntaxin 11	6q24.1
FHL-5	*STXBP2(UNC18B)*	MUNC18–2	19p13.3-p13.2
Acquired HLH			
Infectious agents			
Autoinflammatory and autoimmune diseases (macrophage activation syndrome)			
Malignant diseases			
Immunosuppression, hematopoietic stem cell and organ transplantation, AIDS			
Metabolic factors			

AIDS=acquired immunodeficiency syndrome; FHL=familial hemophagocytic lymphohistiocytosis; HLH=hemophagocytic lymphohistiocytosis.

HLH occurs due to various genetic abnormalities and often presents during infancy and early childhood, but can occur into the seventh decade of life. It is associated with an autosomal recessive inheritance pattern, and in a majority of cases, the gene mutations are responsible for fixed defects in cytotoxic cell function (Table 1).

Secondary HLH is less age-restricted, and although it can occur in young children, it is more common in older children and adults who present with no known genetic cause or family history of HLH. It is a very heterogeneous disorder and is often associated with various infections and malignant, metabolic, and rheumatologic conditions. The list of potential etiologies is long and includes infections (eg, Epstein-Barr virus [EBV], herpes simplex virus, cytomegalovirus, avian influenza),[3-5] rheumatologic diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, Kawasaki syndrome, adult-onset Still's disease),[6,7] malignancy (eg, natural killer [NK]-cell leukemia, peripheral T-cell lymphoma, EBV in T-cell lymphoma, B-cell lymphoma, and a variety of other lymphomas),[8,9] acquired immune deficiency states (eg, after organ transplantation), and drugs.[10]

In patients who present with secondary HLH, treatment of the underlying cause can lead to control and resolution of HLH. Nevertheless, the process of resolution is not well understood or thoroughly defined. If HLH recurs in the absence of any underlying causes, it is most likely that the patient has primary HLH. However, labeling patients as having either primary or secondary HLH is often not possible (eg, cases without a known genetic defect or family history) and does not appear to add much value with respect to patient management.

Thus, a careful search for underlying disease triggers should be performed in all patients and, most importantly, initial treatment should not be delayed or altered based on these categories. It is helpful to think of HLH along a spectrum of disease, where distinction between primary and secondary HLH has become more blurred, as patients who develop the disease after childhood are often found to share some of the same genetic defects as those who present with primary HLH.

Pathophysiology

Both familial and secondary forms of HLH share the histologic feature of hemophagocytosis, which results from dysregulation of the immune system. The ensuing molecular pathway ultimately leads to organ failure, unless appropriate treatment is instituted. More recent work with whole-gene analysis expression has shown downregulation of proapoptotic signals and genes related to innate and adaptive immune responses, along with the upregulation of genes coding for proinflammatory cytokines and antiapoptotic factors.[11] Primary HLH occurs secondary to genetic defects in genes important in the cytolytic secretory pathway that cause perforin and granzymes to induce apoptosis in target cells (Table 1). These preformed proteins are delivered to the synaptic junction between cytolytic cells (NK-cells and cytotoxic T lymphocytes [CTLs]) and their targets.[12] Thus, dysfunction of these proteins causes dysregulation and depression of CTL and NK-cell function, which are responsible for the homeostatic removal of cells that are superfluous or dangerous to the organism.

Despite recent advances, the pathogenesis of HLH requires further investigation. Pathogenesis of secondary HLH remains unclear, although patients with this form are increasingly found to have heterozygous changes or polymorphisms in the familial proteins. The current understanding of HLH on a molecular level is based on specific key cellular processes, including cytokine storm with elevations of IL-2, IL-6, TNF-α, and IFN-γ secondary to an inflammatory cytokine release,[13] and mediator molecules, such as prostaglandins,[14] which lead to the overactivation of antigen-presenting cells (histiocytes, macrophages) and CD8+ T cells. This uninhibited process thereby leads to activated CTLs and the migration of T-helper cells, resulting in end-organ damage.[15] It is believed that this phagocytic, non-neoplastic activation leads to marked histiocytic proliferation, hypercytokinemia, and T-cell immunosuppression.[16,17] Thus, the pathways that lead to impaired immune activation in acquired forms of HLH require further study. Most likely, the mechanisms underlying secondary forms of HLH are multifactorial. They may involve an imbalance between infected cells and immune effector cells, immune dysfunction from immunosuppressive medications, or low populations of NK cells, and, additionally, interference in the cell cytotoxic function by viruses. As has been shown in patients with sepsis, the expression of both pro- and anti-inflammatory cytokines may lead to the apoptosis of cells of the innate and adaptive immune systems.[18]

Mortality

Left untreated, the prognosis of HLH is poor and generally fatal. Therefore, prompt recognition and timely treatment are critical. Mortality in secondary HLH has been reported to vary from 8–22% in rheumatologic HLH to 18–24% in EBV HLH.[4] Delay in the diagnosis of multiorgan involvement is associated with a poorer prognosis in both primary and secondary HLH patients, and prompt treatment must be instituted to prevent end-organ irreversible damage. Unfortunately, many of these patients will succumb to bacterial and/or fungal infections from prolonged neutropenia, multi-organ damage, or cerebral dysfunction.

Clinical Features

The clinical features of HLH are due to 3 cellular pathways: 1) hyperactivation of CD8+ T lymphocytes and macrophages; 2) proliferation, ectopic migration, and infiltration of these cells into various organs; and 3) hypercytokinemia with elevated levels of various cytokines, resulting in progressive organ dysfunction.[12]

These cellular mechanisms lead to a polysyndromic presentation of HLH, including the findings of fevers, cytopenias, hepatosplenomegaly, liver abnormalities, coagulation disorders, encephalopathy, hypertriglyceridemia, hyperferritinemia, coagulation disorders, and hyponatremia. The symptomatic presentations of both primary and secondary HLH are often overlapping, and many patients presenting with secondary HLH are at risk of dying from disease sequelae. A retrospective analysis found that the presence of fever was the only factor that was statistically significant in determining prognosis.[15]

Diagnosis

In 1994, the Histiocyte Society formed a standard definition of HLH as part of the HLH-94 clinical trial. It has since been revised as part of the HLH-2004 trial and is the definition most commonly employed for diagnostic purposes (Table 2). Five out of 8 criteria are necessary to make a diagnosis of HLH. The utility of this approach has been questioned due to the lack of specificity of the various criteria. However, it is the presence of multiple criteria, along with the progression and magnitude of the abnormalities, which reflects the severity of the condition. Examples of this concept include the level of hyperferritinemia and the elevation of the α-chain of the soluble IL-2 receptor (sCD25). Measuring levels of sCD25 (sIL2r), which reflects the activation of T cells, is useful in diagnosis and follow-up, as very high levels are rarely seen outside of HLH. Recent findings have shown age-related differences in the normal levels of sIL2r, which are not yet reflected in the published criteria and should be considered in future work.[19]

The detection of hemophagocytosis, a hallmark of activated macrophages in the bone marrow, is supportive for diagnosis (Figure 1). Bone marrow biopsies are often neither specific nor sensitive for conclusive diagnosis. In patients who present with symptoms of HLH, computed tomography of the chest and abdomen, as well as a bone marrow aspiration and biopsy, are valuable in diagnosing underlying malignancy.

Newer laboratory data have recently shown the utility of monitoring levels of soluble hemoglobin scavenger receptor (sCD163) in patients with HLH. CD163, a receptor for hemoglobin-haptoglobin complexes, is a marker for the activation of alternative pathway scavenger macrophages. Levels of this molecule in HLH patients are markedly higher than those found in patients with malignancy, infections, and autoimmune conditions.[20] Thus, monitoring levels of sCD25 and sCD163 can be effective in tracking HLH disease activity.[21] Utilizing these laboratory tests can aid in the early diagnosis and prompt treatment initiation of HLH.

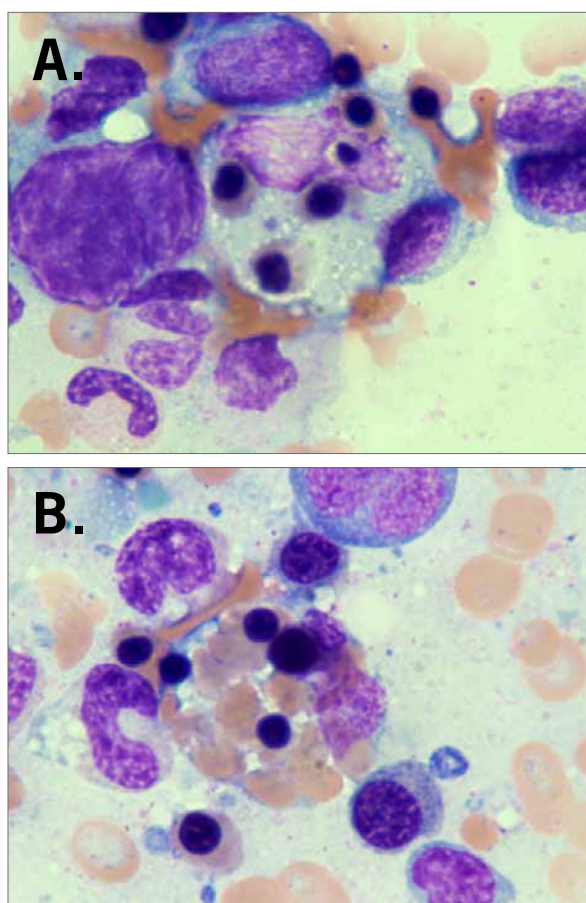**Table 2.** Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis According to the HLH-2004 Protocol

A diagnosis of HLH can be made if either criteria 1 or 2 is met:
1. Molecular diagnosis consistent with HLH
2. Clinical and laboratory criteria (at least 5/8 criteria should be fulfilled)
- Fever
- Splenomegaly
- Cytopenia ≥2–3 cell lines in peripheral blood (hemoglobin <9 g/100 mL, platelets <100 × 10⁹/L, neutrophils <1.0 × 10⁹/L)
- Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥3.0 mmol/L, fibrinogen ≤1.5 g/L)
- Hemophagocytosis in bone marrow, spleen, CSF, or lymph nodes. No sign of malignancy
- Decreased or absent NK-cell activity (according to local laboratory reference)
- Ferritin ≥500 µg/L
- sCD25 (soluble IL-2–receptor) ≥2,400 U/mL
Supportive evidence includes: Cerebral symptoms with moderate pleocytosis and/or elevated protein Elevated transaminases Elevated bilirubin Elevated LDH

CSF=cerebrospinal fluid; HLH=hemophagocytic lymphohistiocytosis; IL=interleukin; LDH=lactate dehydrogenase; NK=natural killer.

Figure 1. Bone marrow sample with hematoxylin-eosin stain. Bone marrow biopsies (A and B) reveal increased number of activated macrophages with prominent hemophagocytosis of hematopoietic elements.

Treatment Approach

The first goal of therapy in adult patients with HLH is to suppress the immune system and quiet the unregulated severe hyperinflammation. The second aim of therapy is to identify and treat the underlying triggers of HLH. With the exception of rheumatologic-associated HLH (macrophage activation syndrome [MAS]), both primary and secondary forms of HLH can initially be treated following the same protocol; as such, there is no need to distinguish primary from secondary HLH at the time of diagnosis. Thereafter, it does become important to make this distinction, as patients with primary HLH will require hematopoietic stem cell transplantation (HSCT).[12]

The HLH-94 protocol combined the treatment strategies of cytotoxicity and immunomodulation with 8 weeks of remission-induction using etoposide (VP-16) and high-dose dexamethasone with or without intrathecal methotrexate (IT MTX) for patients in whom central nervous system (CNS)-HLH did not remit after 2 weeks of dexamethasone, followed by systemic/continuation therapy with cyclosporine A. A more recent modification in 2004 (HLH-2004 protocol) intensifies treatment with cyclosporine A at the beginning of induction and adds hydrocortisone to intrathecal methotrexate with the hope of preventing reactivation of HLH. As these agents often produce various levels of end-organ dysfunction, it is important to monitor for drug toxicity in order to differentiate treatment-related events from HLH progression. Without a final interpretation of HLH-2004 available, the risks and benefits of adding cyclosporine in this format remain unconfirmed. Patients with primary HLH receive maintenance therapy until an HSCT donor can be found for definitive treatment and potential cure. Using the HLH-2004 protocol followed by allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is most frequently advocated for patients with primary, inherited HLH (typical age, <18 years) and for patients with any severe form of HLH.[22]

Treatment Modalities

It is critical to treat any underlying disorders that may contribute to active HLH. Generally, treatment of early adult-onset HLH involves immunosuppression with corticosteroids and/or cyclosporine A to control unregulated inflammation. Corticosteroids may be used as monotherapy for secondary causes of HLH; however, the physician should expect to broaden treatment if the disorder does not respond or progresses. In highly suspicious cases, treatment may be initiated before obtaining final results of all diagnostic studies (including genetic testing), as many are often incomplete, time consuming, and unreliable. Dexamethasone, which can cross the blood-brain barrier, is the preferred corticosteroid. Cyclosporine A has been shown to be highly effective in patients not responding to corticosteroids.

EBV is the most common infection associated with HLH. In EBV-HLH, etoposide is often an effective agent that must be added before disease response is achieved. In a large Japanese series involving patients with EBV-HLH, survival was significantly better if etoposide was initiated early and if at least 4 doses of etoposide were administered.[4] Etoposide appears to be effective for both EBV-HLH and for some cases of rheumatologic-associated HLH.[12] Another agent that has been shown to be effective in EBV-HLH is rituximab (Rituxan, Genentech/Idec Pharmaceuticals), which can eliminate EBV-infected B cells.[23] Treatment with intravenous immunoglobulin (IVIG) can also be helpful in containing viral infections.

Lymphoma is the most common cause of malignancy-associated HLH (MA-HLH). It is more common in adults, and at least 24 cases have been reported in the literature of lymphoma associated-HLH (LA-HLH) during and after treatment for B- and T-cell ALL.[24] A Japanese data analysis identified LA-HLH as the most common cause of secondary HLH. There are few data directly comparing prognosis in adult and pediatric cases, but the prognosis is poor in adults with LA-HLH. In this data analysis, prognosis was significantly worse in adults with EBV-HLH compared to children.[25] The same therapy is indicated in both pediatric- and adult-HLH, and an aggressive escalation in treatment (within hours, days), and even HSCT, should be considered in nonresponders. Delayed diagnosis of MA-HLH is common, and prognosis has been reported to be poor. Thus, high-dose chemotherapy and HSCT can improve survival in patients with LA-HLH.[26]

A promising combination therapy for patients who present with bacterial infection and/or autoimmune-HLH, as well as for patients who cannot tolerate intensive chemotherapy due to old age or disease severity, includes cyclophosphamide, vincristine, and predni-

sone.[27] Another regimen based on a French study offers comparable survival to etoposide-based therapies. In this protocol, patients receive prednisolone, antithymocyte globulin (ATG), and cyclosporine A, which is followed rapidly by HSCT. [28] Overall survival was identical to HLH-94 at 55%; however, comparison of the 2 studies revealed a higher initial response rate to ATG, but also a higher relapse rate. Since there has not been a randomized head-to-head trial comparing this therapy to either HLH-94 or HLH-2004, the standard of care remains the etoposide/dexamethasone immunochemotherapy until further results are obtained. Currently, 2 pilot studies are trying to determine if better disease control to an HSCT endpoint can be achieved by combining various features of the ATG and HLH-94 protocols. There are also reports of successful treatment using certain monoclonal antibodies, such as daclizumab and infliximab.[29,30]

Splenectomy, which has been shown to be useful in confirming underlying etiology, may be of value in patients whose disease is refractory to standard therapy and in patients with splenomegaly.[31] Splenectomy has been utilized in the treatment of uncontrollable coagulopathy and persistent pancytopenia in patients with splenic enlargement.[32] Its use has not been heavily studied in sHLH patients.[33] Combining other common therapies, such as glucocorticoids, IVIG, or chemotherapy, is required, as hyperinflammation is not local to the spleen but rather systemic.

Not all patients require full protocol treatment. For example, patients with rheumatologic-associated HLH (MAS) often respond to corticosteroids alone or corticosteroids with cyclosporine A and/or intravenous immunoglobulin.[34] Cyclosporine A has shown particularly promising results in the treatment of MAS. Other agents that have been shown to be effective in treatment of this disorder include TNF-inhibiting agents, IL-1 inhibitors, and anti–IL-6 antibodies; however, these therapies can also trigger the disorder.[19]

Treatment Monitoring

Following initiation of treatment, patients must be closely monitored for signs of improvement and/or deterioration, as well as potential complications and drug toxicities.[35] Patients often have a rocky and volatile treatment course, which may lead to alterations and customization of therapy. Treatment may be weaned per protocol in patients who respond well, whereas dexamethasone doses and etoposide frequency may need to be increased in patients with disease reactivation. HLH relapse and increased severity of disease correlate with deterioration of liver function and blood counts, as well as increases in serum ferritin, sCD25, and sCD163 levels.[36] Salvage

therapy should be considered if a patient does not have, at minimum, a partial response within 2–3 weeks of therapy initiation. Furthermore, an infectious workup should be pursued in patients with recurring fever and increased inflammatory markers after an apparent response.

Patients with CNS involvement and/or mental status changes during treatment should receive a complete workup that includes a neurologic exam, lumbar puncture, and magnetic resonance imaging (MRI). In addition, weekly methotrexate with hydrocortisone should continue until cerebrospinal fluid (CSF) abnormalities and symptoms resolve. Since CNS involvement in HLH suggests a genetic etiology, and this disease feature is associated with substantial risks for long-term morbidity, HSCT is recommended as definitive treatment, especially in patients who do not have MAS and underlying CNS infections.[37] In addition, cyclosporine A can induce a posterior reversible encephalopathy syndrome (PRES) that may be difficult to distinguish from CNS inflammation.

Recommendations

The diagnosis of HLH needs to be considered in the differential diagnosis for any patient presenting with unexplained cytopenias, hepatosplenomegaly, and prolonged fevers. Hemophagocytosis seen on bone marrow is supportive of diagnosis. Human immunodeficiency virus infection, toxic chemical exposures, and prior treatment with immunosuppressive agents or radiation are other causes of these symptoms and should be excluded.

HLH in adults is a disorder about which little is known. Acquired forms of HLH can occur in otherwise healthy adults, whereas HLH often presents in its inherited (familial) form in children. Although the mechanisms underlying the hyperinflammation are unknown, in adults, acquired HLH is often associated with infections, rheumatologic diseases, and metabolic conditions. Treatment of HLH in adults includes immunosuppressive agents, immunomodulating agents, cytostatic drugs, and biologic response modifiers. In patients who are stable and mildly to moderately ill, consideration can be given to treating the underlying trigger with disease-specific therapy with or without corticosteroids plus close follow-up. In cases of severe disease, an aggressive therapeutic approach is recommended and should be initiated prior to obtaining all diagnostic study results.

Conclusion

HLH is a challenging disease to treat. Mortality is high, even among patients who are treated according to the HLH-2004 protocol. Thus, early recognition and treatment of this disorder is essential to decrease associated morbidity and mortality. Goals for the future include biomarker identification, genetic profiling, understanding the mechanism of sHLH, and modification of the current treatment protocol. Whenever possible, patients with HLH should be enrolled in clinical trials.

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