Hemophagocytic syndrome

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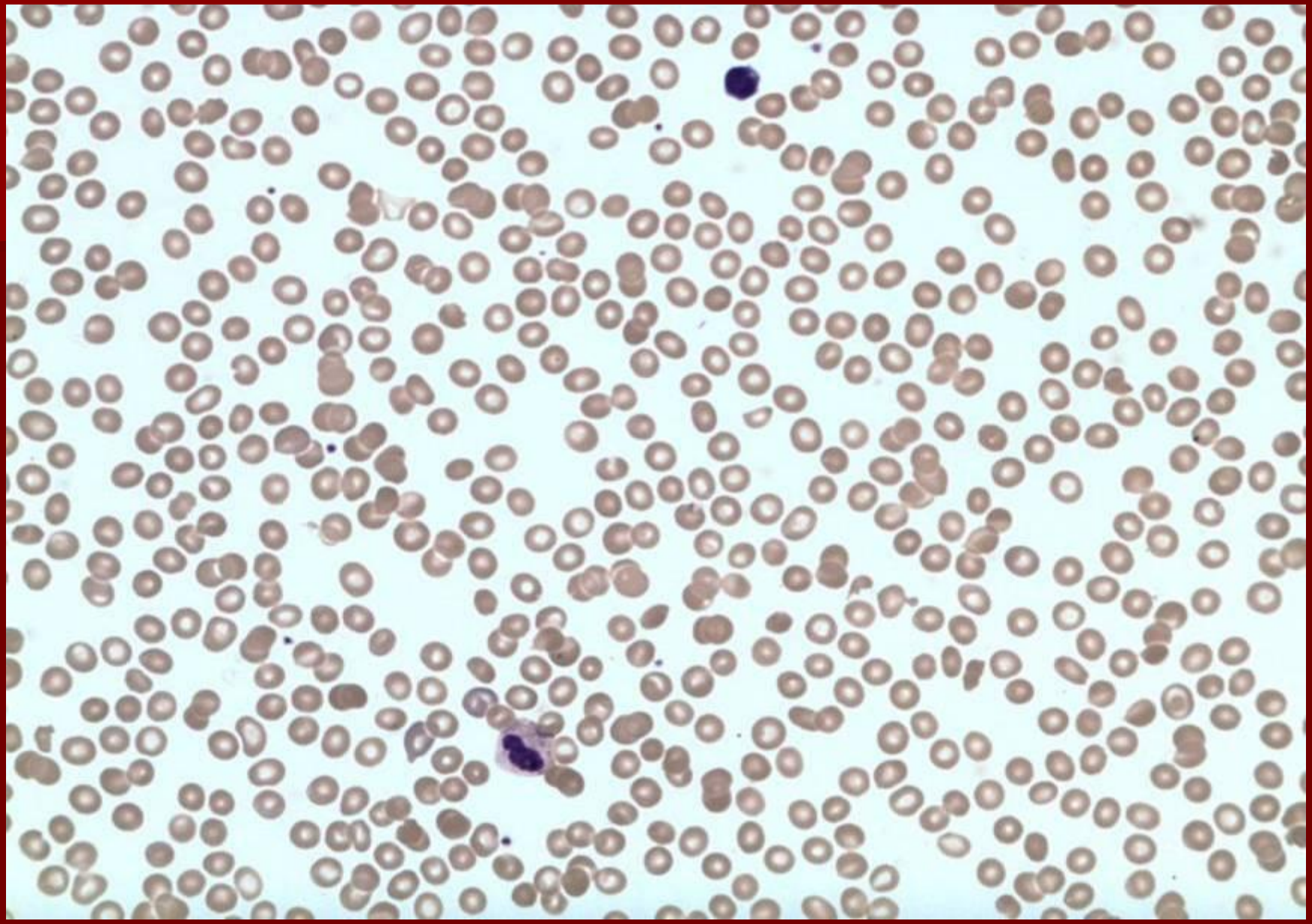
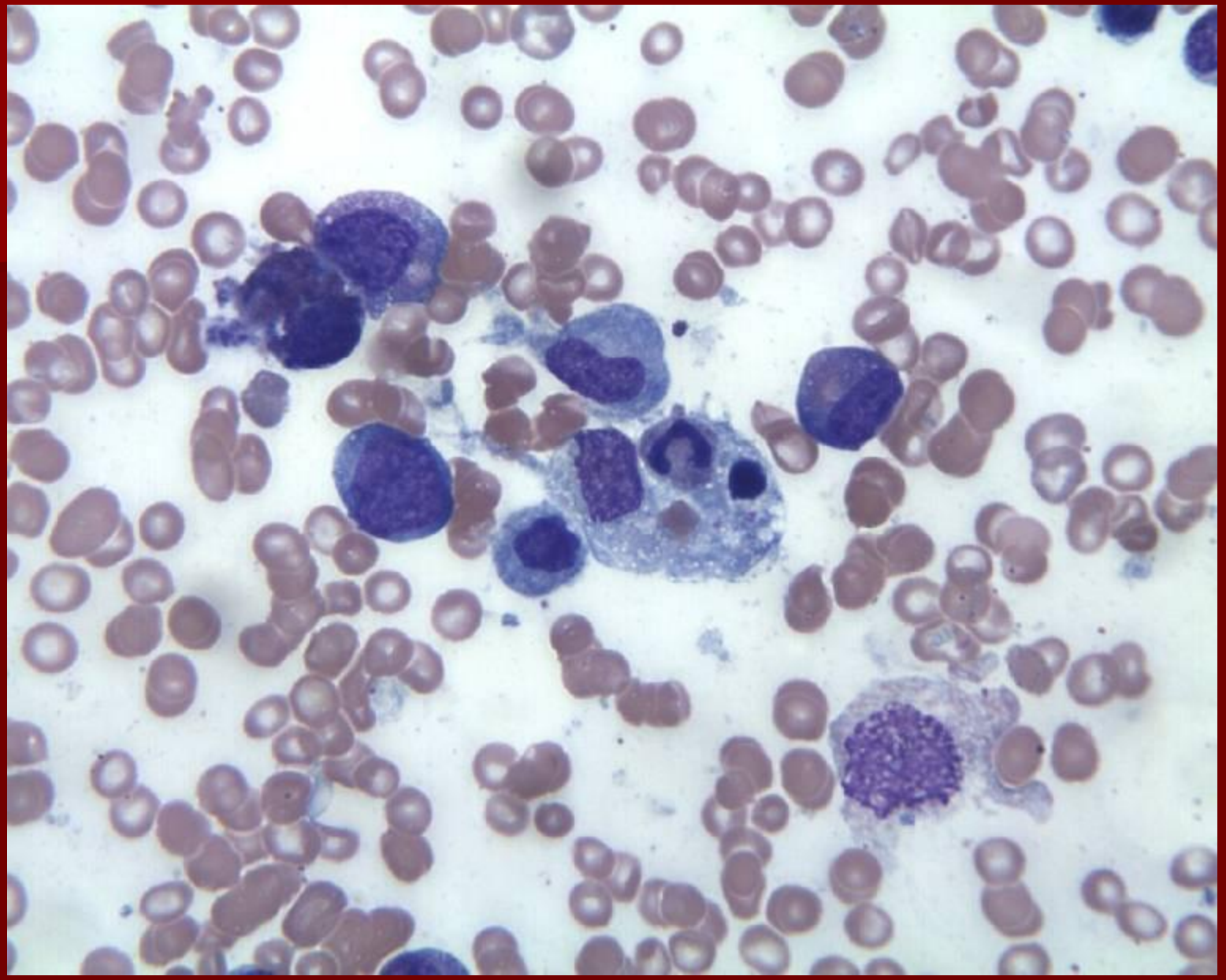
Case Study

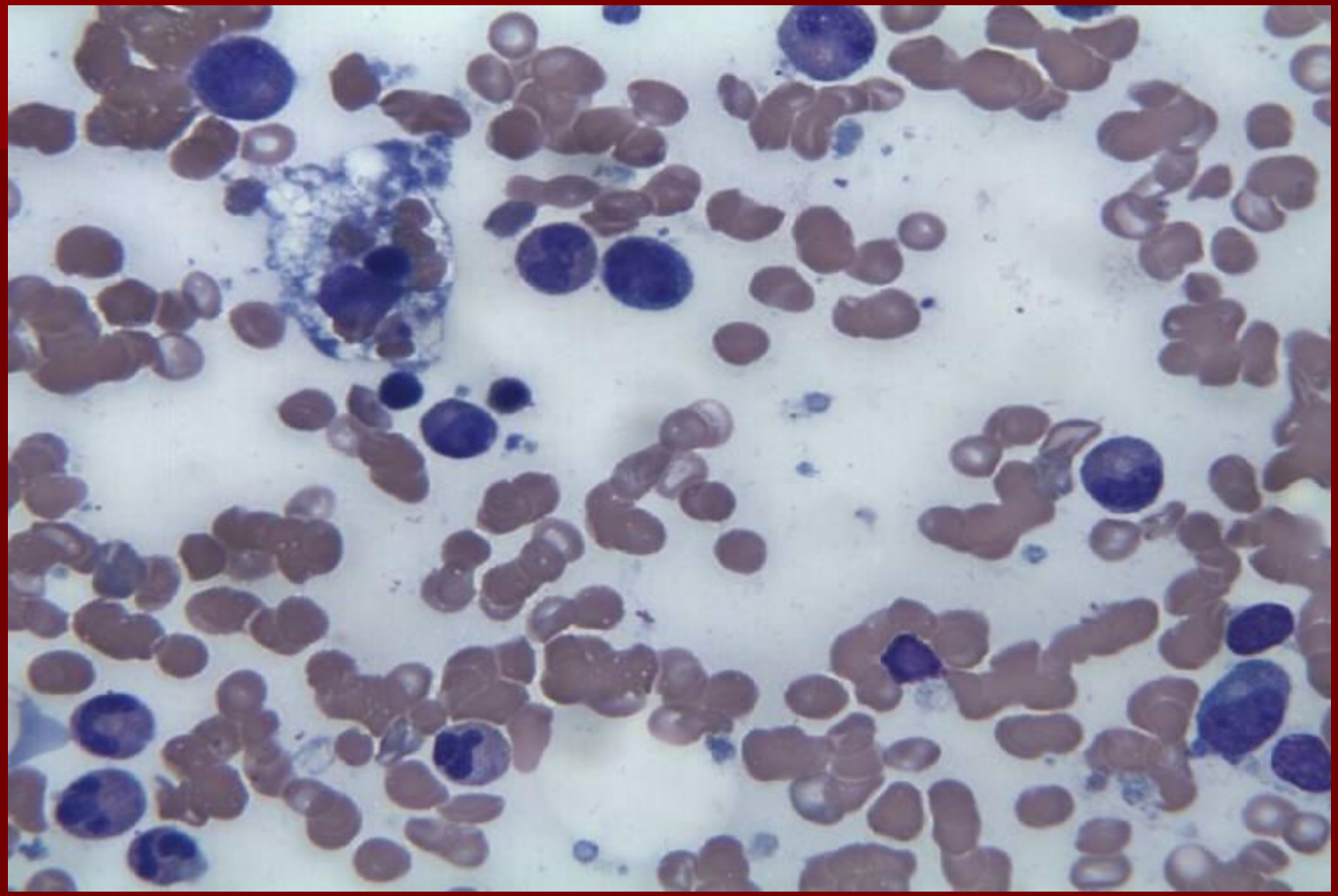
- 9 y/o male with 2-week history of fevers, cough, dyspnea, vomiting
- Lymphadenopathy, pancytopenia
- Viral pneumonia-like picture



Peripheral blood



Bone marrow aspirate



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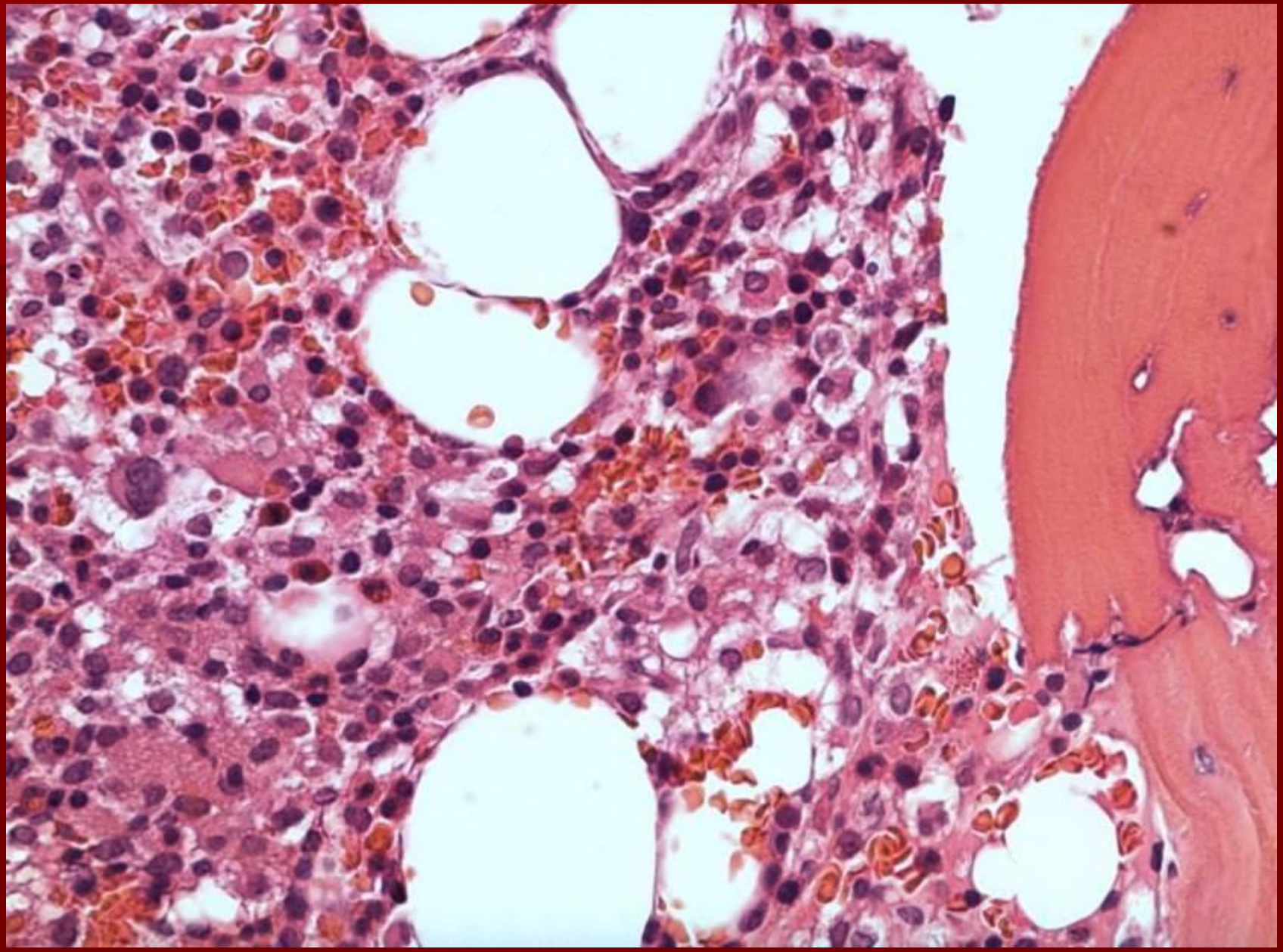
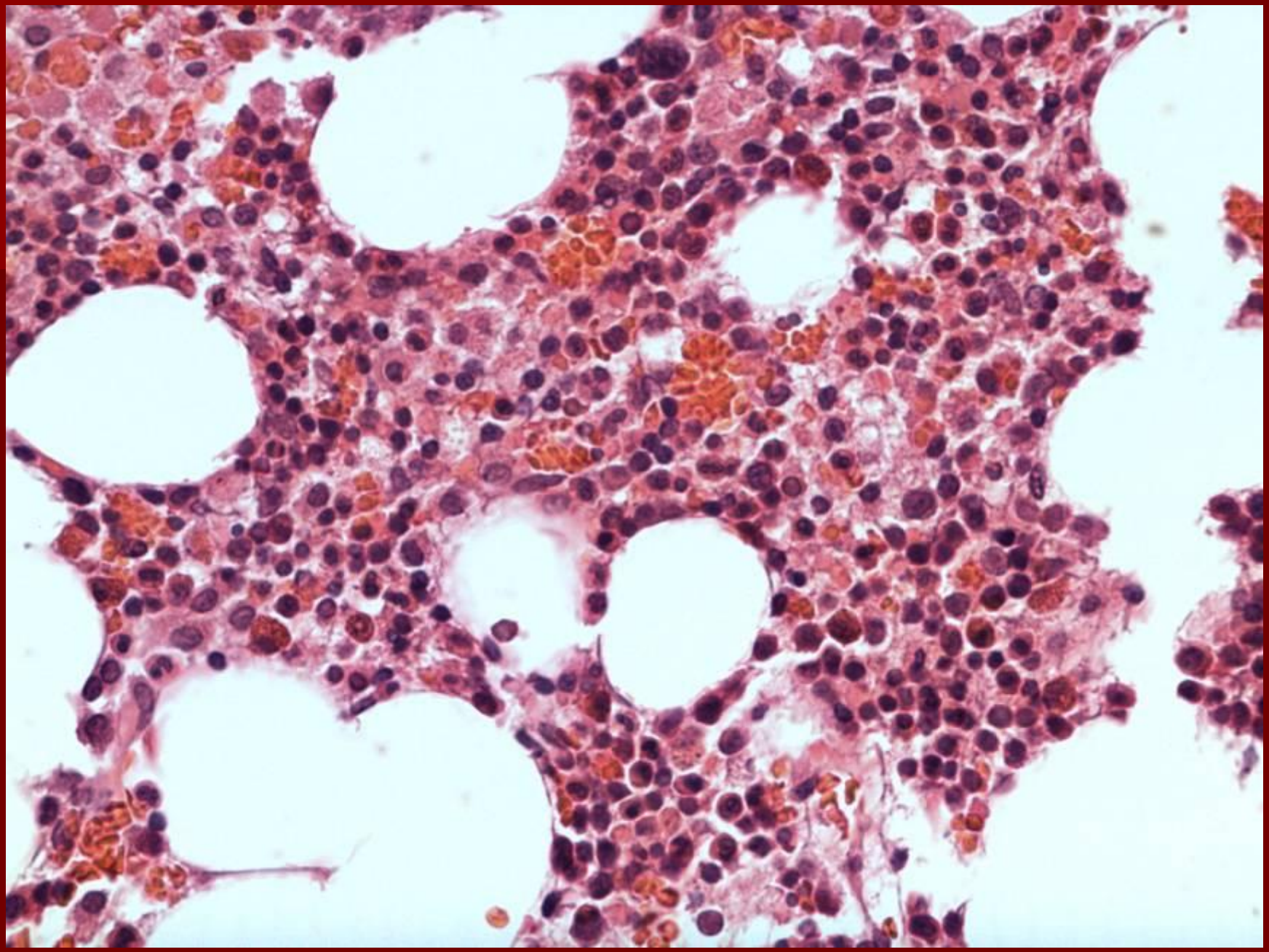


Bone marrow biopsy



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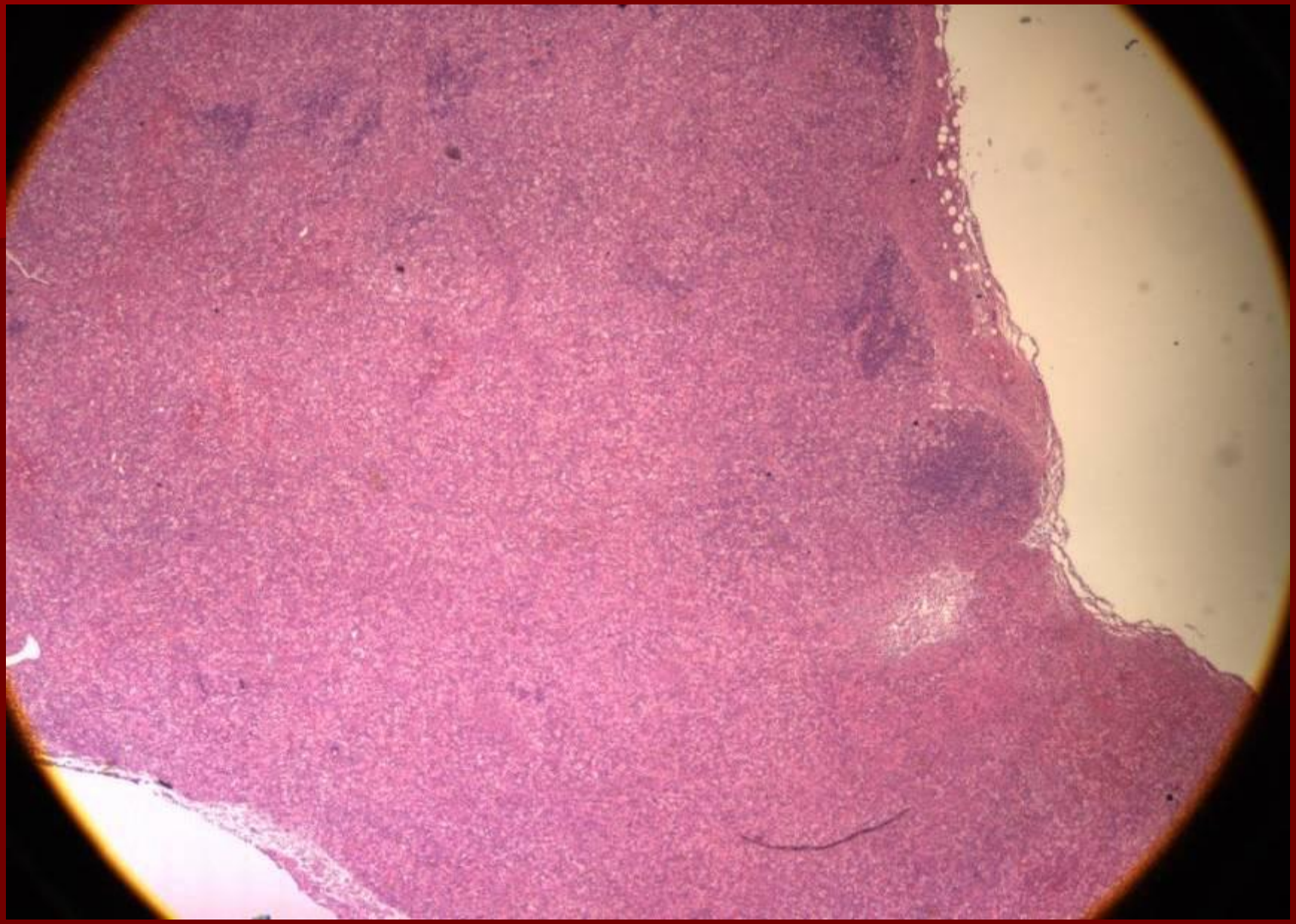
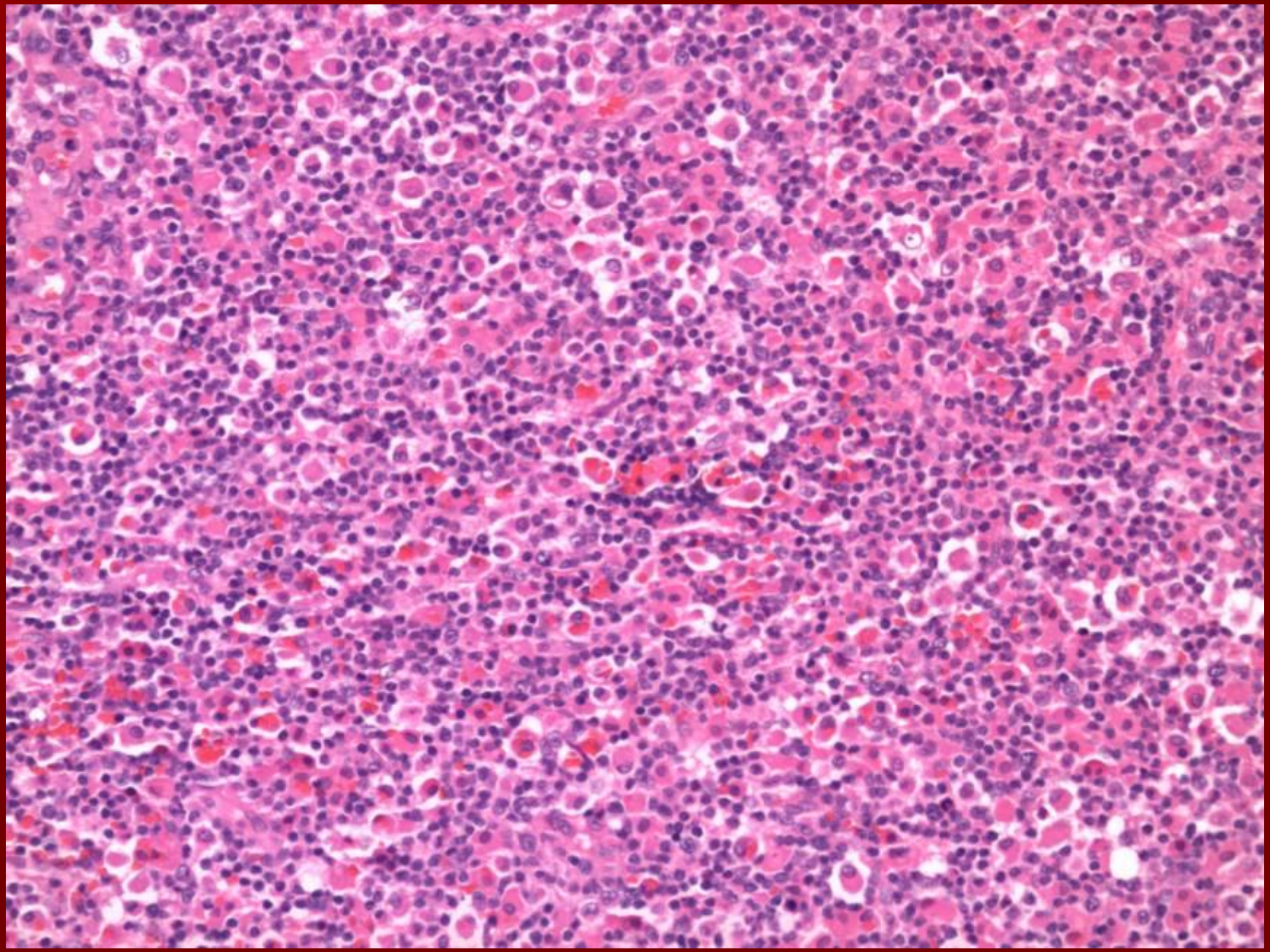
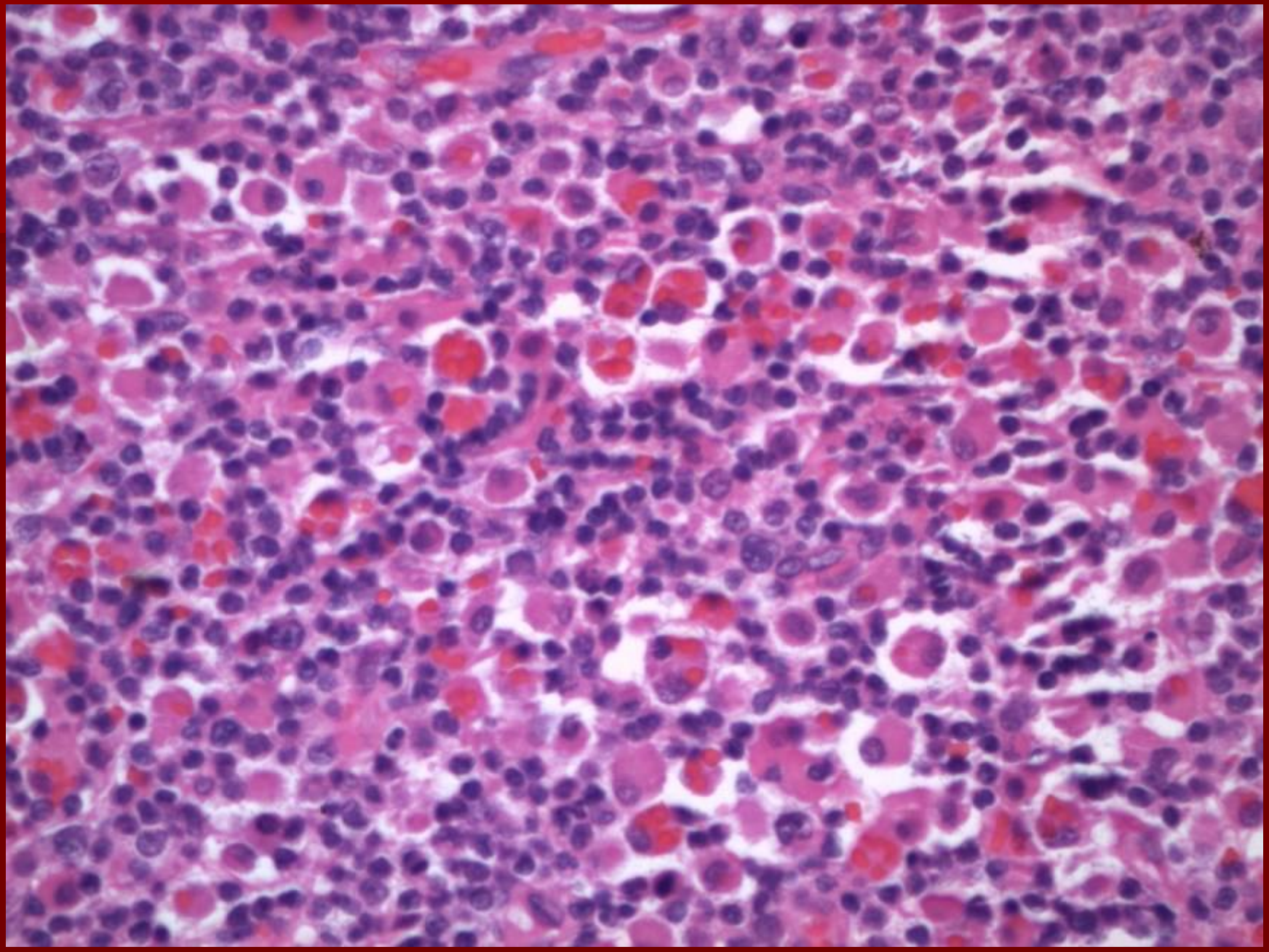
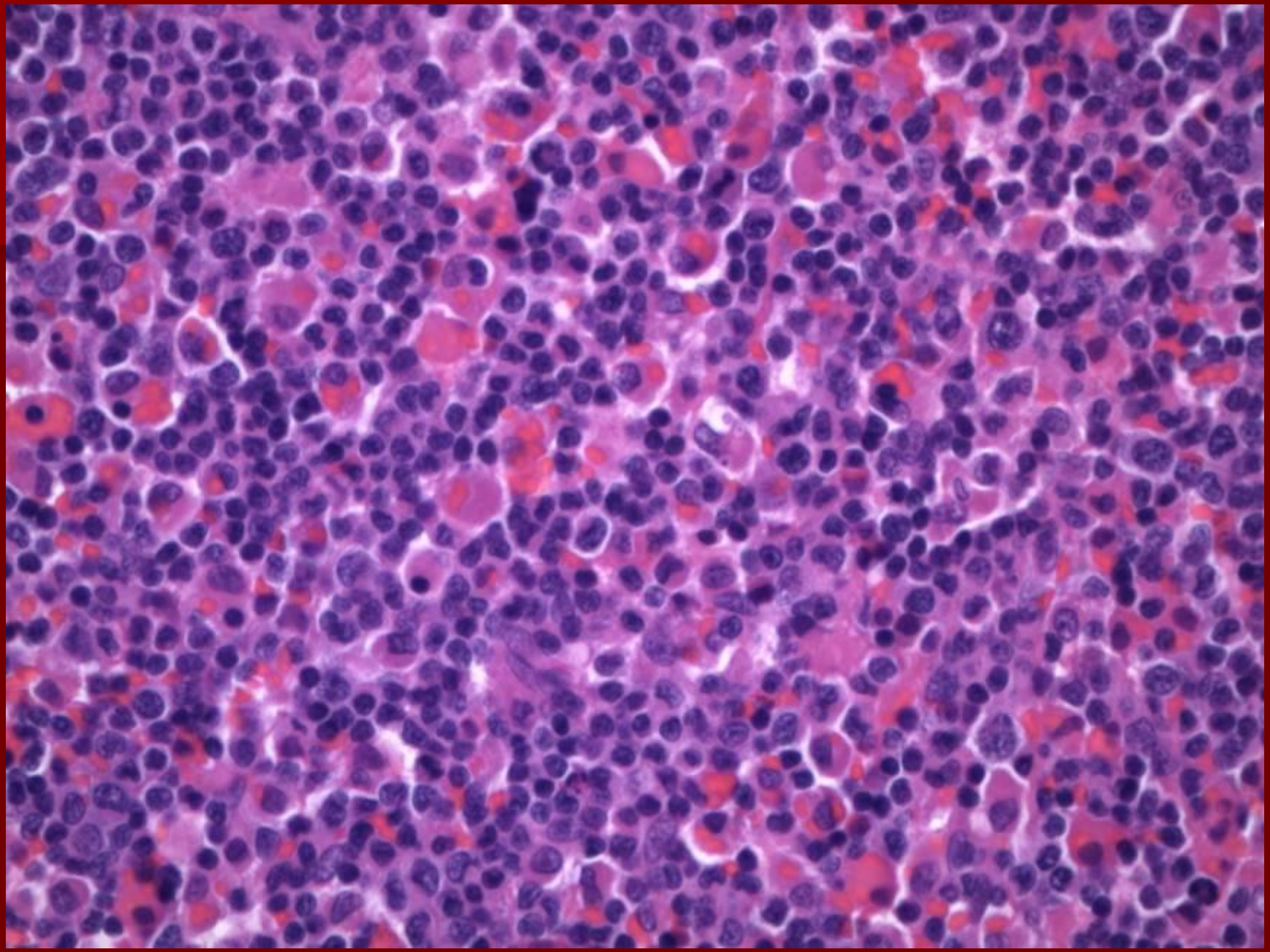


Lymph node biopsy







Case Study - Diagnosis

- Lymph node: Hemophagocytic lymphohistiocytosis, etiology undetermined
  - Negative for CMV, EBV, Parvovirus
- Bone marrow: Extensive hemophagocytosis
  - No leukemia or lymphoma

- Viral-associated hemophagocytic syndrome (VAHS)
  - HHV-6 serology = 3.56 (>1.11)
- Transferred to MDACC

Syndrome Definition

- "Hemophagocytosis" – Process by which macrophages engulf RBCs, WBCs, platelets and their precursors
- Hemophagocytic syndrome = Hemophagocytic lymphohistiocytosis (HLH)
  - Two main groups: Genetic and acquired
  - Highly active yet ineffective immune response that is life-threatening

HLH – Clinical Criteria

- Cardinal sx: Fever, cytopenias, SM (LAD, skin rash, CNS)
- Laboratory findings
  - Elevated triglycerides, ferritin, transaminases, bilirubin, sCD25 (alpha chain of soluble IL-2 receptor)
  - Decreased fibrinogen
- Histopathology: Hemophagocytosis seen in spleen, BM, LN, CNS, skin, liver (but not always present)

Table 3. Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).*

1. Familial disease/known genetic defect
2. Clinical and laboratory criteria (5/8 criteria)

   Fever

   Splenomegaly

   Cytopenia ≥ 2 cell lines
   Hemoglobin < 90 g/L (below 4 weeks < 120 g/L)
   Neutrophils < 1×10^9 /L

   Hypertriglyceridemia and/or hypofibrinogenemia
   fasting triglycerides ≥ 3 mmol/L
   fibrinogen < 1.5 g/L

   Ferritin ≥ 500 µg/L

   sCD25 ≥ 2400 U/mL §

   Decreased or absent NK-cell activity

   Hemophagocytosis in bone marrow, CSF or lymph nodes

Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH > 1000 U/L

HLH - Pathophysiology

- Proliferation of activated macrophages/histiocytes that phagocytose RBCs, WBCs, platelets
- Nonmalignant, but fatal without treatment
- Not clonal
  - Contrast with Langerhans cell histiocytosis

HLH - Pathophysiology

- Theory: Inappropriate immune reaction caused by proliferating, active T cells and macrophages with inadequate apoptosis of immunogenic cells
- Impaired cytotoxic function of NK cells and CTLs
  - Decreased NK activity with persistent T-cell activation
- Cytokine hypersecretion, inflammatory response
  - IFN-gamma, TNF-alpha, IL-6, IL-10, M-CSF
  - Responsible for clinical signs, cytopenias, coagulopathy, high triglycerides
  - Infiltrate tissues and lead to necrosis and organ failure

Table 1. Classification and underlying conditions of hemophagocytic lymphohistiocytosis (HLH).

Genetic HLH

- Familial HLH (Farquhar disease*)
  - Known gene defects (perforin, munc 13-4, syntaxin 11)
  - Unknown gene defects
- Immune deficiency syndromes
  - Chédiak-Higashi syndrome (CHS)
  - Griscelli syndrome (GS)
  - X-linked lymphoproliferative syndrome (XLP)

Acquired HLH

- Exogenous agents (infectious organisms, toxins)
  - Infection-associated hemophagocytic syndrome (IAHS)
- Endogenous products (tissue damage, metabolic products)
- Rheumatic diseases
  - Macrophage activation syndrome (MAS)
- Malignant diseases

* Familial HLH was first described by Farquhar and Claireaux in 1952

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- AR inheritance
- Present as young children
- Poor prognosis

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- AR inheritance
- Chronic pyogenic infections
- Oculocutaneous albinism

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- AR inheritance
- Silver hair

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- Predilection for fatal EBV-induced mononucleosis
- Hypogammaglobulinemia
- Risk for lymphoma

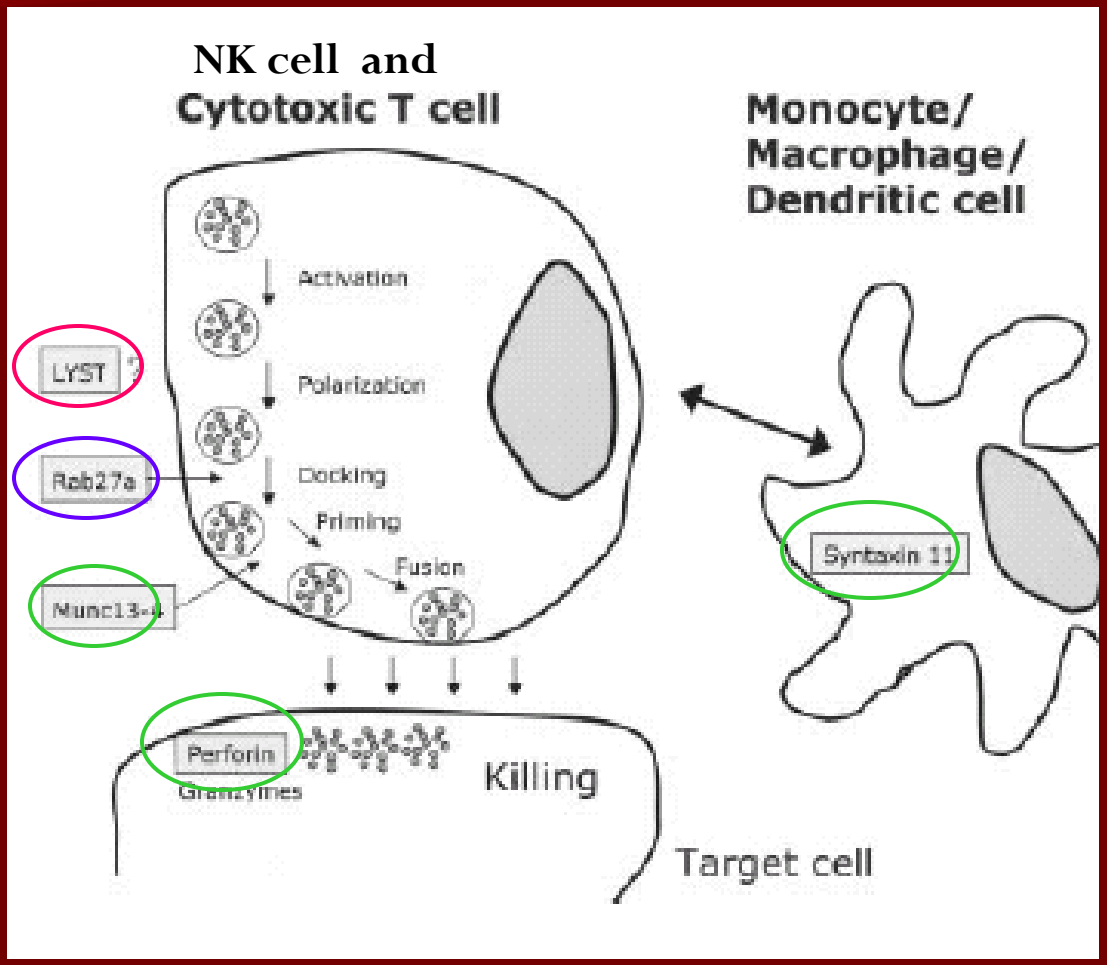
Mechanisms of Genetic HLH:

Defective cytotoxic function

Table 2. Genetic defects in hemophagocytic lymphohistiocytosis.

Disease	Chromosome Location	Associated Gene	Gene Function
FHLH-1	9q21.3-22	Not known	Not known
FHLH-2	10q21-22	PRF1	Induction of apoptosis
FHLH-3	17q25	UNC13D	Vesicle priming
FHLH-4	6q24	STX11	Vesicle transport; t-SNARE
GS-2	15q21	RAB27A	Vesicle transport; small GTPase
CHS-1	1q42.1-q42.2	LYST	Vesicle transport; not further defined
XLP	Xq25	SH2D1A	Signal transduction and activation of lympho-cytes

Abbreviations: FHLH, familial hemophagocytic lymphohistiocytosis; GS, Griscelli syndrome; CHS, Chédiak-Higashi syndrome; XLP, X-linked lymphoproliferative syndrome



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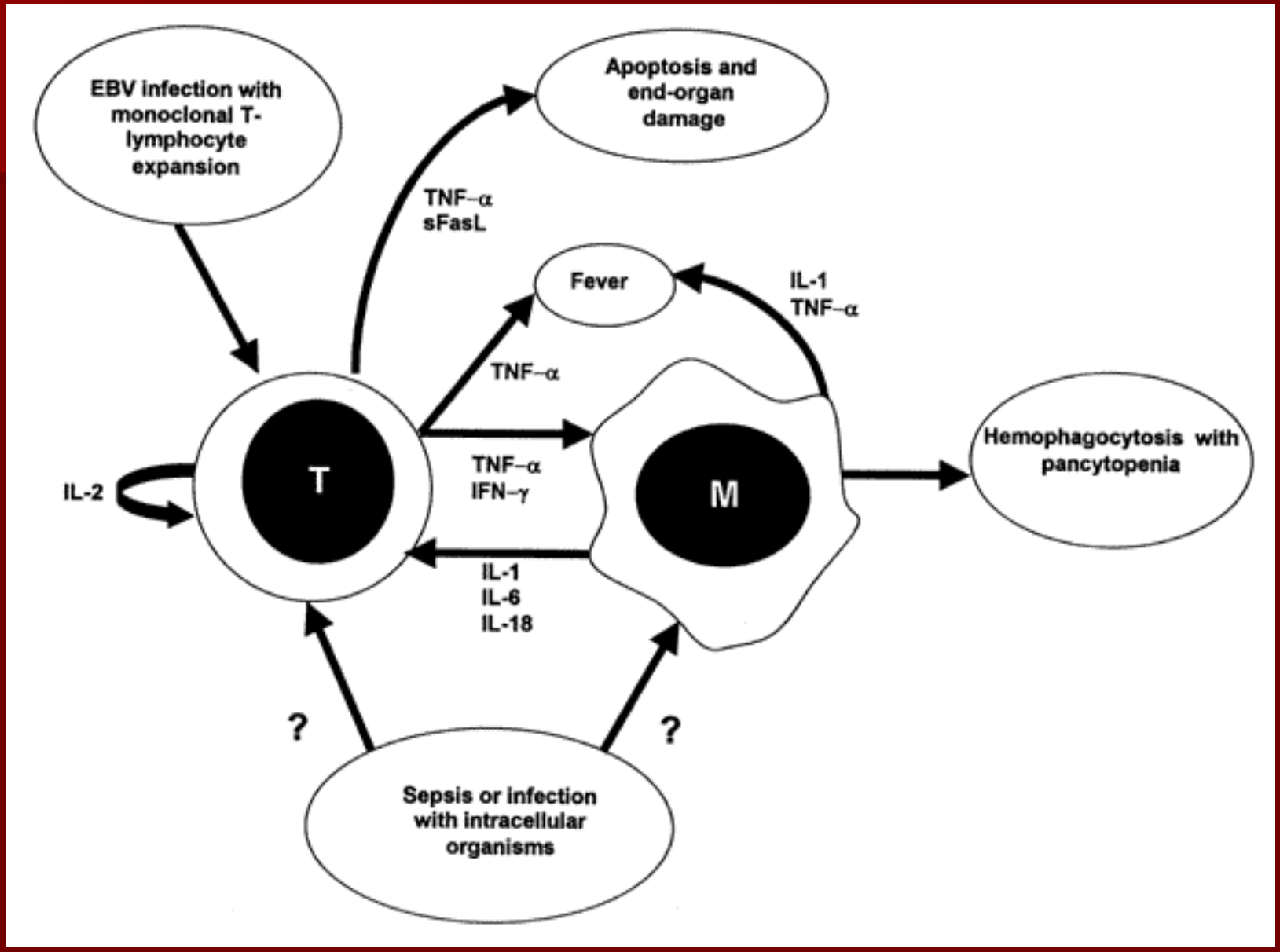
- After strong immune activation
- Little incidence data

Mechanisms of Infection-associated HLH



HLH and Infection

- Viruses, bacteria, parasites, spirochetes, mycobacteria, fungi
- Difficulty distinguishing acquired from familial
  - Familial cases may be precipitated by infection
  - May mimic an infectious illness

HLH and Infection

- Impractical to exclude all possible infectious causes
- If HLH criteria are met, then screen for EBV, CMV, parvovirus B19, HIV
- History should guide testing
  - HIV infection: Pneumococcus, Pneumocystis, Histoplasma, *Penicillium marneffei*, T-cell lymphoma
  - Animal exposure: Brucella, Rickettsia
  - Travel exposure: Leishmania, malaria

HLH and other Associations

- Malignancy
  - T-cell lymphoma
- Autoimmune diseases
  - Macrophage activation syndrome
  - Juvenile RA, Still's disease, SLE

HLH - Laboratory

- CBC, AST/ALT, bilirubin, TG, ferritin, coags (fibrinogen)
- Bone marrow: Insensitive
  - May be negative in 2/3 of initial aspirates
  - Dysplastic RBCs → myelodysplasia
- sCD25 >2400 U/ml
  - Highly specific serum parameter
- NK cell perforin expression by flow cytometry
- Genetic testing
  - PRF1, Munc13-4 available at Cincinnati Children's Hospital

HLH - Treatment

- Immediate goal: Immune suppression
  - Corticosteroids
  - Dexamethasone: Preferred, Xs BBB > prednisolone
  - Cyclosporin A: prevents T cell activation
  - Etoposide: Critical for EBV-infected pts, inhibits EBNA synthesis in EBV-infected cells

- Genetic HLH: Bone marrow transplant

More Information

- The Histiocyte Society
- www.histio.org

References

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