Approach to Hemolytic Anemia

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Objectives

• List the laboratory indications of hemolysis, and distinguish between intravascular and extravascular hemolysis.

• List the differential diagnosis of hemolytic anemia.

• Diagnose the various types of hemolytic anemia according to the appearance of the peripheral blood film, and ancillary laboratory tests.
Objectives- cont’d

• Distinguish hereditary spherocytosis from acquired spherocytic anemia using appropriate tests, and list the possible causes of the latter.

• Distinguish the types and mechanisms of microangiopathic hemolytic anemia using appropriate tests.
What Is Hemolytic Anemia?

• Anemia due to shortened survival of red cells in the circulation
• Normal RBC lifespan is 120 days, therefore it is useful to think of hemolytic anemia as representing RBC survival of less than 100 days
How Is Hemolytic Anemia Classified?

**Intravascular**
- Microangiopathy
- Transfusion rxns
- Infection
- PCH, PNH
- Hypotonic Solutions
- Snake bites

**Extravascular**
- Intrinsic to the RBC
  - Enzymes
  - Membrane
  - Hemoglobin
- Extrinsic to the RBC
  - AIHA
  - Liver Disease
How Is Hemolytic Anemia Classified?- cont’d

Inherited
- Enzyme defects
- Membrane defects
  - One exception
- Hemoglobinopathies

Acquired
- All the rest
- One membrane defect that is acquired is PNH
How Do Patients With Hemolytic Anemia Present?

- New onset of pallor and anemia
- Jaundice
- Gallstones
- Splenomegaly
How is Hemolytic Anemia Diagnosed?

• Two main principles
  – One is to confirm that it is hemolysis
  – Two is to determine the etiology
Lab Tests To Confirm Hemolysis

- Elevated absolute reticulocyte count
- Elevated LDH (note elevation is more pronounced in intravascular hemolysis)
- Elevated Indirect Bilirubin
- Decreased Haptoglobin
- Urine Hemosiderin - useful in the diagnosis of intravascular hemolysis
Lab Tests To Confirm Hemolysis

- the combination of LDH and haptoglobin is 83 percent sensitive and 96 percent specific in the diagnosis of hemolytic anemia
Atypical Presentations

- Hemolysis without anemia
  - Compensated hereditary spherocytosis
- Hemolytic anemia without reticulocytosis
  - AIHA with autoantibodies against erythroid precursors
- Ineffective erythropoiesis
  - Megaloblastic anemia
  - Myelodysplastic syndrome
  - Leukoerythroblastic reaction
The key to the etiology of hemolytic anemia is…

- The history AND
- The peripheral blood film
Patient History

• Lifelong or family history
• Medication/Drug precipitants
  – G6PD
  – AIHA
• Acute versus chronic
• Concomitant medical illnesses
• Clinical presentation
Peripheral Blood Film

- Morphology can help guide further investigation
- Therefore it is important that the blood film is reviewed
Case 1

- 68-year-old male
- African descent
- Seen by a physician for bladder discharge
- Urinalysis showed numerous WBC and positive leukocyte esterase
- Diagnosis of UTI made
- CBC normal
- Patient started on TMP/SMX I ds BID
Case 1- continued

- 2 weeks later, patient was admitted for a cystoscopy
- CBC is as follows:

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Hb</strong></td>
<td>70 g/L</td>
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<tr>
<td><strong>MCV</strong></td>
<td>99 fL</td>
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<tr>
<td><strong>MCH</strong></td>
<td>32 pg</td>
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<tr>
<td><strong>MCHC</strong></td>
<td>320 g/L</td>
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<tr>
<td><strong>RDW</strong></td>
<td>20 %</td>
</tr>
<tr>
<td><strong>Retic</strong></td>
<td>230 x 10⁹/L</td>
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Case 1- continued

(C) American Society of Hematology
Case 1-cont’d

- LDH 600 U/L (normal up to 200)
- Total bilirubin 45 umol/L
- Direct bilirubin 4 umol/L
- Haptoglobin < 0.1 g/L
• What is the diagnosis?
• How do you prove it?
Case 1- continued

• The most likely cause of the anemia is hemolysis secondary to G6PD deficiency
  – Hemolysis picture- low hemoglobin, high retic, high-normal MCV
  – G6PD deficiency- typical history, patient is male and of an at-risk ethnic background
Case 1- continued

- What other diagnostic tests are needed?
  - Tests to confirm G6PD
    - Heinz body prep
    - G6PD level- can NOT do this test right now, however it should be done once the hemoglobin normalizes to confirm diagnosis
Case 1- continued

• G6PD deficiency
  – One of the most common causes of hemolysis
  – X-linked = disease in males
  – Usually persons of African or Mediterranean descent
  – Usually history of getting an offending drug
    • Antibiotics, antimalarials, etc
  – Management is supportive
  – G6PD protects RBC against oxidative damage
Case 2

- 18 year old female
- “always has been anemic”
- Recently also started on iron supplements for “iron-deficiency”
- No family history of anemia, but there is a family history of splenectomy
Case 2- cont’d

• On exam
  – Vitals stable
  – scleral icterus
  – Spleen tip is palpable
  – Rest of the exam is unremarkable
Case 2- continued

WBC normal
Platelets normal

LDH 400 U/L
Total bilirubin 45 uM/L
Direct bilirubin 4 uM/L
Haptoglobin < 0.1 g/L

Hb | 80 g/L
MCV | 99 fL
MCH | 36 pg
MCHC | 400 g/L
RDW | 20 %
Retic | $300 \times 10^9$/L
• What is the diagnosis?
• How do you prove it?
Ddx of Spherocytic Hemolytic Anemia

- Hereditary Spherocytosis
- Autoimmune Hemolytic Anemia
- Way to distinguish between the two:
  - Direct Antiglobulin Test
- In this case the DAT was negative
  - Hereditary spherocytosis
Spherocytic Hemolytic Anemia

• If the DAT had been positive:
  – With IgG- warm autoimmune hemolytic anemia
    • Drugs
    • Autoimmune disease
    • Lymphoproliferative disease
    • idiopathic
Spherocytic Hemolytic Anemia

• If the DAT had been positive with complement- cold AIHA
  – EBV infection
  – Mycoplasma infection
  – Lymphoproliferative disease
  – idiopathic
Case 3

- 36 year old female G1P1
- She had a normal vaginal delivery about 6 hours ago
- Now has post-partum hemorrhage
- Taken to the OR for a D&C
- Post-op starts to bleed from IV sites and from urinary catheter
Case 3- continued

WBC 14 normal diff  
Platelets 14 x 10⁹/L  
LDH 1000 U/L  
Total bilirubin 45 uM/L  
Direct bilirubin 4 uM/L  
Haptoglobin < 0.1 g/L

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• What is the diagnosis?
• How do you prove it?
Ddx of Microangiopathic Hemolytic Anemia

- Thrombotic thrombocytopenic purpura
- Hemolytic Uremic Syndrome
- Disseminated Intravascular Coagulation
- Way to distinguish between these:
  - History- acute DIC associated with bleeding
  - Lab tests- D-dimer, fibrinogen, INR, aPTT
Case 3-continued

• In this case, the diagnosis was DIC secondary to an amniotic fluid embolus

• Patient improved with blood products and supportive care over 24 hours
Case 4
Case 4- cont’d

• What is the diagnosis?
  – Liver disease
Summary of Important Morphological Findings in Hemolytic Anemia

- **Spherocytes**
  - AIHA, hereditary spherocytosis
- **Schistocytes**
  - With thrombocytopenia- TTP or DIC
  - Without thrombocytopenia- heart valve hemolysis
- **Blister Cells**- oxidative damage- G6PD
- **Acanthocytes**- Liver disease
Conclusions

• Hemolytic anemia can be recognized by the clinical picture
  – History and physical
  – Lab tests to confirm hemolysis
  – Peripheral blood film to guide further tests