A Case of DRESS/HLH Overlap syndrome

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49 year old male diagnosed with seronegative rheumatoid arthritis, started on sulfasalazine and prednisone
49 year old male diagnosed with seronegative rheumatoid arthritis, started on sulfasalazine and prednisone

1/29

ED visit - fevers, malaise, HA, cough, abd pain, diarrhea.
CT C/A/P - no acute findings
Labs - ferritin 719, CRP 51, LFTs wnl
Dx: CAP
Tx: cefdinir and doxycycline
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2/3

ED visit - persistent symptoms
Labs - ferritin 550, CRP 54, LDH 900, AST 108, ALT 84
Dx: Suspected Covid PNA
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2/20

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Patient Presentation

49 year old male diagnosed with seronegative rheumatoid arthritis, started on sulfasalazine and prednisone.

- **1/29**: 49 year old male diagnosed with seronegative rheumatoid arthritis, started on sulfasalazine and prednisone.
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- **2/3**: ED visit - persistent symptoms
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  - Dx: Suspected Covid PNA
  - Tx: none

- **2/20**: ED visit - persistent symptoms
  - CT A/P - splenomegaly, lymphadenopathy
  - Labs - ferritin 3870, CRP 185, LDH 4155, AST 510, ALT 526
  - Admitted to OSH

- **2/27**: ED visit - persistent symptoms
  - Labs - ferritin 3870, CRP 185, LDH 4155, AST 510, ALT 526
  - Admitted to OSH
Patient Presentation

PMH:
- HTN
- Seronegative RA

PSH:
- None

Allergies:
- Allopurinol - facial edema
- Febuxostat - facial edema

Medications:
- Sulfasalazine and Prednisone

Social History:
- Denies cigarette smoking or illicit drug use
- Stopped alcohol use several months ago
- Lives with nephew
- Currently unemployed, previously worked as an aerospace mechanic
- No recent travel or exposure to animals

Family History:
- No significant family history
Patient Presentation

Physical Exam:

• **Vitals:** Temp 37.3, BP 144/91, HR 114, RR 18, SpO2 100%
• **General:** Well-developed male; **appears tired and uncomfortable**
• **HEENT:** Sclera anicteric, oropharynx without erythema, exudates, or ulcers; no cervical lymphadenopathy
• **CV:** Tachycardic, normal S1 and S2; no murmurs
• **Pulm:** CTAB; no wheezes or crackles
• **Abdomen:** Soft, non-distended; no rebound or guarding; **mild discomfort to RUQ palpation, palpable splenomegaly**
• **Extremities:** Warm and well perfused x4, no peripheral edema, radial and pedal pulses 2+
• **Neuro:** CN III-XII grossly intact; no focal deficits
• **Skin:** Poorly demarcated erythematous rash of face and anterior chest
Labs

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Alk Phos - 182
ALT - 434
AST - 345
Total bili - 3.8
INR - 1.4
PTT - 37

Abs Eosinophils - 110
Labs

Triglycerides - 226
CRP - 19.1
ESR - 28
LDH - 1317
Ferritin - 6883
Haptoglobin - 194
Soluble IL-2 receptor - 7252

Other workup for autoimmune, rheumatologic, infectious (viral, bacterial, and fungal), hepatitis, and malignancies, including lymphoma were negative
Imaging/Pathology

CT Chest/Abdomen/Pelvis -
Mild enlargement axillary lymph nodes, splenomegaly with scattered periportal, portacaval and prominent iliac and inguinal lymph nodes
PET CT - Hypermetabolic lymph nodes throughout the neck, chest, abdomen, and pelvis with enlarged and abnormally avid spleen
Bone marrow biopsy - Cellular marrow with trilineage hematopoiesis, increased megakaryocytes, blasts, and small aggregates of T-cells consistent with reactive process. There are rare macrophages showing hemophagocytosis
Imaging/Pathology

Skin biopsy - Spongiotic and lichenoid dermatitis with mixed inflammation consistent with a reaction to a medication
Hemophagocytic Lymphohistiocytosis

- Inflammatory endpoint for a variety of conditions
  - Autoimmune diseases
  - Malignancies
  - Infections
  - Few case reports of drug induced HLH
- High morbidity and mortality, estimated rates 20-40%
- Retrospective cohort study on HLH patients
  - Infection (41.1%)
  - Malignancy (28.8%)
  - Autoimmune disease (6.8%)
  - Transplant (2.7%)
  - Idiopathic (17.8%)
Hemophagocytic Lymphohistiocytosis

Diagnostic criteria (at least five of the following):

- **Fever ≥ 38.5° C**
- **Splenomegaly**
- **Cytopenia, with at least 2 of the following**
  - Hemoglobin <9 g/dL
  - Platelets <100,000/microL
  - Absolute neutrophil count <1000/microL
- **Hypertriglyceridemia (fasting triglycerides >265mg/dL) and/or hypofibrinogenemia (<150 mg/dL)**
- **Hemophagocytosis in bone marrow, spleen, lymph node, or liver**
- **Low or absent NK cell activity**
- **Ferritin >500 ng/mL**
- **Elevated soluble IL-2 receptor alpha (CD25)**
- **Elevated CXCL9**
Hemophagocytosis

- Hemophagocytosis not a pathognomonic feature of HLH
- Seen in other hyperinflammatory conditions
- Unclear role in HLH
DRESS

- Drug induced hypersensitivity reaction characterized by a cutaneous eruption
- Registry of Severe Cutaneous Adverse Reactions scoring system (RegiSCAR)
  - Fever ≥ 38.5°C
  - Enlarged lymph nodes in at least two different body areas
  - Eosinophilia
  - Atypical lymphocytes
  - Skin involvement
    - Rash/biopsy suggestive of DRESS
    - Extent ≥ 50% BSA
  - Organ involvement
  - Resolution > 15 days
  - Exclusion of other causes (If HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood cultures neg)
DRESS/HLH Overlap Syndrome

- Immune dysregulation
- Fever
- Rash
- Multi-organ involvement
- Association w/ viral infection/reactivation
- Hemophagocytosis
- Elevated inflammatory markers

DRESS
- 2 cases per 100,000 pts
- Drug-specific CD4 & CD8 T cell activation
- Eosinophilia
- Lymphadenopathy
- Atypical lymphocytosis

HLH
- 1.2 cases per 1,000,000 pts
- Excessive Macrophage and CD8 T cell activation
- Cytopenias
- Splenomegaly
- Hyperferritinemia
- Soluble CD25 elevation
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DRESS/HLH Overlap Syndrome

- Literature review over the last decade shows a small number of documented DRESS/HLH Overlap syndromes, with 21 cases
  - 11/21 cases involved infection/reactivation of herpesviridae
  - 10/21 without such features suggesting prolonged period of immune dysregulation with DRESS or HLH could induce the other
Acknowledgements

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Dr. Jeremy Smith
References: