Drug induced hemolysis: transfusion management

Interactive case study

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Case 1

- Male patient, 50 y

- History
  - Nil

- Chief Complaint
  - General malaise
  - Fatigue
  - Loss of appetite
  - Vertigo
  - Headache
## Case 1 – Lab work

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (Hemoglobin)</td>
<td><strong>10,2 g/dl</strong></td>
<td>12,9 – 16,4</td>
</tr>
<tr>
<td>MCV (Mean corpuscular volume)</td>
<td><strong>112,7</strong></td>
<td>82,4 – 97,3</td>
</tr>
<tr>
<td>Reticulocyte (Immature red blood cell)</td>
<td>14 / 1000 RBC</td>
<td>4,4 – 15,5</td>
</tr>
<tr>
<td>LDH (Lactate dehydrogenase)</td>
<td>357 U/L</td>
<td>313 – 618</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0,5 mg/dl</td>
<td>0,2 – 1,3</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>1,72 g/l</td>
<td>0,26 – 1,85</td>
</tr>
</tbody>
</table>
Is this drug induced hemolytic anemia?

- Yes
- No
- I don’t know
### Hemolytic anemia

#### Red Blood Cells

- **One RBC contains 1 billion molecules of oxygen**
- **2 to 3 million RBCs are made each second**
- **RBCs circulate for 120 days**
- **There are millions of RBCs in one drop of blood**
- **RBCs take 20 seconds to circulate the body one time**

#### Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>= or ↓</td>
</tr>
<tr>
<td>MCV</td>
<td>↑</td>
</tr>
<tr>
<td>Reticulocyte</td>
<td>↑</td>
</tr>
<tr>
<td>LDH</td>
<td>↑</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>↑</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>↓</td>
</tr>
</tbody>
</table>

Goodnough LT. Am J Hematol 2015
Case 2

Second Chance
Just Ahead
Case 2

- Male patient, 50 y

History
- Nil

Chief Complaint
- General malaise
- Fatigue
- Loss of appetite
- Vertigo
- Headache

Examination
- Hemodynamic stable
- Slight icterus
# Case 2 – Lab work

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (Hemoglobin)</td>
<td>7.7 g/dl</td>
<td>12.9 – 16.4</td>
</tr>
<tr>
<td>MCV (Mean corpuscular volume)</td>
<td>101.7</td>
<td>82.4 – 97.3</td>
</tr>
<tr>
<td>Reticulocyte (Immature red blood cell)</td>
<td>78 / 1000 RBC</td>
<td>4.4 – 15.5</td>
</tr>
<tr>
<td>LDH (Lactate dehydrogenase)</td>
<td>2857 U/L</td>
<td>313 – 618</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>4.0 mg/dl</td>
<td>0.2 – 1.3</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>&lt; 0.05 g/l</td>
<td>0.26 – 1.85</td>
</tr>
</tbody>
</table>
Is this drug induced hemolytic anemia?

- Yes
- No
- I don’t know
Is this drug induced hemolytic anemia?

- Hemolytic anemia?

- **Drug** induced hemolytic anemia?
  - Pharmaceutical drug or medicine, is a chemical substance used to treat, cure, prevent, diagnose a disease or promote well-being.

- History

- Case 2 patient: “painkiller”
  - Acetaminophen
  - Ibuprofen

Garratty G. Blood reviews, 2010
Can hemolytic anemia only be induced by drugs?

- Yes
- No
- I don’t know
Hemolytic anemia

- Non – xenobiotic related

- Xenobiotic related
  - Direct red cell destruction
    - Venoms (snake, spider)
    - Hypotonic solutions
  - Microangiopathic (eg clopidogrel, cyclosporine, tacrolimus)
  - Oxidative damage
  - Autoimmune hemolytic anemia

Garratty G. Blood reviews, 2010
Carnovale C. Int J Clin Pharm, 2015
Drug induced hemolysis

Immune mediated versus oxidative (metabolic)
Immune mediated hemolytic anemia

- Trigger antigen antibody reaction
- Varying degree hemolysis
Immune mediated hemolytic anemia

- Association 150 drugs

- Drug dependent
  - Hapten
  - Drug-antibody immune complex

- Drug independent (auto-antibodies)

Fig. 1. Proposed unifying hypothesis of drug-induced antibody reactions. The thicker, darker lines represent antigen-binding sites on the Fab region of the drug-induced antibody. (A) Drugs (haptens) bind loosely (or firmly) to cell membranes, and antibodies can be made to the drug (producing in vitro reactions typical of a drug adsorption [penicillin-type] reaction); (B) membrane components, or mainly membrane components (producing in vitro reactions typical of autoantibody); (C) or part-drug, part-membrane components (producing an in vitro reaction typical of the so-called immune complex mechanism).
Oxidative hemolytic anemia

- Enzymatic defects
  - Glucose 6-phosphatedehydrogenase deficiency

Luzzatto L. B J Hematology, 2014
Oxidative hemolytic anemia

- X-linked genetic
- > 140 mutations in G6PD gene
- Genetic heterogeneity

Different levels enzymatic activity

<table>
<thead>
<tr>
<th>Class</th>
<th>Level of deficiency</th>
<th>Enzyme activity</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Severe</td>
<td>Chronic nonspherocytic hemolytic anemia in the presence of normal erythrocyte function</td>
<td>Uncommon; occurs across populations</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
<td>Less than 10 percent of normal</td>
<td>Varies; more common in Asian and Mediterranean populations</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>10 to 60 percent of normal</td>
<td>10 percent of black males in the United States</td>
</tr>
<tr>
<td>IV</td>
<td>Mild to none</td>
<td>60 to 150 percent of normal</td>
<td>Rare</td>
</tr>
<tr>
<td>V</td>
<td>None</td>
<td>Greater than 150 percent of normal</td>
<td>Rare</td>
</tr>
</tbody>
</table>

G6PD = glucose-6-phosphate dehydrogenase.
Information from references 1 and 7.

Frank JE. Am Fam Physician, 2005
Oxidative hemolytic anemia

- Acute hemolysis
  - Infection
  - Fava beans
  - Oxidative drug

- Degree hemolysis depends on
  - Drug dose
  - G6PD activity
  - Red cell ageing

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<table>
<thead>
<tr>
<th></th>
<th>Definite association</th>
<th>Possible association</th>
<th>Doubtful association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimalarials</td>
<td>Primaquine</td>
<td>Chloroquine</td>
<td>Mepacrine Quinine</td>
</tr>
<tr>
<td></td>
<td>Pamaquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Sulfanilamide</td>
<td>Sulfadimidine</td>
<td>Aldesulfone</td>
</tr>
<tr>
<td></td>
<td>Sulfacetamide</td>
<td>Sulfasalazine</td>
<td>Sulfadiazine</td>
</tr>
<tr>
<td></td>
<td>Sulfapyridine</td>
<td>Gibenclamide</td>
<td>Sulfafuroazole</td>
</tr>
<tr>
<td></td>
<td>Sulfinpyrazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfones</td>
<td>Dapsone</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Nitrofurantoin</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Antipyretic or analgesic</td>
<td>Acetamiide</td>
<td>Aspirin</td>
<td>Paracetamol Phenacetin</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Nalidixic acid</td>
<td>Ciprofloxacin</td>
<td>Aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Nifuradil</td>
<td>Chloramphenicol</td>
<td>Dextrorubicin</td>
</tr>
<tr>
<td></td>
<td>Methylothionium</td>
<td>Vitamin K analogues</td>
<td>Probenecid</td>
</tr>
<tr>
<td></td>
<td>Phenazopyridine</td>
<td>Ascorbic acid</td>
<td>Dimercaprol</td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole</td>
<td>Mesalazine</td>
<td></td>
</tr>
<tr>
<td>Other chemicals</td>
<td>Naphthalene</td>
<td>Acalypha indica extract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,4,6-trinitrotoluene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reprinted from ref 1 with permission.

Table 2: Drugs and chemicals associated with substantial haemolysis in patients with G6PD deficiency

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Cappellini MD. Lancet, 2008
Diagnosis

Your test results are in, and you're full of surprises!
Is there an unique discriminative test between immune mediated or oxidative hemolytic anemia?

- Yes
- No
Direct antiglobulin test (DAT)

- Direct Coombs test
- Critical step evaluation hemolysis
- Determination IgG and/or complement bound on RBC

Positive: immune-dependent
Negative: immune-independent

Zantek ND. Am J Hematol, 2012
Diagnosis drug induced hemolytic anemia

- Careful history drug exposure
- DAT

- Immune-dependent
  - Antibodies
    - Reference labs
    - Drug or metabolites

- Immune-independent
  - G6PD activity (generation NADPH)
    - Fluorescent spot test
    - Quantitative spectrophotometric assay
Management
Treatment for immune mediated hemolytic anemia includes minimum

- Cessation of offending drug
- Red blood cell transfusion
- Steroids
- All of the above
Treatment for oxidative hemolytic anemia includes minimum

- Cessation of offending drug
- Red blood cell transfusion
- Vitamine E (anti-oxidant)
- All of the above
Treatment drug induced HA

- Discontinuation of offending drug
  - Dose-dependent effect (enzymatic)
  - Drug-dependent antibodies (immune)

- Immune-mediated
  - Steroids: no effect

- Oxidative
  - Vitamin E and selenium (antioxidants): no benefit

- Transfusion RBC (severe anemia)
Transfusion trigger
Tranfusion trigger in drug induced hemolytic anemia is

- Hb $\leq 10$ g/dl
- Hb $\leq 8$ g/dl
- Hb $\leq 7$ g/dl
- Clinical decision
Hb value ... OR ... patient

- Physiological status
  - \( DO_2 = CO \times CaO_2 \)
  - \( DO_2 = (SV \times HR) \times [(1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)] \)

- Goal
  - Avoid organ ischemia
  - Avoid organ dysfunction

- Restrictive transfusion better than liberal
  - Same mortality
  - Less transfusion-related complications

Goodnough LT. Am J Hematol 2015
Spahn DR. Transfus Med Hemother 2015
### Transfusion trigger

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Transfusion trigger</th>
<th>Evidence quality</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU patients</td>
<td>Hb ≤ 7 g/dl</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Postoperative</td>
<td>Hb ≤ 8 g/dl or symptomatic</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Hb ≤ 8 g/dl or symptomatic</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>Acuut coronary syndrome</td>
<td>None</td>
<td>Very low</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

Guidelines AABB - 2012
Transfusion for drug induced anemia

- Clinical decision
  - Physiological status (CO, Hb, SaO₂)
  - Clinical circumstances
    - Pre-existing anemia
    - Massive hemolysis
    - Ongoing hemolysis

- Guidance

<table>
<thead>
<tr>
<th>Hb</th>
<th>Signs brisk hemolysis</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 g/dl</td>
<td></td>
<td>Blood transfusion</td>
</tr>
<tr>
<td>&lt; 9 g/dl</td>
<td>Yes</td>
<td>Blood transfusion</td>
</tr>
<tr>
<td>7 – 9 g/dl</td>
<td>No</td>
<td>Observe for 48 h</td>
</tr>
</tbody>
</table>
Case 2 - continued

- DAT negative

- G6PD deficiency
  - No infection
  - No fava bean
  - Must be drug induced ...
    ... unable to identify drug

- No transfusion
Take home messages

- Work-up anemia

 DIAGNOSIS OF ANEMIA

- MCV* <80
  - Ferritin
  - Iron Deficiency Anemia
    - Sickle Cell Thalassemia etc.
  - Hb Electrophoresis +
  - Sideroblastic Anemia
    - Lead poisoning
  - Coombs -
  - Hb Electrophoresis +
    - Sickle Cell Thalassemia etc.

- MCV 80-100
  - Ferritin
  - Chronic Disease

- MCV >100
  - B12↓
  - Folic acid RBC folate↓
  - Folic acid Deficiency Liver disease
  - Megaloblastic Anemia
  - Aplasia, Myelofibrosis
  - Coombs +
  - Hb Electrophoresis -
    - Autoimmune Hemolytic Disease
  - Hb Electrophoresis +
    - Spherocytosis
    - Ovalocytosis
    - G6PD**

*MCV = Mean Corpuscular Volume of Erythrocytes
**G6PD = Glucose-6-phosphate dehydrogenase Deficiency
Take home messages

- Careful drug history
- Treatment = cessation of exposure
- Transfusion clinical decision
Thank you for your attention