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Clinical report

Hemophagocytic lymphohistiocytosis: Analysis of 18 cases☆

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ABSTRACT

Background and objective: *Hemophagocytic lymphohistiocytosis* (HLH) is a serious condition, caused by an improper regulation of the immune response to different stimuli of the immune system. Early diagnosis and treatment are a challenge for the clinician.
Patients and method: We conducted a retrospective study at our institution between 2010 and 2015, of adult patients diagnosed with HLH, in accordance with the criteria of the Histiocyte Society, analysing their clinical characteristics, diagnostic and etiological studies and the outcome.
Results: Eighteen patients were analysed. Median time to diagnosis was 24 days. We found neoplastic aetiology in 8 cases (7 hematologic), while it was infection-related in 6 (4 visceral leishmaniasis), and an inflammatory disease in one. In the remaining 3, an underlying cause for the HLH was not found. Course of treatment was corticosteroids in 16 patients, associated with cyclosporine in 2 of them, one received immunoglobulins, while another received etoposide with tacrolimus.
Conclusions: We emphasize the scarce use of etoposide therapy, the currently recommended treatment. Overall mortality was 44%, mainly associated with neoplastic aetiology (67 compared to 16.6% mortality in infection-related aetiology, $P < .05$).

Linfohistiocitosis hemofagocítica: análisis de 18 casos

Palabras clave:
Síndrome hemofagocítico
Síndrome de activación macrofágica
Adulto
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RESUMEN

Antecedentes y objetivo: La *hemophagocytic lymphohistiocytosis* (HLH, «linfohistiocitosis hemofagocítica») es una entidad grave, producida por una incorrecta regulación de la respuesta inmunológica frente a diversos estímulos del sistema inmunitario. Su diagnóstico y tratamiento precoz suponen un reto para el clínico.
Pacientes y método: Hemos realizado un estudio descriptivo retrospectivo de los pacientes adultos diagnosticados de HLH, según los criterios de la *Histiocyte Society*, entre los años 2010 y 2015 en nuestra institución, analizando sus características clínicas, el estudio diagnóstico-etiológico y su evolución.
Resultados: Se analizaron 18 pacientes. La mediana de tiempo al diagnóstico fue de 24 días. La etiología fue neoplásica en 8 casos (hematológica en 7), infecciosa en 6 (leishmaniasis visceral en 4), inflamatoria en uno, y en los 3 restantes, idiopática. Se realizó tratamiento en 16 pacientes con corticoides, asociando ciclosporina en 2, inmunoglobulinas en uno, y etopósido con tacrolimus en otro.
Conclusiones: Destacamos la escasa utilización de etopósido en el tratamiento dirigido, el actualmente recomendado. La mortalidad global fue del 44%, asociada a la etiología neoplásica principalmente (67 frente a 16,6% de mortalidad en la etiología infecciosa, $p < 0,05$).

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a serious immune system disorder, described in 1939 by the paediatricians Scott and Robb-Smith[1]. The underlying pathogenetic mechanism is an uncontrolled activity of the mononuclear-phagocyte system with secondary release of cytokines, responsible for the basic clinical manifestations of the syndrome (fever, progressive cytopenia and hepatosplenomegaly). The HLH is classified into primary, with a genetic basis and development mainly during childhood, and secondary or acquired. The latter is usually diagnosed in adulthood and is triggered by infectious, inflammatory or neoplastic processes.[2] The presence of a stimulus maintained by an antigen (Ag) and the inability of the immune system to remove it leads to a sustained stimulation between Ag-presenting cells and cytotoxic T cells, as well as the Toll-like receptors and interferon (IFN)-γ. Furthermore, changes in degranulation involving perforin and granzyme release defects at the synapse between NK cells and Th1 lymphocytes with macrophages result in an abnormal immune process regulation. This leads to macrophage hyperactivation and proinflammatory cytokines hypersecretion (IFN-γ, TNF-α, interleukin [IL] -1, IL-4, IL-6, IL-8, IL-10 and IL-18), which constitute the so-called cytokines storm responsible for the clinical and laboratory findings, tissue damage and progressive multiorgan failure.[3]

The incidence of HLH in adult patients is unknown, but reported cases have clearly increased in recent years. The prognosis is generally poor, with early diagnosis and treatment being the most important factors affecting survival. Our study aims to establish the prevalence, clinical profile, aetiology and prognosis of adult patients with HLH in our healthcare setting.

Materials and methods

This is a retrospective observational study of cases with a final clinical, cytological and/or pathological diagnosis of HLH in adults over 18 years of age between 2010 and 2015 at the Hospital 12 de Octubre in Madrid. To this end, an active search was performed in electronic health records and Haematology and Pathology services databases using the terms "haemophagocytosis", "hemophagocytic syndrome" or "macrophage activation syndrome".

Medical records with a diagnosis of HLH were reviewed, using for case definition the current *Histiocyte Society* criteria established in 2004 (*HLH-2004 trial*, Table 1).[4] The following variables were recorded: epidemiological data, personal history, clinical symptoms and signs, and HLH-related laboratory abnormalities. The etiologic study performed, treatment administered and patient outcome was collected. An analysis of frequencies and descriptive statistics was performed through SPSS® version 15.0.

Table 1
2004 HLH-trial diagnostic criteria.

Molecular diagnosis compatible with HLH
Mutations in genes PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A or XIAP
OR
Five of the following criteria:
Fever higher than or equal to 38.5 °C
Splenomegaly
Cytopenia (at least 2 of 3)
Hb < 9 g/dl
Platelets < 100,000/mm^3
Neutrophils < 1000/mm^3
Hypertriglyceridemia (>265 mg/dl) or hypofibrinogenemia (<150 mg/dl) or both
Haemophagocytosis in BM, lymph nodes, spleen or liver
Low NK cell activity or absence
Ferritin > 500 ηg/ml
Increased soluble CD25, >2400 U/ml

Source: Henter et al.[4]

Results

Of the 62 medical records identified, only 18 (29%) met the criteria according to *HLH-2004 trial*. The incidence of the disease in our healthcare setting in the adult patient is 18 cases/690,000 admissions/5 years.

Clinical characteristics and diagnostic criteria

As shown in Table 2, 72.2% of patients with HLH were men with a mean age of 51 years (22–88), of Spanish nationality (89%). Most of them were healthy, except 2 who were recently diagnosed with HIV infection with detectable viral load and CD4 < 500/mcL without antiviral treatment. Symptoms at baseline were unspecific, with high prevalence of fever (100%) and anorexia (83%), followed by respiratory (44%) and gastrointestinal (39%) symptoms. Hepatosplenomegaly was frequent on physical examination, lymphadenopathy was found in 55.6% of patients. All had bicytopenia, with thrombocytopenia being the most prevalent (88.6%), followed by anaemia (44.4%). 100% had increased blood ferritin (10/18 [55%] above 2,500 ng/ml), 55% increased triglycerides (>265 mg/dl) and only 16.7% decreased fibrinogen (<150 mg/dl). The concentration of soluble CD25 was elevated (>2500 IU/ml) in 90% of patients for whom its determination was requested. NK cells activity was not determined in any case. Study of lymphocyte populations were requested in 45% of patients, the NK population being decreased in 87.5% of them. Fifteen patients out of 18 (83%) had haemophagocytosis in bone marrow (Fig. 1).

Table 2
Baseline characteristics of patients and clinical, laboratory and bone marrow findings.

	n/No.	%
Sex		
Male	13/18	72.2
Female	5/18	27.8
Clinical presentation		
Fever (>38 °C)	18/18	100
Anorexy	15/18	83
Splenomegaly	13/18	72.2
Hepatomegaly	11/18	61.1
Lymphadenopathy	10/18	55.6
Sweating	9/18	50
Respiratory symptoms	8/18	44.4
Gastrointestinal symptoms	7/18	38.9
Weightloss	6/18	33.3
Headache	5/18	27.8
Bleeding	1/18	5.6
Rash	1/18	5.6
Arthromyalgia	1/18	5.6
Lab findings		
Ferritin (>500 ng/ml)	18/18	100
Thrombocytopenia (<100,000/mm^3)	16/18	88.9
Hypertriglyceridemia (>265 mg/dl)	10/18	55
Anaemia (<9 g/dl)	8/18	44.4
Abnormal liver profile (>3 N)	8/18	44.4
Hyponatremia (<135 mEq/l)	7/18	38.9
Hypofibrinogenaemia (<150 mg/dl)	3/18	16.7
Neutropenia (<1000/mm^3)	2/18	11.1
Soluble CD25 requested	10/18	55.6
Increased CD25 (>2400 U/ml)	9/18	90
Bone marrow haemophagocytosis	17/18	94
Bone marrow biopsy	11/18	61
Bone marrow aspirate	6/18	33