HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) DUE TO CCHF

معرفی بیمار

- بیمار خانم ۴۷ ساله بدون بیماری خاصی در گذشته با شرح حال تب, سردرد, میالژی و خواب الودگی مراجعه میکند بدنبال این مشکلات بیمار دچار هموپتیزی, ملنا ,هماتمز و سپس خونریزی واژینال میشود.

- در شرح حال بیمار دو روز قبل ازشروع علائم ,ذبح گوسفندو حدودا ۵ روز قبل از آن گزش کنه را هیستوری میدهد

- در معاینات انجام شده بیمارتب ندارد فشار خون ۹۰ ,ضربان ۸۰و تعدادتنفس در حد ۲۵ دارد
- بیمار رنگ پریده و خواب الود ولی هوشیار است اکیموز در ساعد دست راست و کشاله ران هر دو طرف دارد و خونریزی از ناحیه واژن مشهود است
- در سونوگرافی بیمار هپاتواسپلنومگالی خفیف گزارش شد

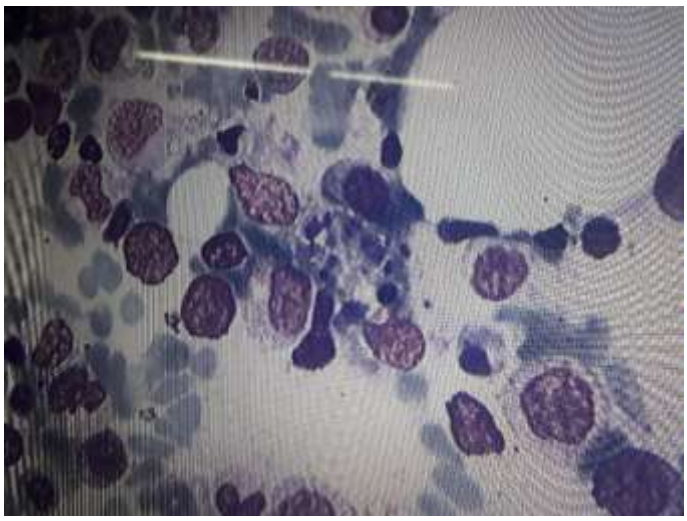
آزمایشات روز اول

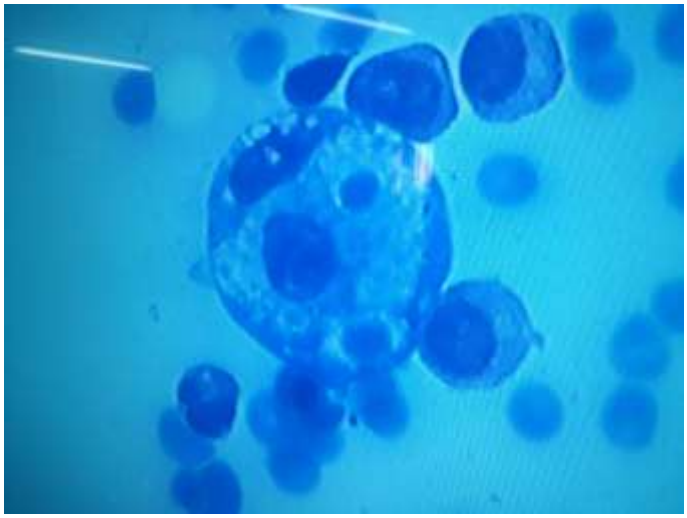
WBC	1200	Na	131
RBC	3.76	K	3.4
Hb	8	AST	558
MCV	71	ALT	136
PLT	66000	LDH	2180
BS	189	INR	1.9
Urea	16	PT	18.5
Cr	0.8	PTT	49

آزمایشات روز دوم

WBC	0.6		BILL	0.8
RBC	3.95		PCT	0.538
Hb	8		Ferritin	11245
PLT	43000	13000	TG	137
AST	2700	4680	HBSAg	negative
ALT	664	710	HIV ab	negative
LDH	3097		HCV ab	negative
CPK	825		Wright	negative

BONE MARROW ASPIRATION





Approach to Hemophagocytic Syndromes

Introduction: background and pathogenesis

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory condition caused by a highly stimulated but ineffective immune response.[1] The incidence is estimated to be approximately 1.2 cases per million individuals per year,[2] but this is almost certainly an underestimate. Broadly, HLH can be classified

- It most frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages. HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases.

- TERMINOLOGY — Terms used to describe HLH and related syndromes have evolved since the original patient was described as having "familial hemophagocytic reticulosis" in 1952.
- Use of the term "primary HLH" to denote the presence of an underlying genetic disorder and "secondary HLH" to denote presence of the HLH phenomenon occurring secondary to another condition has caused a great deal of confusion among clinicians. Both primary and secondary HLH can be triggered by infections or other immunologically activating events, and gene mutations can be found in individuals of any age and with any family history. In practice, distinction between primary and secondary HLH is not essential for the initial diagnosis and management

PRIMARY HLH, ALSO CALLED FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (FHL)

Table 1. Genetic defects leading to HLH*

Disease	Gene	Defect
FHLH1	Unknown	
FHLH2	*PRF1*	Vesicle content
FHLH3	*Munc13.4*	Vesicle priming
FHLH4	*STX11*	Vesicle docking and fusion
FHLH5	*STXBP2*	Vesicle docking and fusion
Chediak-Higashi	*LYST*	Vesicle trafficking
Griscelli II	*RAB27a*	Vesicle fusion or fission
Hermansky-Pudlak II	*AP3B1*	Vesicle trafficking
XLP1	*SH2D1A* (*SAP*)	Multiple effects including $CD8^+$ T/NK-cell cytotoxicity
XLP2	*BIRC4* (*XIAP*)	Multiple signaling pathways

- ●Secondary (sporadic, acquired) HLH has generally been used to describe those without a known familial mutation; adults; and those for whom a clear trigger of the HLH episode has been identified (eg, viral illness, autoimmune disease, lymphoma). However, this term can create confusion because many patients with "secondary HLH" do in fact have a genetic defect associated with the syndrome (eg, heterozygous defect, mutation resulting in partial protein expression), and many patients with primary HLH experience symptoms in response to one of these triggers.

- ●Macrophage activation syndrome – Macrophage activation syndrome (MAS) is a form of HLH that occurs primarily in patients with juvenile idiopathic arthritis or other rheumatologic diseases

- PATHOPHYSIOLOGY
- Immunologic abnormalities — HLH is not a malignancy; it is a syndrome of excessive inflammation and tissue destruction due to abnormal immune activation and excessive inflammation. In general, the excessive inflammation is thought to be caused by a lack of normal downregulation of activated macrophages and lymphocytes

THE CELL TYPES INVOLVED IN THE PATHOGENESIS OF HLH INCLUDE THE FOLLOWING:

- **Macrophages** – Macrophages are professional antigen presenting cells derived from circulating monocytes; they present foreign antigens to lymphocytes. In HLH, macrophages become activated and secrete excessive amounts of cytokines, ultimately causing severe tissue damage that can lead to organ failure

- **●Natural killer cells and cytotoxic lymphocytes** – Natural killer (NK) cells constitute 10 to 15 percent of lymphocytes. NK cells eliminate damaged, stressed, or infected host cells such as macrophages, typically in response to viral infection or malignancy, in an MHC-unrestricted manner

- Cytotoxic lymphocytes (CTLs) are activated T lymphocytes that lyse autologous cells such as macrophages bearing foreign antigen associated with Class I histocompatibility proteins. Most CTLs express CD8

- In HLH, NK cells and/or CTLs fail to eliminate activated macrophages. This lack of normal feedback regulation results in excessive macrophage activity and highly elevated levels of interferon gamma plus other cytokines

- Consistent with this mechanism, most patients with HLH exhibit impaired cytotoxic function of NK cells and CTLs, coupled with excessive activation of macrophages

- Hemophagocytosis – In addition to antigen presentation and cytokine production, macrophages can also phagocytize host cells. Hemophagocytosis refers to the engulfment (literally "eating") of host blood cells by macrophages. Hemophagocytosis is characterized by the presence of red blood cells, platelets, or white blood cells (or fragments of these cells) within the cytoplasm of macrophages. It can be seen on biopsies of immune tissues (lymph nodes, spleen, liver) or bone marrow aspirates/biopsies. 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.

- Triggers – Patients with HLH can have a single episode of the disease or relapsing episodes. The initiating trigger for an acute episode is often an infection or an alteration in immune homeostasis. The two broad categories of triggers include those that cause immune activation, and those that lead to immune deficiencyInfection is a common trigger both in those with a genetic predisposition and in sporadic cases.

- especially with Epstein-Barr virus (EBV)

Table 2
HLH Subtypes and Common Disease Associations

Infection	Reported Associations
Viral	Herpesviruses (EBV, CMV, HHV-8, HSVI, HIV, HTLV, adenovirus, HAV, HBV, HCV, measles, mumps, rubella, dengue, hantavirus, parvovirus B19, enterovirus, influenza
Bacterial	*Staphylococcus aureus, Campylobacter* spp, *Fusobacterium* spp, *Mycoplasma* spp, *Chlamydia* spp, *Legionella* spp, *Salmonella typhi, Rickettsia* spp, *Brucella* spp, *Ehrlichia* spp, *Borrelia burgdorferi, Mycobacterium tuberculosis*
Fungal	*Candida* spp, *Cryptococcus* spp, *Pneumocystis* spp, *Histoplasma* spp, *Aspergillus* spp, *Fusarium* spp
Parasitic	*Plasmodium falciparum, Plasmodium vivax, Toxoplasma* spp, *Babesia* spp, *Strongyloides* spp, *Leishmania* spp
Malignancy	
Hematologic	Peripheral T-cell/NK-cell lymphomas, ALCL, ALL, Hodgkin lymphoma, multiple myeloma, acute erythroid leukemia
Nonhematologic	Prostate and lung cancer, hepatocellular carcinoma
MAS	Systemic-onset juvenile idiopathic arthritis, Kawasaki disease, systemic lupus erythematosus, seronegative spondyloarthropathies

ALCL, anaplastic large-cell lymphoma; ALL, acute lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; MAS, macrophage activation syndrome; NK, natural killer.

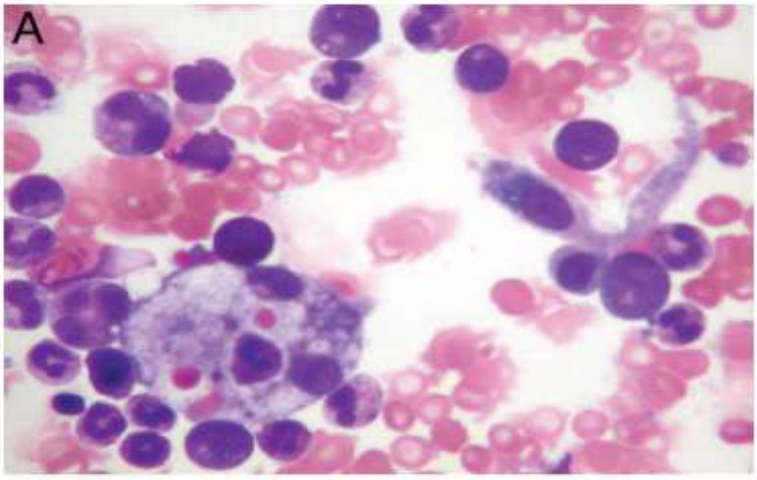
Clinical Characteristics	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6	Case-7	Case-8	Total n (%)
Fever	+	+	+	+	+	+	+	+	8 (100%)
Jaundice	_	_	+	+	+	+	+	_	5 (62%)
Breathlessness	_	_	+	+	+	_	+	_	4 (50%)
Rash	_	_	_	+	+	_	+	_	3 (37%)
Body ache	+	_	+	+	_	+	_	_	4 (50%)
Abdominal pain	_	_	+	+	_	+	_	_	3 (37%)
Joint pains	_	_	+	_	_	+	_	_	2 (25%)
Headache	_	_	_	_	_	_	+	_	1 (12%)
Seizures	_	_	_	_	+	_	_	_	1 (12%)
Pallor	+	+	+	+	+	+	+	_	7 (87%)
Icterus	_	+	+	+	+	+	+	_	6 (75%)
Hepatomegaly	_	_	+	+	+	+	+	_	5 (62%)
Splenomegaly	+	+	+	+	+	+	_	_	6 (75%)
Lymphadenopathy	_	_	+	+	+	_	+	_	4 (50%)
Pedal odema	+	_	_	+	_	_	+		3 (37%)
Etiology	Not known	Not known	Tuberculosis	Lymphoma	EBV	Dengue	Scrub typhus	JIA	6 (75%)

[Table/Fig-1]: Shows patients clinical characteristics and physical findings at the time of diagnosis as HLH.

- CLINICAL FEATURES
- Initial presentation — HLH presents as a febrile illness associated with multiple organ involvement. Thus, initial signs and symptoms of HLH can mimic common infections, fever of unknown origin, hepatitis, or encephalitis. With few exceptions, the clinical features are similar regardless of whether an underlying genetic defect has been identified

Table 1. Diagnostic Guidelines for HLH

The diagnosis of HLH requires a molecular diagnosis consistent with HLH or 5/8 of the below criteria
1) Fever
2) Splenomegaly
3) Cytopenias affecting ≥ 2 lineages a. Hemoglobin <9 g/dL b. Platelets $<100 \times 10^9$ /L c. Neutrophils $<1.0 \times 10^9$ /L
4) Hypertriglyceridemia and/or hypofibrinogenemia a. Triglycerides ≥265 mg/dl b. Fibrinogen ≤150 mg/dl
5) Hemophagocytosis in bone marrow, spleen, or lymph nodes
6) Low or absent NK-cell activity
7) Ferritin ≥ 500 µg/L
8) Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml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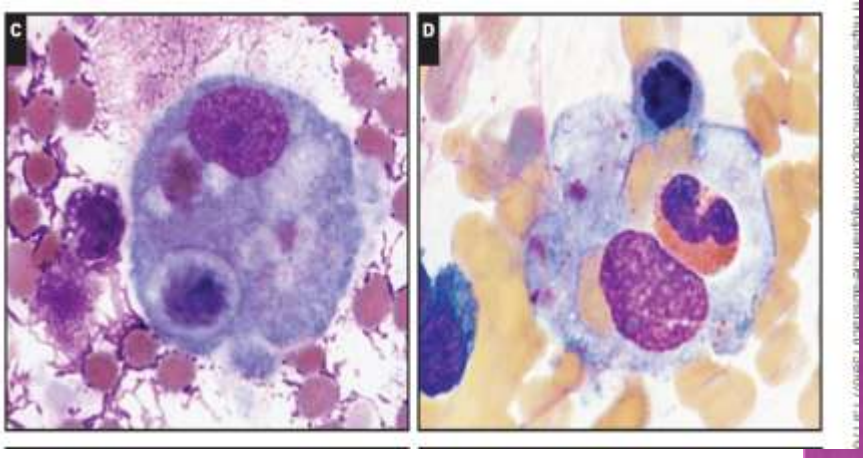
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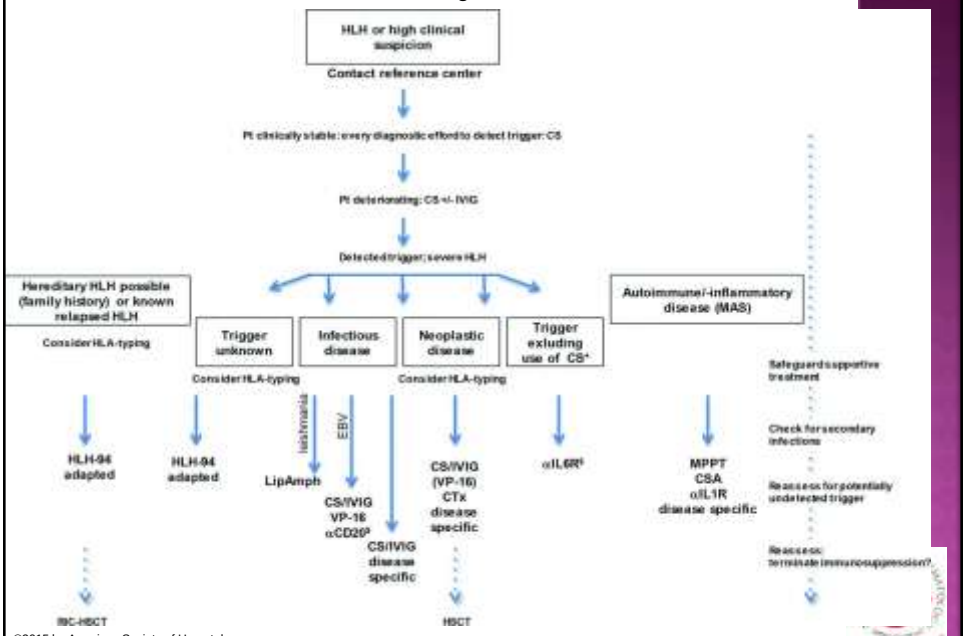
D

Treatment algorithm for aHLH.



- **The treatment of crimean-congo hemorrhagic fever with high-dose methylprednisolone, intravenous immunoglobulin, and fresh frozen plasma.**
- Erduran E[1], Bahadir A, Palanci N, Gedik Y.
- Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne disease caused by Nairovirus, and it is sometimes characterized by reactive hemophagocytic histiocytosis (HLH). The reasons for reactive HLH are macrophage-activating syndrome and disseminated intravascular coagulation due to cytokine storm, liver dysfunction, and endothelial damage by the virus. In this study, the effectiveness of high-dose methylprednisolone (HDMP) (5 to 30 mg/kg/d), fresh frozen plasma (FFP), and intravenous immunoglobulin (IVIG) was investigated in patients with CCHF associated with reactive HLH. Twelve patients with CCHF in association with reactive HLH were included in the study. The patients were successfully treated with HDMP to suppress the macrophage activation, FFP to treat disseminated intravascular coagulation, and IVIG to treat severe thrombocytopenia. No patients received ribavirin. Fever reduced in 1.6 ± 0.8 days, WBC count increased above 4.500/μL in 4.0 ± 2.4 days, platelet count increased above 150.000/μL in 8.5 ± 2.5 days, and D-dimer level decreased under 1 mcg/dL in 5.8 ± 3.6 days. Consequently, HDMP, FFP, and IVIG may be effective in patients with CCHF associated with reactive HLH during hemorrhagic period of the disease.

Crimean-Congo hemorrhagic fever: Five patients with hemophagocytic syndrome

Nuriye Tasdelen Fisgin,[1*] Tunc Fisgin,[2] Esra Tanyel,[1] Levent Doganci,[1] Necla Tulek,[1] Nil Guler,[3] and Feride Duru[2]

Three pediatric and two adult Turkish patients with Crimean Congo Hemorrhagic Fever (CCHF) induced hemophagocytic syndrome (HPS) were admitted to Ondokuz Mayis University Hospital, which is in the Middle Black Sea Region of Turkey. All of them had remarkable hemophagocytosis in the bone marrow with severe bleeding symptoms along with the other known clinical and laboratory findings of CCHF. We would like to present these patients and to discuss the pathophysiology and the effect of acquired HPS on the severity of the disease. Am. J. Hematol. 83:73–76, 2008.