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Case Report Open Access

Hemophagocytic lymphohistiocytosis in a patient with systemic lupus erythematous

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Hemophagocytic lymphohistiocytosis (HLH), is a disorder seen more often in children and is life-threatening in terms of over- activation of macrophages, and T cells resulting in cytokine storm. HLH can be familial or secondary to infections, malignancy, immunosuppression, and autoimmune conditions, such as systemic lupus erythematosus (SLE). Here, we report a 10-year old female with previously diagnosed SLE who hospitalized because of fever and pancytopenia.

Keywords: Systemic lupus erythematosus; Hemophagocytic lymphohistiocytosis (HLH); Cytokine storm; Pancytopenia

Introduction

Systemic lupus erythematosus (SLE), is an autoimmune disease with various presentations ranging from mild to severe including arthritis, fever, pleuritis, alopecia, malar rash, oral ulcers, lymphadenopathy and fatigue. SLE has remitting relapsing nature. Genetic susceptibility and environmental factors, such as estrogen, UV, smoking and vitamin D insufficiency playroles in flare-ups [1,2]. Most common auto- antibodies include anti-ds DNA, and anti-nuclear antibodies (ANA) [1]. Anemia is common in childhood SLE [3,4]. Thrombocytopenia and leukopenia may be in terms of the disease itself or as treatment adverse effects. Hemophagocytic lymphohistiocytosis (HLH) manifestsas fever, hepatosplenomegaly andlymphadenopathy. Bone marrow biopsy reveals histiocytosis. The occurrence of HLH in SLE patients is very uncommon. Hence, we reported a rare case of very young female with SLE, whose manifestations led to diagnsis of HLH.

Case Presentation

A ten-year-old Baluch girl with known SLE was initially seen in the pediatric department with early symptoms including mouth ulcers, hair loss, positive ANA, low complement levels, and thrombocytopenia. Her treatment regimen was prednisolone 7.5 mg/day, azathioprine 25 mg/day, and hydroxychloroquine 100 mg/day. She was hospitalized in Shahid Sadoughi hospital because of high grade fever (39ºC) and pancytopenia. She complained of severe cough, abdominal pain, back pain, loss of appetite, weakness, lethargy, and constitutional symptoms, such as tachycardia. Abdominal examination showed splenomegaly with the size of 3 fingers below subcostal margin. Based on the above findings, the patient underwent various studies. In laboratory studies, the patient had hemoglobin of 8.7 mg/dL, white blood cell (WBC) count of 2000/mm^3, and platelet count of 80000/mm^3. lactic dehydrogenase was reported as 1420 U/L and ESR as 20 mm/h. In the urine analysis protein: 3+, RBC: 12-15 and WBC: 10-12 was shown. For this reason, a 24-hour urine test was performed and the results were reported as follows: volume: 2550 ml, creatinine: 0.4 mg, protein: 1063 mg. Immunologic tests were reported a positive

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anti-ds DNA (3.89 U/ml), and a C3 and C4 levels of 21.7 mg/dl and 118 mg/dl, respectively. Based on the pancytopenia as well as other laboratory findings, the patient underwent Bone marrow aspiration/ bone marrow biopsy (BMA/BMB). Hemphagocytic activity within histiocytes was reported by the pathologist which suggested the possibility of HLH (Figures 1,2).

Magnetic resonance imaging of the patient's brain showed cerebral atrophy. The diagnosis of Covid-19 was made based on the patient's ongoing high fever, respiratory symptoms such a prolonged cough, and the results of a chest computed tomogram scan that revealed pulmonary infiltrates. Spinal fluid polymerase chain reaction (PCR) was negative for herpes simplex virus. Despite negative Covid-19 PCR test, the patient was treated with Remdesivir (regarding common possibility of false negative test) and Caspofungin. Based on experts opinion two inravenous (IV) pulses of intravenous immunoglobulin (IVIG) (27.5 gram), cyclosporine and ganciclovir was prescribed. The patient underwent cardiac counseling due to tachycardia, which was treated for heart failure in terms of reduced Ejection Fraction (rEF) (EF: 20%), although after two days and normalization of EF, treatment continued with only furosemide and spironolactone. The patient's consciousness increased after continuing to receive IVIG, although she still showed agitation and confusion. Finally, the patient's therapy was maintained at home in accordance with the patient's adequate O^2 saturation as well as owing to her prolonged agitation and the danger of an exacerbation of her mental health issues. Finally, based on the clinical and laboratory findings, and BMA/BMB results and considering the HLH-2004 criteria proposed by Henter et al. [13] including, persistent fever ≥ 38.5°C, hemoglobin < 9 g/L and platelets count < 100×109/L, hemophagocytosis in the bone marrow, decreased consciousness and splenomegaly, the patient was diagnosed with HLH.

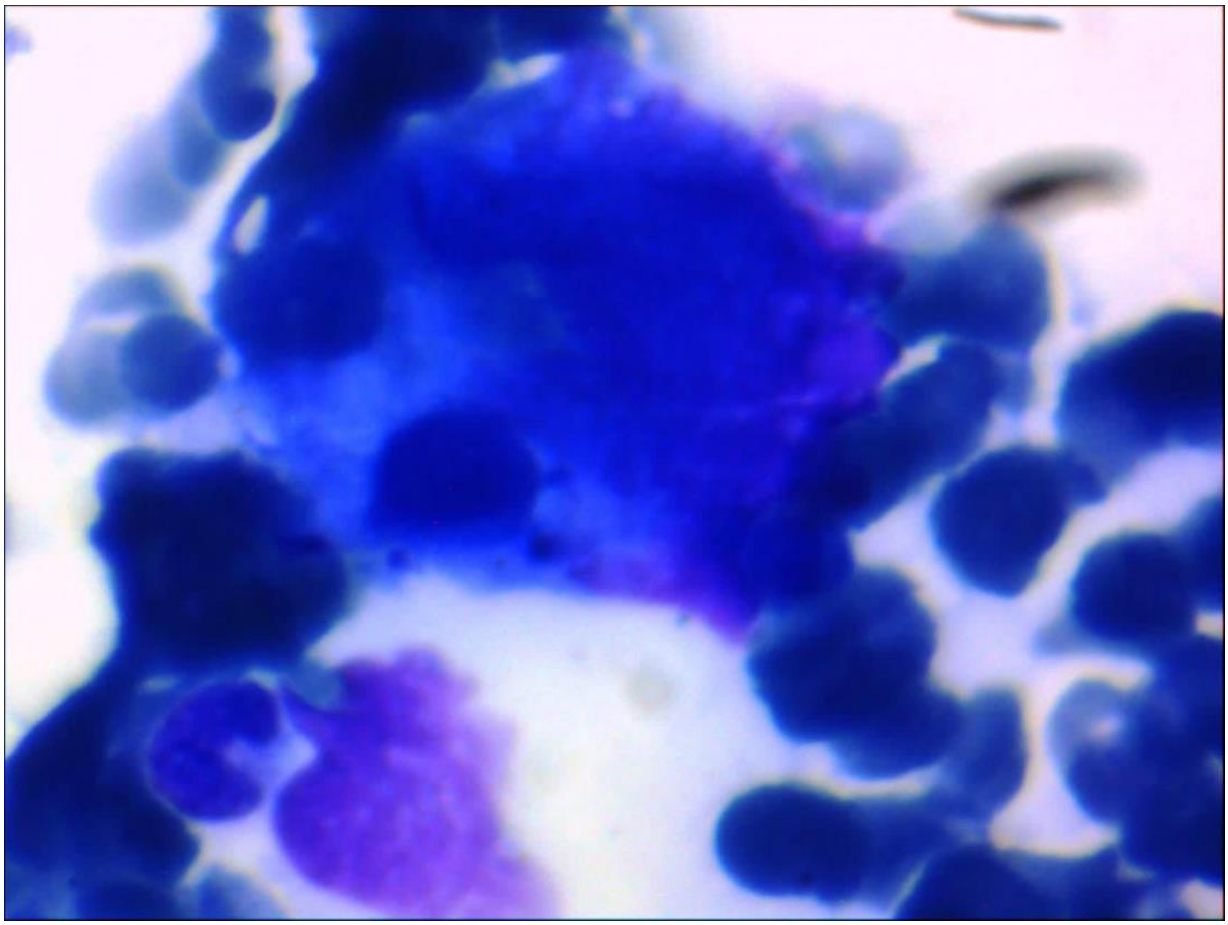

Figure 1. This figure demonstrates hemophagocytosis of erythroid precursor cells (Wright Giemsa stain)

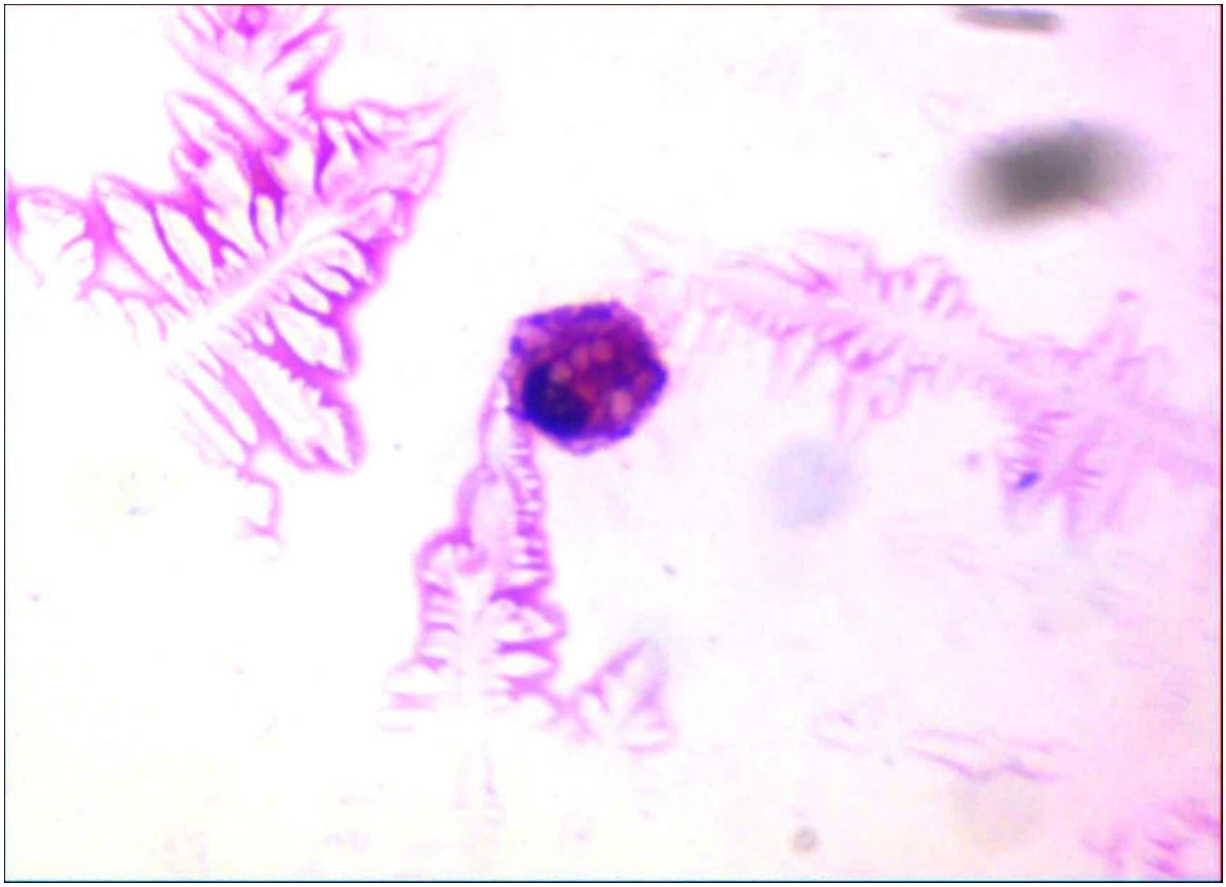

Figure 2. Smear shows phagocytosis of numerous red blood cells by a macrophage

Discussion

HLH is an uncommon hematologic disorder seen more often in children. Laboratory abnormalities include, lymphocytosis, macrophages hyper-activation and cytokine storm. It is classified as one of the cytokine storm syndromes. HLH could be inherited or acquired [5] and should be considered in any severely ill patient presenting with pancytopenia, and fever [6]. HLH clinically manifests with high persistent fever, jaundice and skin rash, decreased consciousness, respiratory distress, and splenomegaly [13]. Pancytopenia, hypo-albuminemia, and elevated ESR are other laboratory findings that may aid in diagnosis. The presence of histiocytosis in bone marrow biopsy samples may indicate HLH [10]. In HLH-2004 diagnostic and therapeutic guideline for HLH, the presence of five or more of the following is necessary for diagnosis [10,11]:

- fever > 38.5 °C)
- splenomegaly
- cytopenia at least at two lineages:

✓ hemoglobin < 9 g/L

✓ thrombocytopenia (<platelet < 100×10^9/L)

✓ neutropenia (WBC < 1×10^9/L)

- elevated triglycerides
- hypofibrinogenemia (fibrinogen ≤ 150 mg/dl)
- hyperferritinemia (ferritin ≥ 500 ng/ml)
- hemophagocytes revealed in bone marrow biopsy, spleen or lymph node tissues
- decreased natural killer cells
- soluble CD25 > 2400 U/ml

Because of the high morbidity and mortality, treatment should be started immediately if HLH is suspected. Effective treatments include etoposide, glucocorticoids, and high-dose IVIG, which target macrophages and histiocytes; cyclosporine A and anti-thymocyte globulins, which target T cells. If an infection was the cause, it has to be properly treated. Hematopoietic stem cell transplant (HSCT) in children without significant CNS involvement was promising [11]. Neuro-cognitive deficits may present years after HSCT, although most will be improved [12]. SLE is a very rare underlying disorder of HLH is very rare, underlying cause of HLH, despite similarities in their pathogenesis.

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Conflict of Interests

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