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CLINICAL UP-DATE

# Hemophagocytic lymphohistiocytosis associated with viral infections: Diagnostic challenge and therapeutic dilemma☆

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**KEYWORDS**
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**Abstract** Hemophagocytic lymphohistiocytosis is a frequently fatal clinicopathologic syndrome in which an uncontrolled and ineffective immune response leads to severe hyperinflammation. It may occur as either a familial disorder or a sporadic condition in association with a variety of triggers: infections, malignancies, autoimmune diseases, and acquired immune deficiencies. However, the most consistent association is with viral infections, especially Epstein–Barr virus. The main clinical features are fever, liver dysfunction, coagulation abnormalities and pancytopenia. Early diagnosis and treatment are important to reducing mortality, but the diagnosis is difficult because of the rarity of the syndrome and the lack of specificity of the clinical findings. Treatment should be directed toward treating the underlying disease and to suppressing the exaggerated inflammatory response through the use of immunosuppressive agents.


**PALABRAS CLAVE**
Linfohistiocitosis hemofagocítica;
Perforina;
Hemofagocitosis,
Infecciones virales

## Linfohistiocitosis hemofagocítica asociada a infecciones virales: reto diagnóstico y dilema terapéutico

**Resumen** La linfohistiocitosis hemofagocítica es un síndrome clinicopatológico de evolución potencialmente fatal, en el que una respuesta inmune no controlada e ineficaz conduce a hiperinflamación. Puede aparecer como una enfermedad familiar o esporádica, asociado a diferentes factores desencadenantes: infecciones, neoplasias, enfermedades autoinmunes o inmunodeficiencias adquiridas, pero la asociación más consistente es con infecciones virales,

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especialmente el virus de Epstein–Barr. Las principales características clínicas son fiebre, disfunción hepática, coagulopatía y pancitopenia. El diagnóstico es difícil debido a la rareza de este síndrome y a la falta de especificidad de los hallazgos clínicos, sin embargo, un diagnóstico y tratamiento precoces son importantes para disminuir la mortalidad. El tratamiento debe ser dirigido al control de la enfermedad subyacente y a suprimir la respuesta inflamatoria exagerada mediante el uso de inmunosupresores.


A previously healthy 16-year-old male with no toxic habits was admitted for sore throat, fever and cervical adenopathies of approximately 6 days of evolution. The Paul-Bunnell test and the Epstein–Barr virus (EBV) immunoglobulin M test were positive. The results of the serology for the human immunodeficiency virus (HIV) and the hepatitis virus were negative. During the stay in the ward, the mononucleosis symptoms presented by the patient on admission progressively worsened. These included hepatosplenomegaly, progressive pancytopenia and a progressive increase in transaminase and bilirubin levels. After blood cultures were taken and other infectious foci were ruled out, treatment was started with glucocorticoids and broad-spectrum antibiotics. Despite this, the patient maintained a continuous high fever and, on the seventh day of hospitalization, experienced renal and respiratory failure and delirium. The blood and urine cultures were negative and the cerebrospinal fluid was normal.

How should this patient be evaluated and treated?

## The clinical problem

This is a patient with an exceptional disease: fulminating hemophagocytic lymphohistiocytosis (HLH), trigged by a common disease, infectious mononucleosis. HLH is a difficult to diagnose disease due to its low incidence and nonspecific clinical manifestations. It progresses as a severe systemic inflammatory syndrome, with a large clinical overlap with sepsis; however, the prognosis and treatment of the 2 diseases are very different. HLH has a poorer prognosis and requires treatment with chemotherapy and, in some cases, bone marrow transplantation, while severe sepsis has a better prognosis and is treated with antimicrobials. The early diagnosis and treatment of HLH can dramatically improve the prognosis; however, the decision to administer immunosuppressants to a patient who has an infectious disease, such as the one we just presented, requires clinical expertise and prudence.

## Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis is a clinical-pathological syndrome in which an uncontrolled and ineffective immune response leads to hyperinflammation. This condition was first described by Scott and Robb-Smith in 1939, who reported 4 cases of a disease that manifested with fever, adenopathies, organomegaly, pancytopenia and histiocytic infiltration of the bone marrow, with an invariably fatal outcome, a condition they called histiocytic medullary reticulosis.[1] Over the last decade, interest in this disease has intensified enormously due to the availability of tools that have enabled significant progress in understanding the molecular mechanisms of HLH. The annual number of citations in PubMed regarding HLH has multiplied by a factor of more than 10.

Historically, 2 phenotypes of HLH have been distinguished: primary and secondary (Table 1).[2]

*Primary HLH* (also called genetic or familial). This phenotype has a high mortality rate, occurs mainly in infants with genetic abnormalities that interfere with the function of cytotoxic T lymphocytes and natural killer (NK) lymphocytes and is transmitted by autosomal recessive inheritance. Two subgroups have been described: familial HLH (FHLH) and the genetic forms associated with primary immunodeficiency, including disorders linked to pigmentary dilution or pseudoalbinism (S. Chediak-Higashi syndrome, S. Griscelli syndrome and S. Hermansky-Pudlak syndrome) and lymphoproliferative disease associated with chromosome X.

*Secondary or acquired HLH*. This is defined as cases of HLH in which no characteristic mutations of the disease are detected and one or several triggers have been identified (Table 2), such as infections (HLH-I),[3] autoimmune and autoinflammatory diseases[4] (in this case called macrophage-activation syndrome [MAS]) and tumors (HLH-T), especially T-cell lymphomas.[5] In general, this phenotype has lower mortality than the primary forma and manifests more frequently in older children, adolescents and adults. Nevertheless, the primary forms are also often precipitated by infections and other triggers, and hypomorphic or heterozygous mutations that cause defects in cytotoxicity have been reported in the secondary forms. The distinction between primary and secondary HLH is therefore becoming increasingly blurred and artificial.

## Epidemiology

The incidence of HLH is difficult to estimate because this condition is probably underdiagnosed. It is a primarily pediatric disease, with increased incidence in children younger than 3 months. A national retrospective study of Japan[6,7] revealed an HLH incidence of 1/800,000 inhabitants/year (56% of cases in children younger than 14 years). The