

ACUTE LUPUS HAEMOPHAGOCYTIC SYNDROME

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ABSTRACT

A 25 year old female who had been on treatment for Systemic Lupus Erythematosus for the last 12 years presented with high grade non-remitting fever and pleural effusion. She had delivered a full term baby girl and soon developed pancytopenia, markedly raised fibrinogen degradation products, deranged coagulation profile, low serum fibrinogen level, raised liver enzymes and grossly raised serum ferritin. Bone marrow examination revealed reactive haemophagocytosis and megakaryoblastosis. Autoimmune disorders can lead to reactive haemophagocytic syndrome which is a treatable entity even if it presents with life threatening complications.

INTRODUCTION

Haemophagocytic Lymphohistiocytosis (HLH) is an entity with both familial and acquired forms. The acquired or Reactive Haemophagocytic Syndrome has been found in patients with Autoimmune Associated Haemophagocytic Syndrome (AAHS), including systemic lupus erythematosus (Acute Lupus Haemophagocytic Syndrome ALHS). Acquired forms of HLH are encountered in association with viral infections, autoimmune diseases, malignant diseases, and acquired immune deficiency states (e.g., after organ transplantation).¹ HLH represents a severe hyper-inflammatory condition with the cardinal symptoms of prolonged fever, cytopenias, hepatosplenomegaly, and hemophagocytosis by activated, morphologically benign macrophages.² A special form of HLH in rheumatic diseases is called macrophage – activation syndrome.³ Biochemical markers include elevated ferritin and triglycerides, and low fibrinogen. In children several inherited immune deficiencies may lead to this syndrome, whereas most adults with HLH have no known underlying immune defect.⁴ Nevertheless, impaired function of natural killer cells and cytotoxic T-cells is characteristic of both genetic and acquired forms of HLH. Frequent triggers are infectious agents, mostly viruses of the herpes group.⁵ Malignant lymphomas, especially in adults, may be associated with HLH.⁶ Initially HLH may masquerade as a normal infection. Patients with HLH, however, cannot control the hyper-inflammatory response which, if untreated, is fatal in genetic cases and in a high percentage of acquired cases.⁷ Awareness of the clinical symptoms and of the diagnostic criteria of HLH is important to start life – saving therapy with immunosuppressive / immunomodulatory agents in time.⁸

CASE REPORT

A 25 years old female who had been on treatment for Systemic Lupus Erythematosus for 12 years presented with high grade non-remitting fever, and increasing dyspnoea for 5 days. She delivered a baby girl a month ago and her disease had since flared up requiring frequent hospitalization. Her pulse was 110 / minute, BP was 120/80, temperature was 102° Fahrenheit. Her liver was palpable 2 cm below the costal margin and splenic tip could also be palpated.

Investigations revealed Hb 7.7g/dl, TLC 2.3×10^9 /l, neutrophils 79%, lymphocytes 16%, monocytes 5%; Platelet count 7×10^9 /l; ESR 9 mm in 1st hour. RBC morphology revealed marked anisocytosis and poikilocytosis with oval macrocytes, schistocytes and microcytes. Red Cell Distribution Width was 21%. There was no evidence of malarial parasite infestation. Direct and indirect Coomb's test were negative and reticulocyte count was 0.8%. Serum ferritin was 5540 µg/l.

PT was 17/13 sec and APTT was 70/33 sec. Fibrinogen Degradation Products were more than 20 µg/ml. Total serum bilirubin was 3.4 mg/dl, with direct bilirubin of 1.9 mg/dl, SGOT was 100 U/l, SGPT 67 u/l, Alkaline phosphatase was 444 U/l, urea was 31 mg/dl, Serum creatinine 0.9 mg/dl, uric acid 2.6 mg/dl. LDH was 9514 U/l. CRP was 25.7 mg/dl.

Blood culture, urine culture were negative, serology for hepatitis B and C was also negative. On ultrasound liver was 16.8cm, spleen was 13.6 cm, there was about 10 ml free fluid in the cul de sac. The right sided lung showed about 100 ml pleural effusion. Echocardiography showed 10 ml of fluid in the pericardial cavity. Pleural effusion was tapped and analysis suggested exudative fluid. Gram stain, ZN stain were negative for microorganisms.

Bone marrow examination revealed hypocellular fragments and trails. Macrophages were increased, morphologically benign and showed haemophagocytosis. Phagocytic vesicles contained red blood cells and normoblasts, neutrophils and platelets. Megakaryocytes also showed emperipoiesis. There was no evidence of leukemia, lymphoma or any other malignancy at the tested site. Patient was offered on pulse steroid therapy. She responded but ten days after admission she developed herpes zoster blisters on left side of neck and chest. There was no neuralgic pain preceding the eruption possibly due to steroids.

Table 1: *Classification and underlying conditions of hemophagocytic lymphohistiocytosis (HLH).⁵*

<i>Genetic HLH</i>
Familial HLH (Farquhar disease)
Known gene defects (perforin, munc 13 – 4, syntaxin 11)
Unknown gene defects
Immune deficiency syndromes
Chédiak – Higashi syndrome
Griscelli syndrome
X-linked lymphoproliferative syndrome
<i>Acquired HLH</i>
Exogenous agents (infectious organisms, toxins)
Infection – associated hemophagocytic syndrome
Endogen products (tissue damage, metabolic products)
Rheumatic diseases
Macrophage activation syndrome
Malignant diseases

Table 2: *Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).⁸*

I. Familial disease / known genetic defect
II. Clinical and laboratory criteria (5/8 criteria)
1. Fever
2. Splenomegaly
3. Cytopenia ≥ 2 cell lines
Hemoglobin < 90 g/L (below 4 weeks < 120 g/L)
Neutrophils $< 1 \times 10^9$ /L
4. Hypertriglyceridemia and/or hypofibrinogenemia
fasting triglycerides ≥ 3 mmol/L
fibrinogen < 1.5 g/L
5. Ferritin ≥ 500 μ g/L
6. sCD25 ≥ 2400 U/mL
7. Decreased or absent NK – cell activity
Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH > 1000 U/L

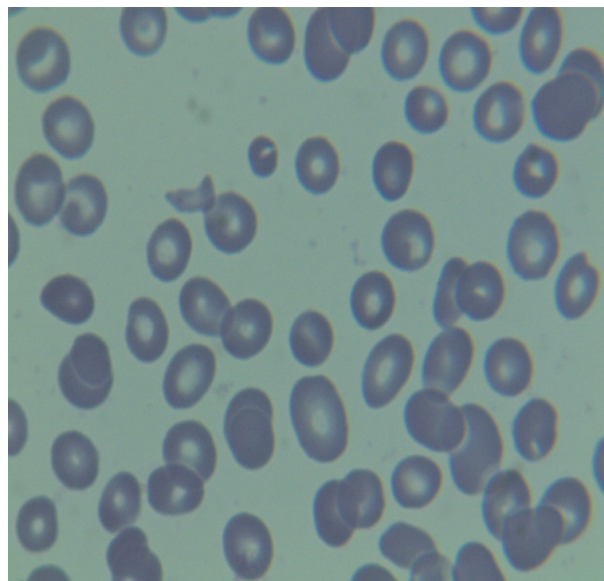


Fig. 1: *Anisocytosis, poikilocytosis, schistocytes in peripheral blood smear (Giemsa stain).*

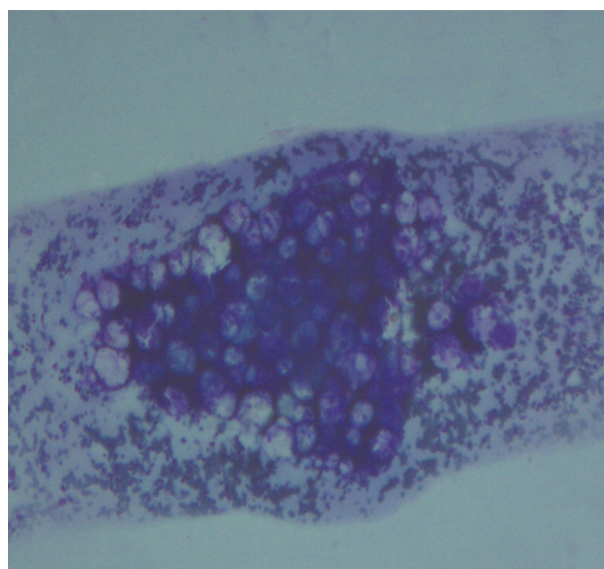


Fig. 2: *Hypocellular bone marrow fragmen (Giemsa stain).*

DISCUSSION

Our patient was on treatment of SLE for 12 years with a waxing and waning symptoms. Her disease flared-up during pregnancy and after delivery she developed high grade fever and pleural and pericardial effusion. Her labs revealed organomegaly, coagulopathy, cytopenias, raised FDPs, deranged LFTs and haemophagocytosis. ESR was paradoxically depressed due to low fibrinogen levels. The triggering event was most likely viral as the course of her disease proved in due time.

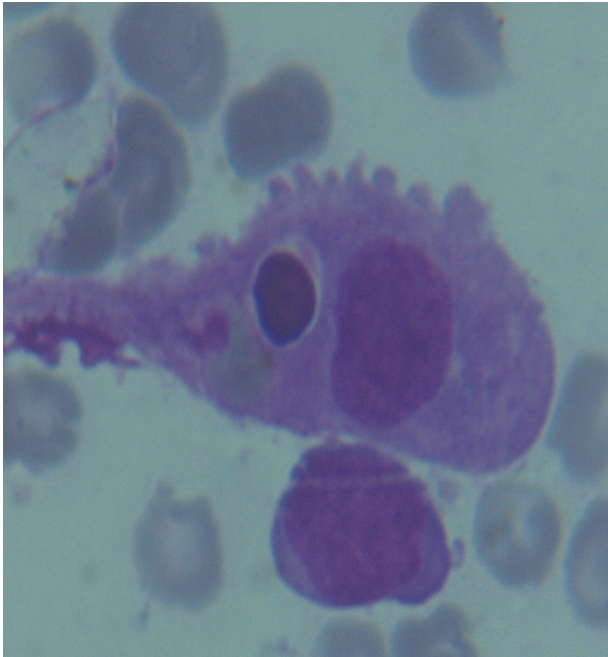


Fig. 3: Lymphocyte ingested by a macrophage, a large immature looking histiocyte underlying the macrophage (Giemsa stain).

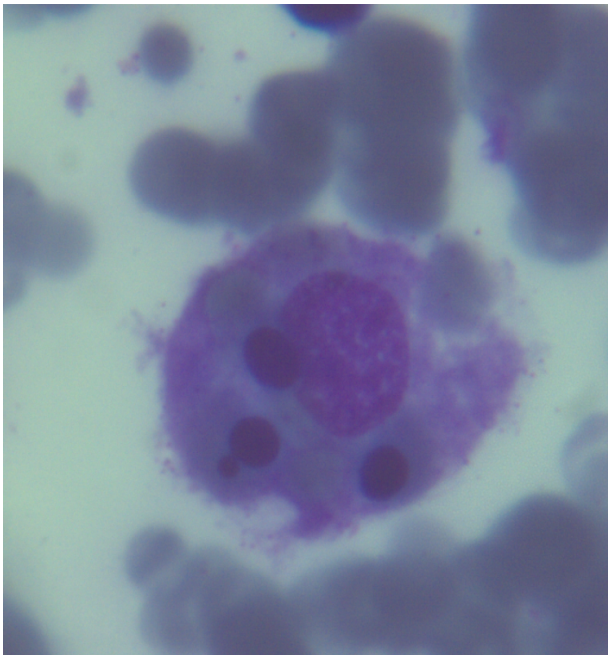


Fig. 4: Macrophage ready to ingest an circled RBC, 3 NRBCs seen in the cytoplasm (Giemsa stain).

HLH patients usually present with mild signs of upper respiratory or gastrointestinal infection and a high fever. The fever often subsides spontaneously and can recur within days to weeks. Transient improvements in thrombocytopenia, with nonspecific

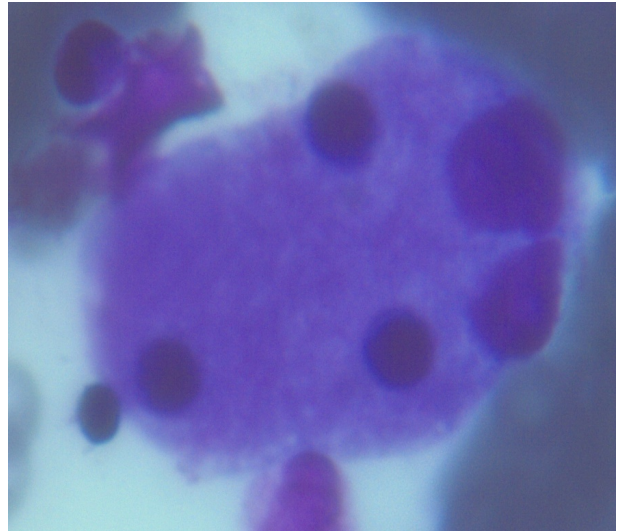


Fig. 5: NRBCs ingested by macrophages (Giemsa stain).

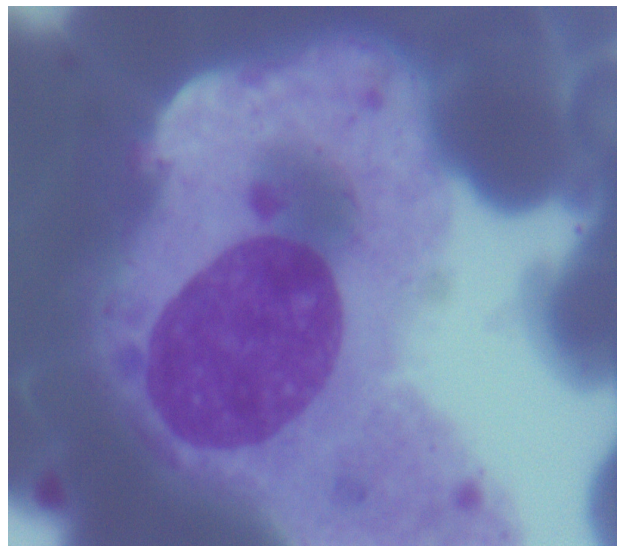


Fig. 6: Platelet phagocytosed in macrophage (Giemsa stain).

measures such as antibiotics and transfusions are seen frequently. However, organomegaly, anemia or other changes commonly persist. Severe, fulminant liver failure with coagulopathy or neurological symptoms may cause delayed diagnosis of HLH. Minimal diagnostic requirements are a complete blood count, liver enzymes, bilirubin, triglycerides, ferritin and a coagulation profile including fibrinogen. All patients should have a bone marrow aspirate. In the majority of cases, hemophagocytosis is not observed in the initial bone marrow aspirate and only increased monocytes and monohistiocytic cells may be present. Two highly diagnostic disease parameters are an increased plasma concentration of the α chain of the

soluble IL₂ receptor (sCD₂₅) and impaired NK cell activity.¹⁰ A hallmark of HLH is impaired or absent function of natural killer cells and cytotoxic T-cells. While many of these cardinal symptoms are found in immune-competent patients in response to an infectious organism, they are more pronounced in patients with HLH. Without treatment, the uncontrolled inflammatory response leads to sustained neutropenia and death from bacterial or fungal infections as well as from cerebral dysfunction. A review of the published cases in children diagnosed with infection associated HLH reported that. EBV was the triggering virus in 74% of the children.⁹

The macrophage activation syndrome (MAS) occurs in children and adults with autoimmune diseases. It is most commonly seen in association with systemic onset juvenile arthritis or adult – onset Still's disease, but also occurs rarely with systemic lupus erythematosus or other entities.¹¹ The clinical picture has all of the characteristic features of HLH. Patients with MAS exhibit the defective NK cell function common to other patients with HLH⁶ MAS generally develops in active phases of the underlying disease. Viruses have been identified as triggering factors, but other inciting factors that have been implicated include non-steroidal anti-inflammatory drugs, methotrexate, and gold – salt injections. Mortality of patients with MAS is between 10% and 20%.¹¹ The search for a triggering infectious agent like Epstein Barr Virus, cytomegalovirus, herpes simplex virus, adenovirus, varicella zoster virus and leishmania is important since most of these organisms are treatable.⁵

It is **concluded** that when an SLE patient presents with prolonged fever, hepatosplenomegaly and cytopenias, he should be investigated for evidence of MAS leading to HLH. Underlying causes for HLH should also be looked for as viral infections and commonly used drugs can trigger the haemophagocytosis.

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