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Case Report

Macrophage Activation Syndrome: About A Case

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Abstract: Macrophage activation syndrome is a rare but a potentially fatal disease. This pathology is defined not only by clinical criteria (fever, splenomegaly), but also by biological criteria (bi or pancytopenia, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia) and cyto histological ones (hemophagocytosis in the bone marrow, in the spleen or in the peripheral lymph nodes). It may be primary or more often reactive to an infectious or a malignant pathology, an immune deficiency, or an autoimmune systemic disease. Its occurrence imposes a quite exhaustive etiological assessment, as the associated diseases are multiple. We report in this work the case of a patient in whom a macrophage activation syndrome secondary to a bacteraemia was diagnosed in the laboratory of Hematology of the Hassan II University Hospital -Fez, and whose evolution was marked by a good response to antibiotic therapy with a regression of clinical symptoms and an improvement of the biological parameters. However, the prognosis for macrophage activation syndrome remains severe with about 50% mortality in the literature. It is therefore considered as a serious condition, with a severe prognosis and a treatment that is still poorly codified**.**

Keywords: Fever, splenomegaly, cytopenia, hemophagocytosis, hypertriglyceridaemia, hyperferritinemia, hypofibrinogenemia.

INTRODUCTION

Hemophagocytosis syndrome, also called macrophage activation syndrome (MAS) or lymphoid-histiocytic activation syndrome, is a rare but potentially fatal disease [1]. The probable evolution towards a fatal multi-visceral failure in the absence of proper diagnosis and management makes it a therapeutic emergency [2].

This disease defined by clinical criteria (fever, splenomegaly), biological criteria (bi- or pancytopenia, hypofibrinogenemia, hypertriglycerida emia, hyperferritinemia) and cyto histological ones (the presence of hemophagocytosis in the bone marrow, spleen or peripheral lymph nodes) is the result of a cytokine dysregulation and a benign lymphoid-histiocytic proliferation [1]. Its diagnosis is mostly based on the bone marrow cytology [3]. Its etiologies, relatively numerous could be divided into two nosological frameworks:

- Primary macrophage activation syndromes: genetically determined diseases affecting mainly newborns and infants (familial lymphohistiocytosis, Chediak-Higashi, Griscelli, HermanskyPudlak type 2, Purtillo)
- Secondary macrophage activation syndromes: that affects mostly older children and adults and also complicates many pathologies: infections, medication, neoplasias, inflammatory or autoimmune systemic diseases [2].

The prognosis of macrophage activation syndrome remains severe with approximatively 50% mortality found in the literature [4-5]. The prognosis depends mainly on the time limit of the treatment initiation, the nature of the underlying pathology, and the existence of an underlying immunosuppression [6]. Our work reports the case of a young woman of 23 years old admitted for the management of an extended fever. The cytological examination of the bone marrow, which has been carried out in the laboratory of Hematology of Hassan II University Hospital in Fez, permitted the diagnosis of a macrophage activation syndrome. Through this case, we will discuss the epidemiology, various clinical and biological signs, treatment and prognosis of this syndrome.

OBSERVATIONS

A 23-year-old patient was admitted at the Hassan II University Hospital in Fez to be cared for an extended fever that was lasting for 8 months. This fever was associated to an intermittent liquid diarrhea, a loss of weight of 10 Kg and an inflammatory pain of the large and small joints.

During her admission, the patient was febrile at 39°C with an alteration of her general condition. On physical exam, she had painful and centrimetric left submandibular angulo lymphadenopathy. The patient had also few centimetric axillary lymphadenopathy that were located in both axillary regions and subcentimetric inguinal lymphadenopathy. A slight splenomegaly was found on palpation exam. The mucous cutaneous examination revealed purpuric tasks on both feet, a maculopapular rash on the left forearm and a slightly one on the abdomen and also an oral thrush. The rest of the somatic examination had shown no others anomalies. The abdominal and pelvic echography showed the presence of a homogeneous splenomegaly of 16 cm.

The biological report revealed normocytic normochromic aregenerative anemia (Hb 8 g / dl) associated with thrombocytopenia at 90.109 / l, a high level of lactate deshydorgenase (LDH) at 604 µl / l, a hypertriglyceridemia at 2.36 mmol / l, a hyper-ferritinemia at 1200 ng / ml, a hypo-albuminemia at 22.5 g / l. The cytologic exam of the bone marrow revealed a rich marrow with the presence of numerous macrophages associated with some images of macrophagic magmas and images of hemophagocytosis compatible with the diagnosis of macrophage activation syndrome [Figure 1, 2, 3].

Table 1: Diagnostic criteria for macrophage activation syndrome, according to [10].

At least five of the following
Fever
Splenomegaly
Cytopenias affecting at least two lines
➢ Hemoglobin< 9 g/dL
➢ Platelets<100000/mm3
➢ Polymorphonuclear neutrophils < 1000/mm3
Hypertriglyceridemia and / or hypofibrinogenemia
➢ Triglycerides> 3 mmol/L
➢ Fibrinogen< 1,5 g/L
Hemophagocytosis in the bone marrow, spleen or lymph nodes
No neoplasia
Low or zero Natural Killer cell activity (according to local laboratory references)
Ferritinemia ≥ 500 g/L
IL-2 soluble receptor ≥ 2400UI/ml

Table 2 :Clinical signs of macrophage activation syndrome, according to [11]

Fever	70—100 %
Splenomegaly	70—100 %
Hepatomegaly	40—95 %
Adenopathies	15—50 %
Skin Rash	5—65 %
Neurological signs	20—50 %

Table 3: Biological signs of macrophage activation syndrome, after [11]

Anemia	90—100 %
Thrombocytopenia	80—100 %
Neutropenia	60—90 %
Hypertriglyceridemia	60—70 %
Hypofibrinogenemia	65—85 %
Elevation of transaminases	35—90 %
Hyperbilirubinemia	35—75 %

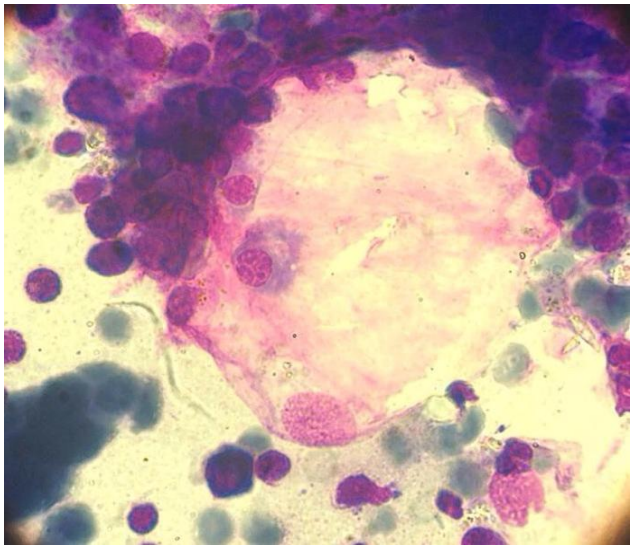

Fig-1: Erythroblast phagocytosis

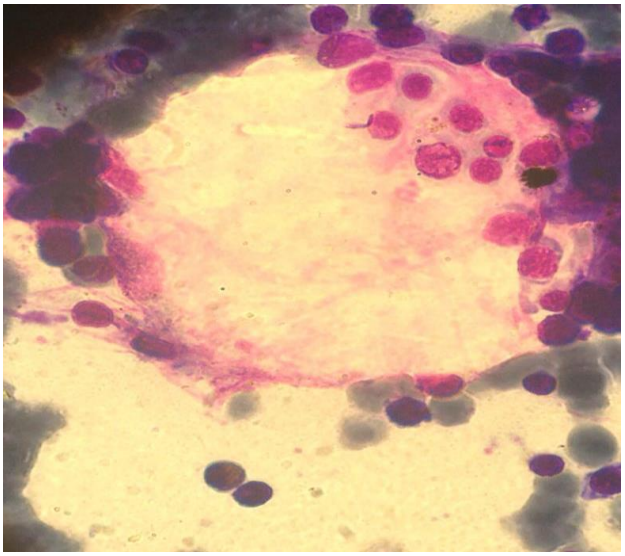

Fig-2: Phagocytosis of lymphocytes and erythroblasts

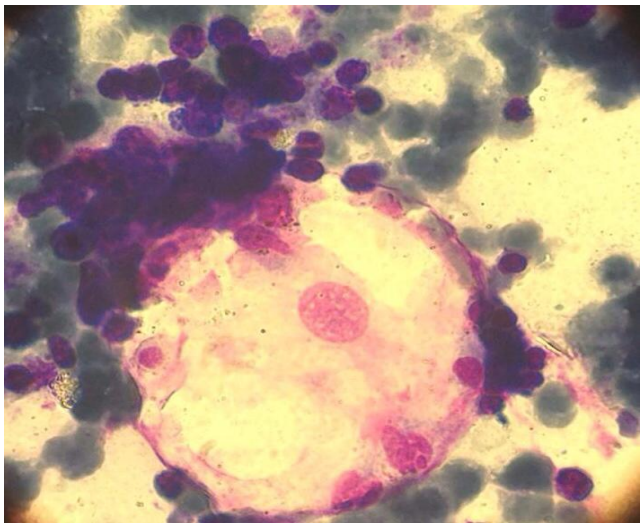

Fig-3: Phagocytosis of neutrophilic polynuclear cells and lymphocytes

In terms of the etiological diagnosis, the serology of the hepatitis B and C, the syphilis, the cytomegalovirus, the rubella, the toxoplasmosis and the leishmaniasis were performed and returned negative. A blood culture, also performed, was positive and had isolated a *Klebsiella pneumoniae*.

The patient was placed on antibiotics based on amoxicillin-clavulanic acid 3 g every day for 10 days. The evolution of the patient was marked by an improvement in the clinical and biological signs.

DISCUSSION

Macrophage activation syndrome is an underestimated pathology [7]. Its annual incidence is around 4 cases per year in subjects over 16 years and it was estimated to be 51.7 cases per year in Japan, by Imashuki, including pediatric and adult macrophage activation syndrome [8, 9]. Whereas it only represents 2.4 cases per year in the pediatric department of Hassan II University Hospital Center in Fez between 2005 and 2009 [10] .To date, the physiopathology of adult macrophage activation syndrome has not been yet fully elucidated. According to Pillet and all [2] this pathology could result from an inadequate immune response of the host due to cytotoxicity and is characterized by uncontrolled lymphoid-histiocytic proliferation and activation (CD8 T lymphocytes and macrophages) inducing a " hyper cytokinetic" dysregulation (IL-1, IL-6, IL-18, TNFα, IFNg).

The diagnosis of macrophage activation syndrome is based on the association of clinical, biological and cytological or histological signs. These diagnosis criteria have recently been redefined and are presented in Table 1 [11]. These criteria were established for the diagnosis of primary forms and are used by extension for the diagnosis of the secondary forms. Clinically, macrophage activation syndrome often occurs as a febrile condition, with splenomegaly and/or hepatomegaly, lymphadenop athy. It can also present skin rash, and neurological signs (Table 2) [12].

On the biological level, numerous abnormalities could be found, though they are not specific [Table: 3]. Indeed, it is their association with clinical signs that leads to evoke the diagnosis of macrophage activation syndrome. In the case of our patient, the clinical picture was marked by a fever, an alteration of the general condition, a peripheral lymphadenopathy, a rash, and a splenomegaly. As for the neurological signs, they were absent.

Biologically, our patient had bicytopenia, increased levels of lactate deshydrogenase and ferritinemia and had also a hypertriglyceridemia. The reference examination for the diagnosis of macrophage activation syndrome is the myelogram. The latter, makes it possible to objectify the intramedullary haemophagocytosis essential to the diagnosis [13]. Thus, it allows not only confirming the diagnosis of the macrophage activation syndrome but it also allows sometimes suspecting or confirming the etiology of this syndrome. In our case, the myelogram found images of macrophagic magmas associated with images of hemophagocytosis. This intramedullary hemophagocytosis may occur in other hematological conditions besides macrophage activation syndrome. It is therefore necessary but not sufficient for the diagnosis of the macrophage activation syndrome and its association with the clinical and biological signs remains, thus, indispensable to the diagnosis [14].

Macrophage activation syndrome is observed in multiple clinical situations: medication side effect , inflammatory disease, systemic autoimmune disease, neoplasia, infectious disease [15]. The infectious origin may be linked to viral, fungal or parasitic infections or, as our patient has been, bacterial ones [16].

Indeed, severe bacterial infections can evolve towards a macrophage activation syndrome, and take the form of multi organ failure. This case is frequently encountered in intensive care units.

Banal bacterial germs (*Staphylococcus spp*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumonia*e and other gram negative bacilli) have been described as the cause behind haemophagocytic syndromes [17]. A prospective study in an intensive care unit showed that a systematic myelogram in thrombocytopenic patients during a septic shock found an hemophagocytosis in 60% of cases [17]. Thus, hemophagocytosis is likely to be underestimated, especially in severe septic syndromes. It may also explain in part the pancytopenia observed in these cases [18].

Currently there are no randomized studies concerning the treatment of macrophage activation syndrome in adults. In addition to symptomatic treatment (transfusions, intensive care) and treatment of the causal disease, the specific therapeutics treatments described in the literature are aimed at decreasing the activation of T lymphocytes and macrophages.

The immunosuppressive treatments used are high-dose corticosteroids (prednisone at 1 mg for kg every day or even bolus of methylprednisolone) and cyclosporine which is used in particular on pediatric patients. The corticosteroids are rapidly effective, but their use may be deleterious in the case of the infectious macrophage activation syndrome [19]. The prognosis of MAS remains severe with about 50% mortality reported in the literature [5]. It depends on several parameters, including the earlier diagnosis, the initiation of an adapted anti-

infective treatment and the positivity of the etiological assessment. It also depends on the presence of an associated neoplastic etiology and the existence of an earlier defective immune status (HIV, immunodepression) [16].An analysis by Karras and Hermine of the main series published up to 2002 found a negative prognosis in 49% of cases [16]. In our case, the patient progressed favorably under antibiotic treatment, with a regression of the clinical symptoms associated to an improvement of the various biological parameters.

CONCLUSION

Macrophage activation syndrome is a rare clinical, biological and anatomopathological entity with a certain life-threatening morbidity, which requires a strict diagnostic approach and multidisciplinary therapeutic management that includes the collaboration of doctors from intensive care units, hematology laboratories and infectious diseases services, in order to determine the best options according to the etiology found and the gravity of the case.

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