MACROPHAGE ACTIVATION SYNDROME IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CASE REPORT

SINDROME DE ATIVAÇÃO MACROFAGICA EM PACIENTE COM LUPUS ERITEMATOSO SISTEMICO: RELATO DE CASO

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ABSTRACT

Macrophage activation syndrome is a complication present in autoimmune diseases, triggered by hyperactivation of the inflammatory cascade, leading to persistent fever, coagulopathy, hepatosplenomegaly, lymphadenomegaly, exanthema and neurological changes, causing multiple organ dysfunction. Its diagnosis has criteria well determined by a score. Its treatment is based on immunosuppressive therapies, using corticosteroids, cyclophosphamide and, in refractory cases, immunoglobulins. The present case study reports a young woman with SLE, presenting macrophage activation in the city of Valença-RJ, with a diagnosis based on the criteria of the "Histiocyte Society score" (2004) and therapy for the condition.

KEYWORDS: As macrophage activation syndrome, systemic lupus erythematosus, lymphocytic lymphohistiocytosis.

RESUMO

A síndrome de ativação macrofágica e uma complicação presente em doenças autoimunes, desencadeada por hiperativação de cascata inflamatória, levando a febre persistente, coagulopatia, hepatoesplenomegalia, linfadenomegalia, exantema e alterações neurológicas, causando disfunção de múltiplos órgãos. Seu diagnostico possui critérios bem determinados por um escore. Seu tratamento se baseia em terapêuticas imunossupressoras, podendo utilizar corticoterapia, ciclofosfamida e em casos refratários, imunoglobulinas. O presente estudo de caso relata quadro de mulher jovem, lúpica, apresentando ativação de quadro macrofágico no município de Valença-RJ, sendo feito diagnostico baseado nos critérios do "*Histiocyte Society score*" (2004) e realizado terapêutica para o quadro.

PALAVRAS-CHAVE: Síndrome de ativação macrofagica, lúpus eritematoso sistêmico, linfohisticitose linfocitica.

1. INTRODUCTION

Macrophage activation syndrome (MAS) or hemophagocytic lymphohitiocytosis is a rare pathology with an incidence of 1 in 50,000 inhabitants, which can be primary or secondary[1].

The primary form of the disease is genetic, being an autosomal recessive alteration that implies the cytotoxic function of lymphocytes. The secondary or acquired form is a complication of autoimmune diseases, mainly juvenile idiopathic arthritis (JIA) and adult still disease, but it can also occur in systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), Kawasaki syndrome (KD) and in juvenile dermatomyositis (JDM). It can be triggered by drugs (anti-inflammatory drugs, methotrexate, sulfasalazine, leflunomide) and infections (viral, bacterial and fungal), mainly by herpes viridae such as Epteins-Barr and Parvovirus B19[2].

Table 1. classification of macrophage activation syndrome.

1-	Primary
2-	familiar
3-	Secondary
a-	Infectious states -virus (varicella zoster, hepatitis A, parvovirus, Epstein-Barr, coxsackie B) - bacteria - Parasites - Fungi
b-	Neoplasms / lymphoproliferative diseases -lymphoma, multiple myeloma, acute leukemia
c-	Autoimmune diseases - juvenile idiopathic arthritis - systemic lupus erythematosus - Kawasaki disease - Adult Still's disease (rare)
d-	Drugs -non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, gold salts, penicillamine, etanercept

Source: Rosa, et al. (2007)[3].

Its pathophysiology involves exacerbated activation of the pro-inflammatory cascade resulting in hypercytokinemia and uncontrolled mononuclear

phagocytic system marked by hemophagocytosis, antigenic presentation and persistent activation of T lymphocytes[1,3].

It is a serious clinical condition that presents with persistent fever, coagulopathy, hepatosplenomegaly, lymphadenomegaly, exanthema, and neurological changes, causing multiple organ dysfunction. Laboratory tests show varying degrees of pancytopenia, changes in liver enzymes, increased lactic dehydrogenase, hypertriglyceridemia, hyperferritinemia, increased inflammatory tests, soluble CD25, soluble CD163, D-dimers, prothrombin time (PT) and partial time prolongation. of activated thromboplastin (aPTT), as well as hypofibrinogenemia and the presence of hemophagocytosis in the bone marrow, spleen, liver or lymph nodes confirms the diagnosis[1,4].

Table 2. Diagnostic criteria for lymphohistiocytic hemophagocytosis (HLH).

	A- Molecular diagnosis compatible with HIH: pathological mutations of PRF1, UNC13D, Munc 18-2, Rab27a, STX11, SH2D1A, or BIRC 4.
	OR
	B- 5 of the eight criteria listed below:
	1- Fever (temperature greater than 38.3°C);
	2- Splenomegaly;
	3- Cytopenias (at least two lineages involved)
	3.1- Hemoglobin < 9g/dL or 10g/dL in newborns
	3.2- Platelets < 100,000 mL
	3.3- Neutrophils < 1,000 mL;
4.	Hypertriglyceridemia (> 265mg/dL) or hypofibrinogenemia (< 150 mg/dL);
5.	Hemophagocytosis in bone marrow, spleen, lymph nodes or liver – no evidence of malignancy;
6.	Decreased or absent NK cell activity;
7.	Serum ferritin > 500mg/dL;
8.	Increased soluble CD25 (> 2,400U/mL)

Histiocyte Society – Treatment Protocol of The Second International HLH Study 2004.

Due to the severity and the high risk of mortality, treatment should be started early, with the first-line administration of high doses of corticosteroids in the form of pulse therapy with intravenous methylprednisolone or oral prednisone 1mg/kg/day. Another medication commonly used in therapy is cyclosporine A, reserved for refractory cases. Other therapeutic modalities can be used, such as intravenous human immunoglobulin, cyclophosphamide, plasmapheresis. It is important for the treatment to control the triggering factor as well as the correction of associated disorders, the most common hydroelectrolytic disorder being hyponatremia[4].

2. CASE REPORT

Patient, 39 years old, female, black, diagnosed with systemic lupus erythematosus for 1 year, using hydroxychloroquine 400mg/day and prednisone 5mg/day at home, was admitted to the emergency department on 09/08/2020, with a report that 2 weeks ago he started with a fever of 40ºc refractory to the use of antipyretics, associated with inappetence and adynamia, evolving with nausea, vomiting and liquid, green diarrhea without blood, mucus or pus and abdominal cramps. She reported using amoxicillin with clavulanate three days on her own before seeking medical attention, with no improvement. Hospitalization was performed, laboratory tests were requested, and symptomatic prescriptions were prescribed. The gastrointestinal symptoms improved, but fever remained. Laboratory investigation showed pancytopenia and hyponatremia; serology for hepatitis B, hepatitis C and HIV negative, as well as serology for cytomegalovirus IgG positive and IgM negative, toxoplasmic IgM negative and IgG negative, serology for herpes simplex reagent IgG and non-reactive IgM, Epstein-Barr non-reactive IgM and Reagent IgG. The other exams showed urinary tract infection with discrete proteinuria and granular casts, chest computed tomography did not suggest an infectious process and USG of the total abdomen without alterations, showing no splenomegaly. Initiated cefepime 2g 8/8h due to febrile neutropenia. The remainder of the investigation demonstrated maintenance of pancytopenia, anti – DNA: non-reactive, anti - SSA RO 240 U/mL and anti – SM 16 U/mL , c3 complement: 46 mg/dL ; c4: 12 mg/dL, direct Coombs: negative, iron: 22 mcg/dL, ferritin: 8250 ng/mL / haptoglobin: 1 mg/dL / reticulocytes: 1.6%/ triglycerides: 348 mg/dL; Aldolase 4.9 U/L; protein electrophoresis with polyclonal increase in the gamma globulin region; microalbuminuria 6.2 mcg/mg creatinine; anti-SM 7.7 U/ml; cardiolipin IgG 2.5 U-GPL/ml; cardiolpin IgA 44 U-APL/ml; cardiolipin IgM 2.9 U-MPL/mL; C3 complement 120mg/dL; complement CH50 154 u/CAE; C4 complement 33mg/dL. Bone marrow aspirate was requested, which showed hemophagocytosis. In view of these results, pulse therapy with methylprednisolone (1g/day for 3 days) was initiated, with the patient's base weight of 66kg, and after prednisone 60mg/day (1mg/kg/day) was started. The patient evolved with worsening of the general condition, tachypnea and adynamia, associated with bullous lesions on the lips, being then transferred to the ICU (INTENSIVE CARE UNIT) and escalated antibiotic therapy to meropenem and vancomycin for 7 days due to nosocomial pneumonia. On the same day, cyclosporine (200mg/day) was started with a therapeutic schedule of 8 weeks. The patient maintained a persistent fever, even after taking the medications, and then therapy with intravenous immunoglobulin was started (2 stages). Still in the ICU, he developed voluminous epistaxis, caused by dry nasal polyp evaluated by otorhinolaryngology. Due to the maintenance of anemia, blood transfusion was performed without complications. The patient evolved with clinical improvement, being transferred to the ward, but maintaining pancytopenia and being opted for a new pulse therapy with methylprednisolone for three days. Patient with clinical and laboratory improvement, was discharged with prescription of prednisone 1mg/kg/day and cyclosporine 200mcg/day, hydroxychloroquine 400mg/day, being then referred to the rheumatology outpatient clinic, where therapy with

azathioprine was started, maintaining hydroxychloroquine and prednisone with stability. of the board and maintaining follow-up with expertise.

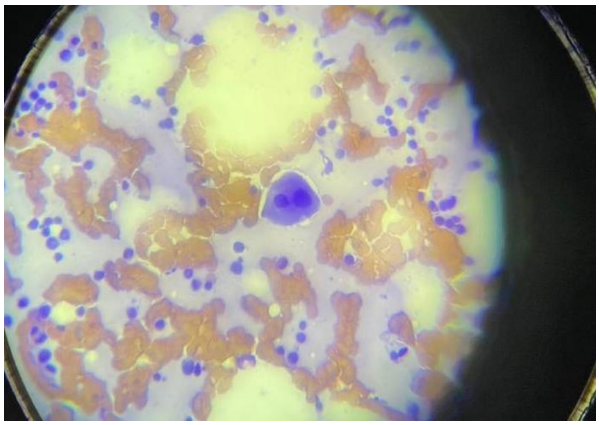

Figure 1. presence of hemophagocytes in the bone marrow aspirate. **Source:** The Author.

3. DISCUSSION

Macrophage activation syndrome is a complication present in rheumatologic diseases, in systemic lupus erythematosus and juvenile idiopathic arthritis, which often progresses with severity. In this work, we describe the condition of a young woman, with lupus diagnosed approximately 1 year ago, who presented a complication as a form of macrophage activation syndrome, evolving with severity during hospitalization, being compatible with the course of the disease and with the epidemiological range. for the appearance in lupus patients[5].

The diagnosis for macrophage activation syndrome in this patient was guided by the previous clinical presentation of lupus, and by the Histiocyte Society Score 6, which presented fever, cytopenia, hypertriglyceridemia, hyperferritinemia, hemophagocytes in the bone marrow aspirate, scoring in 5 of the 8 criteria, it was not possible to evaluate the genetic study, dosage of NK cell activity and CD25 count at the service. Among the criteria researched, there was no score for splenomegaly, seen with no changes in abdominal ultrasound[3,5].

The treatment of macrophage activation syndrome initially consists of suspending base drugs, correction of hydroelectrolytic and coagulation disorders, as well as other associated disorders. The mainstay of therapy is immunosuppression with corticosteroids, usually performed in the form of pulse therapy with methylprednisolone at a dose of 30mg/kg/day for 3 to 5 consecutive days. As a second-line drug, we have cyclosporine, which is used in cases that are refractory to corticosteroid therapy, being used at a dose of 1 to 3 mg/kg/day. The use of intravenous immunoglobulin can be used, usually at a dose of 2g/day, but its benefit must be weighed due to the possibility of immunosuppression with an increase in the number of cases of opportunistic diseases, which can worsen the outcome of the condition[3]. In the present report, correction of associated disorders was performed, such as hydroelectrolytic disorders and treatment of an infectious focus, followed by pulse therapy with methylprednisolone at a dose of 1g/day for 3 days, with no satisfactory response. In view of the failure of the first attempt with stent therapy, cyclosporine was started at a dose of 200mg/day (3mg/kg/day) and, due to severity, immunoglobulin was associated, which was performed in two stages[2,4].

He progressed with improvement, but after finishing the immunoglobulin, while still on cyclosporine, he presented new cytopenia and a new pulse therapy with methylprednisolone 1g/day for three days associated with cyclosporine which was already in use was performed, showing a satisfactory

4. CONCLUSION

Despite its rarity, macrophage activation syndrome is a diagnosis to remember in patients with sudden onset of persistent fever, hepatosplenomegaly, acute liver failure and pancytopenia. Due to its severity, rapid diagnosis and early therapy are required. In addition, it is well known for its correction with rheumatologic

5. REFERENCES

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