

# Hemophagocytic Lymphohistiocytosis

## An Update on Diagnosis and Pathogenesis

Flavia G. N. Rosado, MD,<sup>1</sup> and Annette S. Kim, MD, PhD<sup>2</sup>

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### Abstract

*Hemophagocytic lymphohistiocytosis (HLH) is a frequently fatal and likely underdiagnosed disease involving a final common pathway of hypercytokinemia, which can result in end-organ damage and death. Although an early diagnosis is crucial to decrease mortality, the definitive diagnosis is often challenging because of the lack of specificity of currently accepted diagnostic criteria and the absence of confirmatory gold standards. Because of the wide range of laboratory assays involved in the diagnosis of HLH, practicing pathologists from a broad spectrum of clinical specialties need to be aware of the disease so that they may appropriately flag results and convey them to their clinical counterparts. Our article summarizes these new advances in the diagnosis of HLH and includes a review of clinical findings, updated understanding of the pathogenesis, and promising new testing methods.*

The first reported case of hemophagocytic lymphohistiocytosis (HLH) was described in 1952 by Farquhar and Claireaux,<sup>1</sup> who called the disease *familial hemophagocytic reticulosis* and described it as a rare familial disorder characterized by a proliferation of histiocytes in solid organs and phagocytosis of blood cells. HLH, also known as hemophagocytic syndrome, is an uncommon systemic inflammatory clinical syndrome associated with numerous conditions, such as neoplastic, infectious, autoimmune, or hereditary diseases. The disease is seen in all ages and has no predilection for race or sex.<sup>2</sup> HLH is caused by a defect in inflammatory signals that results in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway. Untreated, approximately 95% of children will die of the disease.<sup>3</sup> Even with currently recommended therapy, HLH is a frequently fatal condition, although spontaneous partial regression has been reported.<sup>4</sup> The early institution of therapy is critical to control the hypercytokinemia that otherwise will lead to end-organ failure and death.

HLH has been traditionally divided into a primary form, which typically manifests in children with documented genetic abnormalities of the cytotoxic function of NK cells and T cells, and a secondary form that tends to occur at older ages in the setting of an associated condition, such as infection and malignancy, without an identifiable genetic abnormality. Upon the realization that genetic defects of HLH can occur at any age,<sup>5,6</sup> that these defects are uncommonly present even in children,<sup>7</sup> and that infections also can be a triggering mechanism in such patients,<sup>6</sup> the designations *primary* and *secondary* have become less relevant. Instead, *genetic* and *acquired* HLH are currently more appropriate designations.<sup>2</sup> The types of HLH and associated diseases are listed in **Table 1** and **Table 2**.

Genetic HLH currently encompasses the cases associated with a discrete genetic abnormality, as listed in Table 1. These patients will show a predisposition to the recurrence of HLH that manifests within the first year of life in 70% to 80% of cases, with only 10% of cases presenting in the neonatal period.<sup>8,9</sup> Late-onset cases have also been described in adolescents and adults as old as 62 years.<sup>2,5,6</sup> Nevertheless, 50% to 60% of childhood HLH cannot be attributed to any known gene defect.<sup>7,8</sup> The genetic form of HLH can be divided into 2 subgroups: familial HLH (FHL) and those associated with another primary immunodeficiency syndrome.

FHL is an autosomal recessive disease caused by several mutations in the NK/T-cell cytotoxic pathway. Perforin defects account for approximately 50% of all FHL cases in North American families.<sup>10</sup> Other genetic causes involve mutations in genes regulating the packaging, transport, or release of cytotoxic granules. A family history of genetic HLH is often absent due to the recessive nature of this disease.<sup>11</sup>

FHL is uncommon. A recent retrospective study estimates the prevalence of HLH in Texas to be at least 1 in 100,000 persons younger than 18 years.<sup>12</sup> In addition, the incidence of FHL varies according to the geographic region. The reported incidence is 1.2 cases per million persons younger than 15 years per year or 1 in 50,000 births in Sweden<sup>13</sup> and 0.342 in 100,000 in Japan,<sup>14</sup> with an annual incidence of 1 in 800,000.<sup>15</sup> In Turkey, the incidence is even higher, at 7.5 in 10,000, due to increased consanguinity and higher frequency of perforin gene defects.<sup>16</sup> A seasonal pattern of disease manifestation has been suggested, with more frequent occurrence in the summer.<sup>17</sup>

HLH is often the first manifestation of another primary immunodeficiency syndrome.<sup>2</sup> Immunodeficiency syndromes known to be associated with HLH include Chédiak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2, and X-linked proliferative syndrome (XLP) (see Table 2).

**Table 1**  
HLH Subtypes and Their Genetic Defects<sup>2,10</sup>

HLH Subtype	Genetic HLH			
	Gene/Protein	Function	Location	% of Familial Cases <sup>70</sup>
FHL1	Unknown	Unknown	9q21.3-locus 6	~10 <sup>10</sup>
FHL2	<i>PFR1</i> /perforin 1	Cell lysis, membrane pore formation	10q21-22	20-50
FHL3	<i>UNC13D</i> /Munc 13-4	Cytolytic granule exocytosis	17q25	~23
FHL4	<i>STX11</i> /syntaxin 11	Intracellular vesicle trafficking	6q24	~1
FHL5	<i>STXB2</i> /syntaxin binding protein 2 or <i>UNC18B</i>	Intracellular vesicle trafficking	19p13	Unknown
Griscelli syndrome type 2	<i>RAB27A</i> /Rab27a	Vesicle docking on microtubules	15q21	
Chédiak-Higashi syndrome	<i>LYST</i>	Vesicle maturation and sorting	1q42.1-q42.2	
Hermansky-Pudlak syndrome type 2	<i>AP3B1</i>	Encoding $\beta$ subunit of AP3, vesicle maturation and transport	5q14.1	
XLP type 1	<i>SHD2D1A</i> /SAP protein	Polarization of cytolytic granules for transport to the immunological synapse	Xp25	
XLP type 2	<i>BIRC4</i> /XIAP protein	Unclear	Xp25	

XLP, X-linked proliferative syndrome.

**Table 2**  
HLH Subtypes and Common Disease Associations

Infection	Reported Associations
Viral	Herpesviruses (EBV, CMV, HHV-8, HSV), HIV, HTLV, adenovirus, HAV, HBV, HCV, measles, mumps, rubella, dengue, hantavirus, parvovirus B19, enterovirus, influenza
Bacterial	<i>Staphylococcus aureus</i> , <i>Campylobacter</i> spp, <i>Fusobacterium</i> spp, <i>Mycoplasma</i> spp, <i>Chlamydia</i> spp, <i>Legionella</i> spp, <i>Salmonella typhi</i> , <i>Rickettsia</i> spp, <i>Brucella</i> spp, <i>Ehrlichia</i> spp, <i>Borrelia burgdorferi</i> , <i>Mycobacterium tuberculosis</i>
Fungal	<i>Candida</i> spp, <i>Cryptococcus</i> spp, <i>Pneumocystis</i> spp, <i>Histoplasma</i> spp, <i>Aspergillus</i> spp, <i>Fusarium</i> spp
Parasitic	<i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , <i>Toxoplasma</i> spp, <i>Babesia</i> spp, <i>Strongyloides</i> spp, <i>Leishmania</i> spp
Malignancy	
Hematologic	Peripheral T-cell/NK-cell lymphomas, ALCL, ALL, Hodgkin lymphoma, multiple myeloma, acute erythroid leukemia
Nonhematologic	Prostate and lung cancer, hepatocellular carcinoma
MAS	Systemic-onset juvenile idiopathic arthritis, Kawasaki disease, systemic lupus erythematosus, seronegative spondyloarthropathies

ALCL, anaplastic large-cell lymphoma; ALL, acute lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; MAS, macrophage activation syndrome; NK, natural killer.

Acquired HLH is often subcategorized into infection-associated HLH, with particular emphasis on Epstein-Barr virus (EBV)-associated disease, malignancy-associated HLH, and HLH in association with autoimmune disease. The term *macrophage activation syndrome* (MAS) is often applied to HLH in this latter setting in the context of rheumatologic diseases, commonly systemic-onset juvenile idiopathic arthritis (soJIA), adult-onset Still disease, and systemic lupus erythematosus.<sup>18,19</sup>

Acquired HLH has also been reported in patients receiving immunosuppressive therapy after transplant<sup>2</sup> or intravesical Bacille Calmette-Guérin therapy.<sup>20</sup> However, opportunistic infections for which these patients are at risk may represent a confounding factor.<sup>11</sup>

Establishing a timely diagnosis of HLH is the critical challenge that physicians face. The symptoms of HLH are nonspecific; thus, the disease is easily underrecognized.<sup>21</sup> The confirmation of a suspected HLH case is also difficult because of a lack of a gold standard confirmatory test. The current diagnostic criteria proposed by the Histiocyte Society in 2004<sup>22</sup> have been criticized for their lack of specificity when applied to critically ill patients.<sup>23</sup> The recently included tests for soluble CD25 (sCD25) and 51-Cr release assay are not available in most medical centers, thus preventing patients from the benefit of an early diagnosis and therapy. The identification of a genetic abnormality is helpful but rarely present.<sup>8</sup>

Despite these difficulties, there have been changes in the understanding, diagnosis, and pathogenesis of HLH, which will be summarized in this review.

## Clinical Findings

HLH should be suspected in cases of an unexplained sudden onset of a systemic inflammatory response syndrome (SIRS), including fever, malaise, hepatosplenomegaly, jaundice, generalized lymphadenopathy, and cytopenias.<sup>22</sup> As many as 65% of pediatric patients also have a nonspecific rash that often takes the form of purpuric morbilliform eruptions, although cases of erythroderma also have been described.<sup>24</sup>

Central nervous syndrome (CNS) symptoms are seen in up to 75% of pediatric cases.<sup>13</sup> These symptoms include seizures, meningitis, encephalopathy, ataxia, hemiplegia, cranial nerve palsies, mental status changes, or simply irritability. There have been reports of isolated CNS symptoms without accompanying systemic findings, termed *cerebral HLH*.<sup>25,26</sup> The recognition of HLH in this setting is often challenging.<sup>27,28</sup> On imaging studies, enhancing nodular parenchymal lesions may be seen, as well as leptomeningeal enhancement, demyelination, and atrophy.<sup>27</sup> There are also isolated reported cases of acute neurological degeneration with subdural hemorrhage detected on computed tomography scans.<sup>29</sup>

The clinical presentation of HLH is different in neonates. Fever in this age group is commonly absent and should not dissuade the clinician from pursuing the diagnosis of HLH.<sup>30</sup> Similarly, hypertriglyceridemia, although frequently seen in adults, has been reported in only 14% of neonates. This difference has been attributed to age-related differences in lipid metabolism.<sup>30</sup> By contrast, coagulopathy, hepatomegaly, and cytopenias should raise suspicion for HLH in this population.<sup>11</sup> Neonatal HLH presenting as isolated fulminant liver failure has been reported.<sup>2</sup>

HLH constitutes a medical emergency at any age. Because of the nonspecific nature of the clinical presentation, this disease is often overlooked, although the patients may be in extremis.<sup>31</sup> Clinicians must be sure to always maintain a high level of suspicion in any patient with unexplained cytopenias and fever, so that appropriate testing can be conducted rapidly (see Diagnostic Criteria section). However, even a suspected case of HLH is difficult to confirm because of the current lack of gold standard confirmatory tests. Laboratory testing can be falsely negative, lack specificity, or involve a turnaround time that is not helpful in a clinical emergency.

## Laboratory Findings

Common laboratory findings associated with HLH include cytopenias affecting at least 2 lineages in the peripheral blood, hypofibrinogenemia, strikingly elevated ferritin levels, and hypertriglyceridemia. Hyperbilirubinemia with elevated transaminases and lactate dehydrogenase levels are also commonly seen and reflect liver dysfunction.<sup>2</sup> In addition, about half of children with HLH have a moderately increased cell count and/or protein content in the cerebrospinal fluid (CSF).<sup>2</sup>

The striking levels of ferritin require an additional comment. A review of ferritin levels in pediatric patients found a cutoff of 10,000 µg/L to be 90% sensitive and 96% specific for HLH.<sup>32</sup> This high cutoff of ferritin significantly maximizes the specificity since elevated ferritin due to other inflammatory conditions occurs typically at lower levels. Measurement of ferritin levels is also particularly convenient since it is a rapid chemistry test performed at almost all hospitals.

Other more esoteric laboratory tests include the 51-Cr release assay and the measurement of sCD25. NK-cell activity is measured by the 51-Cr release assay, in which patient NK cells that have taken up the radionuclide are stimulated to degranulate. Release of the radionuclide is expected to be reduced or absent in HLH.<sup>33</sup> The reported sensitivity of these tests approaches 100%.<sup>31</sup> CD25, the α subunit of the interleukin 2 receptor (IL-2R), is a marker of activated lymphocytes that also release sCD25. This sCD25 can be measured by an enzyme-linked immunosorbent assay and also has been proven

useful in the diagnosis of MAS in soJIA.<sup>34</sup> Because of the technical challenges of employing a radionuclide in the former assay and the infrequent utilization of both, these assays are currently available in only a few medical centers in the United States, limiting their utility in time-critical clinical scenarios.

## Histopathologic Findings

Histopathologic findings of HLH typically include a prominent and diffuse accumulation of lymphocytes and mature macrophages, which occasionally exhibit hemophagocytosis **Image 1**. Although classically seen in the bone marrow, these infiltrates also have been described in the spleen, lymph nodes, liver, skin, lungs, meninges, CSF, and, rarely, the subcutaneous tissue.<sup>35-38</sup>

In the bone marrow, hemophagocytosis of mature and immature hematopoietic cells is characteristic, in addition to myeloid and erythroid hypoplasia, as well as variable megakaryocytic hyperplasia. Hemophagocytosis, especially on aspirate smears, must be distinguished from physiologic erythroblastic islands, which can resemble erythrophagocytosis. Concurrent findings related to the overlying triggering process also may be seen. For instance, in cases of acute infection, the bone marrow may display plasmacytosis, increased immunoblasts, or granulomas.<sup>36</sup> Malignant neoplasms, commonly B-, T-, and NK-cell lymphoma as well as Hodgkin lymphoma, are often masked by the abundant histiocytosis.<sup>36</sup>

In the liver, there is Kupffer cell hyperplasia,<sup>39</sup> as well as a portal and sinusoidal cytotoxic T-cell infiltrate expressing CD3, CD8, and granzyme B with variable hemophagocytic histiocytes.<sup>40</sup> The pattern is commonly described as similar to chronic persistent hepatitis,<sup>37</sup> although other patterns that are leukemia-like, giant cell hepatitis-like, or storage disease-like have also been described, depending on the predominant cell type.<sup>40</sup> Variable degrees of endothelialitis of portal and central veins and lymphocytic bile duct injury appear to correlate with the clinical severity.<sup>40</sup>

The microscopic visualization of hemophagocytosis is simply one of the possible diagnostic criteria **Table 3**. It does not necessarily need to be present to establish a diagnosis of HLH. In fact, hemophagocytosis is often cyclical, and thus a given biopsy specimen may yield negative results at first examination.<sup>37</sup> In such cases, repeat biopsies may be helpful. In addition, morphologic evidence of hemophagocytosis is not a specific finding for HLH. In 1 report, HLH was demonstrable in up to 60% of patients with severe sepsis who did not fulfill criteria for HLH, whereas another report found microscopic evidence of HLH in one-third of the patients who died in the intensive care unit with sepsis and multiorgan failure.<sup>41,42</sup> The explanation for this occurrence lies in the suppression of the function of NK cells that occurs in severe sepsis, particularly

in sepsis associated with viral infections.<sup>43,44</sup> Elevated sCD25/sIL-2R was also detected in those patients. Thus, these studies suggest a significant overlap in severe sepsis and HLH, with a final common pathway leading to hemophagocytosis. These findings raise the question of whether even some cases of infection-associated HLH are in fact simply the extreme end of the inflammatory spectrum of sepsis.<sup>23,45</sup>

## Diagnostic Criteria

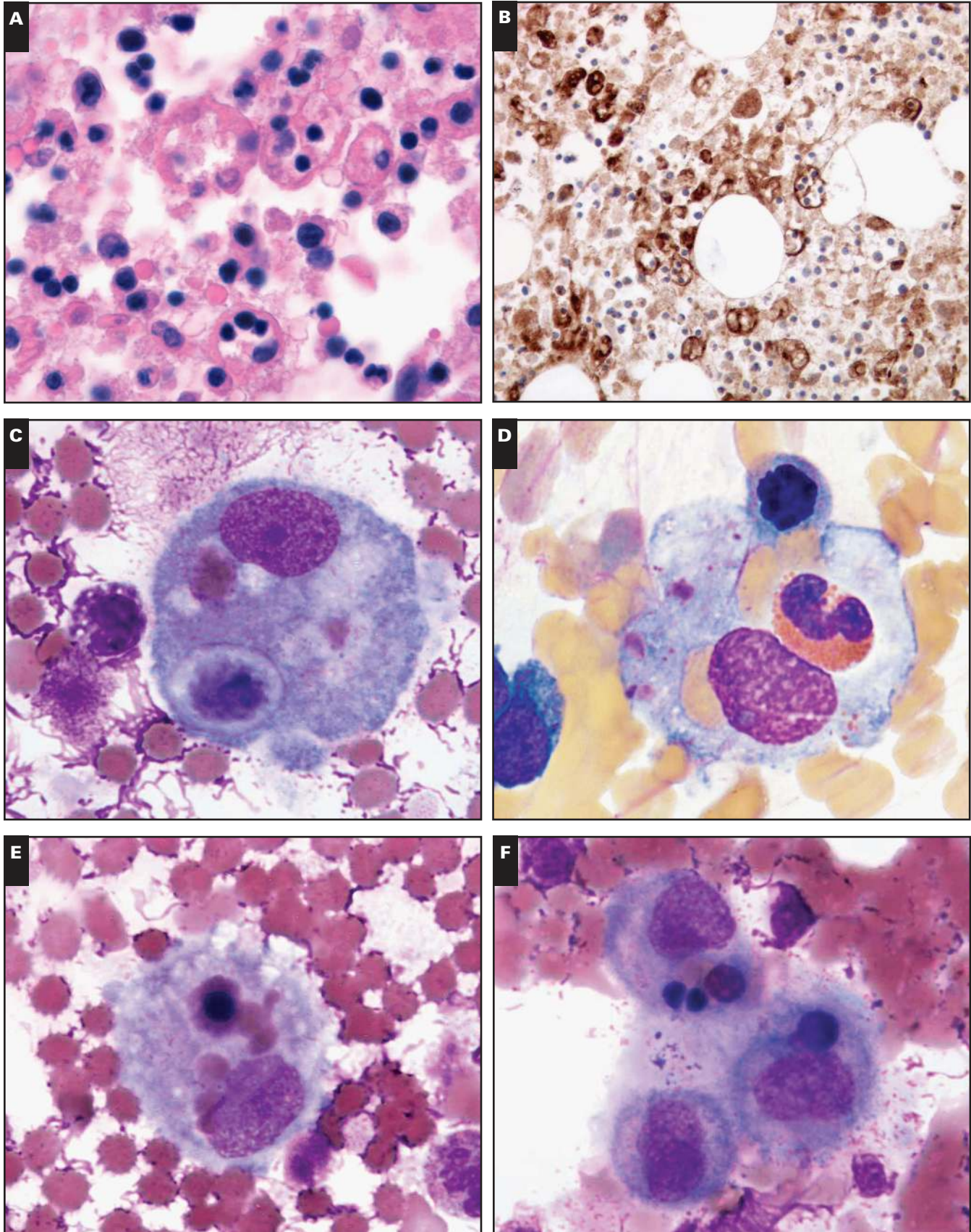
Based on these common clinical and laboratory findings, diagnostic criteria for HLH were proposed in 1991<sup>3</sup> and updated in 2004<sup>22</sup> to include NK-cell activity measured by the 51-Cr release assay, sCD25, and elevated ferritin (Table 3). These criteria, generated based on studies of FHL,<sup>3</sup> are the only guidelines available for the diagnosis of acquired HLH.

The diagnostic criteria include fever; splenomegaly; cytopenias affecting at least 2 of 3 lineages in the peripheral blood; hyperferritinemia greater than 10,000 µg/L; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes (see Image 1); low or absent NK-cell activity determined by the 51-Cr release assay; and high levels of sCD25. Five of these 8 criteria are required for diagnosis, although in patients with an established genetic abnormality (eg, FHL mutations), the diagnosis can be established without meeting the 5 criteria.<sup>46</sup> The diagnostic criteria are listed in Table 3.

The 2004 diagnostic criteria for HLH do not apply to MAS because of the overlap of clinical and laboratory findings between HLH and autoimmune diseases.<sup>47</sup> Modified diagnostic criteria for MAS have been suggested by Ravelli et al,<sup>47</sup> who proposed a change in baseline laboratory findings as an indication of MAS in conjunction with the appropriate clinical symptoms. In the absence of arthritis, a very high C-reactive protein, only moderate cytopenias, reduced erythropoiesis, increased granulopoiesis with a left shift, and a high level of interleukin 1β might suggest MAS.<sup>48</sup> Ongoing projects are being conducted to validate these criteria.<sup>47</sup>

## Mutation Analysis

The perforin gene mutation was the first genetic defect to be described in association with HLH in 1999.<sup>49</sup> The perforin protein is one of the major cytolytic proteins in cytotoxic cells,<sup>50</sup> and mutations involving perforin gene 1 (*PRFI*) account for 20% to 50% of familial cases of HLH (FHL2) (see Table 1).<sup>51</sup> Mutations in other genes involved in the perforin pathway account for the other types of FHL—namely, *UNC13D* (FHL3),<sup>52</sup> *STX11* (FHL4),<sup>53</sup> and *STXBP2* or *UNC18B* (FHL5).<sup>54</sup> A potential gene locus on chromosome 9q21 is associated with FHL1.<sup>55</sup> The types of FHL are summarized in Table 1.



**Image 1** **A**, Bone marrow biopsy specimen demonstrating nucleated forms within macrophages and background cellular debris (H&E,  $\times 1,000$ ). **B**, CD68 stain on a bone marrow biopsy specimen highlighting the nuclei of numerous engulfed cells within macrophages (CD68,  $\times 400$ ). **C-F**, Various images of hemophagocytosis on a bone marrow aspirate (Wright-Giemsa,  $\times 1,000$ ).

**Table 3**  
**Diagnostic Criteria of Hemophagocytic Lymphohistiocytosis (HLH)**

Molecular diagnosis of HLH or the presence of at least 5 of 8 criteria:

1. Fever
2. Splenomegaly
3. Cytopenias (affecting at least 2 lineages in the peripheral blood)  
 Hemoglobin levels <90 g/L (in infants <4 weeks old,  
 hemoglobin <100 g/L)  
 Platelets <100 × 10<sup>9</sup>/L  
 Neutrophils <1.0 × 10<sup>9</sup>/L
4. Hypertriglyceridemia and/or hypofibrinogenemia:  
 Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)  
 Fibrinogen ≤1.5 g/L
5. Documented hemophagocytosis in the bone marrow, spleen,  
 or lymph nodes
6. Low or absent natural killer cell activity
7. Ferritin ≥500 µg/L
8. Soluble CD25 (ie, soluble interleukin-2 receptor) ≥2,400 U/mL

Mutation analysis should be requested for all cases of confirmed or suspected HLH, even when an associated infectious disease has already been identified.<sup>2</sup> The demonstration of a characteristic genetic defect alone can be used to make the diagnosis of HLH in the appropriate clinical setting, without the need to fulfill 5 of the 8 diagnostic criteria.<sup>46</sup> It should include the analysis of the known FHL mutations (*PRF1*, *UNC13D*, *STX11*, and *UNC18B*) at a minimum.<sup>56,57</sup> When XLP is suspected (eg, upon documentation of EBV infection), mutation analysis for *SH2D1A/SAP* and *BIRC4* also must be included.<sup>57</sup> Specific testing for the other types of immunodeficiency syndromes, such as Chédiak-Higashi syndrome, Griscelli syndrome type 2, or Hermansky-Pudlak syndrome type 2, may be warranted in the appropriate clinical setting.

Heterozygous patients for the perforin gene mutation may manifest the disease despite having normal perforin expression levels.<sup>58</sup> Children with a strong family history of HLH also may be offered the test prophylactically.<sup>57</sup> Prenatal and preimplantation diagnosis is possible by genetic analysis once the gene defect within a family is known. Prenatal diagnosis was first performed in 2 unrelated Turkish families harboring a perforin mutation.<sup>59</sup>

Importantly, HLH cannot be ruled out solely on a negative mutation study, since at least half of childhood and most adult cases cannot be attributed to any known mutation.<sup>7,8</sup>

### Flow Cytometry

Flow cytometry recently has been added to the arsenal of screening tools for HLH, although it is not currently cited in any formal diagnostic algorithms. It is based on the detection of perforin expression in all cytotoxic cell types by intracellular staining. Thus, the absence of perforin staining reflects the presence of homozygous perforin gene mutations, and even heterozygous carriers also demonstrate abnormal perforin staining patterns.<sup>60</sup> This method has enabled a 2-hour screen for FHL2 in the medical centers that use this technique.<sup>60</sup>

However, the fact that some mutations do not result in significant reduction of the protein levels and that disease can sometimes occur in heterozygous patients limits flow cytometry's sensitivity to perforin defects. In addition, alternative defects in gene regulation unrelated to HLH may affect protein expression, which affects the specificity of the study.<sup>57</sup> Despite these limitations, the fast turnaround time of flow cytometry makes it advantageous over mutation analysis.

Mutations in other genes related to granule trafficking and exocytosis also can be determined by quantifying the expression of surface CD107a (LAMP-1) on peripheral blood mononuclear cells following stimulation with phytohemagglutinin or anti-CD3.<sup>61</sup> CD107a is normally released to the surface of cytotoxic T cells and NK cells upon exocytosis; thus, the absence of CD107a expression on the cell surface may be indicative of defects throughout the pathway involving secretory granule migration, docking, priming, or fusion.<sup>61</sup> A similar technique is used for the detection of *SAP/SH2D1A* expression.<sup>62</sup>

### Differential Diagnosis and Pitfalls

The main differential diagnosis of HLH is SIRS due to other causes. In addition, HLH has been mistaken for neonatal hemochromatosis<sup>63</sup> or as metabolic disease in infants presenting with extreme organomegaly or high triglycerides.<sup>2</sup> HLH has been reported as difficult to diagnose in patients with underlying Kawasaki syndrome.<sup>64</sup> Langerhans cell histiocytosis is also in the differential diagnosis, but in HLH, the expanded population of histiocytes is not clonal.<sup>65</sup> Infections with *Leishmania donovani* are known to mimic the syndrome clinically, although hemophagocytosis should not be seen in the bone marrow. The findings in lymph node biopsy specimens may mimic those of malignant lymphomas.<sup>2</sup>

### Pathophysiology

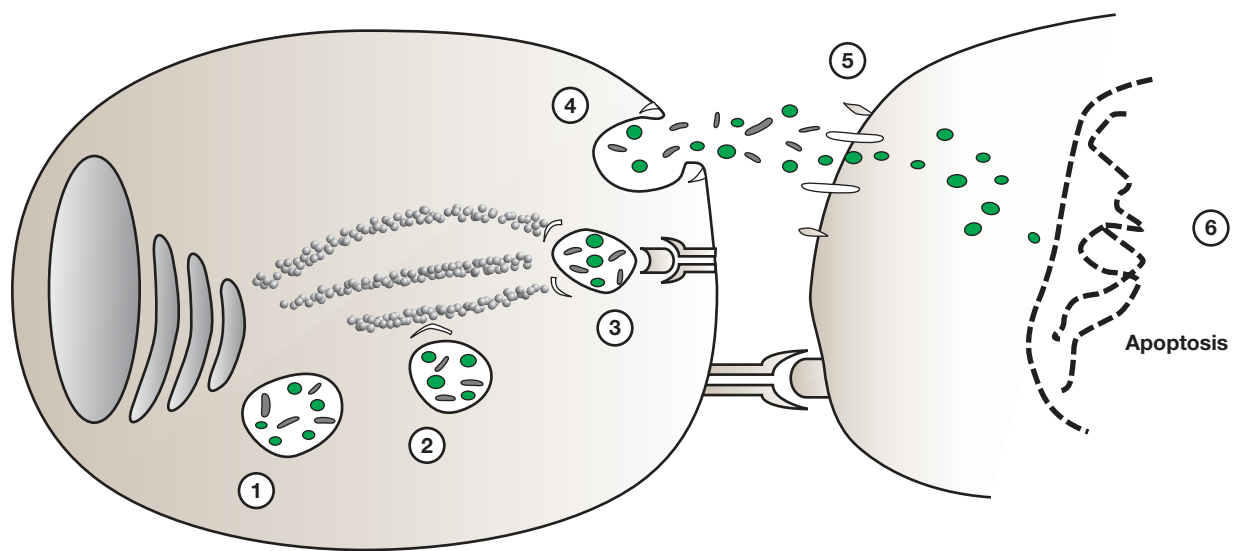
The pathogenesis of HLH was at first thought to be the result of an inability to clear infections in immunodeficient patients.<sup>19</sup> Subsequent descriptions of HLH in immunocompetent patients worked to disprove such theory. More recently, the identification of cytotoxic pathway mutations as the primary cause of genetic HLH has elucidated to some extent the mechanism of this disease. It is thought that all forms of HLH are due to some form of impairment in the function of cytotoxic T lymphocytes (CTLs) and NK cells, although the exact mechanism is less clear for nongenetic forms of HLH.<sup>31</sup>

The inability to clear the antigenic stimulus and thus turn off the inflammatory response is what ultimately leads to the hypercytokinemia characteristic of HLH.<sup>66</sup> In a healthy individual, antigens will initiate an inflammatory cascade, with

the release of Th1 cell cytokines (interferon  $\gamma$  [IFN- $\gamma$ ], tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ], granulocyte-monocyte colony stimulating factor) that will stimulate macrophages, NK cells, and CTLs to proliferate. NK cells release granules that contain perforin and granzymes.<sup>31</sup> Perforin is a key cytolytic protein that acts by inserting itself in the membrane of the target cell and creating pores that lead to osmotic lysis of the target cell.<sup>67</sup> Furthermore, perforin is necessary for the uptake of granzymes in the target cell that will then catalyze protein degradation. These combined actions induce apoptosis of the target cell, remove the antigenic stimulation, and signal the termination of the inflammatory response.

Loss of this normal cytotoxic function of NK cells and CTLs can cause decreased production of the contents of the cytotoxic granules or inhibit the proper formation and release of these granules in the immunologic synapse. These latter steps rely on an intact cytoskeleton and microtubules involved in docking and fusion of the granules into the cell membrane. All the genetic defects described in FHL involve either inadequate levels of perforin itself (FHL2) or improper granule exocytosis (FHL3-5 and immunodeficiency syndromes) **Figure 1**.

In acquired HLH, the exact means by which the function of NK cells and CTLs is impaired are less clear. Suppressed



Mechanism	Type of Genetic HLH
① Immature granule containing perforin and granzyme is formed.	FHL2—perforin gene mutation
② AP3 aids in the maturation of the granule. Granule docking on microtubules is mediated by Rab27a.	Hermansky-Pudlak syndrome type 2 Griscelli syndrome type 2
③ Granule exocytosis is mediated by Munc13-4, expressed on the granule along with syntaxin 11 and Munc18-2, expressed on the cell membrane.	FHL3, FHL4, FHL5
④ The SAP protein mediates appropriate granule polarization and the cytotoxic proteins are released in the synapse.	X-linked lymphoproliferative disorder
⑤ Perforin inserts itself in the target cell membrane, creating a pore.	FHL2—perforin gene mutation
⑥ Granzyme enters the target cell through the pore and induces apoptosis.	

**Figure 1** Schematic depicting a cytotoxic lymphocyte (either T or natural killer, left) and a target cell (right). Within the cytotoxic lymphocyte are some of the key steps in the packaging of cytotoxic granules (step 1), their transport (step 2), their fusion with the membrane (step 3), and the secretion of their contents (step 4). In the target cell, formation of the perforin-lined pore is shown (step 5), as well as introduction into the target cell of various cytotoxic granules (step 6). Below the schematic are listed the key players in each of these processes and the type of genetic hemophagocytic lymphohistiocytosis (HLH) that is associated with mutations of these key players.

T-cell function by viral infections,<sup>31</sup> similar to that seen in EBV infection,<sup>68</sup> is a plausible mechanism.

If antigen removal is inefficient, as in individuals with HLH-causing mutations in the cytotoxic pathway, the inflammatory stimulus will not be terminated, resulting in a final common pathway in HLH of uncontrolled hypercytokinemia with sustained macrophage activation and tissue infiltration.<sup>66,69,70</sup> Hypercytokinemia and lymphohistiocytosis explain most of the symptoms and laboratory findings of this disease, driven by an accentuation of the Th1 response. Elevated levels of Th1-type cytokines have been seen in patients with HLH, including TNF- $\alpha$ , IFN- $\gamma$ , and interleukin 18.<sup>71</sup> Under the influence of these Th1-type cytokines, macrophages become activated.<sup>71</sup> The chronic stimulation by TNF- $\alpha$  and IFN- $\gamma$  results in not only chronic activation of the macrophages but also nonphysiologic behavior of those macrophages.<sup>72</sup> The macrophages in HLH have been shown to ingest without involvement of the typical receptor profile of interactions. In addition, the macrophages ingest nonphysiologic quantities and do not induce apoptosis of the ingested cells. However, pancytopenia is likely the consequence of high levels of TNF- $\alpha$  and IFN- $\gamma$  produced by Th1-type T cells rather than solely due to hemophagocytosis.<sup>71</sup> TNF- $\alpha$  and IFN- $\gamma$  act on hematopoietic precursors to suppress both early and late stages of hematopoiesis and induce apoptosis in hematopoietic cells.<sup>73</sup>

TNF- $\alpha$  and IFN- $\gamma$  also inhibit lipoprotein lipase, leading to elevated triglycerides.<sup>2</sup> Activated macrophages secrete plasminogen activator that results in high plasmin levels, hyperfibrinolysis, and a decrease in fibrinogen.<sup>11</sup> Ferritin production is also upregulated in the macrophages secondary to increased levels of heme-oxygenase, a heat shock protein expressed in response to inflammatory cytokines and endotoxin.<sup>74</sup> Hepatosplenomegaly, with increased transaminases and bilirubin, and neurologic symptoms are the consequence of organ infiltration by activated lymphocytes and histiocytes.<sup>75</sup> Fever is induced by interleukin 1 and interleukin 6 produced by activated macrophages, and sCD25 is increased in HLH in response to the activation of Th1 cells.

## Genetic HLH

The various forms of genetic HLH all center on critical defects in the function of the NK or cytotoxic T cells. Five types of FHL are described (Table 1). FHL1 is due to chromosome arm 9q mutations and accounts for approximately 10% of the familial cases.<sup>10,57</sup> The responsible gene at that locus and its function have not yet been identified.

FHL2 is caused by mutations in *PRF1*. This mutation accounts for approximately 20% of familial cases worldwide, with a somewhat higher prevalence in Turkey (30%), Japan

(40%), and North America (approximately 50%).<sup>10</sup> The type of perforin mutations is unique in some populations, suggesting that these abnormalities occurred in temporally and geographically distinct ancestors.<sup>10</sup> African American patients tend to carry the same 50delTA perforin mutation. In Japan, the most common perforin mutation is 1090-1091delCT (62.5% of perforin mutations); the second most common mutation is 207delC (37.5% of perforin mutations).<sup>76</sup> Turkish families express the Trp374X perforin mutation at a high frequency, which is associated with early disease onset, and Italian families express the A91V sequence variant.<sup>10</sup>

In FHL3, mutation in the *UNC13D* gene leads to an abnormal expression of Munc 13-4, a protein involved in proper fusion of the cytotoxic granules with the cell membrane.<sup>2</sup> In Japan, the frequency of *UNC13D* mutations is quite high, including 6 of 16 patients with FHL in 1 study.<sup>77</sup>

FHL4 is due to mutation in the *STX11* gene, leading to the abnormal expression of syntaxin 11, a protein also involved in granule exocytosis. It is involved in vesicle transport through interactions with t-SNARE, the attachment protein receptor present in the cell membrane, and leads to defective granule exocytosis with normal polarization.<sup>78</sup> Although mutations in *STX11* are thought to be responsible for much of FHL in the Middle East, 1 survey found such mutation in only 1% of North American patients.<sup>70</sup>

The more recently described FHL5 is associated with mutations in the syntaxin binding protein 2 (*STXBP2* or *UNC18B*), which regulates intracellular vesicle trafficking.<sup>54</sup> The remainder of FHL cases are caused by mutations in as yet unidentified genes.<sup>7</sup>

Similar to FHL3, FHL4, and FHL5, impaired granule exocytosis can also be seen in some primary immunodeficiency syndromes, with an associated defect in NK/T-cell function and a predisposition to the development of HLH (Table 3).<sup>79</sup> In Griscelli syndrome type 2, mutation in the *RAB27A* gene results in decreased GTPase and impaired vesicle docking on microtubules.<sup>80</sup> Interestingly, this mutation also has been seen in patients without evidence of Griscelli syndrome type 2 and may represent a somatically acquired mutation.<sup>81</sup> In Chédiak-Higashi syndrome, the putative mutation is in the *LYST* gene, which encodes for a protein involved in vesicle maturation and sorting.<sup>82</sup> In Hermansky-Pudlak syndrome type 2, mutations in the *AP3B1* gene, encoding the  $\beta$  subunit of the adapter protein complex AP3, are implicated in defective vesicle maturation and protein transport.<sup>83</sup> In XLP, the defective genes are *SH2D2IA* (XLP type 1) or *BIRC4* (XLP type 2), which encode for the proteins SAP and XIAP, respectively. Abnormal expression of SAP, the signaling lymphocytic activation molecular (SLAM)-associated protein, has been recently linked to an impaired polarization of cytolytic granules.<sup>84</sup> The role of XIAP, the X-linked inhibitor of apoptosis protein, in the pathogenesis of HLH is unclear. Other immunodeficiency



syndromes associated with an increased risk of HLH are Wiskott-Aldrich syndrome,<sup>85</sup> DiGeorge syndrome,<sup>86</sup> and severe combined immunodeficiency syndrome,<sup>87</sup> but the exact mechanism in these cases has yet to be determined.

## Acquired HLH

Acquired HLH is not associated with any known genetic abnormality or immunodeficiency syndrome. It was first described years after the genetic form, in 1979 by Risdall and colleagues,<sup>88</sup> in adults with a viral infection following organ transplantation. However, later it became clear that HLH also occurs in immunocompetent patients. Although thought to arise in adults, it is now accepted that acquired HLH may occur at any age, including children.<sup>2</sup> In fact, some authors advocate that this form is more common in children than the genetic form.<sup>2</sup>

The true incidence of acquired HLH is unknown, and a study suggests that HLH may be significantly underrecognized in many adult critical care units.<sup>21</sup> The pathogenesis is not as well understood as in genetic HLH. It is possible that, in adults with a previously unexpressed HLH genotype, the disease becomes apparent in response to a major immunologic challenge.<sup>31</sup> There are certainly reported cases of genetic HLH with mutation of the *PRF1* gene that previously had been deemed acquired based on age.<sup>89,90</sup>

A large variety of underlying conditions have been reported in association with HLH, commonly infection and malignancy, although metabolic diseases and medical therapy also have been implicated (see Table 2).<sup>75</sup>

## Infection-Associated HLH

HLH associated with infection was originally described in patients under iatrogenic immunosuppression.<sup>91,92</sup> Infections are commonly implicated triggers of genetic HLH; therefore, the identification of an infection does not discriminate between genetic and acquired forms.<sup>22,93</sup>

A number of infectious organisms have been associated with HLH (see Table 2). Viral infections of the herpesvirus family are frequently reported,<sup>2</sup> particularly cytomegalovirus and EBV infections, with EBV regarded as the pathogen that most commonly triggers infection-associated HLH (see further discussion below).<sup>94</sup> Herpes simplex virus infections are associated with up to 30% of neonatal HLH in Japan.<sup>30</sup> Human herpesvirus 8-associated HLH has been described in 13 patients, mostly occurring in the setting of Kaposi sarcoma or multicentric Castleman disease.<sup>95</sup>

Other viruses reported in association with HLH include hepatitis viruses, adenovirus, measles, mumps, rubella, dengue,

hantavirus,<sup>96</sup> parvovirus B19,<sup>97</sup> and enterovirus.<sup>98</sup> Influenza-associated HLH has also been reported.<sup>35</sup>

HLH may also be the first manifestation of a human immunodeficiency virus (HIV) infection.<sup>99</sup> Around 10% to 20% of bone marrow biopsy specimens in patients with HIV before initiation of highly active antiretroviral therapy showed hemophagocytosis; however, it is not known whether these patients fulfilled other criteria for HLH.<sup>100</sup> The fact that viral infections may interfere with the function of cytotoxic T cells represents a possible mechanism of infection-associated HLH.<sup>75</sup>

The incidence of bacterial-associated HLH varies between studies.<sup>101,102</sup> Bacterial organisms include *Staphylococcus aureus*, as well as various Gram-negative and atypical bacteria such as *Campylobacter* spp, *Fusobacterium* spp, *Mycoplasma* spp, *Chlamydia* spp, *Legionella* spp, *Salmonella typhi*, *Rickettsia* spp, *Brucella* spp, *Ehrlichia* spp, and *Borrelia burgdorferi*.<sup>96</sup> As many as 36 cases of HLH have been published in association with tuberculosis.<sup>96,103</sup>

Among parasitic infections that trigger HLH, malaria (*Plasmodium falciparum* and *Plasmodium vivax*), toxoplasmosis, babesiosis, and strongyloidiasis have also been described in HLH.<sup>96</sup> Fungal infections include *Candida*, *Cryptococcus*,<sup>104</sup> *Pneumocystis*, *Histoplasma*,<sup>105</sup> *Aspergillus*, and *Fusarium* species.<sup>96</sup> These are more frequent in patients with immunosuppression due to HIV infection, lymphoma, and chronic steroid use, as well as in transplant recipients.<sup>106</sup> *Leishmania* is a frequent nonviral agent reported in children.<sup>107</sup> The mechanism by which these various infectious organisms cause HLH is poorly understood, with the exception of EBV-associated HLH.

## EBV-Associated HLH

EBV has been identified as the triggering virus in 74% of children in whom infectious agents were identified.<sup>102</sup> EBV-associated HLH is most often seen in East Asian countries. In Japan, the estimated incidence is at least 25 cases per year in the pediatric population, with a peak incidence occurring between 1 and 2 years and with a slightly higher frequency in girls.<sup>94</sup> This higher geographic prevalence points to possible genetic factors involved in the pathogenesis of EBV-associated HLH. It may also be related to the higher prevalence of EBV and EBV-infected T cells in Asians or to better detection and diagnosis of HLH in Asian hospitals.<sup>108</sup>

Most patients with EBV-associated HLH present with a prolonged atypical infectious mononucleosis–like course, although some will develop an abrupt, rapidly fatal disease.<sup>78</sup> Although EBV-associated HLH appears to be more common in the setting of reactivation,<sup>94</sup> its occurrence in some immunocompetent children or young adults with classic mononucleosis suggests also an association with primary EBV infections.<sup>109</sup>

In primary EBV infection, EBV infects and replicates primarily in CD21+ B cells.<sup>110</sup> Occasionally, T cells are also infected.<sup>111</sup> However, unlike in chronic persistent EBV infection, in which infected NK cells and CD4+ T cells are more frequent, in EBV-associated HLH, infected CD8+ T cells predominate.<sup>112,113</sup> The infection of the cytotoxic CD8+ T cells by EBV is believed to impair the proper function of these T cells, thus setting up the basic mechanism of a cytotoxic pathway defect characteristic of HLH.<sup>108,112,114</sup>

Clonality studies have shown that a significant number of patients with EBV-associated HLH have a clonal proliferation of T cells, particularly patients with recurrent disease.<sup>115,116</sup> The clonal expansion is also indicated by the presence of homogeneous viral terminal repetitive sequences in both EBV-associated HLH<sup>108,117</sup> and EBV-positive T-cell lymphoma.<sup>118</sup> These findings shared by both T-cell lymphomas and EBV-associated HLH are intriguing given the strong association between the 2 diseases.

EBV infection is also the commonly implicated trigger in genetic HLH. In particular, the pathogenesis of EBV-associated HLH is similar to that of XLP, and EBV infection can easily tip a compensated XLP immune system into HLH by further compromising an impaired pathway. In XLP, mutations in the *SAP/SH2D1A* gene lead to abnormal levels of SAP protein.<sup>94,119-121</sup> Normally, the SAP protein acts as a negative regulator of the SLAM/ERK signal pathway for T-cell activation to secrete cytokines such as IFN- $\gamma$  and TNF- $\alpha$ .<sup>120,122,123</sup> EBV affects infected T cells by inhibiting *SAP/SH2D1A* gene expression through the action of EBV latent membrane protein 1 (LMP1), thus resulting in an enhanced cytokine secretion.<sup>118,124</sup> When coupled with an underlying mutation of *SAP*, EBV infection of XLP T cells would further abrogate negative regulation of cytokine production. In addition to the role of LMP1, EBV also causes immortalization of infected T cells by blocking apoptotic signaling through TNF- $\alpha$ /TNF receptor 1 in the infected B and T cells via the activation of the nuclear factor- $\kappa$ B signal pathway. Thus, the persistent effect of EBV predisposes these patients to have recurrent episodes of HLH.<sup>68</sup>

### Malignancy-Associated HLH

Malignant neoplasms are commonly seen in association with HLH in both children and adults. It may be the presenting clinical picture of an underlying malignancy, or it may develop during the treatment for a malignancy.<sup>102</sup> An incidence of 20% has been reported in the pediatric population. A concomitant triggering infection is common and contributes to mask the underlying malignancy.<sup>102</sup>

Hematologic malignant neoplasms account for the majority of cases, although solid tumors such as prostate, lung, and hepatocellular carcinoma have also been described.<sup>125-127</sup> Mediastinal neoplasms such as germ cell tumor and thymomas

are known associations.<sup>102</sup> Among the hematologic neoplasms, peripheral NK/T-cell lymphomas, anaplastic large-cell lymphoma, and acute lymphocytic leukemias are often implicated.<sup>31,102</sup> Hodgkin lymphoma, multiple myeloma, and acute erythroid leukemia have also been reported.<sup>102,128,129</sup> HLH is rarely seen in patients with non-Hodgkin B-cell lymphomas.<sup>2</sup>

Given the current understanding of the pathogenesis of other types of HLH, a possible mechanism of malignancy-associated HLH may be the impairment of the cytotoxic pathway by the neoplasm through neoplastic changes in the cytotoxic cell itself or through malignancy-associated immune dysregulation. The strong association with NK/T-cell lymphomas and other EBV-related malignant neoplasms points to a possible common mechanism shared by cases of nonmalignant EBV-associated HLH.

### Macrophage Activation Syndrome

MAS is the name of HLH that arises as a complication of autoimmune diseases. The estimated prevalence ranges from 7% to 13% of children with soJIA or Still disease.<sup>19</sup> Other autoimmune diseases have also been reported in association with HLH, including Kawasaki disease, systemic lupus erythematosus, and seronegative spondyloarthropathies in adults.<sup>2</sup>

MAS was first described in association with a pediatric rheumatic disease in 1985, although first descriptions may have been as early as the mid-1970s.<sup>19</sup> Although these patients may exhibit many of the clinical features of HLH, severe coagulopathy and cardiac impairment have been reported as common manifestations.<sup>2</sup>

As mentioned previously, because of the overlap of clinical and laboratory findings between HLH and the rheumatologic process, modified diagnostic criteria for HLH must be applied in the case of MAS, based on a change from baseline laboratory values.<sup>47</sup> For example, soJIA is often associated with anemia, hyperferritinemia,<sup>130</sup> and leukocytosis,<sup>131</sup> even in the absence of MAS, requiring a high index of suspicion to make a diagnosis of MAS.<sup>19</sup> Patients with soJIA-associated MAS typically have lower levels of ferritin than in bona fide HLH, albeit still elevated above normal.<sup>132</sup> However, patients may be afebrile and cytopenias may be less severe, at least initially.<sup>2</sup>

The mechanism of MAS is presumably the impaired function of NK/T cells, similar to the other types of HLH.<sup>19,133</sup> Patients with MAS have been shown to exhibit decreased expression of perforin or the *SAP* gene, mimicking the defects associated with familial HLH and XLP, respectively.<sup>2</sup>

### Treatment and Prognosis

The therapy of HLH aims to suppress the exaggerated immune response through the use of immunosuppressive agents. The 2004 treatment protocol formulated at the second

international meeting of the Histiocyte Society recommends an 8-week induction therapy with corticosteroids, etoposide, and cyclosporine A as the backbone of HLH treatment.<sup>22</sup> Corticosteroids are used to suppress the hypercytokinemia, cyclosporine A adds the inhibition of T-cell activation, and etoposide further blocks cell division and cell proliferation. Stem cell transplant (SCT) is indicated in selected cases. Treatment with SCT improves 3-year survival from nearly 0% to 50% in familial cases,<sup>134</sup> with reduced-intensity regimens showing better results.<sup>135</sup> Some cases have been reported to be cured with SCT.<sup>134-136</sup> In cases of infection-associated HLH, malignancy-associated HLH, or MAS, the immediate treatment of the underlying disease is indicated.<sup>2</sup>

The prognosis of genetic HLH without treatment is poor, with a median survival of 1 to 2 months<sup>137</sup> and a less than 10% probability that the patients survive for 3 years.<sup>8</sup> MAS in soJIA has a reported mortality of 8% to 22%.<sup>19</sup> In acquired HLH, there is more variability in severity and outcomes than in genetic HLH,<sup>2</sup> although the prognosis may be worse in malignancy-associated HLH.<sup>78</sup> The overall reported mortality for acquired HLH exceeds 50%.<sup>9,102</sup>

Among all the viruses associated with HLH, EBV carries the worst prognosis, with a reported mortality ranging from 25% to 100%.<sup>102,114</sup> However, the addition of etoposide in the therapy regimen has yielded good results, especially if initiated within the first 4 weeks.<sup>138</sup>

Following a confirmed episode of HLH, it is important to rule out a genetic defect of FHL or primary immunodeficiency syndrome, which are associated with a high risk of recurrence and necessitate SCT for any prospect for a long-term cure. Until the transplant, these individuals should be monitored closely for reactivation, especially in the CNS.<sup>10</sup> However, because of the possibility of as yet undetected mutations or underlying acquired conditions, even patients with a negative genetic workup need to be followed closely for recurrence. In adults, the diagnosis of HLH should prompt investigation for an underlying malignancy, regardless of an associated infectious trigger.<sup>29</sup>

## Conclusion

HLH is an uncommon but likely underdiagnosed disease. The mortality is uniformly high, and a timely diagnosis is imperative. Infections are common triggers in both genetic and acquired HLH. There have been recent advances in understanding the pathogenesis of genetic HLH, for which genetic tests are available and treatment protocols have shown to improve prognosis.<sup>22</sup> With better understanding of the pathogenesis of this disease subtype, newer and more specific testing may become available as well as novel targeted therapies.

However, these advances are largely limited to genetic HLH, and the mechanisms of acquired HLH remain somewhat

of an enigma. Most studies of prevalence and response to treatment in HLH were conducted in the pediatric population, which is known to most commonly carry the genetic form of HLH. Therefore, it is unknown whether the HLH that presents in the adult population with no known genetic defect or immunodeficiency behaves in a similar manner. A recent study in adults ultimately determined that extremely ill patients may present with findings that are indistinguishable from HLH.<sup>139</sup> Additional studies are required to address whether acquired HLH truly exists as its own disease or is simply the final common pathway of an exhausted immune system that is about to collapse. These studies should help direct research aimed at improving diagnostic methods and treatment.

From the <sup>1</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, NY, and <sup>2</sup>Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN.

Address reprint requests to Dr Kim: Dept of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, 1301 Medical Center Dr, 4603A TVC, Nashville, TN; e-mail: [annette.s.kim@vanderbilt.edu](mailto:annette.s.kim@vanderbilt.edu).

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