Diagnostic Challenges of Hemophagocytic Lymphohistiocytosis

Zaher K. Otrock,[1] Naval Daver,[2] Charles S. Eby[1]

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by excessive activation of the immune system, resulting in overproduction of inflammatory cytokines. Patients usually present with high fever, cytopenias, hyperferritinemia, and hepatosplenomegaly, and their disease process ranges from mild to fatal multiorgan failure. HLH is a heterogeneous group of disorders that can be triggered by infections, neoplasms, or autoimmune diseases. The HLH diagnosis can be difficult to confidently confirm in critically ill patients while waiting for pathology or reference laboratory results to return, delaying the diagnosis with significantly worsened outcomes. The current HLH-2004 diagnostic guidelines were originally developed for pediatric cases and were not validated to diagnose secondary HLH, whether in children or adults. In addition, some laboratory findings that are common among HLH patients such as hypoalbuminemia and elevated liver enzymes are not represented in the HLH-2004 guidelines. Even more challenging for clinicians is that many of the diagnostic features of this syndrome are nonspecific. For example, the clinical presentation of HLH can meet the diagnostic criteria of systemic inflammatory response syndrome, viral infections, or neoplastic diseases. It is necessary to revisit the diagnostic criteria for HLH by validating the clinical and laboratory findings in large prospective HLH prospective clinical trials or by establishing registries. This will improve our understanding of HLH, help validate and develop newer, more specific, and more rapidly obtainable diagnostic criteria, and, eventually, result in earlier therapy with more consistent monitoring of the response.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 17, No. S1, S105-10
Keywords: Adult, Criteria, Diagnosis, HLH, Sepsis

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, but potentially fatal, clinical syndrome characterized by excessive activation of the immune system, resulting in overproduction of inflammatory cytokines.[1] Although more common in children, HLH can affect adults of all ages. The estimated annual incidence in children is 1 to 10 per 1 million children in Europe and the United States.[2,3] Patients usually present with high fever, cytopenias, hyperferritinemia, and hepatosplenomegaly, and their disease process ranges from mild to fatal multiorgan failure.[4] The presence of hemophagocytosis in a tissue specimen is a characteristic feature of HLH; however, hemophagocytosis might not be identified in the initial stages of disease and bone marrow or tissue hemophagocytosis is not specific enough to accurately predict HLH.[5,6]

[1]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO
[2]Department of Leukemia, MD Anderson Cancer Center, Houston, TX

Submitted: Jan 23, 2017; Accepted: Feb 28, 2017

Address for correspondence: Charles S. Eby, MD, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110
E-mail contact: eby@wustl.edu

HLH is a heterogeneous group of disorders. In the primary ("familial") form, which occurs mostly in children, the disease is associated with mutations, particularly in the perforin gene.[7] Secondary ("acquired") HLH typically occurs in adults with acquired defects in cytotoxic T lymphocytes and natural killer cell function.[8] HLH can be triggered by underlying infections (especially viral), hematologic malignancies (especially T- and B-cell lymphomas and acute leukemia), or autoimmune triggers. In some cases, an underlying trigger will not be identifiable.

Diagnostic Criteria

The first HLH diagnostic guidelines were published by the Familial Hemophagocytic Lymphohistiocytosis (FHL) Study Group of the Histiocyte Society in 1991.[9] The criteria were proposed based on common clinical and laboratory findings among Swedish children aged < 15 years who had developed FHL.[2] These diagnostic criteria were based on 5 salient features, including fever (duration $\geq$ 7 days with peaks of $\geq 38.5°C$), splenomegaly (> 3 cm below the costal margin); cytopenias affecting ≥ 2 of 3 lineages in the peripheral blood and not caused by hypocellular or dysplastic bone marrow (neutrophils $< 1 \times 10^9$/L, hemoglobin < 9 g/dL, platelet count $< 100 \times 10^9$/L), serum triglycerides ≥ 2.0 mmol/L and/or

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2017.02.017

serum fibrinogen ≤ 150 mg/dL, and hemophagocytosis in the bone marrow, spleen, or lymph nodes.

In 1994, the same group from Sweden proposed the first treatment protocol (HLH-94) for FHL that combined chemotherapy and immunotherapy.[10] This protocol was later coupled with bone marrow transplantation for selected higher risk primary HLH patients, with improved survival in children with FHL.[11] The cumulative experience in treating FHL led to a new treatment protocol, HLH-2004 (etoposide, dexamethasone, cyclosporine, and intrathecal methotrexate), which used the updated and expanded HLH diagnostic criteria.[12] The 5 criteria in the 1991 guidelines remain valid. In addition, 3 additional criteria thought to be central to HLH pathophysiology from improved understanding of the disease process were added: serum ferritin ≥ 500 μg/L, soluble interleukin-2 (sIL-2) receptor-α ≥ 2400 U/mL, and low or absent natural killer (NK) cell activity. Of these 8 criteria, 5 must be fulfilled to confirm an HLH diagnosis. An exception to this is that a molecular diagnosis consistent with HLH is sufficient to confirm the diagnosis of primary HLH, regardless of the findings for the other criteria.[12]

No information is available regarding the clinical utility of the last 2 criteria (ie, sIL-2 receptor and NK cell activity). The HLH diagnostic criteria and requirement for 5 of the 8 to be present to diagnosis FHL appear to have been determined empirically and should be considered more as expert guidelines than as clinically validated and reproducible diagnostic criteria. Moreover, HLH patients frequently manifest additional clinical and laboratory findings other than those presented in the diagnostic guidelines. Also, some of these additional laboratory findings can occur earlier in the disease course, and the assays for these might be more rapidly available in local laboratories. For example, in our review of a large cohort of adult HLH patients, > 80% of patients presented with hypoalbuminemia, elevated liver enzymes, and coagulopathy.[13] Coagulopathy and hypoalbuminemia were also reported by others to be prevalent in HLH patients compared with in control groups.[14] These laboratory findings were not included in the HLH-2004 guidelines.

Problems With the Diagnostic Criteria: Assessment of Parameters

The current HLH diagnostic guidelines were originally developed for pediatric patients with FHL. According to Henter et al,[2] the initial goal was to determine the incidence of FHL in Sweden.[2] Their patient population included children aged < 15 years who had FHL, although "no generally accepted definition of FHL" was used. Most of these children had died by the time of the study, and the investigators had to rely on retrospective clinical and laboratory data and autopsy reports for the histopathologic diagnosis. The study included only 32 children from 1971 to 1986, from whom a combination of commonly recurring clinical, laboratory, and pathologic criteria evolved to become the HLH-91 diagnostic criteria.[9]

These criteria were not originally validated to prospectively diagnose HLH in general and certainly not to diagnose secondary HLH, whether in children or adults. The updated HLH-2004 criteria were an extrapolation of the previous criteria, with the addition of 3 diagnostic guidelines following the HLH-2004 treatment protocol for children with HLH aged < 18 years.[12] In addition, most HLH studies and reviews had focused on pediatric patients, with a relative scarcity of published information available on adult HLH until recently.[13,15-17] The sensitivity, specificity, and accuracy of the laboratory and clinical parameters included in the HLH-2004 diagnostic guidelines have not been evaluated or validated in the context of adult HLH. In these sections, we review the sensitivity and specificity of the clinical, laboratory, and histologic criteria used to assess acutely ill patients for HLH.

Fever

Fever is induced by overproduction of IL-1. It is a very common finding in HLH and is usually high and unremitting. Of the 32 children with data included in the 1991 guidelines proposal, fever was documented in 91% of cases at the initial presentation and in 100% at some point in the disease course in patients diagnosed with HLH.[2] In adults with HLH, fever will be detected in 96% of cases.[18] Although sensitive, fever is not specific to HLH and is one of the most common medical signs in hospitalized patients. It can be caused by many medical conditions, including infections, connective tissue diseases, malignancies, and drugs.[19,20]

Splenomegaly

Splenomegaly is an early marker of HLH, present in 84% of pediatric cases[2] and 69% of adults.[18] It is caused by infiltration of lymphocytes and macrophages and is part of the constellation of lymphohematopoietic organomegaly seen in HLH, which can manifest as hepatomegaly and other adenopathies. Splenic enlargement can be detected by clinical examination, as well as using more sensitive and quantitative imaging studies such as ultrasonography and computed tomography. However, the spleen can become enlarged for many reasons other than HLH, including immune response hypertrophy and immune infiltration, such as with infection; red blood cell destruction hypertrophy, such as hemoglobinopathies; congestion from portal hypertension; infiltration from hematopoietic progenitors in myeloproliferative neoplasms; tuberculosis; connective tissue diseases; sarcoidosis; and neoplastic involvement, such as in lymphomas, myelodysplastic syndromes, and acute leukemias.[21,22] The causes of splenomegaly in retrospective studies in the United States were, in decreasing order of frequency, hematologic diseases, hepatic diseases, infections, congestive or inflammatory diseases, and primary splenic diseases.[23,24]

Another caveat to consider when diagnosing HLH is that a patient might have pre-existing splenomegaly due to a primary disease (acute infection or lymphoma) and, subsequently, might develop signs and symptoms concerning for HLH. Splenomegaly in that setting was a manifestation of the primary disease, which might have triggered HLH and should be considered in the diagnosis of HLH. The current HLH criteria do not delineate a difference between these 2 settings.

Cytopenia

Anemia and thrombocytopenia are more prevalent than neutropenia in HLH patients, and they usually develop early in the disease course.[18,25] Anemia and thrombocytopenia will be identified in about 67% and 78% of adult HLH cases, respectively, at any