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HLH Syndrome: A Case Report

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Abstract: ***Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome .It is the consequence of a severe, uncontrolled hyperinflammatory reaction that in most cases is triggered by an infectious agent. Frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages .Its incidence is estimated to be 1.2 cases per 10,00,000 individuals per year. A 42 year old male with fever since 1 month, generalized weakness since 20 days, high colored urine since 5 days with no risk factors, no significant family history and so significant past history. On Examination: Temperature-101*F, Pulse: tachycardia and BP normal. Pallor and icterus were present, hepatosplenomegaly noted, ascites was present and other systems examination was normal. Postinfectious HLH is likely underdiagnosed in critically ill patients. A priority should be placed on rapid evaluation, with the goal of starting treatment as soon as possible as it has an impact on prognosis.***

Keywords: lymphohistiocytosis, aggressive, hyperinflammatory, postinfectious

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome[1] .It is the consequence of a severe, uncontrolled hyperinflammatory reaction that in most cases is triggered by an infectious agent. Frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages .Its incidence is estimated to be 1.2 cases per 10,00,000 individuals per year[2].

2. Case Report

A 42 year old male was admitted with complaints of fever, generalized weakness and high colored urine . Illness started 1 month back with complaints of high grade fever followed by easy fatigability since 20 days and high colored urine since 5 days. Past history and family history were not significant, Personal history - married and has two children (both are healthy), patient had no addictions.

Clinical examination: He was conscious, coherent and cooperative. Patient was febrile with a temp of 101*F and pulse was 98bpm, BP-100/60 mmhg. Pallor, icterus and pedal edema were noted, no cyanosis and clubbing.
CNS: Normal, CVS:S1S2+, P/A: hepatosplenomegaly+ , ascites+, RS: b/lNVBS.

Investigations: CBP revealed pancytopenia, LFT: Total bilurubin -2.6 mg/dl, Direct bilurubin – 2.2 mg/dl, Indirect bilurubin – 0.4 mg/dl, AST-206 U/lit, ALT – 52 U/lit, ALP – 292 U/lit, Serum proteins-4.6gm/dl, Serum Albumin – 1.5gm/dl, Serum globulin – 3.1 gm/dl, direct coombs test-positive, blood cultures, virals-negative, LDH-1932u/l, S.Ferritin->2000ng/ml, fibrinogen-900mg/dl, serum trigycerides-190mg/dl, Peripheral smear-rbc: hypochromasia with anisocytosis comprising of microcytes, macrocytes, normocytes and tear drop cells, bone marrow: hemophagocytes were present, USG abdomen – hepatosplenomegaly and moderate ascites, rapid test for MP –ve, Serial LFT reports T.bilirubin-7.2mg/dl , D.bilirubin-6.4mg/dl,I. bilirubin-0.8mg/dl, T.bilirubin-10.1mg/dl, D.bilirubin-8.7mg/dl, I.bilirubin-1.0mg/dl.

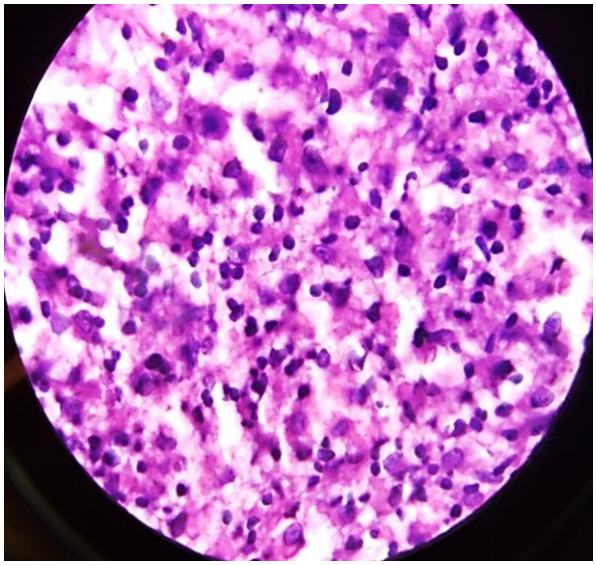

Figure 1: Bone marrow under oil immersion: showing histiocytes containing erythrocytes, granulocyte precusors, neutrophils and lymphocytes.

3. Treatment

Patient was started on wysolone (according to weight basis), levofloxacin and ursodeoxycholicacid. Clinical improvement was seen after 1 week. Patient was advised to continue wysolone at the time of discharge and was followed up weekly. His blood work and clinical signs and symptoms improved.

4. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is classified into genetic HLH and acquired HLH. Genetic variant is usually encountered in infants while the acquired form affects all age groups.[3]

Table 1: Classification of HLH

Genetic HLH	Gene
FHL	
FHL-1	Unknown
FHL-2	*PFR1*
FHL-3	*UNC13D*
FHL-4	*STX11*
FHL-5	*STXBP2(UNC18B)*
Immunodeficiency syndromes	
CHS	*LYST*
GS-2	*RAB27A*
XLP-1	*SH2D1A*
XLP-2	*BIRC4*
Other rare immune defects such as HPS-2, SCID, ITK, and CD27 deficiency	
Acquired HLH	
Infectious agents	
Autoinflammatory and autoimmune diseases (MAS)	
Malignant diseases	
Immunosuppression, HSCT, organ transplantation, AIDS	
Metabolic diseases	

HPS2 indicates Hermanksy-Pudlak Syndrome 2; and SCID, severe combined immunodeficiency.

H score is essential to diagnose HLH . 5 out of 8 criteria should be present to diagnose a case as HLH syndrome. It is common for a patient to exhibit only three or four of the eight diagnostic criteria but also have CNS symptoms, hypotension, and renal or respiratory failure To address this issue, a modification of the diagnostic criteria has been proposed In this approach, diagnosis requires three of four clinical findings (fever, splenomegaly, cytopenias, hepatitis) Plus one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or very decreased NK cell function). We also consider such criteria sufficient for diagnosis.[4]

Although it can be a marker of excessive macrophage activation and supports the diagnosis of HLH, hemophagocytosis alone is neither pathognomonic of, nor required for, an HLH diagnosis.[5]

Immune response in healthy subjects and uncontrolled, ineffective immune response in patients with genetic HLH.[6] Perforin and granzymes are secreted via cytotoxic granules, leading to apoptosis of the target cell. Processing of cytotoxic granules requires several steps, including polarization, docking, priming, and fusion with the cell membrane. Genes mutated in FHL-3, FHL-4, and FHL-5 and in the immunodeficiency syndromes CHS and GS-2 encode proteins that are crucial for these processes.

Fever is caused by interleukins and TNFα. Ferritin is secreted by activated macrophages, which also produce increased levels of plasminogen activator, leading to hyperfibrinolysis. Cytokines suppress lipoprotein lipase and hematopoiesis.[1]

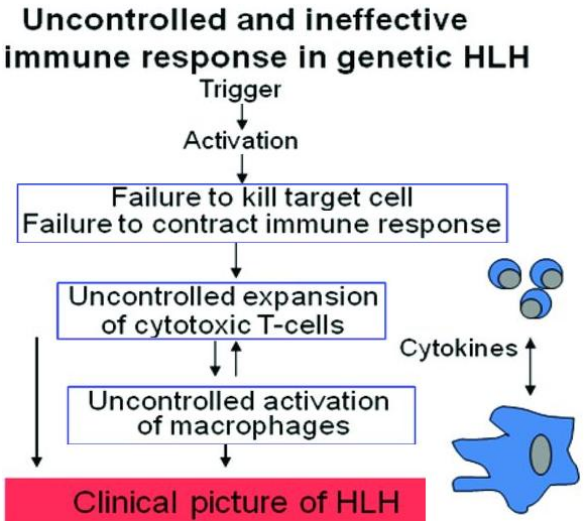

Figure 1: Clinical Picture of HLH

Neurologic abnormalities have been observed in one-third of patients with HLH. The types of abnormalities include seizures,altered mental status and ataxia. It is common for a patient to exhibit only three or four of the eight diagnostic criteria, but also have CNS symptoms, hypotension, and renal or respiratory failure

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Table 2: Diagnostic guidelines for HLH

Number	Criteria
1	Fever
2	Splenomegaly
3	Cytopenias affecting two or more lineages HB <9 g/dl Platelets <100,000/cumm Neutrophils <1000/cumm
4	Hypertriglyceridemia and/or hypofibrinogenemia TG >265 mg/dl Fibrinogen <150 mg/dl
5	Serum ferritin >500 μg/l
6	Hemophagocytosis in bone marrow, spleen, or lymph nodes
7	Decreased NK cell activity
8	Soluble IL-2 receptor >2400 U/ml

HLH diagnosis requires a molecular diagnosis consistent with HLH or 5/8 above criteria. HLH - Hemophagocytic lymphohistiocytosis; Hb - Hemoglobin; TG - Triglyceride; NK - Natural killer; IL-2 - Interleukin-2

Table 3. Principles of treatment in HLH

Suppression of hyperinflammation (immunosuppression, immunomodulation)	Corticosteroids, IV immunoglobulins, cyclosporin A, anticytokine agents
Elimination of activated immune cells and (infected) APCs (CTLs, histiocytes)	Corticosteroids, etoposide, T-cell antibodies, (antithymocyte globulin, alemtuzumab), rituximab
Elimination of trigger	Anti-infectious therapy
Supportive therapy (neutropenia, coagulopathy)	Antifungals, antibiotics, plasma
Replacement of defective immune system	HSCT

Differential Diagnosis

Macrophage activation syndrome (MAS) should be thought of as HLH in the setting of a rheumatologic disorder rather than as a separate syndrome[8]

Infection/sepsis (Unlike HLH, which is often triggered by a viral infection, sepsis is typically caused by a bacterial or fungal microorganism an extremely high ferritin and elevated lactate dehydrogenase level are predictive of HLH)[9]
Liver disease/liver failure (Unlike liver disease, HLH is a multisystem disorder. Those with HLH typically have more extensive organ involvement, cytopenias, extremely high ferritin, and neurologic findings. Cytokine profiles seen in HLH are not typically seen in primary liver disease)[10]
Multiple organ dysfunction syndrome (An extremely high ferritin or dramatically increasing ferritin is more consistent with HLH than with MODS)[11]

5. Conclusion

Postinfectious HLH is likely underdiagnosed in critically ill patients. Persistent, otherwise-unexplained thrombocytopenia in apparently “septic” patients who do not improve with standard treatment should alert the clinician. A priority should be placed on rapid evaluation, with the goal of starting treatment as soon as possible

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