Hemophagocytic lymphohistiocytosis (HLH) was first described in 1939 by Scott and Robb-Smith. At that time, it was known as histiocytic medullary reticulosis (HMR), and was originally thought to be a form of atypical Hodgkin’s disease. Scott and Robb-Smith described four cases of adult patients who exhibited similar clinical courses of fever, lymphadenopathy, splenomegaly, and hepatomegaly, and later in their disease courses they developed jaundice, purpura, anemia, and leukopenia. Postmortem examination of these patients revealed histiocytes phagocytosing erythrocytes. In addition, Scott and Robb-Smith examined six other case reports of patients with similar findings; these patients were between the ages of 26 to 69 years, and both genders were affected. Thirteen years later, in 1952, Farquhar and Claireaux described two siblings with HMR who both presented in infancy with rapidly progressing organ failure resulting in fatality.

In this review, the etiologies of HLH are explored, as well as the resulting pathogenesis, clinical manifestations, and subsequent diagnosis and treatment.

ETIOLOGY AND EPIDEMIOLOGY
HLH can be broadly categorized into primary and secondary forms, with respective subtypes. Primary HLH, also known as familial HLH (F-HLH), has autosomal recessive inheritance and incomplete penetrance. A number of genetic mutations have been identified that result in F-HLH, although some genetic lesions are still unknown (Table 1). In addition, certain immunodeficiency syndromes and hereditary disorders are closely linked to HLH, including Chediak-Higashi syndrome and Griscelli syndrome-2, as well as X-linked lymphoproliferative syndromes types 1 (XLP1) and 2 (XLP2), Hermansky-Pudlak syndrome type II, and Wiskott-Aldrich Syndrome.

F-HLH is most commonly diagnosed during the first year of life. The incidence in children younger than age 1 year is 1.1 per 100,000, with a median age of onset of 5.1 months. However, being older than age 1 year does not exclude the diagnosis of F-HLH. For example, there are cases of late-onset F-HLH among teenagers with defects in PRF1. The frequency of HLH subtypes differs between populations. Mutations of PRF1, UNC13D, and STX11 were identified in 80% of patients with HLH who were of Turkish descent, as well as in 30% of German patients. In patients with F-HLH in North America, the PRF1 mutation is the most common, followed closely by UNC13D and STXBP2.

Secondary, or acquired, HLH is usually associated with infectious, oncologic, rheumatologic, or other underlying causes. The most common infection associated with acquired HLH is Epstein-Barr virus (EBV). In Japan, 40% of all
patients with HLH have an associated EBV infection. Curiously, when EBV is associated with HLH, the predominantly infected cells are T cells or B and T cells equally, as opposed to primarily B cells. Respiratory syncytial virus, rotavirus, and adenovirus infections are also implicated causes of secondary HLH. If HLH develops in the presence of malignancy, it is known as malignancy-associated hemophagocytic syndrome (MAHS). In one study of 52 children with MAHS, 60% of cases were associated with non-Hodgkin’s lymphoma (primarily T-cell type), followed by acute leukemias, myelodysplastic syndromes, Langerhans cell histiocytosis, and histiocytic sarcoma. When HLH is observed in the context of rheumatological diseases, secondary HLH is commonly known as macrophage activation syndrome (MAS), and is most often found as a complication of systemic juvenile idiopathic arthritis (sJIA). MAS has been found to occur in at least 7% to 13% of sJIA patients. However, it can also be associated with systemic lupus erythematosus, mixed connective tissue disease, and other rheumatic diseases. HLH has also been observed in the setting of immune suppression after transplant, including kidney, liver, and hematopoietic stem cell transplants. Cases of HLH have occurred after prolonged periods of total parenteral nutrition that include soluble lipids, in which case it is known as fat overload syndrome. Moreover, a case of HLH was reported in a neonate in association with mitochondrial respiratory chain disorder.

**PATHOPHYSIOLOGY**

Much of what is known about the pathophysiology of HLH has been discovered in the context of F-HLH. The exact mechanisms underlying the pathophysiology of secondary HLH are not yet completely elucidated and are likely multifactorial. Altered function of natural killer (NK) cells and cytotoxic T lymphocytes (CTL) with accompanying dysregulated response to antigen presenting cells (APCs), are common to the pathogenesis of the varied HLH subtypes. In patients with an intact immune system, NK cells and CTLs kill infected cells and APCs via a perforin-dependent pathway. The former possess secretory lysosomes composed of perforin and granzymes. Jenkins et al. demonstrated in their mouse and human cell models that when an NK cell recognizes an APC, it becomes activated, forming an immunological synapse (IS) between the two cells. Perforin and granzymes are transported along this synapse toward the APC. The IS is also responsible for releasing inflammatory cytokines and chemokines, which further facilitate the immune response. Working together with perforin, granzymes facilitate apoptosis of the APC or infected cell. The dying cell then releases a caspase-dependent enzymatic cascade which destroys the IS, and thereby downregulates the immune response.

Patients with F-HLH have defects in this perforin-dependent and granzyme-dependent pathway, resulting in the inability of the NK cells or CTLs to down-regulate the immune response. For example, patients with F-HLH type 2 have mutations affecting perforin. Additionally, those with F-HLH types 3, 4, and 5 harbor mutations affecting secretory lysosome processing, transporting, docking, and exocytosis. It has been suggested that heterozygous variants in genes related to this pathway contribute to the development of secondary HLH. For example, in MAS, Kaufman et al. demonstrated that of 14 MAS cases associated with sJIA, 5 were heterozygous for at least one mutation in the known genes related to F-HLH. However, in other forms of secondary HLH, the initial pathogenesis remains to be elucidated. In EBV-HLH, it is still unknown if susceptibility to developing secondary HLH is caused by genetic predisposition or EBV-induced immunological dysregulation, although infection of T cells by
the virus is associated with development of HLH. This could be secondary to the observation by Lay et al. that infection of T cells by EBV increases expression of tumor necrosis factor-alpha and interferon-gamma, leading to increased macrophage activation.

Despite the variations in the predispositions or inciting factors of HLH, after NK cells, lymphocytes, and macrophages become increasingly activated and they secrete high levels of cytokines and chemokines, which results in the clinical and laboratory findings.

Interleukins and tumor necrosis factor-alpha generate fever. Cytokines suppress lipoprotein lipase, leading to hypertriglyceridemia. Macrophages secrete ferritin, leading to increased plasminogen activator, resulting in hyperfibrinolysis and hypofibrinogenemia.

SIGN AND SYMPTOMS

The signs and symptoms of HLH can be nonspecific, ranging from persistent fevers to sepsis physiology, so the index of suspicion must be kept high to make the diagnosis. The main symptoms associated with HLH include prolonged high fever, hepatosplenomegaly, and cytopenias. Other clinical findings include hepatitis, neurological symptoms (such as seizures, meningismus, decreased level of consciousness), rash, pulmonary dysfunction, and lymphadenopathy. Central nervous system (CNS) involvement should also be a consideration when diagnosing HLH. Changes in mental status, especially during the initial stages of therapy, should be immediately addressed. During this time, there is a risk of posterior reversible encephalopathy syndrome, which is characterized by headache, confusion, seizures, and visual loss, and associated with cyclosporine use and hypertension.

Laboratory findings exhibit a myriad of abnormalities, including cytopenias (affecting at least two cell lineages in the peripheral blood), hyperferritinaemia, hypertriglyceridemia (especially in secondary HLH), hypofibrinogenemia, elevated serum transaminases, hyperbilirubinemia, abnormal coagulation studies, hyponatremia, and hypoproteinemia.

Ferritin levels >500 ng/mL should raise the suspicion for HLH; and a ferritin level >10,000 ng/mL was shown to be 90% sensitive and 96% specific for HLH.

DIAGNOSIS

Diagnosis of HLH can be established by either molecular means or by meeting clinical and laboratory criteria. A combination of high index of suspicion, clinical presentation, and basic laboratory findings could point the clinician toward a diagnosis of HLH, promoting prompt referral for quick treatment.

Primary HLH can be diagnosed by clinical findings, although genetic testing alone is sufficient. However, it should be noted that the latter is not an expedient process, and one should focus more on clinical findings when immediate diagnosis is required. Genetic testing is also commonly used for siblings and to confirm a suspected diagnosis; it is important to distinguish HLH from sepsis, as estimated survival is <10% when left untreated.

It is important to note that in practice, patients with secondary HLH due to a known rheumatologic condition (usually MAS) may not meet full criteria for HLH. In light of the high morbidity and mortality associated with MAS, rheumatologists may begin empiric treatment for suspected MAS in patients with a known predisposing condition (especially systemic onset JIA), even in the absence of a definitive diagnosis.

Hemophagocytosis can also be found in bone marrow, spleen, and lymph nodes, as well as in the cerebrospinal fluid, and prevalence can range from 25% to 100%. However, this finding is nonspecific and can also be observed in

| TABLE 2. Diagnostic Guidelines for HLH |
| Molecular diagnosis or |
| The patient fulfills at least 5 of the following 8 diagnostic criteria: |
| 1. Fever |
| 2. Splenomegaly |
| 3. Cytopenias (affecting ≥2 of 3 cell lineages) |
| i. Hemoglobin level <9 g/dL |
| (≤10 g/dL in infants younger than age 4 weeks) |
| ii. Platelets <100 × 10^9/mL |
| iii. Neutrophils <1 × 10^9/mL |
| 4. Hypertriglyceridemia and/or hypofibrinogenemia |
| i. Fasting triglyceride level of ≥2 mmol/L (≥265 mg/dL) |
| ii. Fibrinogen level of ≤1.5 g/L |
| 5. Hemophagocytosis in bone marrow or spleen or lymph nodes, and no evidence of malignancy |
| 6. Low or absent natural killer-cell activity |
| 7. Ferritin level of ≥500 mcg/L |
| 8. Soluble CD25 level of ≥2,400 U/mL |

Abbreviation: HLH, hemophagocytic lymphohistiocytosis. Data from Henter et al.22
In addition to this regimen, other therapies may be considered that are directed at the underlying disease causing HLH. When faced with EBV-associated HLH, rituximab may be helpful; intravenous immunoglobulin can also be appropriate for most viral associations. Anakinra, an interleukin-1 inhibitor, was also found to be associated with decreases in C-reactive protein and ferritin in a small cohort of pediatric intensive care patients.

It is also useful in patients diagnosed with MAS in association with sJIA. Among children with MAS secondary to systemic onset JIA, careful and complete treatment of the underlying rheumatologic disease is of paramount importance. This treatment typically encompasses biologic interleukin-1 or interleukin-6 antagonists, such as anakinra or tocilizumab, in combination with steroids and cyclosporine to specifically treat MAS. In pediatric and adult patients with refractory HLH, alemtuzumab, an antibody directed against CD52 expressed by T cells and histiocytes, was found to be helpful in a single-center study.

SUMMARY

In conclusion, although HLH is a life-threatening medical condition, the signs and symptoms, including prolonged fever and hepatosplenomegaly, can be nonspecific. The index of suspicion must be kept high, especially in the context of certain clinical disorders, such as rheumatologic, infectious, and hematologic diagnoses and immunosuppressed states. The treatment is multipronged and aimed at reducing the hyperinflammatory response while simultaneously targeting the underlying pathologic mechanism. Early diagnosis with timely management is imperative as the survival rate is dismal if left untreated. New therapies are warranted, as almost 50% of patients succumb to HLH despite optimal treatment.

REFERENCES


