A hemolytic quandary
HPI

31 year old woman with 4 days of

• URI symptoms
• Yellowing skin
• Dark urine
• Decreased exercise tolerance
Additional History

- PMH/PSH: None
- Medications & Allergies: None
- Social History:
  - Physician Assistant
  - Marathon runner
  - No tobacco, alcohol or drugs
- Family History: Noncontributory
Physical exam

Vitals T 98.6 F | BP 110/80 | P 90 | RR 16 | O₂ 100%

- General: No distress
- HEENT: Sclera icteric, posterior pharynx normal
- Lungs: Clear to auscultation
- Cardio: RRR, no murmurs, pulses 2+, JVP normal
- Abdomen: No distention, no hepatosplenomegaly, no tenderness to palpation
- Extremities: Warm, dry, no edema
- Skin: Jaundice
- Lymph: No lymphadenopathy
- Neurologic: Well oriented, non-focal
Laboratory data

MCV 101
PMN 50%
Lymph 30%
Mono 5%
Eos 1%

AST 25 U/L
ALT 36 U/L
Alk phos 68 U/L
Tbili 7.0 mg/dL
Indirect Bili 6.0 mg/dL
Albumin 4.0 g/dL
Protein 6.8 g/dL

Haptoglobin undetectable
LDH 1130

Ca 9.0
Mg 2.2
Phos 4.0

PT/PTT/INR/Fibrinogen Normal

Urinalysis
Amber
4+ urobilinogen
Small blood
No RBCs or WBCs
Summary

31 y/o healthy woman with no past medical history presenting with sudden onset of jaundice and exercise intolerance found to be severely anemic with an isolated indirect hyperbilirubinemia, elevated LDH, and undetectable haptoglobin consistent with acute hemolytic anemia
**Acute Hemolysis**

**Extrinsic (Acquired)**
- Immune Hemolysis
  - Primary (e.g. AIHA)
  - Secondary (e.g. Vasculitis, leukemia, lymphoma, medications, infections)

- Mechanical Trauma
  - Mechanical valves
  - Hemangiomas
  - Thrombotic thrombocytopenic purpura, HUS
  - Malignant hypertension
  - Running, bongo drumming (*March hemoglobinuria*)

**Intrinsic**
- Membrane Disorders
  - Spherocytosis, elliptocytosis
  - Paroxysmal nocturnal hemoglobinuria

- Hemoglobinopathies
  - Thalassemia
  - Sickle cell disease

- Enzyme Disorders
  - G6PD deficiency
  - Pyruvate kinase deficiency
  - Hexokinase deficiency
  - Lead poisoning (via pentose phosphate shunt)

- Splenomegaly

- Infection
  - Malaria, sepsis
Further diagnostic work up

- Reticulocyte index: 42%
- Peripheral smear:
  - < 1% schistocytes
  - Occasional bite cells
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Negative/Normal Studies

- Iron studies, B12, folate
- PNH screen
- Coombs test
- HIV, hepatitis A/B/C
- Osmotic fragility
- G6PD
- Pyruvate kinase
- Hexokinase
- Hemoglobin electrophoresis
- ANA
- Pregnancy test
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Summary

31 y/o young woman with severe acute symptomatic hemolytic anemia of unknown etiology with bite cells on peripheral smear.
The bite cell
Bite cells

• Quite specific for Heinz body oxidative hemolytic anemia
Additional History

• Dietary History
  – Recently started a strict vegan diet and had been eating large amounts of fava beans

• Family history
  – Strong Italian family heritage
Favism ?
Further diagnostic work up

Negative/Normal Studies

- Iron studies, B12, folate
- PNH screen
- Coombs test
- HIV, hepatitis A/B/C
- Osmotic fragility
- G6PD
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- Hemoglobin electrophoresis
Dilemma

• Clinically c/w favism
  – Acute hemolysis
  – Family history
  – Recent consumption of fava beans
  – Presence of bite cells

• But normal G6PD level
  – What next?
High G6PD Prevalence Countries
PENTOSE PHOSPHATE PATHWAY
G6PD
Which is responsible for
Glutathione
Which fights
Free radicals
Which damage red blood cells
G6PD Genetics

• X-linked recessive

• Rarely expressed with oxidative hemolysis in females but can occur if the conditions are right.
G6PD expression in heterozygote females

- Baseline mutation
- Variable X – inactivation (mosaicism)
- Oxidative load

G6PD expression/hemolysis
## Drugs and G6PD

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<thead>
<tr>
<th>Medication</th>
<th>Williams Hematology(^8)</th>
<th>Nelson Textbook of Pediatrics(^9)</th>
<th>Harrison's Principles of Internal Medicine(^10)</th>
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<td>Vitamin K analogues</td>
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</table>

### Key Drugs
- **Dapsone**
- **Nitrofurantoin**
- **Sulfamethoxazole**
Fava beans

• Also known as
  – Fever beans
  – Horse beans
  – Many others

• Confer oxidative stress on the body through several molecules whose mechanisms have not been completely elucidated.
Infections and G6PD

- Bacterial Infections
- Viral Infections
- Rickettsial Infections
- Others

Oxidative Stress
G6PD Oxidation Reduction

Drugs | Food | G6PD

Oxidation | Reduction

[Image of G6PD] [Image of blood cell]
Erythrocyte maturation and G6PD
Clinical Course

• Anemia and hyperbilirubinemia progressively improved to normal as an outpatient without intervention

• Repeat testing showed G6PD levels as outpatient were moderately decreased confirming the diagnosis
Management

• Avoid oxidative stressors
  – Fava beans and oxidative drugs

• Folic acid potentially beneficial during acute hemolysis

• Antioxidants have been trialed but no proven benefit and no current medications to prevent oxidative hemolysis

• Consider neonatal screening versus simple trigger avoidance in progeny
Conclusions

- G6PD deficiency is a known cause of acute intermittent oxidative hemolytic anemia
- Rarely expressed in women it can occur in certain circumstances
- Bite cells have a narrow differential diagnosis and should raise diagnostic suspicion for oxidative hemolysis and G6PD deficiency
- G6PD levels maybe normal initially


QUESTIONS ?