Reactive haemophagocytic syndrome in a systemic lupus erythematosus patient – case report

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ABSTRACT

The macrophagic syndrome or reactive haemophagocytic syndrome (RHS) is a complication resulting from systemic inflammatory diseases and may also be related to malign neoplasias, immunodeficiencies and to a variety of infections caused by virus, bacteria, and fungus. It is characterized by an excessive activation of macrophages and histiocytes along with intense hemophagocytosis in bone marrow and reticulum-endothelial system, causing the phagocytosis of erythrocytes, leukocytes, platelets, and their precursors. The clinical manifestations are fever, hepatosplenomegaly, lymphadenomegalies, neurological involvement, variable degrees of cytopenias, hyperferritinemia, liver disorders, intravascular coagulation, and multiple organs failure. We report a rare case of recurrent RHS complication in a systemic lupus erythematosus male patient after two years. Although extremely rare it has evolved with an improvement after a pulse methilprednisolone and cyclophosphamide therapy.

Keywords: reactive macrophage syndrome, hemophagocytic lymphohistiocytosis, systemic lupus erythematosus.

INTRODUCTION

The reactive haemophagocytic syndrome (RHS), well-known as hemophagocytic lymphohistiocytosis, is a potentially lethal, rare, clinical, and pathological condition characterized by a massive production of proinflammatory cytokines, which causes clinical manifestations and frequently results in multiple organs failure. The clinical picture presents fever, hepatosplenomegaly, pancytopenia, limphadenopathy, neurological involvement, and comsumption coagulopathy.[1,2] It can be associated with systemic infections, immunodeficiencies, lymphoproliferative, and autoimmune diseases. Among the inflammatory diseases the juvenile idiopathic arthritis with systemic onset is the most frequently described disorder.[3–5] Its clinical presentation in juvenile systemic lupus erythematosus (SLE)[6] and in juvenile dermatomyositis[7] is sporadic.

We report a case involving a patient diagnosed with SLE who presented with two RHS episodes. The clinical picture was controlled with the recognition of complication and appropriate treatment based on corticotherapy, pulses of cyclophosphamide (CPM) and cyclosporine.

CASE REPORT

A 49-year-old male patient presented with polyarthralgia, weight loss of 15 kg in a year, evening fever, night sudoresis, positive antinuclear factor, pointed pattern (1:200), anti-RNP antibodies (1:500), positive anti-Ro and anti-Sm antibodies, polyclonal hypergammaglobulinemia, hemolytic anemia, and 1 g/24 hours proteinuria. He was diagnosed with SLE and treated using pulse therapy associated with methylprednisolone (three pulses) and CPM (12 monthly pulses), followed by prednisone and azathioprine, obtaining a controlled disease.

Four years later the patient returned reporting daily fever (39°C–40°C) for a month, generalized weakness, dorsalgia, sudoresis, and discrete weight loss, when he was readmitted to hospital for better investigation. The routine laboratory examinations showed increased levels of transaminases, leukopenia,

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Table 1
Laboratory findings at admission during hospital stay

Date	HCTO	HB	PTL	LC	ESR	GOT/GPT	LDH	Hyperferritinemia
10/20/2005	39.1	12.1	120,000	3,990	74	104/60		
10/26/2005	32.4		102,000	3,650		287/156	808	
10/31/2005					85	96/93		15,900
11/01/2005								9,314
11/03/2005	26.8	8,58	91,000	3,480	65	118/82		
11/08/2005	22.8		116,000	3,700	104	100/77		
11/10/2005	26.7		171,000	5,510	100	63/77		7,590
12/16/2005	39.2	12.1	207,000	6,700	37			422

HCTO: hematocrit; HB: hemoglobin; PTL: platelets; LC: leucocytes; ESH: erythrocyte sedimentation rate; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyruvic transaminase; LDH: lactate dehydrogenase.

thrombocytopenia, positive direct Coombs, elevated erythrocyte sedimentation rate, hyperferritinemia, in addition to a 1240-mg proteinuria level in 24-hour specimen of urine along with negative blood culture and urine culture (Table 1).

The echocardiogram revealed grade I diastolic dysfunction with a mild increase in the volume of right heart cavities associated with a slight tricuspid incompetence and 37-mmHg pulmonary arterial pressure. It was detected hepatomegaly. The peripheral blood exam showed anisopoikilocytosis, tear shaped erythrocytes, acanthocytes, neutrophils presenting the Pelger-Huet anomaly, and a mild thrombocytopenia. The bone marrow aspiration procedure revealed erythroid hypoplasia, interrupted maturation with a discrete dyserythropoietic anemia, presence of histiocytes which have phagocytes absorbing erythroid and myeloid line cells, normal hypogranular myeloid cells, and megakaryocytes. The patient improved his clinical picture after being treated with methylprednisolone pulse therapy.

Two years later the patient returned with worsening of overall health status, presenting fever up to 40°C and dyspnea to minimal efforts which started 18 days before his return. He was admitted to the hospital and the antibiotic therapy was introduced evolving with disorientation. The patient underwent cranial computed tomography which presented no changes. The cerebrospinal fluid (CSF) analysis showed 101 cell/m^3, with 94% mononucleated cells, 100 mg/dL protein and 22 mg/dL glucose. The patient underwent therapy with acyclovir.

The patient presented an increase in hepatic enzymes, pancytopenia, moderate anemia and hyperferritinemia. CSF cultures were negative for fungi, acid-fast bacilli, bacteria, mycobacteria, and cytomegalovirus. The patient evolved to acute lung edema and to acute respiratory distress, being performed orotracheal intubation and mechanical ventilation. It was introduced the pulse of methylprednisolone therapy for three days with no significant improvement. Cyclosporine has been gradually introduced for controlling the clinical picture. The patient was discharged from hospital and treated with low doses of corticoids and cyclosporine.

DISCUSSION

We describe a rare case involving a patient with SLE who developed an episode of RHS with recurrence of this complication after two years. There are several triggering factors but the infectious processes are important starting elements for this complication.[8,9]

The clinical manifestations can be explained by overproduction of pro-inflammatory cytokines (interleukin 1, tumoral necrosis factor, gamma-interferon, among others), which are responsible for this severe complication.[10–12]

The diagnostic difficulty is due to the fact that disease activity shares common signs and symptoms, in addition to clinical pictures associated with infectious agents.[13,14] According to many authors the presence hiperferritinemia is a highly suggestive sign of reactive macrophage disease and this factor associated with the bone marrow aspirate has defined RHS clinical features.[15] The patient presented the diagnostic criteria for hemophagocytic syndrome proposed by the Histiocyte Society[16] and by Imashuku,[17] Tsuda,[18] and Ishikura,[8] characterized by the presence of fever, cytopenia, hyperferritinemia, an increase in lactate dehydrogenase, and prominent hemophagocytosis in bone marrow aspirate. Although the SLE in itself may trigger this severe complication,[19] we can not exclude the possibility that an infectious clinical picture may have been the starting point in our patient's second episode, considering that the CSF clinical features were compatible with viral

infection. The clinical features such as fever, pancitopenia, and hiperferritinemia have also suggested the possibility of recurrent RHS which improved after immunosupression, but with no confirmation due to lack of exams showing the clinical picture as peripheral blood studies and myelogram. In many cases is not possible to determine the triggering etiological factor of hemophagocytosis.

Good responses to the pulse methylprednisolone and cyclophosphamide therapies following the cyclosporine treatment have already been described in medical literature presenting satisfactory results in many case reports.[8]

The difficulty for excluding an associated infection delays the beginning of immunosuppressive therapy, which is critical for treatment and for this incident evolutionary process. Hemophagocytosis must be suspected in patients with systemic inflammatory diseases such as SLE and those patients who present with clinical and/or laboratorial manifestations suggestive of RHS.

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