Hemophagocytic Lymphohistiocytosis (HLH)

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KEYWORDS

RV, Pacing, Left Ventricular, Dyssynchrony, Contraction, Speckle tracking

ABSTRACT

HLH is a reactive process resulting from prolonged and excessive antigen-presenting cell activation [1]. Hemophagocytosis is a hallmark of activated macrophages/histiocytes. The predominant clinical findings of HLH are fever (often hectic and persistent), cytopenia, hepatitis, and splenomegaly. A case of HLH in a 32-year-old female with no past medical history was presented in the current paper. She was admitted to the medical department with a fever and thrombocytopenia for evaluation. After failure to respond to a brief course of empiric antibiotics, the patient was extensively investigated and finally diagnosed with HLH (bone marrow aspiration showed occasional hemophagocytes). She was started on steroids but, failed to respond and so immunosuppressant drugs were added to the therapy.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH), which has many genetic causes, is characterized by multi-system inflammation. HLH is a reactive process resulting from prolonged and excessive activation of antigen presenting cells (macrophages, histiocytes) and CD8+ T cells. Hemophagocytosis, which is mediated through the CD163 heme-scavenging receptor, is a hallmark of activated macrophages/histiocytes and is the characteristic finding for which the disorder was named. The majority of genetic causes identified to date affect the cytotoxic function of NK and T cells, crippling immunologic mechanisms that mediate natural immune contraction. The predominant clinical findings of HLH is fever (often hectic and persistent), cytopenia, hepatitis and splenomegaly. Due to the life-threatening implications of the diagnosis of genetically determined HLH, antiinflammatory therapy, often consisting of steroids, etoposide or antithymocyte globulin (ATG), should be instituted promptly, followed by curative hematopoietic cell transplantation. Secondary HLH, associated with autoimmune disorders or viral infections in teens and adults, also carries a significant mortality rate and should be managed in consultation with specialists familiar with the diagnosis and treatment of such disorders.[1] Until recently, it was widely believed that symptoms of HLH due to genetic causes generally arose during infancy and early childhood. With the more widespread availability of genetic testing, it is apparent that the first significant episode of HLH can occur throughout life, from prenatal presentations through the seventh decade.[1] In our case the patient was 32 years old with no past medical history.

Case presentation

32 years old female with no past medical history, she presented with history of 1 week waxing and waning fever, night sweat, along with mild breathing difficulty and palpitation, however there was no history of weight loss nor loss of appetite. She denied any history of bleeding from any site and there was no gastrointestinal or urinary complaints.

She is married but with no kids, she is not a smoker but drinks alcohol occasionally. She works as a nurse in a private clinic.

She was admitted in the medical department with fever and thrombocytopenia for evaluation.

Complete Blood Count shows thrombocytopenia and mild anemia, in view of the mildly elevated inflammatory marker a brief course of IV antibiotic was started which showed no response, meanwhile, a full infectious work up was done including COVID-19, CMV, EBV, Dengue, TB or Malaria which was all negative. Autoimmune screening showed negative ANF, Anti DNA, and ENA profile.

Bone Marrow Aspiration was done and showed cellular, trilineage hematopoiesis along with prominent macrophage and occasional haemophagocytosis (figure1-2).

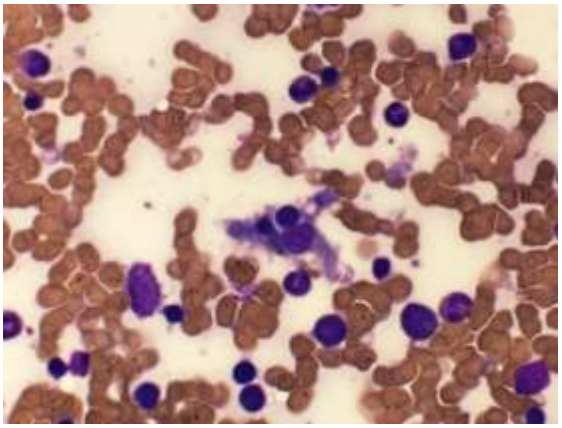

Figure 1: patient peripheral blood film showing phagocytation of white cell

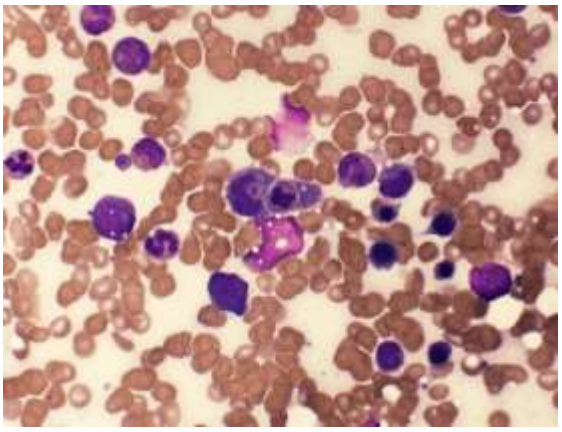

Figure 2: patient peripheral blood film showing phagcytation of red blood cell

Investigations

Her last lab reveals white cell count 4.8, hemoglobin 10.9, platelet 42,

bilirubin 0.6, alkaline phosphatase 180, ALT 62, albumin 3.5, AST 41, PT 11.9, INR 1.12, APTT 37.3, LDH 1253□742, fibrinogen 316.57, procalcitonin 0.93, CRP 68.3, Creatinine 0.7, Urea 25. Blood culture and Bone marrow culture negative.

Bone marrow aspiration mylegram is as follows: Lymphocytes-13%, neutrophils-26%, Mylocytes-13%, Metamyelocytes-06%, Eoosinphils-05%, Erythroid-31%, Monocytes-04%, plasma cells-02%. The erythroid series is predominantly normoblastic. The myeloid series shows adequate sequential maturation and differentiation of cells. There is no left shift, there is no dyspoiesis, and there is no increase in blasts, lymphocytes are unremarkable. Plasma cells are prominent (2-3%), have a mature morphology. Megakaryocytes have a normal morphology and appear mildly increased. Occasional small clusters of megakaryocytes are noted. Prominent macrophage and occasional haemophagocyte (figure 1-2).

Differential Diagnosis

The main differential diagnosis is a normal infection in an immune-competent patient.[2]

Hepatosplenomegaly, fever and blood count changes are signs of acute leukemia (which can be excluded by a bone marrow examination), but also of multisystem Langerhans cell histiocytosis

(LCH).[2]

Unremitting fever, lymph node enlargement, and organomegaly may be caused by large-cell anaplastic lymphoma (LCAL), formerly called malignant histiocytosis. [2]

Treatment

Aims of treatment

The immediate aim in the treatment of any patient with HLH is to suppress the severe hyperinflammation that is responsible for the life-threatening symptoms. A second aim is to kill pathogen-infected antigen-presenting cells to remove the stimulus for the ongoing, but ineffective activation of cytotoxic cells.[3]

Hyperinflammation, caused by hypercytokinemia, can be suppressed successfully by corticosteroids, which are cytotoxic for lymphocytes, inhibit the expression of cytokines and chemokines . and also interfere with the production of CD95 ligand and differentiation of dendritic cells .Since dexamethasone crosses the blood brain barrier better than prednisolone, it is preferred for treatment. Cyclosporin A inhibits activation of T-lymphocytes by interfering with the cyclophilin pathway . As a single agent, it proved to be effective for maintaining remission and for children with MAS Immunoglobulins probably act by cytokine- and pathogen-specific antibodies. Etoposide, which was introduced to the treatment of HLH in 1980 ,is highly active in monocytic and histiocytic diseases. Antithymocyte globulin in combination with steroids and cyclosporin A was used successfully in France [3]

Our case has been started on methylprednisolone 250 mg daily. She completed 3 doses then switched to prednisolone 50mg daily. Her temperature improved along with her platelet count.

2. Result and Discussion

She was started on methylprednisolone 250mg daily and she completed 3 doses after which she was switched to 50mg daily. Temperature improved, along with her platelet count. Three weeks later the patient was seen in the hematology clinic with a platelet count 40 along with anemia and so was admitted for etoposide infusion, meanwhile during the course of treatment the patient developed severe leukopenia for which prophylactic voriconazole along with levofloxacin was started until white cell count returned to normal.

Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH) as established in the HLH-2004 protocol of the Histiocyte Society. HLH diagnosis can be established by fulfilling five of the eight proposed criteria [3] table 1.

Table 1 diagnostic critiria for HLH as established in HLH-2004 protocol of histocyte society.[3]

The diagnostic of hemophagocytic lymph histiocytosis can be established by fulfilling five of the eight following criteria.
Clinical criteria
Fever (>7 days)
Spleen enlargement
Laboratory criteria
Bicytopenia without marrow hypoplasia, including
Hemoglobin<9g/L
Platelet count<100×10^9/mm^3

Neutrophil count<$1\times10^9/mm^3$

Hypertriglyceridemia (>3,0mmol/L, fasting value) and/or hypofibrinemia(<1,5g/L)

Hyperferritinemia (<500microgram/L)

Low/absent natural killer cells activity

Increased soluble CD-25 levels (>2400IU/mL)

Histological criteria

Hemophagocytosis

In our case the patient has six criterion out of eight.

A report of a case of hemophagocytic lymphohistiocytosis (HLH) with severe pulmonary complication and acute respiratory distress syndrome (ARDS) hospitalized in intensive care unit (ICU) in 2014,[4]

A report of adult patients with acute liver failure caused by HLH have increased, and HLH should be suspected in patients with acute liver failure of indeterminate cause. Although the efficacy of the treatment strategy recommended by the HLH 2004 remains to be confirmed in adult patients with acute liver failure caused by HLH, early diagnosis and prompt combined treatment with steroids and cyclosporin A or etoposide should be emphasized.[5]

Learning Points/Take-Home Messages

Any prolonged fever with no definite source of infection and not responding to antibiotics, HLH should be considered a differential diagnosis.

During the assessment of fever and bi-cytopenia hematologist should be alert to search for hemophagocytes during Bone marrow aspiration assessment

Even in the case of HLH, the possibility of associated sepsis should be kept in mind.

Consent to participate

Informed written consent to participate in the study was obtained from all recruited patients.

Consent for publication

Not applicable.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions:

Fadi Mohammad Mobarrak, FARID ULLAH KHAN shared in the study idea, collection and analysis of data and finalizing the results.

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Not applicable.

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