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Medical Journal of Clinical Trials & Case Studies
ISSN: 2578-4838

Hemophagocytic Lymphohistiocytosis (HLH) - The Enigma

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Case Report

Volume 3 Issue 4

Received Date: July 22, 2019

Published Date: August 27, 2019

DOI: 10.23880/mjccs-16000237

Abstract

We report a case of Hemophagocytic lymphohistiocytosis in a 12 year old child. The clue to diagnosis was made by examination of bone marrow biopsy which showed hemophagocytosis. The disease is under reported and it mandates certain criteria for making diagnosis with hemaphocytosis being one of them. In particular in a resource limited set up where advanced complex tests could not be done, careful morphological assessment plays a pivotal role.

Keywords: Hemophagocytic lymphohistiocytosis; Bone Marrow; Histiocytosis

Introduction

We report a case of Hemophagocytic lymphohistiocytosis (HLH) in a 12 year old child as we received his bone marrow examination slides for opinion. Hemophagocytic lymphohistiocytosis (HLH) is potentially fatal hematological disorder characterized by hyperinflammatory response associated with activation of cytotoxic T and Natural killer (NK) cells and macrophages, manifesting as fever, pancytopenia, jaundice and hepatosplenomegaly [1]. Early detection of this complex disease is crucial for a favorable prognosis which requires collaborative efforts of physician and pathologist.

The disease was first reported by Farquhar and Daireaux in 1952 that referred it as familial hemophagocytic reticulosis[2].The etiology can be genetic or acquired [2] seen in all ages with no predilection for race or sex. The genetic HLH comprise of the cases associated with the presence of genetic abnormality that manifests within first year of life [3,4]. The HLH subtypes include FHL1, FHL2 (CPFR1/Perforin 1), FHL 3 (UNC13D/Munc 13-4), FHL 4(STX 11/Syntaxin 11), FHL 5(STXB2/Syntaxin binding protein2 or UNC 1BB), Chediak Higashi Syndrome (LYST), Hermansky Pudiak Syndrome type 2 (AP3B1), Grescelli syndrome type 2 (RAB27A), XLP type 1 (SHD2D1A/SAP Protein) and XLP type 2 (BIRC4/X1AP) protein [1,5]. The studies in literature have suggested the role of perforin and NK/T cells cytokine pathways in familial HLH cases [6,7]. Perforin deficiency results in poor defence mechanism against intracellular pathogens alongside decreased NK cell activity causes T cell activation resulting in cytokine storm leading to macrophage activation [8]. Dengue transmitted by the mosquito Aedes aegypti affects millions of people worldwide every year. Dengue induced HLH is potentially fatal condition and requires timely diagnosis [9].The signs and symptoms of HLH are non specific posing diagnostic difficulties. There are no specific laboratory tests available for diagnosing HLH [10]. HLH should be suspected in cases with sudden onset of fever, hepatomegaly, jaundice, generalized lymphadenopathy and cytopenias [11]. HLH is a medical emergency; with lack of gold standard confirmatory tests it is prudent for the clinician to maintain a high level of suspicion in patients with no bullous cause of cytopenias and fever.

The diagnosis of HLH according to histocytic society protocol entitled HLH establishes if five out of the following eight diagnostic criteria are [11]

1. Fever > 7 days
2. Splenomegaly
3. Cytopenia > 2 lineage
a. Hemoglobin < 9 g/dl
b. Neutropenia , ANC < 1000/mm^3
c. Platelet count <1, 00,000/mm^3
4. Hypertriglyceridemia (>265 mg/dl) or Hypofibrinogemia (1.5 g/l)
5. Hemophagocytosis (Bone marrow, Spleen, Lymph node)
6. Low absent NK cell activity
7. Hyperferritinemia (> 500 mcg/L)
8. Increase soluble CD25 > 2400units/ml

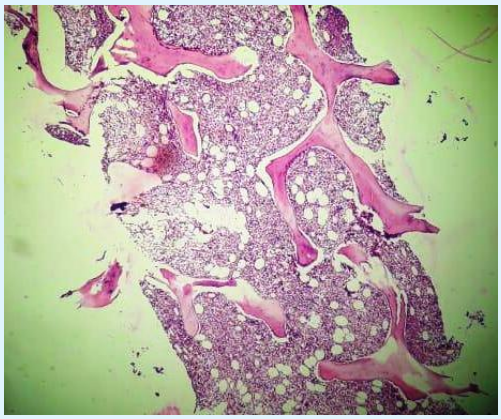

Figure 1: Bone marrow biopsy (H & E, 100 x) showing hemophagocytosis.

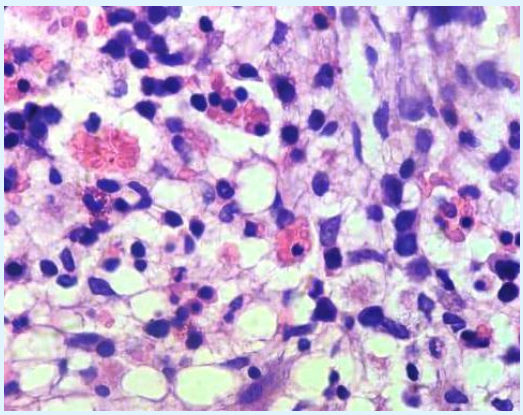

Figure 2: Bone marrow biopsy (H & E, 400 x) showing hemophagocytosis.

The bone marrow examination revealed hemophagocytosis as shown in Figures 1&2. Other ancillary tests were done and 6 out of 8 criteria were full filled before making a diagnosis of HLH. NK cell activity and CD25 were not done due to lack of facility however remaining criteria were full filled. The demonstration of bone marrow hemophagocytosis is a sensitive test however due to lack of specificity it cannot be incorporated as a screening tool [12]. The 2004 guidelines on the diagnosis of HLH by Henter, et al. [11] suggest histopathological examination of other organs in cases where bone marrow in inconclusive including spinal fluid and liver tissue. In the absence of specific novel marker and non specific flow cytometry the diagnosis of HLH remains challenging [13].

The case emphasize on careful microscopic examination of bone marrow coupled with clinic pathological correlation to arrive at correct diagnosis in a multidisciplinary team work.

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