LYMPHOHISTIOCYTOSIS MASQUERADING AS DRESS

Aseem Sood MD

University of Maryland Medical Center
Midtown Campus

History of present illness

27-year old female in art school

Past medical history of anxiety and temporal lobe epilepsy, diagnosed two weeks earlier by electroencephalogram and started on lamotrigine.

History of present illness

One week before presenting to the ED:

flu like symptoms,

headache she described as worst of her life,

nausea & vomiting,

photophobia,

joint pains.

History of present illness

Few days before presenting to the ED:

Developed persistent fevers up to 39.9 C,

Maculopapular rash, began on hands and spread rapidly to trunk

History of present illness

- Travelled to Japan few months earlier

- No known sick contacts

- Childhood vaccinations up to date,
  No recent vaccinations

No Known Drug Allergies

Home Medications: Duloxetine & Lamotrigine

Drinks occasionally. No illicit drug use

PHYSICAL EXAM

Vitals: T 39.7 C, HR 100, BP 95/52, RR 24, SpO2 92%

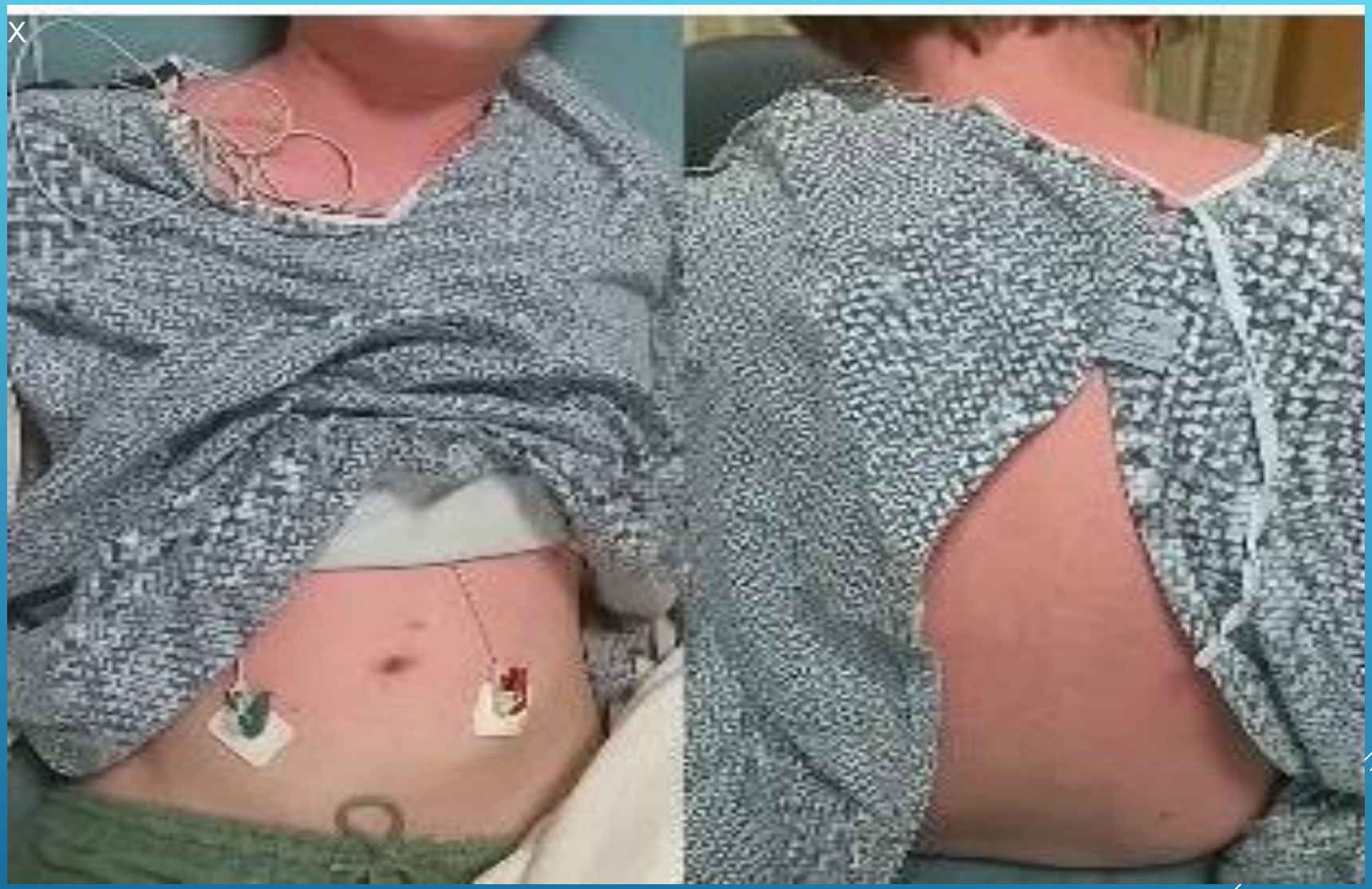
Gen: Young, anxious diaphoretic female in mild distress from pain. Alert and oriented x3.

HENT: Neck stiffness. Oral mucosa moist;
no erythema or exudates

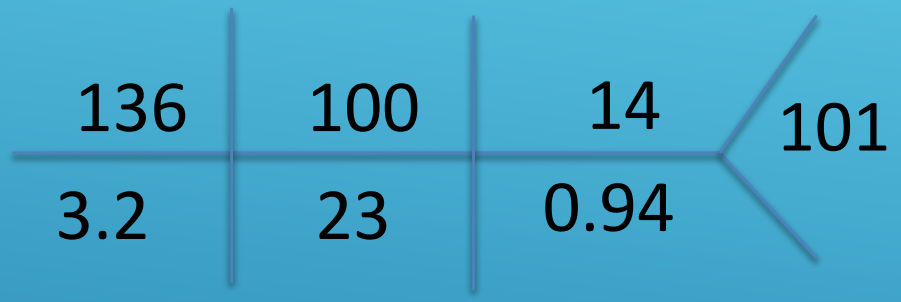
PHYSICAL EXAM

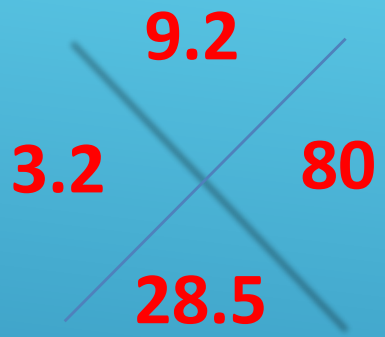
MSK: Limited ROM BL wrists, shoulders, knees, and ankles due to pain.

Skin: Erythematous, confluent, blanchable
diffuse maculopapular rash



LABORATORY RESULTS





Granulocytes: >90%

Lymphocytes: 7.7%

Monocytes: <1%

Basophils: 0%

Eosinophils: 0.3%

AST: 528; ALT: 658

ALP: 954

Rheumatologic

+ANA; anti-DsDNA (-)

Fasting Lipid Profile:

Chol: 116; LDL: 120, HDL: 18,TG: 292

IMAGING STUDIES

Head CT

No acute intracranial abnormalities

CXR

No acute intrathoracic abnormalities

Working Diagnosis

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome

Often occurs 2-6 weeks after initiation

Estimated 10% mortality

Drug Reaction with Eosinophilia and Systemic Symptoms

Lamotrigine is the third most common drug associated with DRESS.

Temporal relation of symptom onset with lamotrigine supported diagnosis of DRESS.

Lamotrigine was stopped on admission

Broad antimicrobials started

Lumbar Puncture:

Clear.

Glucose: 76,

Protein: 290

WBC 520 [93% PMN]

Gram Stain:

PMN, no bacteria

HSV 1&2 DNA (-)

Microbiology:

Pharyngeal Group A streptococcus (+)

Rapid Influenza A & B: (-)

EBV qualitative DNA PCR (+)

Clinical Deterioration

Altered mental status, bilateral pulmonary edema, worsening liver function and urine output

Coagulation tests:

PT: 22.0 PTT: 79.9

Elevated D Dimer

Fibrinogen: 162 (low)

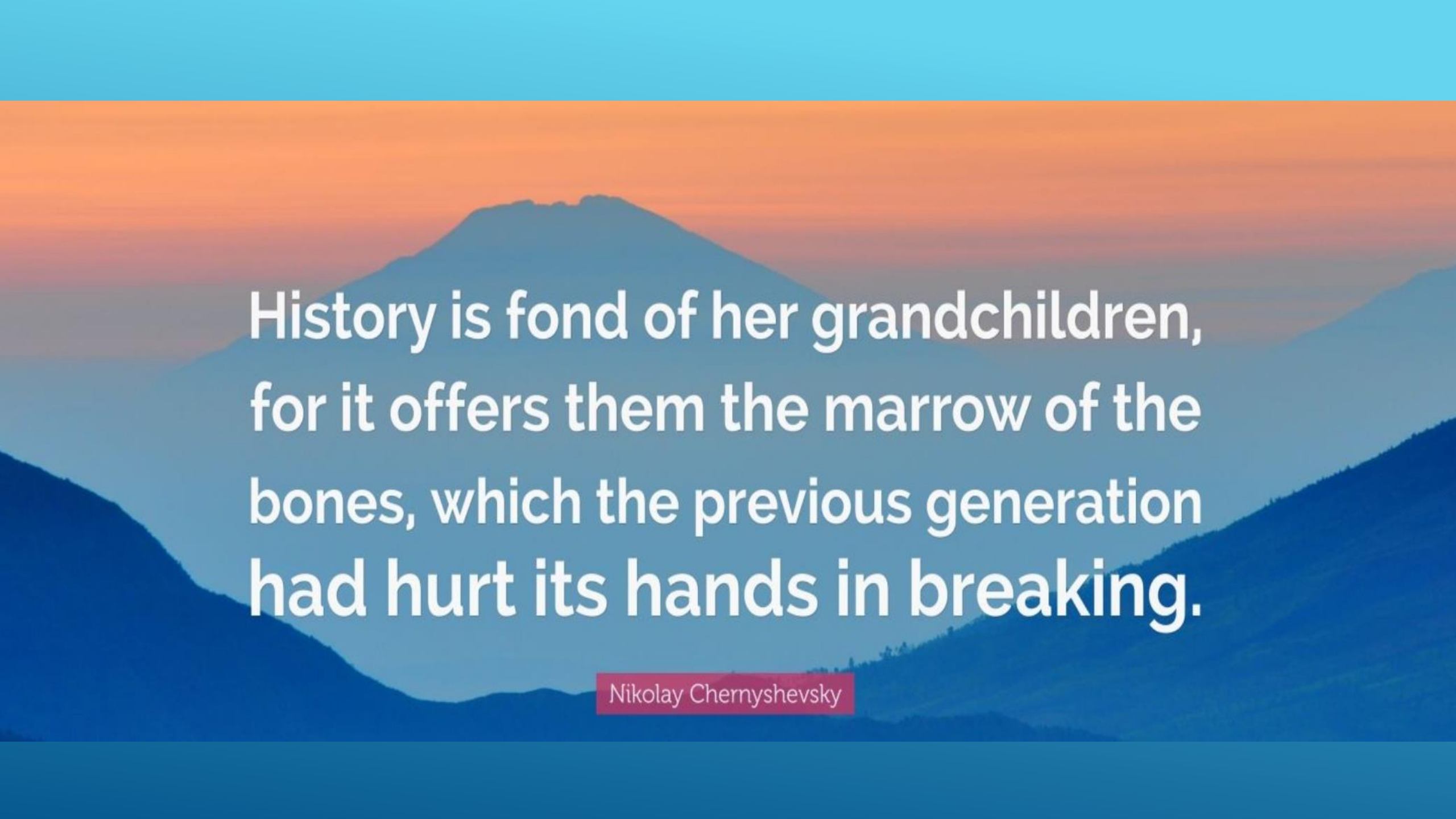
Challenging Our Working Diagnosis

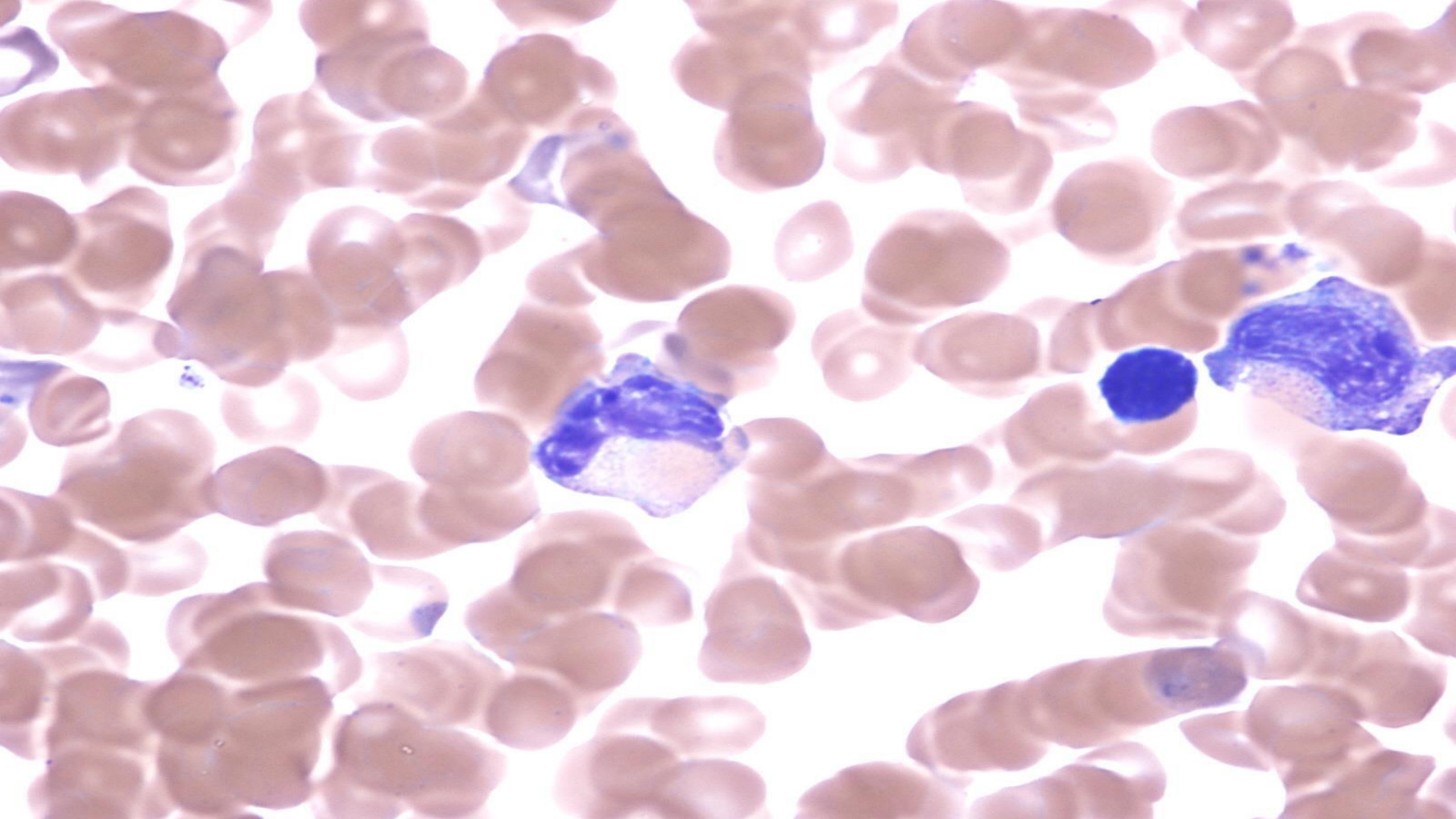
Patient has pancytopenia rather than eosinophilia.

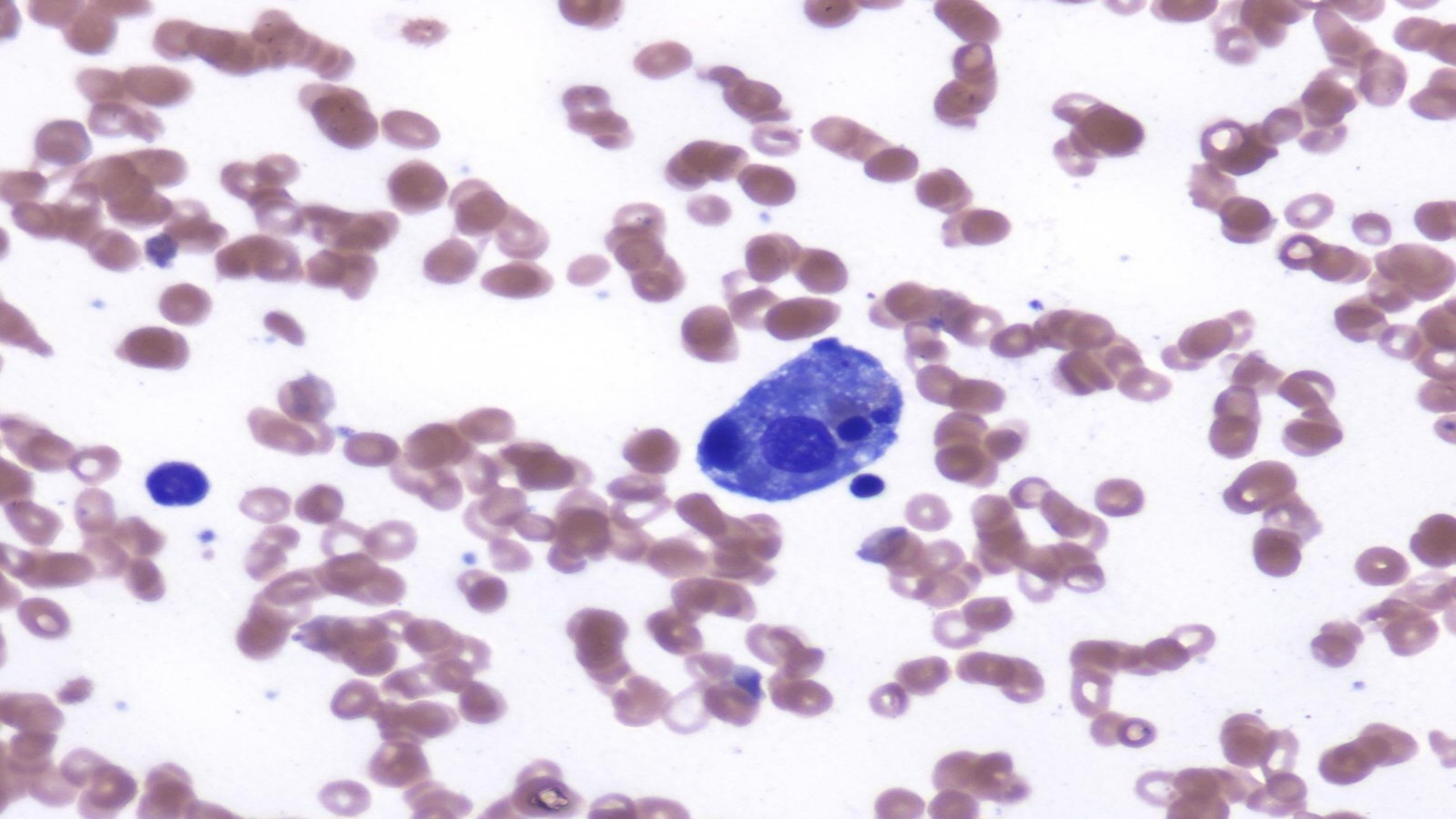
Minority of patients with DRESS can lack eosinophilia

The Suggestion of a Medicine Intern

- Ferritin: 18,154 ng/mL


History is fond of her grandchildren,
for it offers them the marrow of the
bones, which the previous generation
had hurt its hands in breaking.
Nikolay Chernyshevsky





★ Fever ≥ 38.5°C ★

2. Splenomegaly

★ Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood) ★

Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)

Platelets < 100 × 10^3/mL

Neutrophils < 1 × 10^3/mL

★ Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia ★ (< 150 mg/dL)

★ Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver ★

6. Low or absent NK-cell activity

★ Ferritin > 500 ng/mL‡ ★

8. Elevated sCD25 (α-chain of sIL-2 receptor)§

2008 Study of 330 patients, *Pediatric Blood Cancer*

Ferritin level over 10,000 ng/mL was 90% sensitive and 96% specific for HLH.

Activated macrophages secrete ferritin.

HLH vs. DRESS

Overlapping Features

FEVER

RASH

Internal Organs involved

FEVER

RASH

Internal Organs involved

Hemophagocytic Lymphohistiocytosis

1.2 cases per 1 million individuals per year

Hyper-proliferation of tissue macrophages called histiocytes, leading to over activation of phagocytosis, cytokine storm,

Estimated 70% of HLH occurs in pediatrics <1 year old

HLH in adults is much less studied.

Secondary (acquired) HLH can present at any age, triggered by infection or malignancy or vaccine.

Remarkably fatal.
Case Series: six month survival of 54% despite therapy.

Ferritin testing is crucial to identifying HLH, as molecular testing (soluble IL-2 receptor, NK cell activity)

is only done at a few national labs and often treatment cannot be delayed awaiting those results.

Identifying HLH made it possible to achieve a fortunate outcome in the case of this young patient.

Body surface dosing IV dexamethasone initiated with gradual complete recovery and discharge home with her family the day before Christmas Eve.

ACKNOWLEDGEMENTS

My patient. For teaching us.

Drs. Raman & Archana Sood

Dr. Robert Dobbin Chow

The teaching faculty of University of Maryland Medical Center Midtown Campus

References

1. Campo M, Berliner N. Hemophagocytic Lymphohistiocytosis in Adults. *Hematol Oncol Clin N Am*. 2015; 29: 915-925.
2. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med 2011; 124:588.
3. Efthimiou P, Kadavath S. Life-threatening complications of adult-onset Still's disease. Clin Rheumatol. 2014: 33; 305-314.
4. Gerfaud-Valentin M, Jamilloux Y, et al. Adult-onset Still's Disease. *Autoimmunity Reviews*. 2014; 708-722.
5. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia 1999; 40:985.
6. Henter JI, Horne A, et al. HLH-2004: Diagnostic and Therapeutic guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*
2007; 48: 124-31.
7. Mahroum N, Mahagna H, et al. Diagnosis and classification of adult Still's disease. *J of Autoimmunity*. 2013: 34-37.
8. Schram A, Berliner N. How I Treat Hemophagocytic Lymphocytosis in