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Case Report

Hemophagocytic Lymphohistiocytosis Presenting as Panniculitis

Rateesh Sareen[1]*, Menka Kapil[1], GN Gupta[2] and Aditi Mittal[3]

[1]D.N.B Pathology, Department of Pathology and Transfusion Medicine, Santokba Durlabhji Hospital, Jaipur, India

[2]Head of Department, Department of Pathology and Transfusion Medicine, Santokba Durlabhji Hospital, Jaipur, India

[3]DM Hematology, Department of Medical Oncology, Santokba Durlabhji Hospital, Jaipur, India

***Corresponding Author:** Rateesh Sareen, D.N.B Pathology, Department of Pathology and Transfusion Medicine, Santokba Durlabhji Hospital, Jaipur, India.

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Abstract

We report a case of Hemophagocytic lymphohistiocytosis in a 16 year old child. The clue to diagnosis was made by peripheral blood same which showed hemophagocytosis. The disease is under reported in a developing country like India as it mandates certain diagnostic criteria which require advanced testing facilities as well as thorough microscopic examination of blood smear and bone marrow. The case presented with penile Panniculitis which is extremely uncommon presentation for this disorder.

Keywords: *Hemophagocytic Lymphohistiocytosis; Cytophagic Histiocytic Panniculitis*

Introduction

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.

Case Report

We report a case of Hemophagocytic lymphohistiocytosis (HLH) in a 16 year old boy who was admitted under medicine department with complains of penile inflammation and pain. Patient had complaints of fever, generalized painful erythematous skin lesions and painful scrotal swelling. The laboratory investigations revealed-BUN- 19 mg/dl, Creatinine- 0.6 mg /dl, Sodium- 131 m mol/litre, Potassium- 3.0 m mol/liter, chloride- 105 m mol/lit, glucose- 99 mg/dl, SGOT- 150 U/L, SGPT- 93 U/L, total Bilirubin- 0.5 mg/dl, Direct Bilirubin- 0.2 mg/dl, Total protein- 5.1 gm/dl, Albumin- 2.2 gm/dl, globulin- 2.9 gm/dl, A/G ratio- 0.76, Alkaline Phosphatase- 214 U/L, Gamma GT- 106 U/L, bleeding time was 2 minute and PT 16.2 seconds with Aptt- 60.1 sec, Vitamin B12 was 443 pg/dl, Ferritin- 4580, Triglyceride level was 229 mg/dl and Fibrinogen level was 0.85 g/L. An automated complete blood count (CBC) demonstrated Hemoglobin- 73 g/L (reference range 130 - 170 g/L), white blood cell count 1.70 x 10^3/L (reference range 4 - 10 x 10^3/L) Platelet count 40 x 10^6/L (reference range 150 - 450 x 10^6/L), Hematocrit 32.4% (reference range- 36% - 46%), Absolute neutrophil count- 1.38 x 10^3/L, Lymphocyte- 0.31 x 10^3/L and Monocyte count- 0.01 x 10^3/L (Figure 1). Scrub typhus IgM was negative, HIV-1-2, HBsAg, HCV, typhoid antigen were negative. Anti MPO, anti PR3 and ANA were negative. Urine examination was unremarkable. Urine and blood culture were negative. Test for brucella was negative.

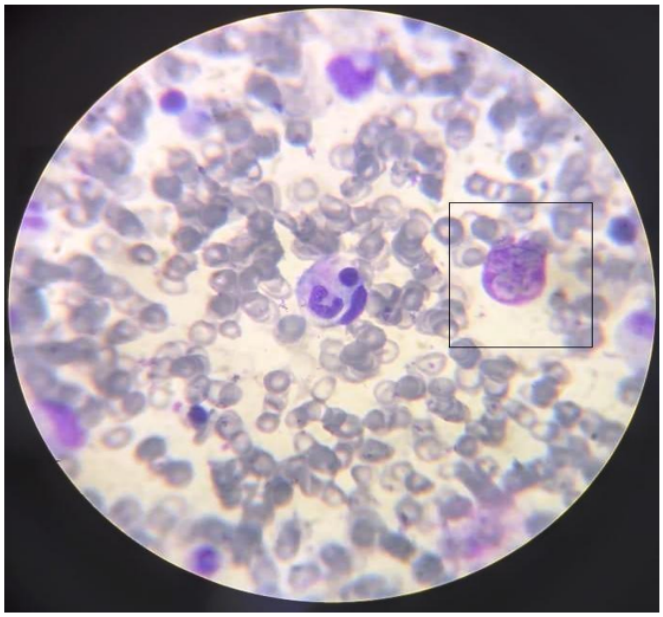

Figure 1: *Peripheral blood smear showing hemophagocytosis (Leishman stain, 1000x).*

A concurrent peripheral blood smear showed normocytic normochromic red blood cells. Test for HIV 1 and 2, Hepatitis B and C viral serology were non-reactive. Malarial smears and rapid malarial antigen test were negative. Routine urine examination did not detect any abnormality. Bone marrow examination and Bcr –ABL testing was advised.

Discussion

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 [1] 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 histiocytic society protocol entitled HLH establishes if five out of the following eight diagnostic criteria are [12]:

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 Hypofibrinogenemia (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 > 2400 units/ml.

Other ancillary tests were done and 5 out of 8 criteria were full filled before making a diagnosis of HLH. (Criteria number 1, 2, 3, 4 and 7). In addition, bone marrow and peripheral blood showed hemophagocytosis (Figure 1). NK cell activity and CD25 were not done due to lack of facility however remaining criteria were full filled. The demonstration of hemophagocytosis is a sensitive test however due to lack of specificity it cannot be incorporated as a screening tool [13]. The 2004 guidelines on the diagnosis of HLH by Henter., *et al.* [14] 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.

The case is interesting as HLH a dreaded disease is rarely associated with Cytophagic histiocytic panniculitis (CHP) with only 40 cases in literature [15]. It was first described in 1980, characterized by infiltration of subcutaneous adipose tissue by benign-appearing T lymphocytes and phagocytic histiocytes ("bean bag cells") [16]. It may be associated with infections as well as malignancies like non-Hodgkin lymphoma.

It is pertinent to mention that cutaneous manifestations are not included in the diagnostic criteria for HLH [17]. The case is unconventional one as HLH was diagnosed prior to the diagnosis of Cytophagic histiocytic panniculitis (CHP) otherwise in other cases where HLH is suspected skin biopsy may be helpful in reaching the final diagnosis of HLH.

The case emphasize on multidisciplinary team work to arrive at correct diagnosis in such challenging cases.

Conclusion

The case emphasize on multidisciplinary approach and team effort in clinching the diagnosis in 16 year old child. The clinician and pathologist both working at tandem where the peripheral blood examination showed hemophagocytosis was picked up by the pathologist

that gave the case a new direction. The battery of diagnostic criteria could only have been used due to mutual decision making, communication and fruitful discussion so that a timely diagnosis of such rare disease is made in an efficient manner.

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