

CASE REPORT

Systemic Lupus Erythematosus and Its Association with Hemophagocytic Syndrome as an Initial Manifestation

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BACKGROUND

Introduction: Hemophagocytic syndrome (HS) is a potentially fatal hyperinflammatory condition characterized by excessive activation of macrophages and T cells. Systemic lupus erythematosus (SLE) is an autoimmune condition that predisposes to HS. The appearance of SLE and HS is rare.

Clinical case: A 16-year-old male presented with fever for one month and lymphadenopathy prior to admission. During evaluation, the patient accumulated 10 points required by EULAR/ACR 2019 for classifying the condition as SLE. Hemophagocytosis was observed in the bone marrow aspirate. The diagnosis of HS secondary to SLE was concluded. Under treatment with intravenous methylprednisolone and mycophenolic acid, symptoms improved and the patient was subsequently discharged.

Discussion: The most typical findings of HS include fever, hepatosplenomegaly, and cytopenias, with lymphadenopathy being the least common. The characteristics of SLE and HS are very similar, making it difficult to differentiate between these two entities.

Conclusion: Although HS is not one of the frequent manifestations of SLE, a high suspicion of its possible association with SLE must be maintained for timely treatment.

Keywords: systemic lupus erythematosus, hemophagocytic síndrome, hemophagocytic lymphohistiocytosis.

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INTRODUCTION

Hemophagocytic síndrome (HS) is a life-threatening disease mediated by the immune system, first described in 1939 by two pediatricians, Scott and Robb Smith. It is caused by alteration in the function of natural killer cells and cytotoxic T cells (1).

Hemophagocytic síndrome is characterized by fever, hepatosplenomegaly, and cytopenias, but also by activated macrophages in hematopoietic organs. It has been given different names, including macrophage activation syndrome, which was used for patients with rheumatological diseases such as juvenile arthritis. In 1992, the Histiocytic Society proposed the name hemophagocytic lymphohistiocytosis (1). Hemophagocytic lymphohistiocytosis is divided into primary and secondary, the latter being subclassified as virus-related, autoimmunity, or neoplasia (Table 1) (1).

Viral infection is the most common trigger in secondary HS. The prevalence of HS is higher in Still's disease compared with SLE (1, 2).

The pathogenesis of secondary HS is not well understood. In most cases, cytotoxic lymphocyte degranulation and toxicity are not affected. However, the balance between antigen-presenting cell activation and cytotoxic T-lymphocyte-mediated control can be disrupted by increased antigen-presenting cell activation. Intracellular pathogens can activate the antigen-presenting cell directly – for example, through activation of toll-like receptors, which could also be stimulated by anti-DNA antibodies in SLE (1, 2).

The most typical findings are fever, hepatosplenomegaly, and cytopenias. Other clinical findings include hypertriglyceridemia, hypofibrinogenemia, liver dysfunction, elevated ferritin levels, lymphadenopathy, edema, and skin rash. Histopathological findings include hemophago-

cytosis, especially affecting the spleen, lymph nodes, and bone marrow (3).

Below we describe the case of a patient who presented HS associated with the initial manifestations of SLE. □

CLINICAL CASE

A 16-year-old man presented with fever for one month prior to admission, generalized fatigue and fever quantified at 39.5° C, associated with predominantly lower extremities mealgias and accompanied by a weight loss of approximately 5 kg as well as axillary and cervical lymphadenopathy. For these reasons, he had visited a private doctor, who prescribed him a seven-day treatment with Doxycycline. There was no post-treatment improvement, with episodes of fever persisting. Therefore, he fixed an appointment with another doctor, prior to which he had a general urine test showing *E. coli* with 400,000 colony-forming units; given that no antibiogram had been done, he was treated with a third generation aminoglycoside and cephalosporin regimen but without any improvement in febrile episodes and with persistence of the previously mentioned adenopathies. Thus, he came to the emergency department of our hospital, where admission was decided in order to explore the persistent fever syndrome.

Upon admission to the unit, he was feverish and presented cervical, axillary and inguinal adenopathies as well as hepatosplenomegaly. Following admission, laboratory analyses were performed, showing hemoglobin 7.8 g/dL, hematocrit 26%, leukocytes 5,900 K/uL, neutrophils 3650 K/uL, lymphocytes 1,500 K/uL, platelets 411,000 K/uL, creatinine 0.9 mg/dL, and DHL 155 U/L.

A tomography of the neck, chest and abdomen was requested, which reported adenopathy in both axillary and inguinal regions with a size of up to 4 cm, and a spleen of 12.1 cm x 5.3 cm. A

TABLE 1. List of diseases and processes associated with hemophagocytic syndrome

Viral infection	Neoplasms	Autoimmune diseases
Epstein Barr	B cell lymphoma	Systemic lupus erythematosus
HIV	Hodgkin lymphoma	Rheumatoid arthritis
Herpes virus	T-cell lymphoma	Vasculitis
Viral hepatitis	Leukemia	Still's disease

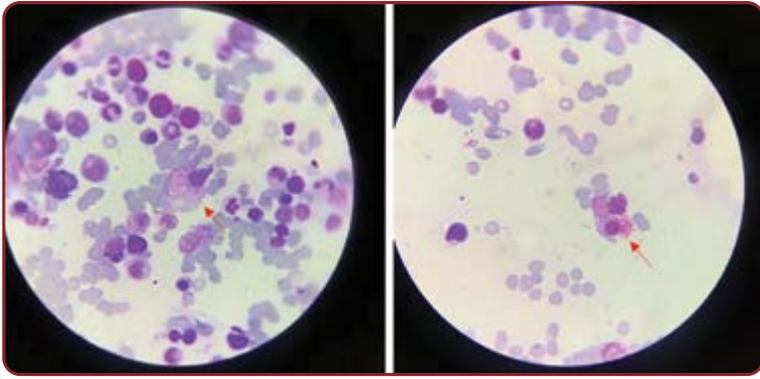


FIGURE 1. A) Hypercellular bone marrow; the arrow indicates a histiocyte phagocytosing myeloid and erythroid precursors; there are no alterations in red and myeloid series. B) The arrow indicates hemophagocytosis of myeloid series.

lymphoproliferative process was suspected, which is why a lymph node biopsy was performed, showing an atypical lymphoid proliferation. Therefore, it was decided to refer him to the Hematology service for a bone marrow aspirate, which was reported as normal cell for the patient's age with the presence of 1-2 megakaryocytes *per field* in the cell count. It showed 37% erythroid precursors, 44% myeloid series, 6% promyelocytes, 11% bands, 18% neutrophils, 8% eosinophils, in addition to the presence of 1% plasma cells, 4% monocytes and 9% phagocytic histiocytes, predominantly erythroid series (Figure 1).

Therefore, he was admitted to the Hematology service with a diagnosis of hemophagocytic syndrome, probably associated with a lymphoproliferative process. However, the immunohistochemical report of the lymph node biopsy showed negative BCL, positive CD20, positive CD 5, negative CD3, with a final report of sinusoidal and follicular hyperplasia, thus ruling out the association with a lymphoproliferative process.

Other laboratory analyses showed ferritin 575.69 ng/mL, Direct Coombs +++, fibrinogen 750.19 mg/dL, triglycerides 230 mg/dL, antinuclear antibodies by chemiluminescence 12.0 (reference, negative <1.5 index, positive >1.5 index), hypocomplementemia C3 41 mg/dL, C4 7.2 mg/dL, rheumatoid factor <15 IU/mL, anti-citrullinated peptide antibody 1.9 U/mL, ANCA c 10.6 UR/mL, ANCA p 3.16 UR/mL, Anticardiolipin IgG 2 GPLU/mL, IgM 2 MPLU/mL, anti double-stranded DNA antibody 44.5 IU/mL (weak positive 35-99 IU/mL), anti-

Smith antibody 60.68 RU/mL (positive > 5.0 RU/mL), beta II glycoprotein IgG 3.22 RU/mL, IgM 3.96 RU/mL, general urine test with density 1.0100, pH 5, protein 30 mg, sediment with 10 leukocytes *per field*, abundant erythrocytes and abundant granular casts as well as a 24-hour urine protein collection reporting proteinuria of 1.7 grams in 24 hours.

Based on the previously described laboratory results, a rheumatologist's opinion was asked.

The diagnosis of hemophagocytic syndrome was made based on findings in the bone marrow aspirate secondary to SLE, which also showed activity at the renal level. Therefore, methylprednisolone pulses were started for three days, accompanied by mycophenolic acid, which led to clinical improvement and fever remission. Thus, the patient was discharged, with the recommendation to take the prescribed treatment based on Azathioprine 50 mg every 24 hours and mycophenolic acid 1 g every eight hours.

During hospitalization, he only met four of the five criteria for HS of the HLH 2004 (Diagnostic criteria of the hemophagocytic lymphohistiocytosis 2004 protocols), but accumulated 10 risk points for the development of HS based on the bone marrow (BM) score. Therefore, previously associated infectious processes were ruled out, leaving the diagnosis of SLE as a secondary cause of HS. □

DISCUSSION

We report the case of a young man whose SLE manifested as hemophagocytic syndrome. His laboratory tests indicated positive antinuclear antibodies, meeting the 10 points required by EULAR/ACR 2019 to classify the condition as SLE (fever two points, proteinuria > 0.5 g/24 h four points, and C3 with C4 under four points). Fever, lymphadenopathy, hepatosplenomegaly, hemophagocytosis and hyperferritinemia met four of the five criteria required by HLH 2004 for HS. However, using the BM score, which has a sensitivity and specificity of 95% and 75%, respectively, the young man accumulated the 10 points necessary to be classified as a patient at risk of developing HS. Therefore, he was diagnosed with SLE that initially manifested with SH (3, 4).

Hemophagocytic syndrome is a clinical syndrome of dysregulatory activation of the immune

TABLE 2. List of diseases and processes associated with hemophagocytic syndrome

	Case 1	Case 2	Case 3	Case 4
Age	10 years	15 years	16 years	57 years
Gender	Female	Female	Male	Male
Fever	Yes	Yes	Yes	Yes
Hepatosplenomegaly	Yes	Yes	Yes	Yes
Hypertriglyceridemia mg/dL	350	418	417	412
Hyperferritinemia ng/mL	45 395	8 440	15 300	15 359
Bone marrow hemophagocytosis	Confirmed	Confirmed	Confirmed	Confirmed
Anti nuclear antibodies	1:320	1:160	1:640	1:1280
Organic involvement of LES	Cutaneous, hematological	Cutaneous, hematological	Hematological, renal	Renal, cutaneous

system and often leads to progressive failure of multiple organs. The main barrier to initiating treatment is misdiagnosis or late diagnosis, which is attributed to the rarity of HS, its variable presentation, and the time required to perform diagnostic tests (4).

Since almost 96% of patients with HS present with fever, early diagnosis is generally based on the doctor's suspicion, because unfortunately, clinical and laboratory abnormalities may not appear on initial presentation. The BM score was developed for the recognition of patients with fever who are at risk of HS and it was not intended to replace the diagnostic criteria for HS, but rather to act as a clinical warning system for the risk of developing this syndrome (4).

The prevalence of HS in SLE has been reported to be 0.9-2.4%. There are few reports of cases in which SLE has manifested as HS (5, 6).

Below we describe some cases in which HS has presented as the initial manifestation of SLE (Table 2) (9, 10).

The characteristics of HS associated with SLE and active SLE are quite similar, so it is difficult to differentiate between these two entities. However, hyperferritinemia is the strongest indicator to separate HS from active SLE. Other common manifestations include hepatosplenomegaly, lymphadenopathy, pancytopenia, cutaneous manifestations, coagulopathy. The presence of thrombocytopenia is considered to be a better

indicator of HS, unlike leukopenia and anemia. However, symptoms, signs and all laboratory parameters together should be used to analyze the case instead of depending on a single parameter for diagnosis (7).

Hemophagocytic syndrome in SLE usually presents in the early stages of the disease or with its onset (8). Treatment of secondary HS is aimed at treating the underlying condition. In HS due to SLE, high-dose steroids and immunosuppressive agents including cyclosporine, cyclophosphamide, and intravenous immunoglobulin are effective (9, 10). Our patient was treated with high-dose steroids and mycophenolic acid, which led to a marked improvement. □

CONCLUSIONS

Hemophagocytic syndrome as the initial manifestation of SLE is extremely rare. However, suspicion of this pathology should be maintained due to its similarity to active SLE. If not all diagnostic criteria for HS are available, it is necessary to classify the patient's risk for the development of this syndrome, which could be supported by the BM score. Treatment of secondary HS is aimed at treating the underlying cause. □

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