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CASE STUDY

MACROPHAGE ACTIVATION SYNDROME AS ONSET OF SYSTEMIC LUPUS ERYTHEMATOSUS: A CASE REPORT

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ABSTRACT: Macrophage activation syndrome (MAS) belongs to the hemophagocytic lymphohistiocytosis group of diseases. It is an anatomo-clinical condition resulting from the inappropriate proliferation and activation of macrophagic cells. This rare but potentially fatal syndrome can be primary or secondary to certain pathologies dominated by infections and neoplasia. In adults, MAS is rarely associated with systemic lupus erythematosus, but it arises as a complication of several systemic autoimmune diseases. Here we report the case of 30-year-old woman who presented with a pruritic rush. She met the Systemic Lupus International Collaborating Clinics (CLICC) criteria for the diagnosis of Systemic Lupus Erythematosus (SLE). The bone marrow showed the presence of abundant hemosiderophages with focal hemophagocytosis. Due to the overlap in clinical findings, SLE-associated MAS might be underdiagnosed. This case represents the importance of prompt diagnosis and treatment of such a potentially fatal clinical syndrome.

KEYWORD: Macrophage activation syndrome, lymphohistiocytosis, Systemic Lupus International Collaborating Clinics, SLE-associated MAS

INTRODUCTION:

Macrophagic activation syndrome (MAS), classified among the group of hemophagocytic lymphohisticytosis (HLH), is a rare reticulo-endothelial system condition that causes an insufficient and exaggerated immune response to the host. It is a rare complication of autoimmune diseases, including systemic lupus erythematous.

Furthermore, MAS is characterized by non-specific activation of the monocyte-macrophage system, which results in activated histiocyte-macrophage proliferation and tissue infiltration, as well as phagocytosis of blood components, resulting in peripheral cytopenia [1]. The incidence of MAS associated with SLE is about 0.9-4.6**%** [1]. The symptomatology is not very specific, presenting with

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several signs and symptoms, including fever, deterioration of the central nervous system, and lethargy. Splenomegaly, hepatomegaly, and hemorrhagic symptoms like purpura. Pancytopenia, elevated liver enzymes, elevated LDH, and high blood triglyceride and ferritin levels are all indicative biochemical markers. Its diagnosis is frequently delayed, and the prognosis is bleak [3]. There is a distinction made between primary macrophagic activation syndromes, which are associated with genetic abnormalities, some of which are known, and secondary macrophagic activation syndromes, which can be induced by a variety of pathologies that have in common a significant stimulation of the immune system, such as viral, bacterial, and parasitic infections, neoplasms with malignant hemopathies at the forefront, and, more rarely, systemic diseases such as systemic lupus [4]. Systemic lupus erythematosus (SLE) is a non-specific auto-immune organ disease that may induce hemophagocytic syndrome (HS). The disease is characterized biologically by the formation of numerous autoantibodies against nucleus constituents, including the disease's native anti-DNA [5]. Macrophagic activation syndrome is a life-threatening consequence of systemic lupus erythematosus that is uncommon and poorly understood. MAS in association with systemic lupus erythematosus is a rare presentation that has mainly been described in case reports and retrospective studies. The goal of this study is to describe a patient who was admitted to the CHU Med VI in Marrakesh's internal medicine department with a macrophagic activation syndrome complicated by systemic lupus erythematosus.

OBSERVATION:

30-year-old woman with no prior medical history went to the emergency room with a pruritic rush that had lasted four days. She was hospitalized in the nephrology department for insufficiency function renal (urea at 0.45 g/L and creatinine at 23 g/L) linked with bicytopenia after experiencing arthralgia for a week in the context of fever, night sweats, and weight loss. She denied any shortness of breath or enlargement of the tongue.

On clinical examination, the patient had a fever of 37.8°C with feverish peaks of over 39°C for eight days. For a few days, the general condition deteriorated to the point of becoming debilitating, with severe asthenia and anorexia.

At the time of presentation, the hemogram revealed normocytic anemia at 9.7 g/dl, leukocytosis at 11.5 G/L (normal range: 4-10 G/L) and thrombocytopenia at 120 G/L (> 150 G/L). We started a laboratory test to rule out the presence of autoimmune, infectious, or neoplastic diseases. The initial biochemical investigations revealed hypertriglyceridemia at 2.6 g/dl (N: 1.5-2g/dl), without hypercholesterolemia, hyponatremia at 135 mmol/L, LDH at 820 U/L (N: 135-225 U/L), CRP at 22 mg/L (N:< 5mg/L), hyperferritinemia at 600 ng/L (N: 30-400ng/L), pancreatic and renal tests were normal. An emergency myelogram was performed due to the detection of angerogenic anemia, which was linked to a variety of clinical and biological issues. The latter objectified a rich marrow with modest granulocytic hyperplasia and, in particular, the presence of many macrophages with hematophagocytosis-like patterns (**figures 1, 2**).

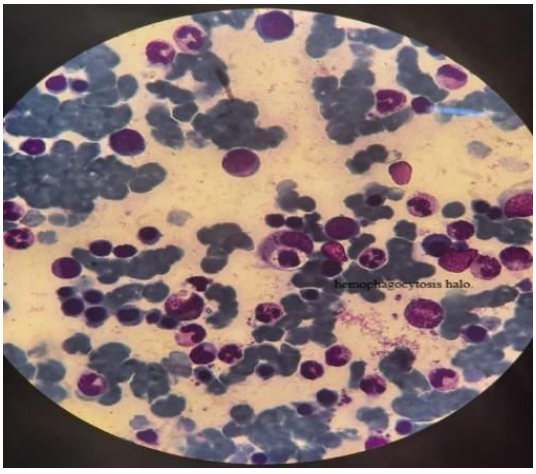

Figure 1: Macrophage phagocytizing an erythroblast and platelets (x100).

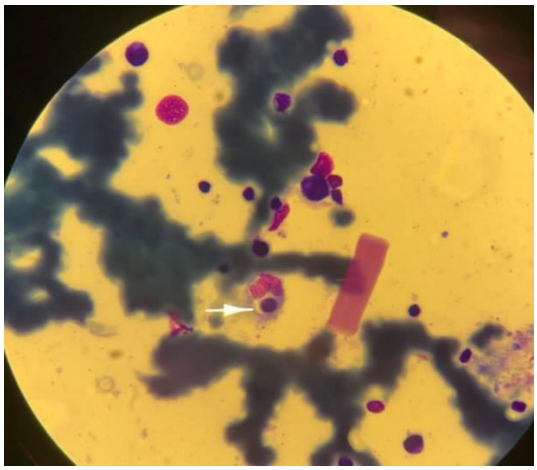

Figure 2: Macrophage phagocytizing an erythroblast. We observe the presence of the hemophagocytosis halo (x100).

The patient was referred to internal medicine for an etiological evaluation and suitable treatment. The dermatological examination revealed lymphadenopathy in the axillae, a discreet erythema of the cheekbones, symmetric arthritis involving hands and wrists, and bilateral pulmonary basal crackles. We had carried out repeated blood and urine cultures in search of an infectious etiology, none of which was contributing. Herpes simplex (HSV-1, HSV-2), Epstein-Barr virus (EBV), cytomegalovirus, hepatitis B and C, HIV 1 and 2 were all negative.

Immunological screening was positive for anti-nuclear antibodies (ANA) (1:620 homogenous), anti-SSA antibodies and positive anti-dsDNA antibodies.

We performed an abdominal ultrasound exam, finding moderate hepatosplenomegaly. A transthoracic heart ultrasound revealed a diffuse pericardial effusion without valvular vegetation, a chest X-ray and sinus X-ray were normal.

The diagnosis of MAS associated with systemic lupus erythematous was retained. The evolution was favorable after the first bolus of corticoid therapy. After the end of methylprednisolone therapy, the patient became apyretic, and skin rash disappeared. The laboratory parameters returned to normal levels within two weeks. The patient was discharged from the hospital and is now under follow-up.

DISCUSSION:

MAS is an inflammatory state in which various pathophysiological pathways are interwoven. The beginning of this disease appears to be associated with aberrant T lymphocyte activation and cytotoxicity (enabling the causal agent to persist) primarily of Th1 and Natural Killer (NK) profiles, with no restriction on their activation capability or cytokine production [2]. The macrophagic response will be stimulated by the large synthesis of pro-inflammatory cytokines [3]. Activated macrophages, on the other hand, produce other cytokines that have a positive feedback loop with lymphocytes, maintaining the amplification loop. Both clinical and biochemical indications of MAS are caused by macrophage activation. The increased production of gamma interferon, IL-6, or IL1 is secondary to fever, which is nearly always an indication of MAS. Phagocytosis, cytokine apoptosis, and myelosuppression all contribute to pancytopenia. Organomegaly is connected to activated macrophages and lymphocytes infiltrating the tissue. Hepatic cytolysis is hypothesized to be caused by intrahepatic macrophage hyperplasia (Kupffer cells).

Hypertriglyceridemia is hypothesized to be caused by inflammatory cytokines inhibiting lipoprotein lipase (TNF-and IL-1) [4]. Erythrophagocytosis, liver injury, and systemic inflammation all contribute to hyperferritinemia [5]. MAS has been found in a variety of inflammatory and systemic illnesses. The most prevalent are still's disease and systemic lupus [6-7]. Immunosuppression caused by the disease and aggravated by immunosuppressive thereby can increase the formation of MAS, which is a rare but significant consequence.

Clinical, biochemical, and cytological or histological criteria are used to diagnose MAS. The French LHH group has published diagnostic criteria, which

include having at least five of the eight criteria to carry out a MAS diagnosis (**Table 1**). Six of the eight requirements were met by our patient [1-8].

Table 1: Diagnostic criteria for macrophagic activation syndrome according to the French group of LHH and presented by the patient.

Diagnostic criteria	Patient
At least five of the eight criteria	
Temperature >38.5°C for 7 days at least	Yes
Spleen enlargement	Yes
Cytopenia affecting 2 or more cell lines	Yes
Hemoglobin <9g/dl	Yes
Platelets <100,000/mm3	Yes
Neutrophils <1000/mm3	Yes
Ferritin >500ug/L	Yes
Hypertriglyceridemia>3mmol/L and/or hypofibrinogenemia (<1.5g/L)	Yes
Soluble IL2 receptor (sCD25)>2400UI/mL	Not realized
NK activity decreased or absent	Not realized
Hemophagocytic cells in bone marrow, spleen, or lymph nodes	Yes

The clinical indications of SLE and MAS can be misled, but the scientific evidence points to a macrophagic activation syndrome, with aregenerative anemia as a key feature. highlighting hemophagocytosis figure on the myelogram is critical in establishing the diagnosis of MAS. Other cytological tests (lymph node aspiration, liver biopsy, ascites fluid examination, cerebrospinal fluid investigation, skin biopsy, lung biopsy, and so on) can be useful but are not frequently performed [9].

We observe a rich marrow with histiocytes and macrophage infiltration, the number of which is gradually increasing. Macrophages are morphologically benign (nucleus not very large, with fine chromatin, sometimes nucleated, with a low nucleocytoplasmic ratio) and contain numerous intracytoplasmic vacuoles containing intact or partially digested figured elements of the blood (erythrocytes, erythroblasts, granulocytes, platelets, lymphocytes) or their hematopoietic precursors. At the same time, a single cell can phagocyte many cell types. However, it is important to remember that hemophagocytosis is a physiological process, and

for some authors, the percentage of macrophages in hemophagocytosis (> 2% for Wong et al [10], and > 3% for Tsuda an al. [11]) is a significant diagnostic criterion. There is no link between the quality of spinal histiocytes and the severity of the condition, according to research [12]. Some authors require a figure without any notion of percentage [4-13].

Other biological conditions, such as aregenerative anemia with hemolysis stigmas, are frequently[14], hypofibrogenemia or thrombocytopenia cause hemostasis problems that develop to disseminated intravascular coagulation [10-15], increased LDH, hepatic cytolysis and hyponatremia. The level of procalcitonin can guide the etiological diagnosis.

Deep pancytopenia, hyperferritinemia, and hypertriglyceridemia are uncommon in lupus and should be considered a sign of MAS, hyperferritinemia in 95.4% of cases [16], increased LDH in 92.3% of cases, hypertriglyceridemia in 89.6% of cases [11] and abnormal liver function tests in 80.8% of cases [17].

The AAN and native anti-DNA antibody assays were both positive in our case. This is consistent with previous research, which found that antinuclear antibodies (ANN) and native anti-DNA antibodies (DNA) were positive in 100% of cases, respectively. Hypocomplementemia was found in 7% of cases. When the SLE was suspected of being cause of MAS, at least one of these immunological abnormalities was discovered.

MAS appears to describe a severe type of SLE with a high risk of recurrence and numerous lupus flares that are difficult to manage even with long-term immunosuppressive medication. MAS linked with SLE had a mortality rate of 9.6%, which is lower than the average seen for all causes of MAS combined (49%).

CONCLUSION:

Macrophagic activation syndrome is an uncommon onset pattern of systemic lupus erythematosus and an unknown cause of fever during the course of the disease. The clinical symptoms of MAS and SLE are often confused, and only laboratory tests such

as ferritinemia, triglyceride determination, and liver enzymes can help distinguish the two. The presence of hemophagocytosis on the myelogram allows us to draw a conclusion.

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