Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

Submitted on: 03/25/2022
Approved on: 06/03/2024

CASE REPORT

Hemophagocytic syndrome as an initial manifestation of systemic lupus erythematosus in childhood

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Keywords:
Lupus erythematosus, systemic, Lymphohistiocytosis, hemophagocytic, Rheumatology, Macrophage activation syndrome.

Abstract

Introduction: Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease of unknown cause. In childhood, it is a rare disease and usually presents with an acute and aggressive form. Hemophagocytic syndrome (HS) or hemophagocytic lymphohistiocytosis (HL) is a serious hyperinflammatory disease, also rare and potentially fatal. **Objective:** To describe a case of SLE in an 8-year-old schoolboy, which presented in a severe form, associated with HS as its first manifestation. **Case report:** An 8-year-old patient with persistent onset of daily fever measured for 20 days, maximum of 39°C, concomitant with decreased appetite, prostration, dyspnea on moderate exertion. Laboratory tests showed moderate anemia, leukopenia, Urine Analysis with proteinuria and hemoglobinuria, with granular and hyaline casts. Echocardiogram showed mild cardiomegaly and mitral and tricuspid insufficiency. In the evolution of the case, it was evaluated by pediatric nephrology, which raised the diagnostic hypothesis of SLE, corroborated after with positive ANA and anti-DNA, and consumption of C3 and C4 complement. Showed hyperferritinemia and hypertriglyceridemia. Due to the signs and symptoms presented, the hypothesis of hemophagocytic syndrome was raised, confirmed on the myelogram with the presence of hemophagocytosis. **Conclusion:** HS is a serious disease, rare when associated with SLE, potentially fatal and difficult to diagnose due to the particularities of its characteristics due to the presence of symptoms similar to each other.

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Resid Pediatr. 2025;15(4). DOI: 10.25060/residpediatr-2025.v15n4-869

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease of still unknown cause, with a predominance in females, and may occur at any age. However, in childhood it is a rare disease and usually presents in an acute and aggressive manner, with greater activity when compared to adults[1,2].

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory disease, also rare and potentially fatal, characterized by an uncontrolled and ineffective immune response of natural killer (NK) cells and cytotoxic T cells[3,4].

First described in 1939 by Scott and Robb-Smith, the syndrome is divided into primary, more common in childhood and mainly caused by genetic defects, and the secondary form, triggered by infections, neoplasms, autoimmune diseases such as SLE, and immunotherapies[3].

The present study aims to describe a case of SLE in an 8-year-old schoolchild, who presented with a severe form associated with HPS as the first manifestation.

CASE REPORT

LKSF, 8 years old, male, born and residing in Porto Velho-RO, sought medical care in early January 2021 with a history of persistent daily fever for 20 days, peaking at 39ºC, accompanied by decreased appetite, prostration, and dyspnea on moderate exertion. He was admitted for further diagnostic evaluation. On admission, he was in fair general condition, pale, with lymphadenopathy in the cervical chains, tachycardia with systolic murmur, flattened umbilical scar, and a palpable liver about 3 cm below the costal margin, without other alterations. Laboratory tests showed moderate anemia, leukopenia, urinalysis with proteinuria and hemoglobinuria, granular and hyaline casts; serologies (dengue, HIV, hepatitis B and C, syphilis, Epstein-Barr, cytomegalovirus, and toxoplasmosis) and AFB were negative. Echocardiography revealed mild cardiomegaly with mitral and tricuspid regurgitation. In addition, he presented an abdominal ultrasound showing mild hepatosplenomegaly and bowel loop dilatation, and a negative rapid test for COVID-19. Furosemide was started due to echocardiogram findings.

Three days after admission, he developed significant worsening of chest pain and dyspnea, especially when supine, with physical exam showing decreased breath sounds in the left middle lobe and absent sounds in the left base. A chest X-ray revealed left hemithorax opacity consistent with pleural effusion, requiring pleural drainage with water seal and initiation of antibiotic therapy. One week later, his condition deteriorated again, with worsening general status, anasarca, proteinuria, and hypertensive peaks. He was evaluated by pediatric nephrology, which raised the diagnostic hypothesis of SLE, later confirmed by positive ANA and anti-dsDNA, and low complement levels (C3 and C4).

During the clinical course, he developed worsening anemia, thrombocytopenia, hyperferritinemia, and hypertriglyceridemia. A renal biopsy was requested, but could not be performed due to severe anemia and patient instability. After 20 days of hospitalization, with worsening respiratory parameters, he was transferred to the ICU, where he underwent pulse therapy with methylprednisolone for 3 days, intravenous immunoglobulin, and antibiotic regimen change. A rapid test for COVID-19 showed reactive IgG and indeterminate IgM. Subsequently, an RT-PCR for SARS-CoV-2 was performed, yielding a negative result. Pediatric cardiology evaluation revealed heart failure, and medications were adjusted.

Blood transfusion was indicated for severe anemia but suspended due to a positive direct Coombs test and incompatibility in cross-matching, with risk of hemolysis. Erythropoietin was started, with diagnosis of severe hemolytic anemia secondary to the autoimmune condition. Given the signs and symptoms, hemophagocytic syndrome was suspected and confirmed by bone marrow aspirate showing hemophagocytosis. Cyclosporine was initiated with good clinical response, resolution of pleural effusion, improvement in autoimmunity tests, hematimetric levels, and proteinuria.

After stabilization, he was transferred to the ward, where he experienced a tonic-clonic seizure episode. As local resources were exhausted and pediatric rheumatology follow-up was required, treatment outside the home city (TFD) was indicated. Cyclosporine was discontinued and cyclophosphamide initiated. The patient returned to his hometown and remains under regular follow-up with our pediatric nephrology service.

DISCUSSION

SLE is a chronic autoimmune disease that can affect any organ. Despite its similarity to the adult presentation, children with SLE show greater severity and impact[1,2,5]. HLH is a severe, aggressive, and potentially fatal hyperinflammatory syndrome, characterized by excessive and ineffective activation and proliferation of lymphocytes and macrophages, resulting in a cytokine storm that causes fever, organ dysfunction, pancytopenia, and coagulopathy[6]. With an autosomal recessive pattern, the syndrome is classified by the Histiocyte Society into primary and secondary forms. The primary form is associated with genetic alterations, occurring mainly in childhood. The secondary form is triggered by factors such as infections, autoimmune diseases, neoplasms, and drugs, and may occur at any age. Infections, especially viral, are the main triggers of HLH. Although uncommon, SLE is an important rheumatologic cause of HLH[6,7]. In systemic autoimmune diseases such as Juvenile Idiopathic Arthritis (JIA), and less commonly SLE, some authors use the nomenclature Macrophage Activation Syndrome (MAS)[4,7,8,9].

In the case reported, the initial clinical picture was consistent with an infectious condition, apparently of pulmonary origin, which led to the initiation of antibiotic therapy

and the need for chest drainage. The unfavorable course of the disease led to ICU admission and raised the hypothesis of severe bacterial sepsis. The involvement of multiple systems, the characteristics and progression of the disease, and the lack of response to antimicrobials led us to investigate other non-infectious causes.

Our patient met the diagnostic criteria for SLE, presenting 6 (serositis, persistent proteinuria, pancytopenia, positive anti-dsDNA and ANA, and seizure) out of the 11 criteria established by the American College of Rheumatology (ACR) (Table 1), the most widely used in pediatric practice. Considering the Systemic Lupus International Collaborating Clinics (SLICC) criteria, he presented 9 (serositis, nephritis, hemolytic anemia, leukopenia, thrombocytopenia, positive ANA and anti-dsDNA, low C3 and C4, and seizure) out of the 17 criteria. For the diagnosis of SLE, the ACR requires 4 or more of the 11 criteria, while the SLICC requires 4 or more of the 17 criteria, with at least one clinical and one immunological criterion, whether simultaneously or sequentially, at any point in time.

HLH has a challenging diagnosis due to several factors, including the involvement of multiple organs, nonspecific signs and symptoms that mimic common infections, and, in the case of SLE and HLH in particular, the coexistence of overlapping symptoms. Diagnosis is based on nonspecific criteria established in the hemophagocytic lymphohistiocytosis protocol (HLH-2004), which requires the presence of at least 5 out of 8 criteria (Table 2), or the presence of a molecular diagnosis with specific genetic mutations associated with HLH. It is worth noting that hemophagocytosis in the initial sample is not required for diagnosis and should be suspected in the presence of fever, hepatosplenomegaly, lymphadenopathy, rash, and neurological alterations[7,10-12].

Regarding the HLH diagnostic criteria, at admission the patient presented with fever, splenomegaly, and bicytopenia. Later, he developed pancytopenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis in bone marrow aspirate. The latter two findings were the main defining factors for our diagnosis[13].

The treatment of patients with HLH aims to suppress hyperinflammation. Therefore, chemotherapeutic agents such as etoposide and/or immunosuppressants such as corticosteroids, cyclosporine A, and immunoglobulin are used. In MAS, the conventional first-line treatment is corticosteroids, since there is a good response to intravenous methylprednisolone pulse therapy, along with cyclosporine A[14,15].

CONCLUSION

HLH is a severe, rare, and difficult-to-diagnose disease characterized by dysregulation of the immune system. Its suspicion is essential in patients with SLE, due to the particularities of their overlapping symptoms.

HLH should be considered even before the full diagnostic criteria are met, in the presence of cytopenias, hyperferritinemia, and unexplained fever, since delaying treatment can cause great harm to the patient due to its high mortality.

Table 1. Criteria for the diagnosis of pediatric Systemic Lupus Erythematosus according to the ACR.

1. Malar rash (erythema)
2. Discoid rash (erythema)
3. Photosensitivity
4. Oral or nasal mucosal ulcers observed by a physician
5. Non-erosive arthritis
6. Pleuritis or pericarditis
7. Nephritis
· Persistent proteinuria greater than 0.5 g/day
· Cylindruria
8. Neuropsychiatric disease
· Psychosis or seizures, excluding drug-induced or metabolic disorders
9. Hematologic disorder
· Hemolytic anemia or leukopenia or lymphopenia on 2 or more occasions
· Thrombocytopenia in the absence of drug-induced thrombocytopenia
10. Immunologic abnormalities
· Presence of anti–double-stranded DNA antibody, or anti-Sm, or antiphospholipid antibody (anticardiolipin IgG or IgM, or lupus anticoagulant), or false--positive VDRL
11. Positive antinuclear antibody (ANA)

Source: SBP.

Table 2. Diagnostic criteria for hemophagocytic syndrome.

1. Fever
2. Splenomegaly (>3 cm)
3. Cytopenias (≥ 2 peripheral blood lineages)
4. Hypertriglyceridemia (>265 mg/dl) and/or hypofibrinogenemia (<1.5 g/dl)
5. Hyperferritinemia (>500 µg/L)
6. Elevated CD25 (>2400 U/ml)
7. Decreased or absent NK cell activity
8. Evidence of hemophagocytosis in bone marrow, spleen, or lymph nodes, with no evidence of malignancy

Hemoglobin <9 g/dl, Platelets <100,000/mm³, Neutrophils <1000/µL.
Source: HLH-2004

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