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Secondary Hemophagocytic Lymphohistiocytosis: Morphological Findings of Spleen and Bone Marrow with Discussion of Management of an Atypical Case

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Abstract

Hemophagocytic lymphohistiocytosis is syndrome due to abnormal and exaggerated immune response to infectious and non-infectious agents. The most common presentation is fever with palpable splenomegaly and pancytopenia. In this case, a young thin girl presented with moderate grade fever and huge splenomegaly (spleen palpable 24 cms below left costal margin) with pancytopenia with severe normocytic anemia. All investigations including serological markers, parasitic a, fungal and bacterial cultures done to know cause of infection , were negative. However, her bone marrow and splenic aspirates were strongly positive for hemophagocytosis. These morphological findings were also confirmed by biochemical results of high triglycerides and low plasma fibrinogen level. This rare case presented to hematology centre and finally diagnosed as hemophagocytic syndrome and treated with HLH-94 protocol, she became afebrile just after one cycle and her splenic size is decreased gradually and pancytopenia is corrected gradually. Now after completion of six cycles of therapy, at the time of writing of paper , she is asymptomatic from more than one year , however she still has mild splenomegaly and mild anemia, but her WBC and platelet counts are corrected completely. She is leading normal transfusion independent and afebrile life. Importance of FNAC of Spleen and bone marrow aspirate in diagnosis of this disease is especially shown in this paper.

Key Words: *Hemophagocytosis, bone marrow, splenomegaly, HLH -94 protocol.*

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an immunological disorder, abnormal and excessive hypercytokinemia mediates the clinical and pathological findings. It has two types: familial hemophagocytosis lymphohistiocytosis (FHLH) and secondary (SHLH) hemophagocytic lymphohistiocytosis; both types clinically manifest with fever, hepatosplenomegaly and pancytopenia. In FHLH variant, involvement of

central nervous system is common. In contrast to FHLH, SHLH may present in any age, has better prognosis, treatment has curative potential and also may subside spontaneously, central nervous system is involved rarely. HSLH syndrome is a rare, but potentially life-threatening immunological disorder caused by massive cytokine release from activated lymphocytes and macrophages [1].

Altered immune response could be due to past infection: viral, bacterial or parasitic, including EBV infection, immune response could not come to baseline after subsidence of infection leading to hemophagocytosis and increased secretion of cytokines. This multisystem inflammatory syndrome especially involving reticuloendothelial system is associated with a range of familial and acquired factors [2]. Persistent moderate to high fever, pancytopenia, hepatitis, splenomegaly and hemophagocytosis in bone marrow (BM), spleen and lymph nodes are common[2]. Apart from clinical and laboratory parameters, morphological findings of spleen and bone marrow are very important for the diagnosis of this rare syndrome.

Case Summary

A girl of 11 years was referred to hematology centre by general physician. She had complaints of high grade fever, abdominal discomfort and severe weakness. On clinical examination, she was thin emaciated, irritated and had raised temperature. She had severe pallor and spleen palpable up to umbilicus (24 cms below left costal margin). She had no icterus, lymph nodes were not enlarged, no cutaneous rashes and joint swelling. She had arthralgia.

Her hematological parameters showed pancytopenia (Table 1, Figure1). Liver function test (LFT) showed mildly raised SGPT and SGOT. Kidney function test (KFT) was within normal range (Table 2). She was further evaluated for serum triglycerides and plasma fibrinogen level (Table 1). Her triglycerides level was raised and fibrinogen level was reduced. Her blood culture for aerobic and anaerobic bacteria and fungus were negative. Bone marrow aspiration and FNAC of spleen were done. Bone marrow smears were cellular with well representation of hematopoietic elements of all series but increased number of activated macrophages, few of them (hemophagocytes) containing red blood cells, platelets and lymphocytes (Figure 2). Hemoparasites were not found. Similarly Splenic aspirate smears showed increased plasma cells, lymphocytes and activated macrophages (Figure 3) .Hemoparasites including malarial parasites and Leishman -Donovan (L. D.) bodies not seen. On the basis of clinical and laboratory findings including morphology of marrow and spleen, diagnosis of hemophagocytic lymphohistiocytic syndrome, acquired type was made. She was further advised serum triglycerides and plasma fibrinogen level. Her triglycerides level was raised and fibrinogen level was reduced. After two units of packed red blood cells transfusion, she was given 8 weeks cycles of etoposide and dexamethasone as per HLH-94 protocol; along with supportive therapy like sulfamethoxasazole – trimethoprim, acyclovir. Within three days of therapy, she became afebrile and gradually size of spleen started decreasing. Her hematological and biochemical parameters corrected gradually (Table 2).

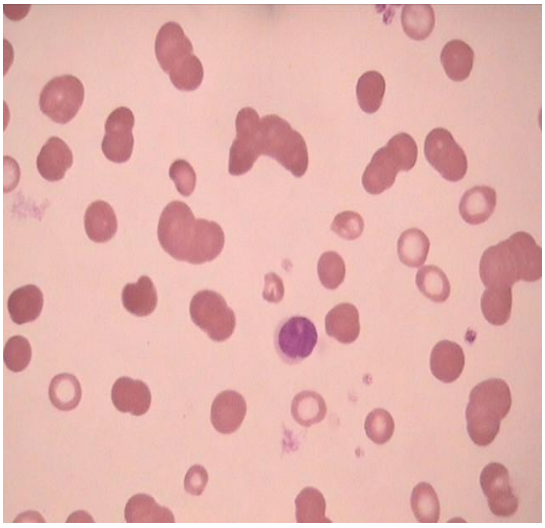

Figure.1 PBS showing pancytopenia (Leishman, 40 x)

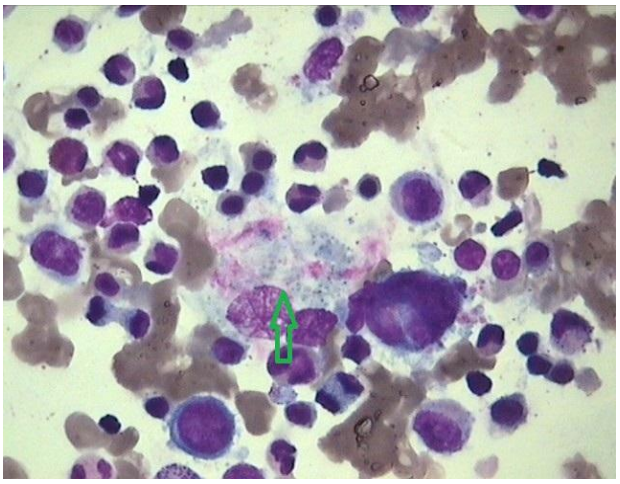

Figure.2. Bone marrow smears showing hemophagocytosis as indicated by green arrow (Leishman, 40x)

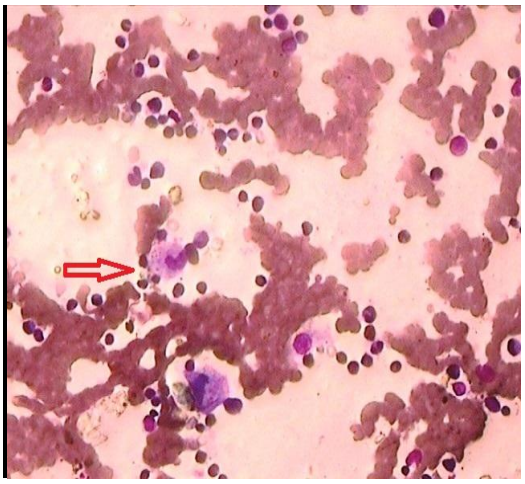

Figure.3 Splenic aspirate revealing activated macrophages as indicated by red arrow (Leishman, 40x)

Table. 1 laboratory parameters of the patient before treatment

Hematological parameters	Patient's value	Normal range
TLC	$2.5x10^3$/UL	$4\text{-}11x10^3$/UL
HB	6 gm/dl	12-17 gm/dl
PLATELET	$80x10^3$/UL	$150\text{-}500x10^3$/UL
ESR	110 mm/hr	0-20mm/hr
Biochemical		
SGPT	25	< 41 IU/L
SGOT	30	< 41 IU/L
Serum creatinine	0.8mg/dl	0.5-1.2 mg/dl
Fasting blood sugar	80	70-100mg/dl
CRP	15	0-5mg/L
Triglyceride	350	<150mg/dl
Fibrinogen	110 mg/dl.	145-348 mg/dl.

Abbreviation: TLC: Total leukocyte count, HB: hemoglobin,

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

Table 2. Hemoparameters after completion of HLH -94 protocol

Parameters	Before treatment	After treatment
TLC	$2.5x10^3$/UL	$4.2x10^3$/UL
DLC	N30 L62 M8	N55 L35 M6 E4
HB	6gm/dl	10.5gm/dl
PLATELET	$80x10^3$/UL	$140x10^3$/UL
CRP	15mg/L	4.5mg/L
Triglyceride	350mg/dl	140mg/dl
Fibrinogen	110 mg/dl.	155mg/dl

Abbreviation: N: neutrophil, L: lymphocyte, M: monocyte, E: eosinophil

Discussion

There are two types of hemophagocytic syndrome, primary and secondary. Primary type is invariably fatal but secondary type could be managed and patient can be cured [1, 5]. Now there is well defined guideline for diagnosis and management for this rare disease. Naturally pyrexia of unknown origin (PUO) with huge splenomegaly having pancytopenia always raise suspicion of Visceral leishmaniasis) (Kalaajar) in State like Bihar. Few clinical and laboratory findings are very useful in the diagnosis , namely moderate grade fever, hypertriglyceridemia in thin patient, decreased plasma fibrinogen in febrile patient , pancytopenia with cellular bone marrow revealing hemophagocytosis and activated macrophage in splenic aspirate [4].

HLH-1994 protocol is very effective in suppressing and correcting abnormal immune response due to lymphohistiocytic cells, decreasing size of spleen, correcting pancytopenia [5,7] .Although in this case, complete normalization of size of spleen could not occur, perhaps due to that anemia is not fully corrected but patient is completely asymptomatic and she is having normal platelet and TLC and DLC from last one year (Table 2).Till the writing the paper, she is on only under clinical observation and having CBC monthly.

Conclusion

HLH is rare immunological disease that classically present with fever, hepatosplenomegaly and pancytopenia, triglyceridemia and or hypofibrinogenemia .Atypical SHLH may present with hypertriglyceridemia and mildly decreased serum fibrinogen level. Secondary SLH has good prognosis with very much curative potential. In this case, HLH-1994 protocol remained very successful and patient became asymptomatic, size of spleen decreased moderately and laboratory parameters became normal except mild anemia persisted. Morphological findings of bone marrow and spleen are diagnostic in presence of suggestive clinical and laboratory parameters. HLH-94 protocol is curative and can be used effectively in OPD setup in small clinic.

Conflict of interest: None

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