World Journal of Advanced Engineering Technology and Sciences
eISSN: 2582-8266
Cross Ref DOI: 10.30574/wjaets
Journal homepage: https://wjaets.com/

(REVIEW ARTICLE)

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Infection-associated hemophagocytic lymphohistiocytosis: A comprehensive review

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World Journal of Advanced Engineering Technology and Sciences, 2025, 16(03), 139–143

Publication history: Received on 29 July 2025; revised on 04 September 2025; accepted on 06 September 2025

Article DOI: https://doi.org/10.30574/wjaets.2025.16.3.1336

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome characterized by uncontrolled immune activation, excessive cytokine release, and phagocytosis of hematopoietic cells by activated histiocytes. HLH is classified as primary (genetic) or secondary (acquired), with infections being the most common trigger of secondary forms. Viral pathogens, particularly Epstein–Barr virus and other herpesviruses, are most frequently implicated, while bacterial (e.g., *Mycobacterium tuberculosis*, *Staphylococcus aureus*, multidrug-resistant *Acinetobacter*), parasitic (e.g., *Leishmania donovani*, *Plasmodium* spp.), and fungal (e.g., *Candida*, *Cryptococcus*, *Histoplasma*, *Aspergillus*) infections are also important contributors. Diagnosis is challenging due to nonspecific features such as prolonged fever, cytopenias, hepatosplenomegaly, and hyperferritinemia, with laboratory markers including elevated soluble IL-2 receptor, ferritin, and soluble CD163 providing supportive evidence. Bone marrow examination demonstrating hemophagocytosis further aids diagnosis. Timely recognition and intervention are essential, as untreated HLH carries uniformly high mortality. Management involves treating the underlying infection and, in severe or refractory cases, combining antimicrobial therapy with immunosuppressive or immunomodulatory agents. This review highlights the spectrum of infection-associated HLH, and its clinical presentation along with diagnostic approach.

Keyboard: Hemophagocytic lymphohistiocytosis; Infection; Macrophages; Histopathological presentation; Diagnosis

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is a rare syndrome characterized by reactive, systemic proliferation of benign histiocytes throughout the reticuloendothelial system. HLH results from defect in inflammatory signals that result in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway wherein activities of lymphocytes and histiocytes are augmented, leading to phagocytosis of hematopoietic cells. HLH can be either primary (genetic), or secondary (acquired HLH) associated with infectious agents, autoimmune diseases, and malignancies. Secondary HLH may develop as a result of strong immunological activation of the immune system, which may be caused by a severe infection. Among the infections, viral pathogens reported to be associated with HLH include Epstein-Barr virus, cytomegalovirus, parvovirus, herpes simplex virus, varicella-zoster virus, measles virus, human herpes virus-8, and human immunodeficiency virus, alone or in combination. HLH may also concur with various bacterial infections, parasite infections, and fungal infections as well as malignancies. It is important to realize that early therapeutic interventions are required when strong clinical suspicion of infection-associated HLH is present to prevent irreversible end organ damage. [1]

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2. Diagnostic criteria

Clinical presentation: The most typical findings of HLH are fever, malaise, hepatosplenomegaly, jaundice, generalized lymphadenopathy, and cytopenias. Neurological symptomsof HLH may be associated with a spinal fluid hyperproteinemia and a moderate pleocytosiswhich may include seizures, meningitis, encephalopathy, ataxia, hemiplegia, cranial nerve palsies, mental status changes, or simply irritability. Other, less common, initial clinical findings include skin rash, maculopapular nodular eruptions and edema. 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. [2]

Laboratory presentation: The symptoms of HLH as "characteristic but non- Specific". Due to the lack of specificity, initial laboratory testing can only provide a guide or support a diagnosis (not establish one). Serum chemistry findings may suggest hemolysis, with hyperbilirubinemia and elevation of transaminases and lactate dehydrogenase. High triglycerides, increased ferritin and decreased fibrinogen are all indicative of an HLH diagnosis providing the physical findings correlate. Other Typical findings in HLH are low natural killer (NK) cell activity and high levels of the alpha chain of the soluble interleukin-2 receptor (sIL-2R, also named sCD25) in serum and CSF. Soluble IL-2R (together with an elevated level of ferritin) is a marker of generalized inflammation, but very high levels of sIL-2R are almost never seen outside of HLH. Suppression of the function of NK cells as well as Elevated sCD25/sIL-2R will be taken as criteria. Another important marker of HLH is soluble CD163 (sCD163). The macrophage hemoglobin scavenger receptor CD163 is restricted in its expression exclusively to cells of the monocyte– macrophage lineage. The extracellular part of the protein is shed into plasma (sCD163), because of proteolytic cleavage upon macrophage activation. Thus, sCD163 is a reliable clinical marker of disorders associated with overwhelming macrophage activity. Because sIL-2R and sCD163 are soluble molecules shed from the surfaces of activated T cells and macrophages, respectively, their levels are likely to increase in the serum regardless of the tissue localization of these cells. [3]

Histopathological presentation: Histopathologic findings of HLH typically include a nonmalignant, mixed lymphohistiocytic accumulation in the reticuloendothelial system. The histiocytes appear activated, and hemophagocytosis. The hemophagocytosis mostly affects erythrocytes but occasionally also platelets and leukocytes. 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. [4]

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. In the liver, there is Kupffer cell hyperplasia, as well as a portal and sinusoidal cytotoxic T-cell infiltrate expressing CD3, CD8, and granzyme B with variable hemophagocytic histiocytes.

3. Diagnosis

A diagnosis that takes into account all the underlying diseases associated with HLH would not be practical, and formal guidelines for evaluating patients with suspected infection associated HLH have not been established.

Nevertheless, all patients meeting the criteria for HLH should undergo initial diagnostic tests that include routine cultures of blood and urine and chest radiography to screen for such infections as miliary tuberculosis. Attempts should be made to screen for infection with EBV, CMV, and parvovirus B19, either through serologic testing or polymerase chain reaction, in-situ hybridization, or (in the case of CMV) immunofluorescent antigen testing. Serologic testing for HIV and human herpesvirus-6 infection should also be considered, and throat and rectal swabs should be taken for viral culture. Because of the association between HLH and fungal infections, lysis-centrifugation blood cultures and fungal antigen testing should be considered for all patients with HLH. Even if an infection known to be associated with HLH has been confirmed, cell marker and T-cell receptor gene rearrangement tests should be performed on bone marrow or other tissue specimens to determine whether an underlying T-cell lymphoma is present. Extensive testing for underlying infecting organisms should be guided by epidemiologic data and the patient's medical history. For example, in a patient with underlying HIV infection, HLH has been associated with infections that commonly affect patients with AIDS (e.g., pneumococcal disease, pneumocystosis, histoplasmosis, and infection with *Penicillium marneffei*) and with T-cell lymphoma. Patients with a history of travel or animal exposure should be screened for such infections as leishmaniasis, brucellosis, rickettsioses, and malaria. In bone marrow transplant patients, attempts should be made to isolate adenovirus from urine, nasopharyngeal and rectal swabs, and tissue specimens. Because so many immunologic, neoplastic, genetic, and infectious disorders may be associated with HLH, clinicians should work closely with pathologists and microbiologists to clearly define precipitating or underlying illnesses. [5]

4. Pathophysiology of infection-associated HLH

The HLH has been associated with a variety of viral, bacterial, fungal, parasitic infections and vaccination. Disseminated infection with an unusual organism in a patient with HLH may represent secondary infection in an immunocompromised patient; however, the resolution of the syndrome following treatment of infection suggests that HLH is secondary to underlying infection. [6]

Table 1 Infections associated with HLH

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	*Staphylococcus aureus*, *Campylobacter* spp, *Fusobacterium* spp, *Mycoplasma* spp, *Chlamydia* spp, *Legionella* spp, *Salmonella typhi*, *Rickettsia* spp, *Brucella* spp, *Ehrlichia* spp, *Borrelia burgdorferi*, *Mycobacterium tuberculosis*
Fungal	*Candida* spp, *Cryptococcus* spp, *Pneumocystis* spp, *Histoplasma* spp, *Aspergillus* spp, *Fusarium* spp
Parasitic	*Plasmodium falciparum*, *Plasmodium vivax*, *Toxoplasma* spp, *Babesia* spp, *Strongyloides* spp, *Leishmania* spp

4.1. Virus-associated hemophagocytic lymph histiocytosis

Viral infections are well-recognized triggers of hemophagocytic lymphohistiocytosis (HLH), with members of the herpesvirus family—particularly cytomegalovirus and Epstein–Barr virus (EBV)—most frequently implicated, EBV being the leading cause of infection-associated HLH. Other viruses associated with HLH include hepatitis viruses, adenovirus, measles, mumps, rubella, dengue, hantavirus, parvovirus B19, influenza, and enteroviruses, while HLH may occasionally represent the first clinical manifestation of human immunodeficiency virus (HIV) infection; notably, hemophagocytosis has been reported in up to 20% of bone marrow biopsies from HIV patients prior to antiretroviral therapy, although fulfillment of diagnostic HLH criteria was uncertain. The underlying mechanism is thought to involve viral interference with cytotoxic T-cell function, which compromises immune regulation and promotes hyperinflammatory responses. EBV-associated HLH is a particularly aggressive form, usually arising during primary EBV infection, but also seen in viral reactivation and even in immunocompetent children or young adults with infectious mononucleosis. In primary infection, EBV predominantly targets CD21+ B cells, though T-cell infection occurs; in HLH, infected CD8+ cytotoxic T cells predominate, and their impaired effector function produces the cytotoxic pathway defect central to disease pathogenesis. Clonality studies demonstrate clonal proliferation of EBV-infected T cells in many patients, especially those with recurrent HLH, and the detection of homogeneous viral terminal repeat sequences in EBV-associated HLH and EBV-positive T-cell lymphoma reveals a striking pathogenic overlap between the two conditions. EBV is also the most frequent trigger of genetic HLH, notably in X-linked lymphoproliferative disease (XLP), where mutations in the SAP/SH2D1A gene reduce SAP protein expression, thereby impairing regulation of SLAM/ERK signaling during T-cell activation and causing uncontrolled cytokine secretion such as IFN-γ and TNF-α. EBV latent membrane protein 1 (LMP1) exacerbates this defect by suppressing SAP expression, while simultaneously activating the NF-κB pathway and inhibiting apoptosis via TNF-α/TNF receptor 1 signaling in infected T and B cells, thereby promoting cell survival and persistent immune activation. The combined effects of impaired cytotoxicity, dysregulated cytokine release, and EBV-driven cellular immortalization explain not only the uncontrolled hyperinflammatory state characteristic of EBV-associated HLH but also the tendency toward recurrent episodes and increased susceptibility to EBV-positive lymphoproliferative malignancies. [7]

4.2. Bacteria-associated hemophagocytic lymphohistiocytosis

Bacteria-associated hemophagocytic lymphohistiocytosis (HLH) has been increasingly recognized, though its incidence varies across studies. A total of 36 cases of tuberculosis-associated HLH have been reported and reviewed, with 60% of patients being male and the median age at presentation being 44 years. Approximately half of these patients had underlying comorbidities, and fever was a universal feature, while organomegaly occurred in about 75% of cases. Notably, 83% of patients demonstrated extrapulmonary tuberculosis, and pancytopenia—particularly thrombocytopenia—was observed in nearly 90%. Of the 36 cases, 29 patients received treatment: nine with antituberculous drugs alone and 20 with a combination of antituberculous therapy and immunomodulatory agents, mainly corticosteroids, though two patients underwent splenectomy and two underwent plasmapheresis. Outcomes were variable, with 12 of 20 patients treated with combination therapy and 7 of 9 patients receiving antituberculous

drugs alone surviving, while all untreated patients succumbed, highlighting the importance of timely therapeutic intervention. HLH has also been reported following intravesical Bacillus Calmette–Guérin (BCG) therapy and even BCG vaccination, further linking mycobacterial antigens to disease pathogenesis.

Beyond mycobacteria, a range of bacterial pathogens have been associated with HLH, including *Staphylococcus aureus*, Gram-negative organisms, and atypical bacteria such as *Campylobacter*, *Fusobacterium*, *Mycoplasma*, *Chlamydia*, *Legionella*, *Salmonella typhi*, *Rickettsia*, *Brucella*, *Ehrlichia*, and *Borrelia burgdorferi* (Lyme disease). Prognosis in bacterial-associated HLH varies: in some cases, it appears more favorable than virus-associated HLH, but when linked to sepsis, outcomes can be rapidly fatal without aggressive antimicrobial therapy and supportive care. Among Gram-negative bacteria, *Acinetobacter baumannii* has emerged as an important nosocomial pathogen due to its ability to survive in a wide range of environmental conditions, its non-fastidious growth, and its intrinsic resistance to many antibiotics. It is now a major cause of bloodstream infections, ventilator-associated pneumonia, urinary tract infections, and wound infections in hospital settings. The emergence of multidrug-resistant *A. baumannii* (MDRAB), first described in Taiwan in 1998, has since become a global health concern. MDRAB strains exhibit resistance to nearly all classes of antibiotics, including carbapenems, cephalosporins, aztreonam, aminoglycosides, and fluoroquinolones, making treatment extremely challenging. Combination regimens such as meropenem with sulbactam have shown partial efficacy, but outcomes remain suboptimal, especially in resource-limited countries where lapses in infection control—such as delayed removal of urinary catheters—contribute to nosocomial spread.

Pathogenetically, HLH represents a non-neoplastic disorder of the mononuclear phagocyte system, characterized by uncontrolled activation of T cells and macrophages, leading to a hyperinflammatory state with excessive cytokine release. First described by Scott and Robb-Smith in 1939 as "histiocytic medullary reticulosis," HLH was initially thought to be a malignant histiocytic disorder until familial forms were later identified, termed familial hemophagocytic lymphohistiocytosis (FHLH). Infections remain the most common triggers of secondary HLH, with viral agents such as EBV, CMV, parvovirus B19, herpes simplex virus, varicella-zoster virus, human herpesvirus-8, and HIV being most prominent; indeed, HLH may occasionally emerge shortly after the initiation of antiretroviral therapy in HIV-infected patients. Other infectious causes include *Brucella*, Gram-negative bacteria, *Rickettsia*, *Leptospira*, *Mycobacterium tuberculosis*, *Plasmodium* spp. (malaria), *Leishmania*, and fungal pathogens. Apart from infections, HLH may arise in the context of autoimmune diseases (e.g., systemic lupus erythematosus, juvenile idiopathic arthritis) or malignancies, particularly T-cell lymphomas. Histopathologically, bone marrow and other involved tissues demonstrate histiocytic proliferation with conspicuous hemophagocytosis. Treatment strategies depend on etiology: familial HLH often requires allogeneic bone marrow transplantation, EBV-associated HLH demands early cytotoxic chemotherapy and/or immunotherapy due to its aggressive course and resemblance to T-cell lymphoma, while non-EBV- or bacteria-associated HLH may resolve with prompt and adequate treatment of the underlying infection.[8]

4.3. Parasite and Fungi associated hemophagocytic lymphohistiocytosis

Parasitic and fungal infections are increasingly recognized as important triggers of hemophagocytic lymphohistiocytosis (HLH). *Leishmania donovani* is one of the most frequent non-viral agents implicated, particularly in children, and can either directly cause HLH or mimic the syndrome by presenting with organomegaly and cytopenias; in such cases, bone marrow aspiration is essential for accurate diagnosis. Leishmaniasis-associated HLH generally responds well to treatment with amphotericin B, leading to cure. Malaria, caused by *Plasmodium falciparum* and *Plasmodium vivax*, has also been reported in association with HLH, along with parasitic infections such as toxoplasmosis, babesiosis, and strongyloidiasis. In patients returning from endemic regions, a thorough travel history is therefore critical to identifying potential infectious triggers. Fungal infections linked to HLH include *Candida*, *Cryptococcus*, *Pneumocystis*, *Histoplasma*, *Aspergillus*, and *Fusarium* species. These infections are more frequently observed in immunocompromised hosts, including patients with HIV, lymphoma, prolonged corticosteroid use, or those who have undergone organ or stem cell transplantation. [9,10]

5. Conclusion

Infection-associated HLH is a life-threatening hyperinflammatory disorder most often triggered by viral, bacterial, parasitic, or fungal infections. Early recognition and prompt treatment of the underlying infection, with immunosuppressive therapy in severe cases, are crucial for survival. Improved diagnostics and clinician awareness remain key to reducing mortality.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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