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Research Article

HEMOPHAGOCYTIC SYNDROME, A RETROSPECTIVE STUDY IN THE MILITARY HOSPITAL MOHAMED V RABAT MOROCCO

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ABSTRACT

Hemophagocytic Syndrome (HS) is an aggressive and life-threatening syndrome of excessive immune activation. It is mostly associated with underlying pathology, it can reveal: immunodeficiency, infections, cancers and auto-immune diseases.

Objective of work: Identify the clinical, biological, etiological and evolutionary features of the HLH.

Methods: A retrospective study of patients with HS syndrome collected in the Hematology Laboratory of the Mohamed V Military Hospital Rabat (MVMHR) in Morocco (between 2013 and 2015).

Results: We identified 7 cases, 4 males and 3 females, middle aged 46 years. The onset of symptoms was brutal in all patients. The splenomegaly and the inflammatory syndrome were found in all cases. The pancytopenia was observed in 6 patients. The hemophagocytosis in bone marrow smear examination was found in all cases. There were infectious underlying causes in 4 cases: one case of visceral leishmaniasis, one case of Staphylococcus *aureus* sepsis, one case of Escherichia *coli* sepsis and one case of glandular tuberculosis. For the other patients, there was a case of follicular lymphoma, a case of Hodgkin lymphoma and a case of myelodysplastic syndrome. The outcome was favorable in 3 cases, 4 patients died.

Conclusion: The HS is an extreme emergency. Clinical and biological signs are not specific; the management should be quick for a better survival.

KEYWORDS: Hemophagocytic syndrome; Macrophage.

INTRODUCTION

The hemophagocytic syndrome (HS) or macrophage activation syndrome has been defined in 1970 as the result of a clinical and biological proliferation and non-specific activation of macrophages reticulohistiocytic system, with phagocytosis of formed elements of blood [1]. Diagnosis is based on the combination of nonspecific clinical and biological signs, requiring cytological or histological research of hemophagocytosis and an exhaustive etiological investigation. Two groups of HS were identified: the primitive HS, rare in adults, the main one is the familial hemophagocytic lymphohistiocytosis FHLH [2]. Secondary or acquired HS for children and adults, complicating many pathologies such as infections, neoplasia, inflammatory diseases or drug treatments. The prognosis is poor, with mortality about 50% from all causes. Acquired HS in adults are not the subject of any

therapeutic consensus. In all cases, the underlying disease should be sought relentlessly and treated.

The occurrence of HS requires an exhaustive etiological investigation. The diagnosis is often negative because there are a lot of diseases associated with this syndrome, and the clinical table is usually dominated by secondary manifestations of HS, obscuring the specific signs of the causal pathology. No clinical symptoms or biological abnormalities are specific to the HS; they can be confused with the underlying pathology that triggered the HS. This raises the question: What conditions should we look at first before a HS of unknown etiology, especially in a country where tuberculosis is endemic and visceral leishmaniasis in adults is not uncommon? Our objective is to analyze, through a retrospective study, clinical and biological features of secondary HS, to determine the underlying pathologies and clarify the evolution and the prognosis.

MATERIALS AND METHODS

This is a retrospective study of clinical cases of HS collected in the hematology laboratory of MVMHR between 2011 and 2015. We have retained folders of patients fulfilling HS modified diagnostic criteria of Henter [1]. Etiological investigation was performed according to the clinical and laboratory guidance. The investigation included as the case may: bone marrow examination, serology of Cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis B and C, and HIV, an immunological tests including antinuclear antibodies, rheumatoid factor and anti citrullinated peptide antibodies, digestive endoscopy, and radiological assessment including a chest X-ray, abdominal ultrasound, and a cervical-thoraco-abdominal computed tomography.

RESULTS

We selected seven cases. It was 4 men and 3 women, mean age 46 years, ranging between 19 and 78 years (Table 1). The onset of symptoms was brutal in all patients, with fever and chills.

On inspection, purpura was observed in three cases, icterus in three cases and a macular rash in two cases. The physical examination showed the presence of splenomegaly in all cases and peripheral lymph nodes in three cases. A bleeding complication was observed in two cases. This was gingival bleeding and epistaxis.

In laboratory tests, there was a biological inflammatory syndrome in all cases. Six patients had pancytopenia. Hypertriglyceridemia and hyperferritinemia were noted in all cases. Increased lactate dehydrogenase with cytolysis were noted in six cases. The sternal puncture was contributory in all cases showing hemophagocytosis.

In our patients, disseminated intravascular coagulation (DIC) was observed in 3 cases.

The HS was associated with an infectious cause in four cases: visceral leishmaniasis, E *coli* septicemia, Staphylococcus *aureus* sepsis and glandular tuberculosis (TB). For other patients, respectively HS was associated with a Hodgkin lymphoma, myelodysplastic syndrome (MDS), and follicular lymphoma (Table 1).
The case of visceral leishmaniasis was treated with Glucantime® with a good clinical and biological evolution. The patients who had lymphoma received chemotherapy. The patient having tuberculosis has received TB treatment. Four patients died, the two sepsis have evolved into septic shock despite appropriate antibiotic therapy, and two patients presented a profound alteration of the general condition following complications from chemotherapy: Hodgkin lymphoma and follicular lymphoma.

DISCUSSION

Many questions remain unanswered currently in the care of acquired HS, especially therapeutic management, which mainly depends on the underlying pathology. A full investigation is needed to identify diseases that trigger the HS to treat them quickly. Few studies have examined the epidemiological features of the disease. In Morocco, its incidence is unknown. This is a pathology likely underestimated. No clinical symptoms or laboratory abnormalities are specific to the HS; they can be confused with the manifestations of the underlying disease [3]. The clinical table is often misleading sometimes brutal with multiorgan involvement. It combines a fever with chills, and altered general condition [4].

General symptoms are always present. Hepatosplenomegaly with lymphadenopathy are observed in 30-70% of cases [5, 6]. All our patients had splenomegaly. The lymph nodes were found in three cases. Rash can be noted in 10 to 20% of cases [5, 6]. In our study, it was observed in two patients. Digestive symptoms are inconstant and non-specific, such as nausea, vomiting, diarrhea and abdominal pain [7], it was noted in our series in the case of E *coli* septicemia. Neurological signs as convulsions or meningeal focalization signs are rare in HS [8]. Pulmonary manifestations are exceptional [9].

There are a lot of laboratory abnormalities in the HS but all nonspecific. It is rather their association which should suggest to the clinician diagnosis of HS. In cell blood count, there is usually a bi or pancytopenia. Thrombocytopenia is the earliest and most common. Its mechanism is rather central, but sometimes peripheral [10]. Anemia is normochromic normocytic, non-regenerative, with intratissular hemolysis stigmata and erythroblastosis. Leukopenia is less common and late onset [5]. Plasma lacticodehydrogenase are constantly increased. There is often an early hypertriglyceridemia, which can reach more than 10 times the normal associated with a significant increase in serum ferritin demonstrating cell lysis by macrophage activation [7]. In our series, hyperferritinemia and hypertriglyceridemia were observed in all patients. Hemostatic disorders are present in the HS in 50 to 70% of cases [7]. This may be an isolated hypofibrinogenemia or associated with the lengthening of thrombin time, prothrombin time and activated partial thromboplastin secondary to activation of coagulation, or even a real DIC, which is a factor of poor prognosis given the risk of bleeding complications that can be deadly [5].

Biological liver abnormalities are found in 40% of cases [11]. This is cytolysis, which may be accompanied by liver

failure. Cholestasis is rather late-onset. In our series, cytolysis was observed in 6 patients.

The diagnosis of HS requires a combination of clinical, biological and histological or cytological signs. The diagnostic criteria have recently been redefined. For a positive diagnosis, we adopted Henter criteria, shown in (Table 2) [1].

Hemophagocytosis can be sought in all organs; the most accessible is bone marrow, liver, lymph nodes and spleen less often. The bone marrow aspiration is the simplest examination to achieve. Hemophagocytosis may be absent at the beginning of the HS and being highlighted after iterative bone marrow examinations [12]. This analysis is recommended for adults when an underlying blood disease is suspected because the hemophagocytosis is not specific to HS.

On the etiological plan, acquired HS may be secondary to several pathologies, infections, especially viral, are top of the list of secondary HS. In our series, the HS was associated with an infectious cause in four cases. In the meta-analysis of Karras et al [7], the HS was secondary to a viral infection in 28.4% of cases. In case of infection with HIV, HS occurs usually in advanced stages of the disease often with opportunistic infections or lymphoma [13].

In a recent review involving 37 cases of HS associated with tuberculosis, 80% of cases were extra pulmonary tuberculosis. The prognosis was severe with mortality up to 50% of cases. Patients, who had not received treatment for TB early, died [14]. In our series, the HS was associated with glandular tuberculosis in one observation.

Bacteria such as Staphylococcus, Pneumococcus, E *coli* and other gram negative bacteria have been described to be the origin of HS [15]. In our series, the HS was associated with Staphylococcus *aureus* septicemia in one case and E *coli* septicemia in one observation. In a prospective study in intensive care unit, bone marrow examination practiced systematically in thrombocytopenic patients with septic shock had objectified hemophagocytosis in 60% of cases [16].

The first line of treatment should be in these cases appropriate antibiotic therapy which alone can control the disease without recourse to corticosteroids and immunosuppressive drugs [17].

Among the parasitical etiologies, fifty cases of visceral leishmaniasis have been reported in association with the HS. This was especially child leishmaniasis; among the 8 cases of leishmaniasis in adults reported in the literature two patients died [18]. In our series, one case of visceral leishmaniasis has been identified. The HS associated with visceral leishmaniasis has some specific features related to the intricacy of the clinical and biological signs leading to a late diagnosis with dramatic consequences [19]. The standard treatment is liposomal amphotericin B®, specific treatment that can be often sufficient to treat the HS [20]. Our patient has been treated with Glucantime ® with a good evolution.

In other cases, the HS can be secondary to some systemic and autoimmune diseases, especially Still's disease, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [21].

Hemophagocytosis may be associated with neoplasia. The frequency of this association is difficult to define; it is variable depending on the series. In Karras's meta-analysis, the HS was secondary to lymphoma in 20% of cases and in 10% of cases to other hematologic or solid tumors. Lymphoma of high grade is the most blood disease observed in case of HS. In 70% of cases, it is a non-Hodgkin lymphoma of T or NK phenotype [9]. In our series there were one case of Hodgkin lymphoma, one case of follicular lymphoma and one case of myelodysplastic syndrome associated with HS. Other malignancies associated with HS have been described, blood diseases such as acute myeloid or lymphocytic leukemia, multiple myeloma, myeloproliferative disorders and various solid tumors [22].

Therapeutically, the management of HS is based on symptomatic treatments, such as hydroelectrolytic balance and blood transfusions, associated with etiological treatment when a cause is demonstrated. Specific treatment referred to antiphagocytic is sometimes necessary, but no controlled studies have been published to date.

The secondary HS prognosis is often very poor despite an adapted etiological treatment. In the study of Karras et al, a fatal outcome was observed in 49% of cases. Mortality was 28.8% in the review of Veerakul et al [23]. In our series, four of our patients died.

The poor prognostic factors in case of HS are age over 30 years, the association with Epstein Barr virus, a lymphoma, a cancer, or therapeutic delay.

Table 1: *Clinical and biological characteristics of our patients*

Patient	Gender	Age	Etiology	CBC	TG g/L	Ferritinemia ng/mL
1	F	52	Leishmaniasis	Pancytopenia	4,3	2018
2	F	22	E.*coli* Septicemia	Pancytopenia	2,9	4089
3	M	37	S *aureus* Septicemia	Pancytopenia	3,3	6877
4	M	19	Tuberculosis	Pancytopenia	3,7	6734
5	M	78	MDS	Pancytopenia	4,1	7836
6	F	65	Hodgkin	Pancytopenia	2,7	2190
7	M	49	Follicular L	Bicytopenia	4,2	4355

Table 2: *Diagnostic criteria of HS*

	Five of the following eight criteria:
1	Fever ≥38.5°C
2	Splenomegaly
3	Peripheral blood cytopenia
4	Hypertriglyceridemia (triglycerides>2,65 g/L) and/or hypofibrinogenemia (fibrinogen <150mg/dL)
5	Hemophagocytosis in bone marrow, spleen, lymph node, or liver
6	Low or absent NK cell activity
7	Ferritin >500 ng/mL
8	Elevated soluble CD25

CONCLUSION

The HS is a very serious pathology, often unrecognized, can be life threatening. Clinical and biological signs are not specific, but rather their association should push the clinician to think about the diagnosis of hemophagocytic syndrome. Using the classification criteria may help to have an early diagnosis and start appropriate treatment quickly. The HS can be secondary to infectious, neoplastic or autoimmune diseases. Infections remain top of the list; an exhaustive infectious check-up is needed because alone an appropriate antibiotic therapy can save the patient.

In endemic areas, tuberculosis and leishmaniasis must be systematically sought. However, even with an etiological treatment, sometimes, the prognosis can be dark.

A better understanding of the pathogenic mechanism would improve the specific treatment and thus save patients resistant to etiological treatment.

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