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A Case Report on Hemophagocytic Lympho Histiocytosis (HLH)

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Abstract: ***Hemophagocytic lympho histiocytosis (HLH) rare immunological disease, that related life- threatening conditions featuring ineffective immunity characterized by an uncontrolled hyperinflammatory response. HLH is often triggered by infection. Familial forms result from genetic defects in natural killer cells and cytotoxic T-cells, typically affecting perforin and intra-cellular vesicles. The mechanism involves an inherited or acquired defect in the handling of antigenic factors (infectious, cancerous, or autoimmune) that leads to a severe systemic inflammatory process due to T-lymphocyte proliferation, cytokine over production and massive macrophage activation). The main symptoms ofHLH are prolonged fever, neutro-and thrombocytopenia, hepatosplenomegaly, and conspicuous laboratory values, such aslow fibrinogen and elevated levels of ferritin, triglycerides andsCD25. HLH is likely under-recognized, which contributes to its high morbidity and mortality. Early recognition is crucial for any reasonable attempt atcurative therapy to be made. Current treatment regimens include immunosuppression, immune modulation, chemotherapy, and biological response modification, followed by hematopoietic stem-cell transplant. A number of recent studies have contributed to the understanding of HLH pathophysiology, leading to alternate treatment options; however, much work remains to raise awareness and improve the high morbidity and mortality of these complex conditions.***

Keywords: Hemophagocytic lympho histiocytosis, immunity, bone marrow transplant, fever, Stem cell transplant

1. Introduction

Haemophagocytic lympho histiocytosis (HLH) is a life-threatening disturbance ofimmunoregulation. HLH comprises primary and acquired forms with different diseaseseverity[1]

Hemophagocytic lympho histiocytosis (HLH) is afrequently fatal and likely underdiagnosed disease involving a final common pathway of hypercytokinemia, which can result in end-organ damage and death. Although an early diagnosis is crucial to decrease mortality, the definitive diagnosis is often challenging because of the lack of specificity of currently accepted diagnostic criteria and the absence of confirmatory gold standards. Because of the wide range of laboratory assays involved in the diagnosis of HLH, practicing pathologists from a broad spectrum of clinical specialties need to be aware of the disease so that they may appropriately flag results and convey them to their clinical counterparts. Our article summarizes these new advances inthe diagnosis of HLH and includes a review of clinical findings, updated understanding of the pathogenesis, and promising new testing methods. **2**

Parameter	Observedvzalue	
	D3	D5
Hb TLC	11.8 7400	10 6008
DLC NLME	39/52 /7/2	39/50 /7/4
Platelets	2, 10000	1, 70000
S. Urea Creatinine	14/0.4	15/0.5
S. Bil/OT/PT	2.8/0.6/357/640	2.3/1.3/180/282
UrineR/M	Negative	
MPcard	Negative	
DENGUE serology		

Hemophagocytic lymphohistiocytosis (HLH), a disorder of the mononuclear phagocyte system, can be classified into two distinct forms: primary HLH (FHL) and secondary HLH. To clarify the epidemiology and clinical outcome for each HLH subtype, we conducted a nation wide survey of HLH in Japan. Since 799 patients were diagnosed in 292 institutions of Japan between 2001 and 2005, the annual incidence of HLH was estimated as 1 in 800, 000 per year. Among them, 567 cases were actually analyzed in this study. The most frequent subtype was Epstein-Barr virus (EBV)-associated HLH, followed by other infection-or lymphoma-associated HLH. Age distribution showed a peak of autoimmune disease-and infection-associated HLH in children, while FHL and lymphoma-associated HLH occurred almost exclusively in infants and the elderly, respectively. The 5-year overall survival rate exceeded 80% for patients with EBV-or other infection-associated HLH, was intermediate for those with FHL or B-cell lymphoma-associated HLH, and poor for those with T/NK cell lymphoma-associated HLH (<15%). Although this nationwide survey establishes the heterogeneous characteristics of HLH, the results should be useful in planning prospective studies to identify the most effective therapy for each HLH subtype. .3

2. Case Presentation

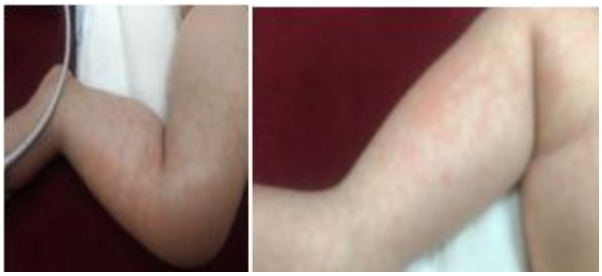
A previously healthy 11-month-old baby girlhospitalized with unexplained sudden onset of a systemic inflammatory response syndrome (SIRS), including fever, abdominal

distension, malaise, hepatosplenomegaly, jaundice, generalized lymphadenopathy. She has not significant previous history of any viral infections. In physical examination found to be all over body minute spot, and parameter summarized in table no.1.

Parameter	Observed value
RespirationRate	18/min
Temperature	101.2f
Pulse rate	88/min
CVS	S1S2+
CNS	Welloriented
Cyanosis	+
Pallor	+
Clubbing	-

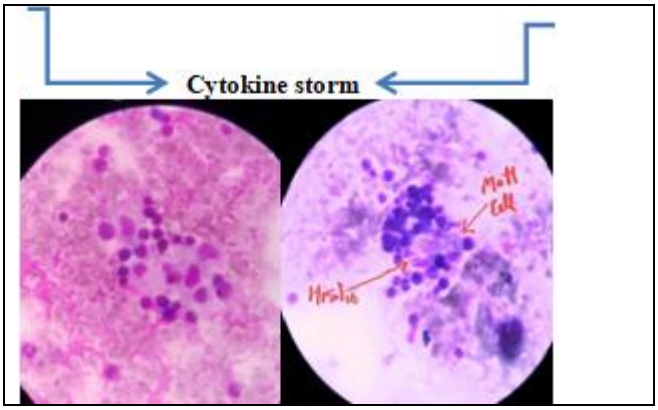
patient was diagnosedwith Hemophagocytic lympho histiocytosis (HLH). The laboratorial value summarized in table no.2

At the of hospitali Table no. 2
According to lab value; she had acute Hemophagocytic lymphohistiocytosis. Patient treated with initial treatment (dexamethasone, etoposide &Azithromycin, UDCA) monitored vals and laboratorial value regularly.



Pathophysiology
An understanding of the defective function of several types of immune cells in HLH has greatly enhanced our knowledge of normal physiology of cytotoxic cells. Several cell types are involved in the pathophysiology of HLH, including macrophages, NK-cells, and cytotoxic T-lymphocytes. Macrophages typically serve as antigen presenting cells to present foreign antigens to lymphocytes for either direct destruction or antibody development. In various forms of HLH, macrophages become activated and secrete cytokines. Cytokines, in turn, can cause organ damage when excreted in excessive amounts. NK-cells directly destroy damaged or infected cells, independent of the major histocompatibility complex (MHC). Cytotoxic T-lymphocytes, while similar to NK-cells, kill autologous cells carrying foreign antigens associated with MHC Class I.

Innate Immunity	Adaptive Immunity
1) Intrinsic hyperactivity	1) Mutations of IL-1 in sJIA
2) Direct activation by EBV	2) Low perforin & NK cell dysfunction in sJIA
3) Overstimulation by self	3) Failure to eliminate Ag DNA in SLE
4) Overstimulation by self	4) Failure of downregulation DNA in SLE
5) IFN-γ	5) Persistent activation & proliferation of T cells & macrophages



Diagnostic Criteria
In HLH-94, the first prospective international treatment study for hemophagocytic lymphohistiocytosis (HLH), diagnosis was based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis). In HLH-2004 three additional criteria are introduced; low/absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels. According to these criteria, are that guidelines for the diagnosis of acquired HLH.

Table 3: Diagnostic Criteria of Hemophagocytic Lymphohistiocytosis
Molecular diagnosis of HLH or the presence of atleast 5 of 8 criteria:
1) Fever
2) Splenomegaly
3) Cytopenias (affecting at least 2 line ages in the peripheral blood) Hemoglobin levels<90g/L (ininfants < 4 weeks old,
4) hemoglobin <100 g/L) Platelets <100 □ 109/L Neutrophils<1.0□109/L
5) Hypertriglyceridemia and/ or hypofibrinogenemia: Fasting triglycerides ≥3.0mmol/L (ie, ≥265mg/dL) Fibrinogen≤1.5g/L
6) Documented hemophagocytosis in the bone marrow, spleen, orlymph nodes
7) Low or absent natural killer cell activity
8) Ferritin ≥ 500mg/L
9) Soluble CD25 (i.e., soluble inter leukin-2 receptor) ≥2, 400U/mL

Investigation

Table 4

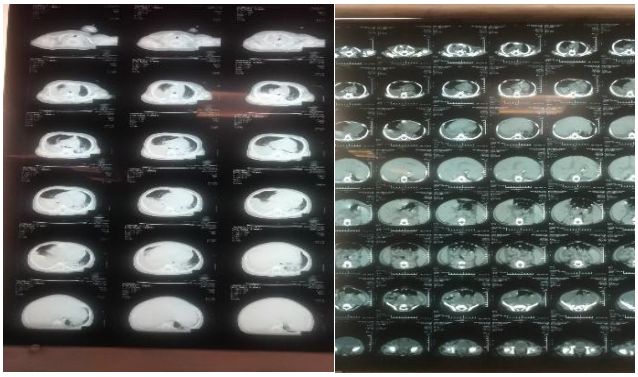
Parameter	Observed value			
	D3	D5	D8	D16
Hb TLC	11.8 7400	10 6008	8.1 4290	7.3 2200
DLC NLME	39/52 /7/2	39/50 /7/4	48/23 /08/1	13/64 /4/1
Platelets	2, 10000	1, 70000	86000	90, 000
S. Urea Creatinine	14/0.4	15/0.5	15/0.2	20/0.3
S. Bil/ OT/PT	2.8/0.6 357/640	2.3/1.3 180/282	4.0/2.2 218/169	5.2/3.1 224/143

CRP / ESR	Positive, Low
Procalcitonin	
Triglyceride	450 (40 – 120)
LDH	440 (260-450)

Ferritin/Fibrinogen	
Bone marrow Studies	
Viral Markers for hepatitis/HIV	NAD

Other investigation-

- CT Scan of Lungs that indicate the moderate effusion on Rt side and minimal effusion on lt side with collapse of bilateral basal lobes
- Abdomen finding show Hepatospleenpmegaly, Moderate ascites



3. Treatment

Main goal of this treatment to suppress the over stimulated immune response through the use of immunosuppressive agents. Day 3 start induction therapy with corticosteroids, etoposide, and cyclosporine. Corticosteroids are used to suppress the hypercytokinemia, cyclosporine A use to inhibit T-cell activation, and etoposide use blocks cell division and proliferation. Stem cell transplant (SCT) is indicated in selected cases. Treatment with SCT improves 3-year survival from nearly 0% to 50% in genetics cases.

The baby girl presented with severe hypoxia, and respiratory and metabolic acidosis, despite pressure-controlled ventilation and attempts of high frequency oscillation ventilation, both at high inspiratory oxygen level. 0 The girl was treated with

- dexamethasone at 10 mg/m 2 (d3 to d 10, reduced/discontinued at d 16),
- cyclosporine A 6mg/kg bd
- etoposide at 150mg/m2 (three doses in total, given on d 2 through d 7
- IV AntibioticsAzithromycinMetrinidazole
- PRBC[at]15ml per kg over 4 hrs
- Albumin infusion 1gm/per infused over 4hrs
- Upgrade to Meropenam 20mg/kg 8 hrly
- UDCA 20mg per kg per day in 2 d. d (Cholestasis management)
- Ventilation / CPAP (Increased respiratory distress)

Supportive Care

- Gastroprotection medication-ranitidine
- Prophylactic cotrimaxazole, oralantimycotic
- Nutritional supplement-Vitamins, Calories, IV Fluid
- Oxygen Support

Other advance modalities

- intravenous immunoglobulin (0.5 g/kg body weight, given on d 2 through d 15) was administered.
- Antithymocyte globulin and rituximab
- HLH-HIT Trail-a combined use of ATG, Etooside, Intrathecal methotrexate and hydrocortisone is currently under studies.
- Allogenic hemotopoietic stem cell tansplantation

Outcome

Few cases of HLH in neonates and infants are reported in the literature. Baby girl hospitalized and treatment may be started on suspicion to avoid loss of timeThe physicians should be aware of the risk and symptoms of HLH, whichmay present the baby girlwas as severe illness in infancy, with signs of HLH and acute respiratory failure. After d 20 of hospitalization, baby girl can not survived this critical condition.

4. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening disease of severe hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages secreting high amounts of inflammatory cytokines. It is a frequent manifestation in patients with predisposing genetic defects, but can occur secondary to various infectious, malignant, and autoimmune triggers in patients without a known genetic predisposition. Clinical hallmarks are prolonged fever, cytopenias, hepatosplenomegaly, and neurological symptoms, but atypical variants presenting with signs of chronic immunodeficiency are increasingly recognized. Impaired secretion of perforin is a key feature in several genetic forms of the disease, but not required for disease pathogenesis. Despite progress in diagnostics and therapy, mortality of patients with severe HLH is still above 40%. Reference treatment is an etoposide-based protocol, but new approaches are currently explored. Key for a favorable prognosis is the rapid identification of an underlying genetic cause, which has been facilitated by recent immunological and genetic advances. In patients with predisposing genetic disease, hematopoietic stem cell transplantation is performed increasingly with reduced intensity conditioning regimes. Current research aims at a better understanding of disease pathogenesis and evaluation of more targeted approaches to therapy, including anti-cytokine antibodies and gene therapy.

5. Conclusion

HLH is an uncommon but under diagnosed disease. The mortality is uniformly high, and a timelydiagnosis is imperative. Infections are common triggers in both genetic and acquired HLH. There have been recent advances in under-standing the pathogenesis of genetic HLH, for which genetic tests are available and treatment protocols have shown to improve prognosis. These studies should help direct research aimed at improving knowledge about HLH diease, clinical presentation, pathophysiology, diagnostic methods and treatment.

Additional studies are required to know patho-genesis of this disease subtype, newer and more specific testing may become available as well as novel targeted therapies.

6. Consent

Written informed consent was obtained from the patient parents for publication of this case report.

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