HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

BY TIMEA A. MAXIM, MD

MAY 2026

LEARNING OBJECTIVES:

By the end of the session, participants will be able to:

- Review the clinical presentations in medical practice.
- Review the pathophysiology of this clinical condition.
- Formulate applicable treatment plans according to the above.
- Determine which medical specialties could become involved for overall medical care.

CONFLICTS OF INTEREST:

I have no conflicts of interest to declare.

CLINICAL QUESTION #1:

What are the diagnostic criteriå for HLH? Can select multiple answers.

A) Fever: Prolonged and high-grade;
B) Splenomegaly;
C) Cytopenias;
D) Hypertriglyceridemia and/or Hypofibrinogenemia;
E) Hemophagocytosis;
F) Low or absent NK-cell activity;
G) Ferritin abnormalities;
H) Elevated soluble CD25 (sCD25).

CLINICAL QUESTION #2:

What are the typical causes of HLH (Hemophagocytic lymphohystiocytosis)?

A) Inherited condition;

B) Viral infections, i.e. EBV;

C) Other infections;

D) Immunosuppression;

E) Malignancy.

F) All of the above.

CLINICAL CASE AT SMMH:

HPI:

28-YEAR-OLD MALE REPATRIATED FROM SAINT MICHAEL'S HOSPITAL ON APRIL 2, 2026 FOLLOWING PROLONGED ADMISSION PREDOMINANTLY FOR HLH. HE INITIALLY PRESENTED TO THE BRACEBRIDGE HOSPITAL ON DECEMBER 17 2025, FOLLOWING 2-DAY HISTORY OF FEELING GENERALLY UNWELL AND A FEW MONTH HISTORY OF DENTAL INFECTION. HE WAS ADMITTED IN DKA TO OUR ICU (FIRST PRESENTATION) AND MANAGED FOR PRESUMED SEPTIC SHOCK.

PMHX:

1. CHOLECYSTECTOMY IN 2009.
2. HEREDITARY SPHEROCYTOSIS

FHX: BROTHER WITH HEREDITARY SPHEROCYTOSIS.

MEDS: NONE.

CLINICAL CASE AT SMMH CONT.:

He was admitted to the ICU for few days, but eventually was transferred to Saint Michael's Hospital on December 20 , 2025 for higher level of care.

His hospital course at St. Michael’s Hospital was complicated by :

- Persistent hyperglycemia → diagnosed with T1DM,
- Recurrent fevers,
- AKI requiring renal replacement therapy,
- Hepatitis B infection, requiring initiation of entecavir,
- Pneumomediastinum and thrombocytopenia,
- Necrotizing pneumonia treated withm eropenem/ ertapenem due to Klebsiella aeruginosa infection,
- Thrombocytopenia eventually led to a diagnosis of HLH (through bone marrow biopsy) for which he had been on IVIG, prednisone taper, etoposide, and ruxolitinib. Initial Onset of HLH brought on by extreme illness and EBV reactivation,
- Sepsis secondary to *Candida dubliniensis* for which he was treated with micafungin for 1 month, completing his course on March 16, 2026,

CLINICAL CASE AT SMMH CONT.:

- Further investigations with TEEs for infective Candida endocarditis, initially revealing a mobile mesh attached to the inferior aspect of the atrial septum-on repeat evaluation this demonstrated lipomatous tricuspid valve mass;
- Development of right IJ DVT;
- Acute GI bleed secondary to colon ulceration felt to be ischemic in nature;
- Hypercalcemia secondary to immobilization managed with pamidronate, calcitonin and zoledronic acid with good response;
- Eventually had a tracheostomy on February 28.;
- Recent tracheostomy on February 28, with recannulation while at RVH in March 2026. By time of discharge he was on cork trials with speaking valve;
- Chronic dysphagia, requiring video swallow study and continuity of care with SLP;
- Severe critical illness myopathy.

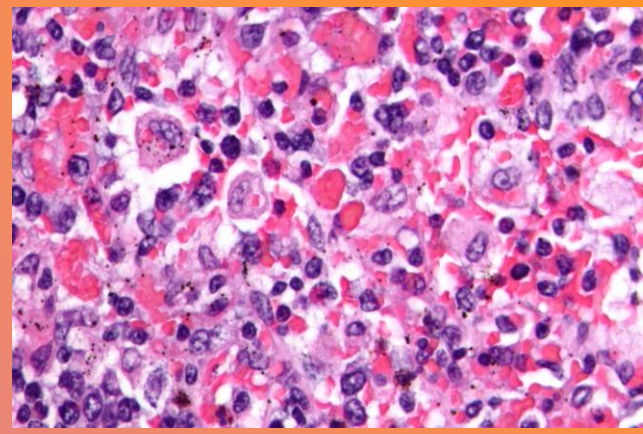
CLINICAL COMPLICATIONS SINCE SMMH TRANSFER:

Initial labs showed the following:

- CMP: BUN 9.8 [H], Cr 45 [L], Na+ 136 [L], K+ 4.3, Cl-102, CO2 29, AG 9.3 [L]. ALT 20.
- CBC: RBC 2.67 [L], Hb 75[L], MCV 80, Plat 153, WBC 5.8.
- Ferritin >1000.

- Acute on chronic anemia, requiring blood transfusions. Received 1pU RBCs while I was on call during the first week of April 2026.
- Lack of clarification on duration of prophylactic ABX, prednisone, and antiviral therapy.
- PT/OT and SLP consults due to severe oropharyngeal dysphagia. NGT feeds were continued.
- Lack of cooperation from patient regarding treatment recommended.

DEFINITION OF HLH:



- - HLH is an aggressive and life-threatening syndrome of excessive immune activation. HLH most often affects infants from birth to 18 months of age, but it also occurs in children and adults of all ages.

  - CAN BE A familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. Infections, malignancies, rheumatologic disorders, and immunodeficiencies are common triggers, both in patients with a predisposing genetic condition and in sporadic cases.

DEFINITION OF HLH CONT.:

- Prompt treatment of HLH is critical for successful outcomes, but the greatest barrier to a successful outcome is often a delayed diagnosis.

- Factors that may delay HLH diagnosis include its rarity, variable clinical presentation, and lack of specificity of the clinical and laboratory findings, which overlap with several other disease states.

INCIDENCE OF HLH:

- It is primarily a pediatric syndrome, but it can occur in patients of any age.

Infants are most commonly affected, with the highest incidence in those <3 months. The male-to-female ratio is close to 1:1. In adults, there may be a slight male predisposition.

Although HLH is predominantly seen in young children, it can be seen in patients of any age, including adults as old as 70 years. There may be an ethnic predisposition for the development of malignancy-associated HLH, with one large study demonstrating a much higher risk in **Japanese and Eastern Asian patients** with malignancy compared with Western patients.

INCIDENCE OF HLH CONT.:

- Up to 1/4 of cases of HLH were originally thought to be caused by **inherited gene variants.** One study reported classic HLH-associated mutations in only 19 % of patients, but 58 % of the other patients had pathogenic variants in other immune-deficiency genes.

- In a study of 65 unrelated families with HLH, gene variants affecting ***STX11, PRF1,*** **and** ***UNC13D*** were found in 20, 18, and 10 % of affected individuals, respectively.

INCIDENCE OF HLH CONT.:

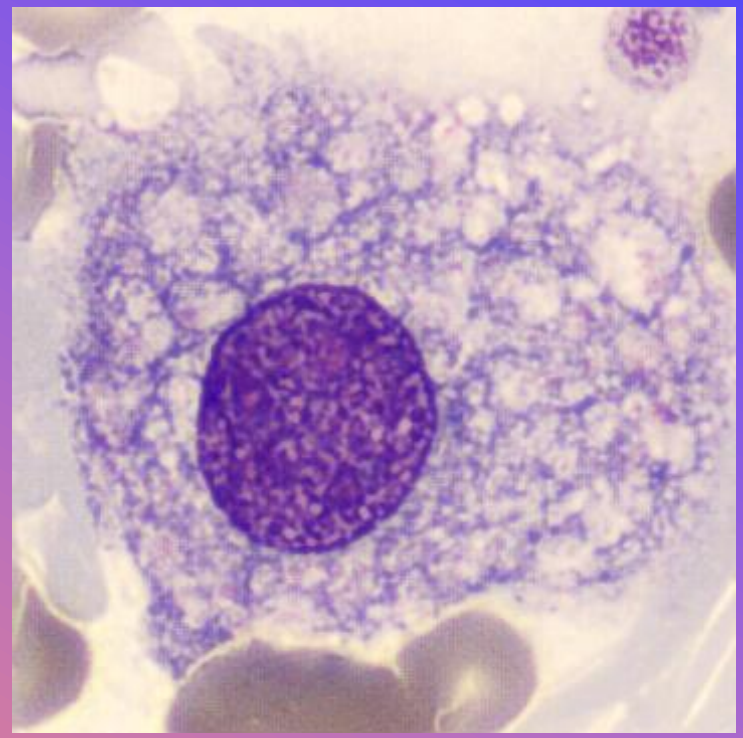
- A review of 224 North American patients with HLH-associated gene variants reported the following distribution of specific gene variants according to race or ethnicity:

  - White Americans – Most likely to be *UNC13D* (47 percent), *STXBP2* (22 %), and *PRF1* (20%);
  - Hispanic Americans – Most likely to be *PRF1* (71% and UNC13D (17%);
  - Black Americans – Most likely to be *PRF1* (98%);
  - Arabs – Most likely to be *PRF1* (36 percent), *UNC13D* (27%), and *STXBP2* (18%).

CELLULAR MECHANISMS OF HLH – A HISTOLOGIC REVIEW:

- **Macrophages –**

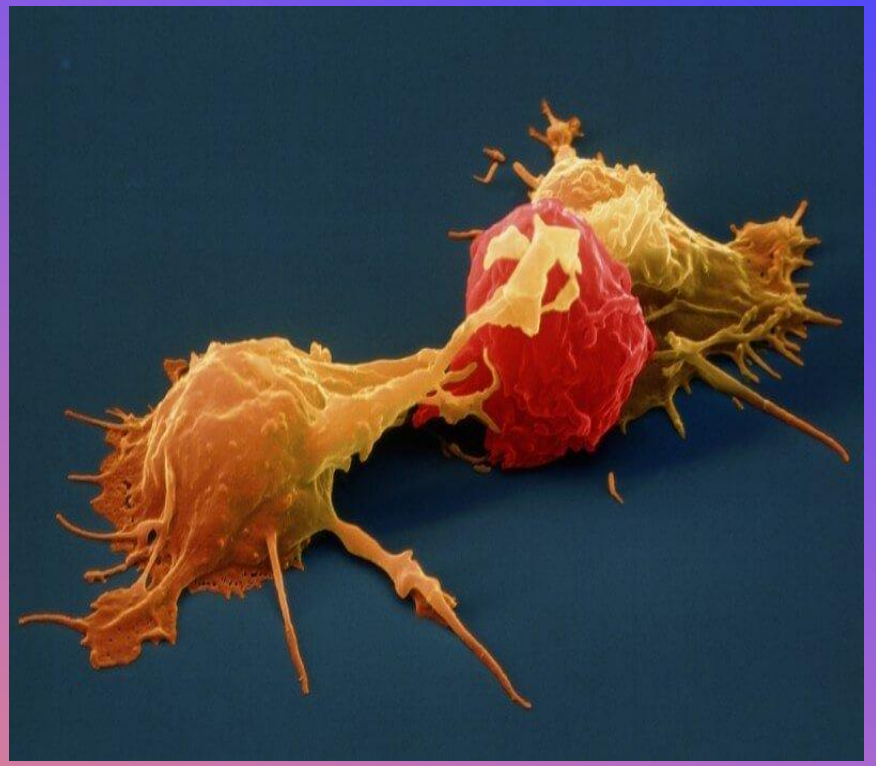
Macrophages are professional antigen-presenting cells derived from circulating monocytes. Macrophages, along with dendritic cells, present foreign antigens to lymphocytes. In HLH, macrophages become activated and secrete excessive amounts of cytokines, ultimately **causing severe tissue damage** that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



CELLULAR MECHANISMS OF HLH CONT.:

Natural killer cells –

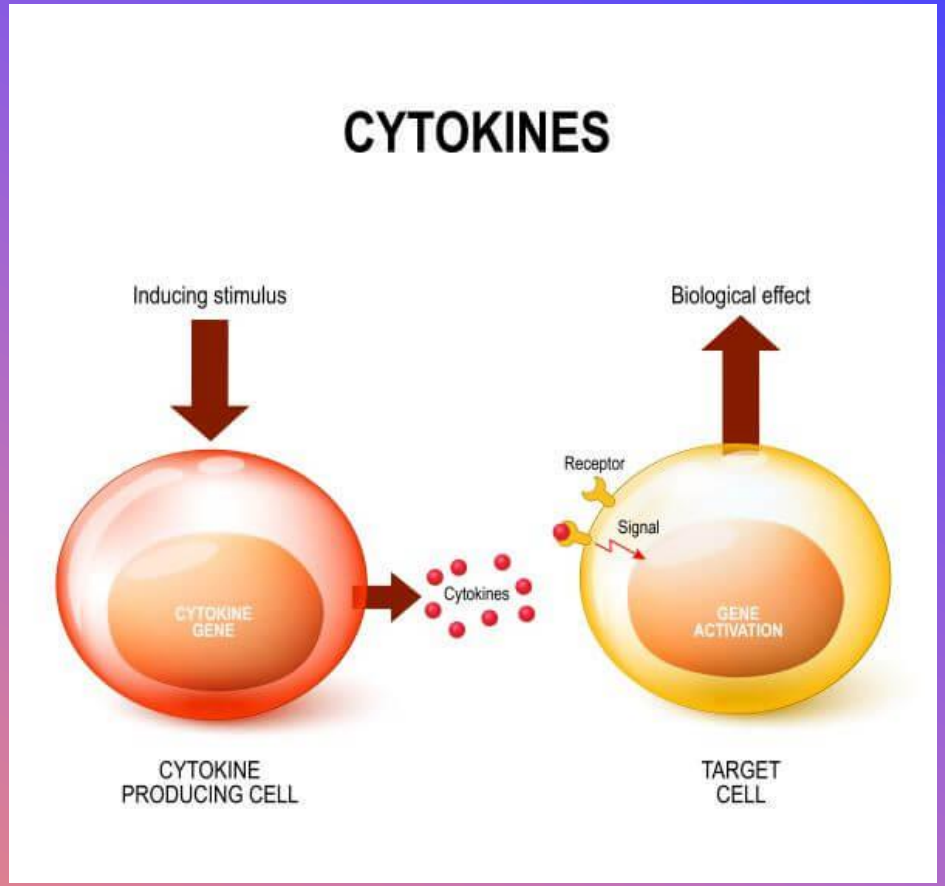
Natural killer (NK) cells constitute 10 to 15% of lymphocytes. NK cells eliminate damaged, stressed, or infected host cells, such as macrophages, typically in response to viral infection or malignancy, in a major histocompatibility complex (MHC)-unrestricted manner.



CELLULAR MECHANISMS OF HLH CONT.:

- **Cytotoxic lymphocytes** –

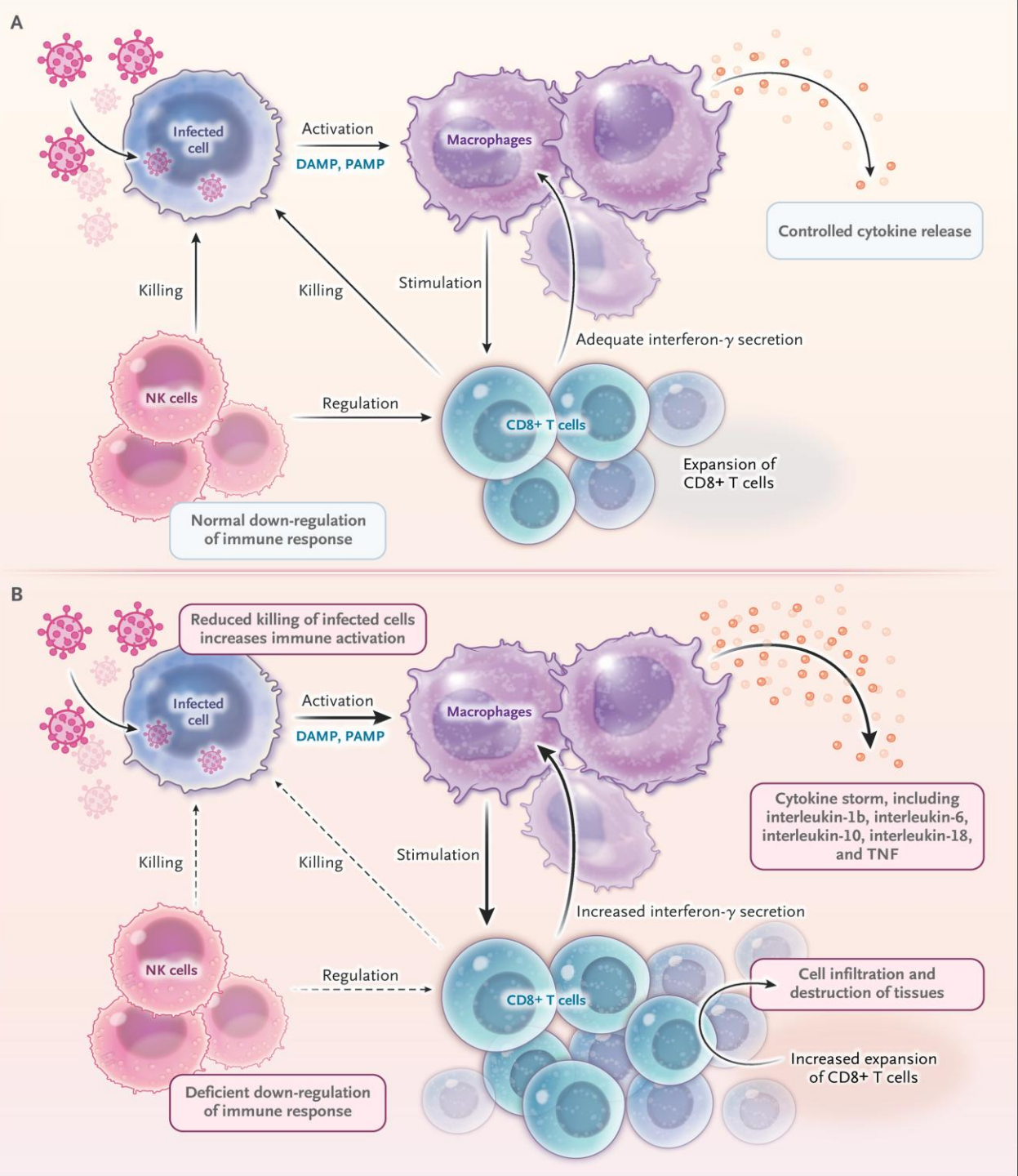
Cytotoxic T lymphocytes (CTLs) are $CD8^+$ activated T cells (primarily expressing CD8) that target and destroy infected or abnormal autologous cells (eg, macrophages), and present foreign antigens in conjunction with class I MHC molecules.



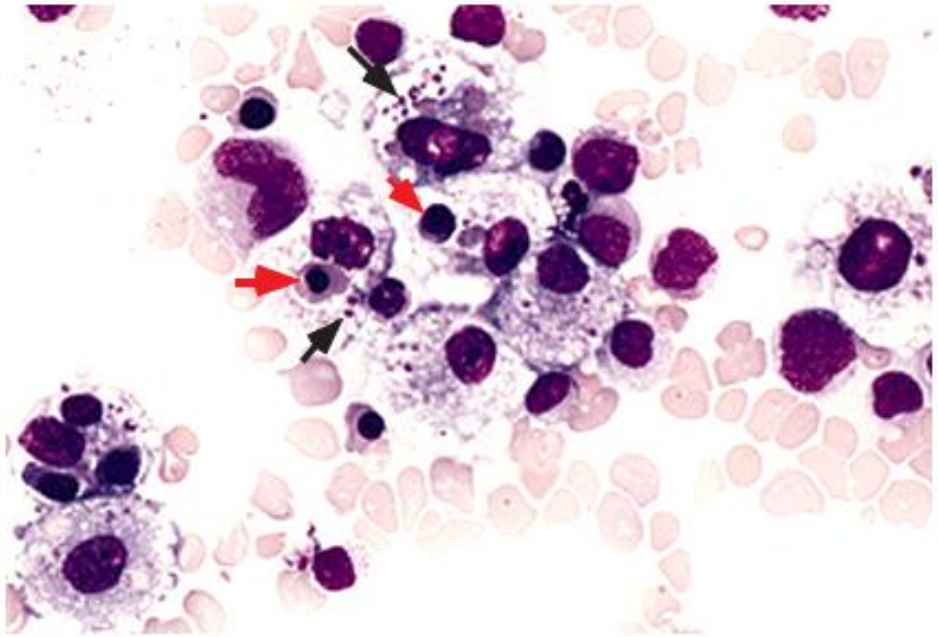
CELLULAR MECHANISMS OF HLH CONT.:

Hemophagocytosis – Hemophagocytosis refers to the engulfment (literally "eating") of host blood cells by macrophages.

Hemophagocytosis can be seen in immune tissues (lymph nodes, spleen, liver) or bone marrow. Although hemophagocytosis can be a marker of excessive macrophage activation and supports the diagnosis of HLH, hemophagocytosis alone is neither pathognomonic nor required for the diagnosis of HLH.



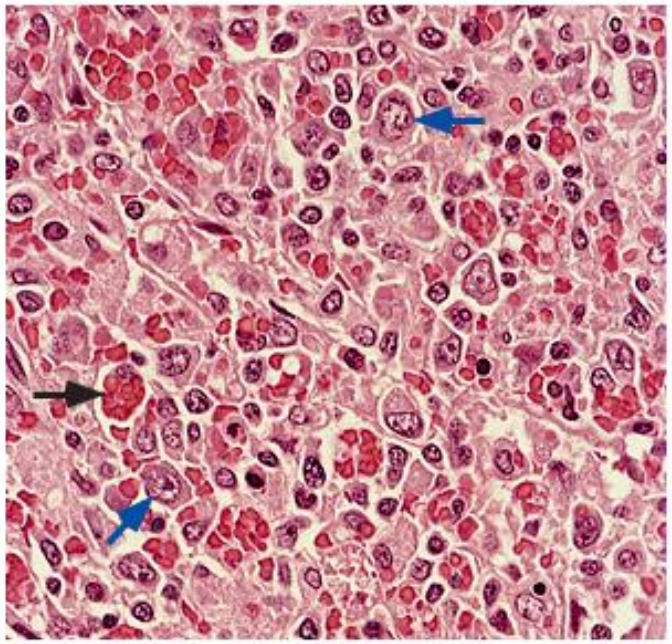
Infection-associated hemophagocytic syndrome



Bone marrow from a child with hemophagocytic syndrome, secondary to Epstein-Barr virus infection. Reactive histiocytes show phagocytosis of nucleated red blood cells (red arrows) and platelets (black arrows). Wright-Giemsa stain.

From: Brunning RD, McKenna RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.

Large T cell lymphoma with reactive hemophagocytosis



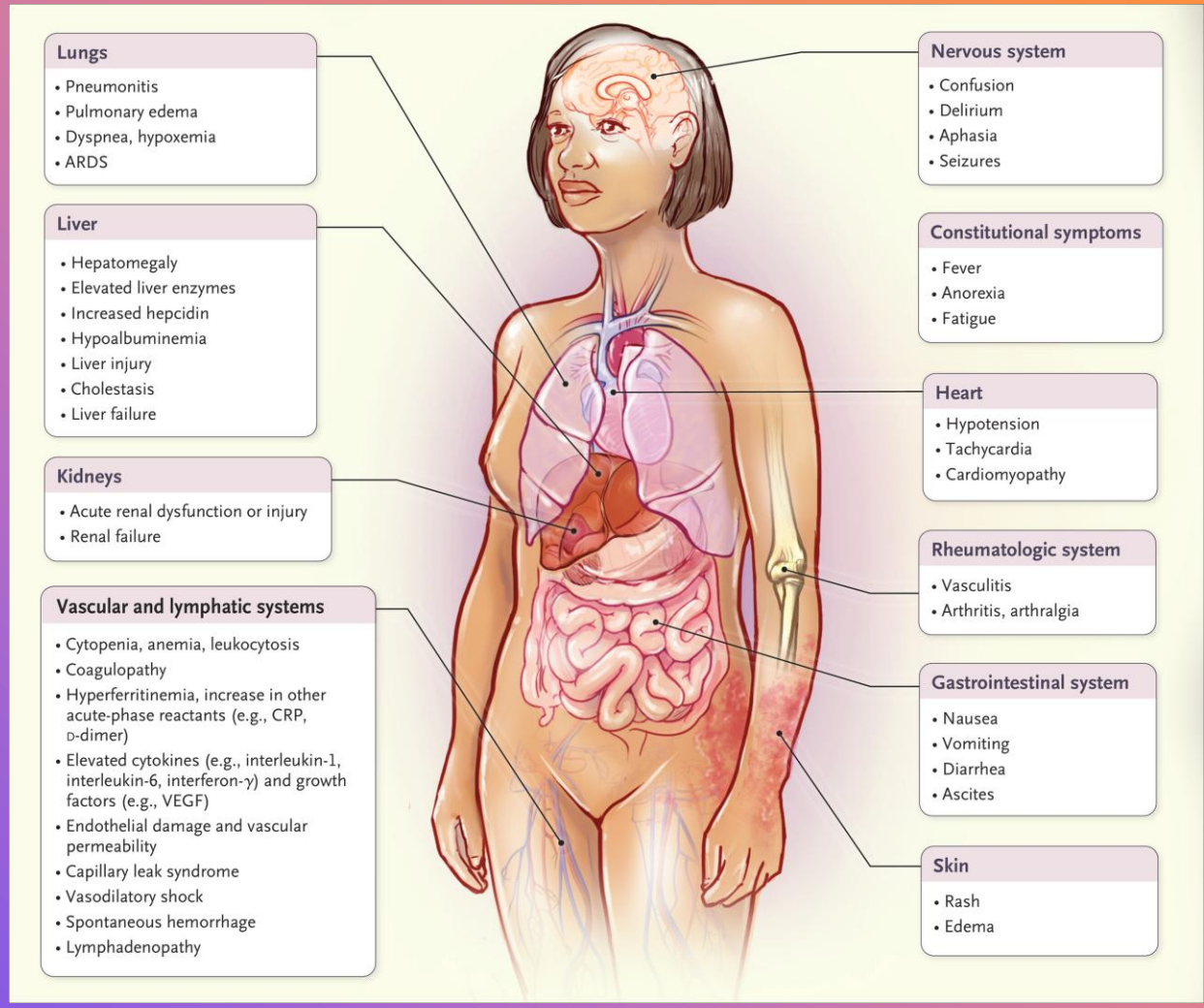
The red pulp of the spleen is diffusely permeated by large lymphoma cells (T lineage, blue arrows) and histiocytes showing erythrophagocytosis (black arrow). The histiocytes have smaller, bland-looking nuclei with delicate chromatin.

From: Warnke RA, Weiss LM, Chan JK, et al. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.

CELLULAR MECHANISMS CONT.:

- **●Cytokine storm –**

  The persistent activation of macrophages, NK cells, and CTLs in patients with HLH leads to excessive cytokine production (cytokine storm) by macrophages and lymphocytes and is thought to be responsible for multiorgan failure and the high mortality of this syndrome.



TYPICAL TREATMENTS FOR HLH:

Treatment of HLH depends on the cause, your age when the disease starts, and how severe the disease is. The acquired form of HLH may clear up when your healthcare provider identifies the cause and treats the disease. Familial-type HLH is usually fatal if not treated. Treatment for familial or persistent acquired HLH may include:

- Chemotherapy;
- Immunotherapy;
- Steroids;
- Antibiotic and/or Antiviral drugs;
- Stem cell transplant if failure to the above. Most curative in most HLH cases.
- Involvement of appropriate medical specialties, such as hematology, infectious disease, immunology, etc.

RETURN TO OUR CLINICAL CASE AT SMMH:

Further updates on Assessment & Plan:

1) HLH-Hemophagocytic lymphohistiocytosis (thought to be triggered by fungemia and possibly EBV infection):

- Will continue prednisone, follow slow taper as ordered and reviewed with PharmD and ruxolitinib. Requires WEEKLY ferritin monitoring for taper guidance. Diagnosed via iliac bone biopsy (Dec. 30, 2025), presumed associated with EBV reactivation. Labs ordered to be done weekly every WED x 9 weeks. Genetic testing results also pending.

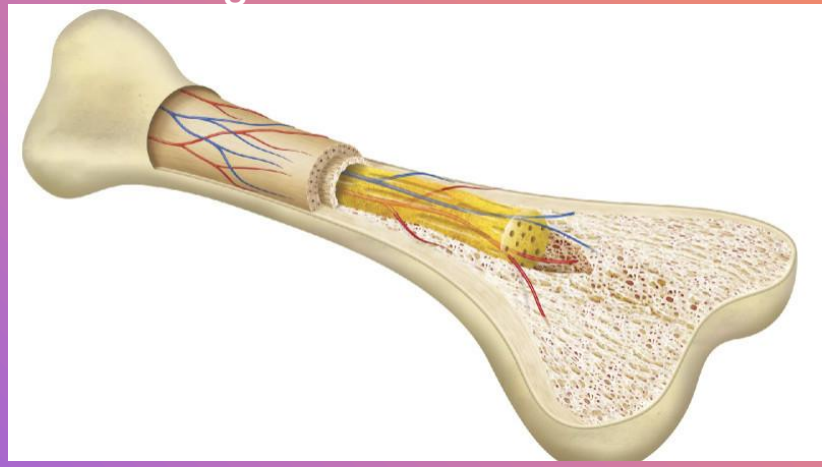
2) Severe Pharyngeal Dysphagia:

- NGT failure overnight. Will remove today as pt. is reluctant to have this continue. Will ensure his original feeds are ingested orally.
- SLP + dietician following closely as well.

TREATMENTS INVOLVED CONT.:

Further updates on Assessment & Plan:

3) Bone Marrow Immunosuppression:
a) Acute on Chronic Normocytic Anemia:
b) Recent GI bleed-secondary to large ulcerated areas in rectosigmoid colon:
- Hb has shown an acute drop. Will trend it, and if require, will proceed with 2U pRBCs. - General surgery states they will become involved if further signs of acute GI bleeding occur.
- FOBT negative - April 14. Is on PPI BID.
- GI/EGD scope done at St. Mike's on Feb.2: likely in the context of anticoagulation and ischemic changes from septic shock.
- Will continue valacyclovir and septra as recommended by ID.
- CT abdo/pelvis - stable splenomegaly - BW r/o hemolysis.



ASSESSMENT & PLAN CONT.:

4) Prolonged Hospital Admission Likely Resulting in Severe Deconditioning / Critical Illness Myopathy:
- Will need aggressive PT/OT and specific dietary requirements.
- Consider more intensive rehab facility in near future.

5) Type 1 Diabetes Mellitus:
Hyperglycemia, improving:
- Currently on lantus 24U in AM and 26U QHS. Increased the bedtime insulin further to 28U to improve glycemic control.
- Will monitor POC glucose closely and adjust accordingly.

6) Hepatitis B:
- Entecavir 0.5 mg PO QD therapy started Jan 23, duration to be clarified. This was found on workup for viral precipitants of HLH --> likely to remain on this for several months.

RETURN TO OUR CLINICAL QUESTIONS:

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C) Other infections;

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E) Malignancy.

F) All of the above.

QUESTIONS AND / OR CONCERNS ?

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THANK YOU FOR YOUR TIME!