

Hemophagocytic Lymphohistiocytosis: About 8 Cases

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Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a clinical-biological entity characterized by a hyperinflammatory state following the deregulation of the cytotoxic immune response, causing histiocytic proliferation with significant hemophagocytic activity in the bone marrow as well as the massive release of inflammatory cytokines. The diagnosis is established by the association of nonspecific clinical and biological signs. The aim of this study was to describe the clinical and laboratory presentation to determine the underlying pathologies and clarify the evolution and the prognosis of adult patients with HLH in our healthcare setting. A retrospective study of patients with HLH was conducted in the Military Teaching Hospital, Rabat, between January 2015 and January 2017. We were able to identify eight patients. Six were men, and the average age at diagnosis was 58 years. Infectious agents were responsible in 3 cases, malignant lymphoma in 3 others, one case of systemic lupus erythematosus, and in the last case etiology remains unknown. Clinical characteristics such as fever (100%), splenomegaly (62,5%), and lymphadenopathy (37,5%) were observed. Laboratory values presented with pancytopenia (62, 5%), thrombopenia and anemia (100%), increased ferritin (100%), lactate dehydrogenase (87, 5%), triglycerides (62, 5%), and decreased fibrinogen (50%). Bone marrow showed hemophagocytis in all cases. The prognosis was poor. Five patients died. Absence of specific signs makes early diagnosis difficult. The prognosis varies according to the series but remains very unfavorable. Studies are needed to assess prevalence and develop a severity score and therapeutic recommendations to improve HLH prognosis.

Keywords: Hemophagocytic lymphohistiocytosis, Infections, Macrophage.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a clinical-biological entity characterized by a hyperinflammatory state following the deregulation of the cytotoxic immune response, causing histiocytic proliferation with significant hemophagocytic activity in the bone marrow as well as the massive release of inflammatory cytokines [1].

The diagnosis is established by the association of nonspecific clinical and biological signs. According to the Histiocyte society, and in the absence of specific genetic tests or family history, the presence of at least 5 out of the 8 criteria is necessary to pose the diagnosis (Table 1) [2].

There are two types of HLH: the primary form, which has a genetic basis and develops during childhood, then the secondary or acquired form that is diagnosed in adulthood and triggered by infections, inflammatory diseases, or neoplasia [3]

Its incidence worldwide is roughly estimated between 0,8 and 4% of the studied bone marrow [4,5]. In almost 50% of cases, the evolution is fatal, highlighting the need for early diagnosis and treatment.

For the primary form, remission may be achieved with immunochemotherapy, and in cases of acquired form by treating the etiology [6,7].

Given its rarity and the scarcity of data in the Moroccan literature, our study aims to describe the clinical and laboratory presentation to determine the underlying pathologies and clarify the evolution and the prognosis of adult patients with HLH in our healthcare setting.

METHODS

This is a retrospective observational study of cases collected in the Laboratory of Hematology at the Military Teaching Hospital Rabat. From January 2015 to January 2017, we identified eight adult patients who were diagnosed for secondary HLH. The criteria for diagnosis were based on the recommendations of the HLH-2004 protocol of Henter *et al.* [2]. For each patient, the case record was reviewed, clinical and laboratory data of the HLH at the time of diagnosis were identified, as were the etiologies triggering the hemophagocytic syndrome. Under Moroccan law no ethical approval is required for a retrospective study.

RESULTS

Clinical features

Of the 8 adult patients, 6 were men and 2 were women. Their average age was 58 years old (range 36-85). The results obtained from the clinical examination and the laboratory results are presented according to the HLH-2004 criteria in Table 2.

Symptoms were unspecific at baseline. The most common observed were fever (100%). Purpura was observed in one case, icterus in two cases. The organomegaly was important, including splenomegaly (62,5%), hepatomegaly (25%), and lymphadenopathy (37,5).

Laboratory findings

All patients had a biological inflammatory syndrome. Three patients had bicytopenia and five had pancytopenia. All had thrombocytopenia and anemia. All patients increased blood ferritin; five patients increased triglycerides, seven increased lactate

deshydrogenase, and four decreased fibrinogen. The bone marrow was contributive in all cases, showing hemophagocytosis (image 1). Three renal failures, and two disseminated intravascular coagulation were observed.

Etiology of HLH

Infectious agents were responsible in 3 cases, malignant lymphoma in 3 others, one case of systemic lupus erythematosus, and in the last case etiology remains unknown. Etiologies are show in table 2.

Treatment and prognosis

All patients received symptomatic treatment at baseline. It involved the correction of hydroelectrolytic disorders and iterative transfusions. The patient with visceral leishmaniasis received meglumine antimoniate. All three patients with malignant lymphoma received chemotherapy. Patient with sepsis received antibiotherapy. Only three patients had well evolved.

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)
<i>Hb < 9 g/dl</i>
<i>Platelets < 100,000/mm3</i>
<i>Neutrophils < 1000/mm3</i>
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 ng/ml
Increased soluble CD25, >2400 U/ml

Table-2: Clinical, biological, and histopathological data for the eight cases of HLH

Patient	1	2	3	4	5	6	7	8
Sex (M/F)	M	M	M	M	F	M	M	F
Age (years)	66	71	36	54	47	84	61	44
Etiology	ML	ML	EBV	VL	ND	ML	SEPSIS	SLE
Fever	+	+	+	+	+	+	+	+
Splenomegaly	+	+	+	+	-	+	-	-
Bicytopenia			+		+			+
Pancytopenia	+	+		+		+	+	
TG	+	+	ND	+	+	-	+	-
Ferritin >500 ng/ml	+	+	+	+	+	+	+	+
Fibrinogen	+	ND	-	ND	+	-	+	+
Hemophagocytis	+	+	+	+	+	+	+	+

M = Male; F = Female; ML malignant lymphoma; EBV = Epstein–barr virus infection; VL= visceral leishmaniasis; SLE = systemic lupus erythematosus; ND = Not determined; + = Present or pathologically increased/decreased; – = absent or normal; TG = Triglycerides.

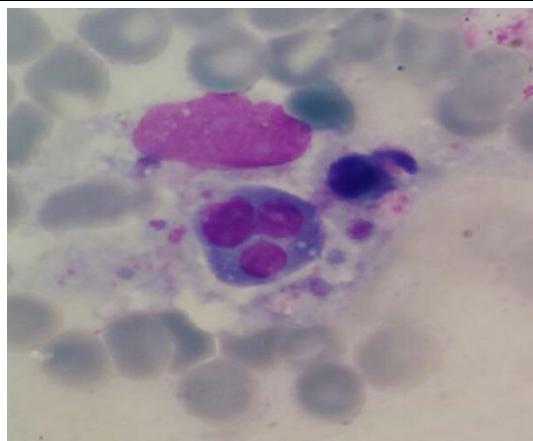


Fig-1: Image of hemophagocytosis in a bone marrow

DISCUSSION

HLH, primary or secondary, is an individualized disease following Risdall's work in 1979 [8,9] and characterized by nonspecific activation of the mononuclear phagocyte system, which leads to tissue proliferation of phagocytosis-activated macrophages of the figurate elements of the blood [10].

This explains the clinical symptomatology and laboratory abnormalities during HLH, as well as organ failure and tissue damage. The prognosis of HLH is pejorative. It evolves towards death in less than 2 months if not treated [11].

HLH is typically characterized by febrile syndrome, organomegaly, bicytopenia or pancytopenia, coagulation disorders, an obvious etiology of HLH, and multivisceral failure [12]. The general signs were present in all our patients. Hepato-splenomegaly with lymphadenopathy are observed in 30 to 70% of cases [13-15]. Five of our patients had splenomegaly and two had hepatomegaly. The adenopathies were found in three cases. A rash or jaundice, can be noted in 10 to 20% of cases [12,15]. In our study, a rash was observed in one patient and the jaundice in two patients. The digestive signs are abdominal pain, diarrhea, and vomiting [8]. None of our patients presented a digestive symptomatology.

In the biological assessment, cytopenias are generally constant according to the studies [8, 10], either in the form of pancytopenia (found in 5 of our patients) or bicytopenia (in 3 of our patients). Thrombopenia, usually less than 100G/l [15], was observed in all our patients. It may be of central as well as sometimes peripheral mechanisms [16]. Anemia, present in seven of our patients is normochromic, normocytic, aregenerative, often deep with hemolysis stigma such as falling haptoglobin, increased LDH and free bilirubin. Its mechanism is either central by intramedullary abortion, partly due to the phagocytosis of erythroblastic precursors, or peripheral by extrahematopoietic erythrophagocytosis [17].

Hyperferritinemia is also constant, usually exceeding 3000 $\mu\text{g/l}$ [18]. It was present in all patients. Hypertriglyceridemia, often early, corresponds to a deficiency of the lipase lipoprotein, inhibited by TNF- α . Five of our patients had hypertriglyceridemia. The increase in Lactate dehydrogenase (LDH) is almost constant, indicative of cell lysis. The average in our series was 887.4 IU/l (range 424-1265).

The bone marrow is often very contributive. It shows a proliferation of activated macrophages which phagocyte red blood cells, leukocytes, platelets and their precursors. Hemophagocytosis may also occur but more rarely in the liver, spleen, and lymph nodes [15]. The bone marrow of all our patients has showed images of hemophagocytosis.

In the HLH-2004 guidelines, three novel diagnostic criteria, namely hyperferritinaemia, elevated sCD25R, and low/absent NK-cell activity, were added to the five criteria in HLH-94 [19]. In our setting, only ferritinemia is performed. Concerning etiologies of the acquired HLH, and according to Larroche [10], the main etiology remains infections (47%), followed by malignant lymphomas (25%). In our study, the underlying diseases of HLH in our patients were infections in three cases (visceral leishmaniasis, EBV infection, sepsis with *Streptococcus pneumoniae*), three malignant lymphoma, one case of systemic lupus erythematosus, and for the last case, etiology remains unknown.

The management of the HLH is first of all symptomatic. It involves an optimization of the hydroelectrolytic balance, antipyretics, and blood transfusions that must be associated to the treatment of underlying diseases. The specific treatment is not yet well codified. Corticosteroids, polyvalent gammaglobulins, ciclosporin and Etoposide were proposed [20].

Despite the etiological treatment, the prognosis of the secondary HLH remains very poor. It depends on

several factors: precociousness of diagnosis, positivity of the etiological assessment, early initiation of an adapted anti-infectious treatment, associated neoplastic etiology and previous immune status (HIV, immunosuppressed). In 50% of the cases, the evolution is towards the death [8]. In our series, five of our patients died.

CONCLUSION

The interest of this study stems from the poor clinical and biological knowledge of this pathology, its multiple etiologies, which lead to difficult management and a still fearsome prognosis. This syndrome has, moreover, an immunological physiopathology which remains very poorly understood. Much progress remains to be made for his understanding. The absence of specific signs makes early diagnosis difficult, but this pathology should not be misunderstood before a febrile pancytopenia in an evocative clinical and biological context. The management of HLH has not yet been validated. This explains in part the fatal evolution in many series despite the treatment instituted. The prognosis varies according to the series but remains very unfavorable especially in the case of HLH with infectious etiology. Several prognostic factors correlated with the severity of the disease are found. Studies are needed to assess prevalence and develop a severity score and therapeutic recommendations to improve HLH prognosis.

What is already know on this topic

- The poor clinical and biological knowledge of this pathology.
- Multiple etiologies, difficult management, and a fearsome prognosis.

What this study adds

- The clinical and the laboratory presentation of the HLH in our Hospital.
- Our experience in the management of this severe disease.

Competing interests

The authors declare no competing interest.

Authors' contributions

All authors contributed to the work and read and approved the final version of the manuscript.

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