The Case of the Disappearing Blood

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Case
Ms. A - History

- 34 yo woman, uncomplicated vaginal delivery of healthy baby on 12/13/2016

- Ongoing post-partum vaginal bleeding

- D+C performed 3/3/2017, given one dose of cefotetan perioperatively

- Hct post-op 32
Ms. A - ER course

- Ongoing bleeding, abdominal pain, syncope x2, presented to outside ED 3/13/17

- CT A/P concerning for hemoperitoneum

- Hct 22

- Taken to OR for urgent laparoscopy to repair uterine rupture

- Evacuation of 1.5L of hemoperitoneum
Ms. A - OR course

• Emergent RBC transfusion ordered

• Type and cross sent, revealed panagluttinin (unable to crossmatch)

• 2 units of O-neg uncrossmatched blood transfused intraoperatively

• Given one dose of cefotetan preoperatively
Ms. A – Post-op Course

- Developed hemoglobinuria postoperatively
- Hct dropped to 16
- OSH concerned for possible transfusion reaction
- Transferred to UWMC
- Hct on arrival 12, Cr 3.6 → admitted to MICU
Peripheral Smear, 100x
Ms. A – Hemolysis Workup

- Retic 4.3% (absolute = 60)
- LDH 4,057; hapto <30
- Panaglutinin, +DAT, IgG 3+ strength (0-4+ scale)
- Eluate was negative
- Alloadsorption → no *underlying* antibodies to common antigens identified
- Sample sent to Red Cross Pomona, CA for further testing.
Ms. A – MICU course

• Given 125mg methylprednisolone IV x 1

• Transfused 3 units phenotypically-matched RBCs

• O negative, matched for 4 out of 6 antigens she lacked

• Hct 12 -> 20 -> 22
Ms. A – Hemolysis Workup

• Red Cross Report:
  – Direct agglutinin test: Pt’s RBCs strongly reactive with anti-IgG, weakly reactive with anti-C3, nonreactive with IgM or IgA
  – Drug Antibody Testing: Pt’s serum was tested against cefotetan-treated and untreated RBCs
  – Serum and eluate reacted strongly with cefotetan-treated RBCs, but not against untreated RBCs

• Results indicate cefotetan tightly bound to RBCs
Drug-Induced Immune Hemolytic Anemia
Drug-Induced Immune Hemolytic Anemia

• Rare (1 / 1 million of the general population)

• Probably underreported

• High fatality rate
  – *Always* include in differential for hemolytic anemia with panreactive antibody screen and negative eluate
### Associated Drugs
(130 discrete drugs implicated as of 2012)

**Table 4. Causes of drug-induced immune hemolytic anemia seen in Dr. Garratty’s laboratories during two different 10-year periods**

<table>
<thead>
<tr>
<th>Drug</th>
<th>1969-78</th>
<th>2003-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa</td>
<td>29 (67%)</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>10 (23%)</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td>17 (19%)</td>
</tr>
<tr>
<td>Cefotetan</td>
<td></td>
<td>24 (28%)</td>
</tr>
<tr>
<td>Piperacillin</td>
<td></td>
<td>32 (37%)</td>
</tr>
<tr>
<td>Platinum-based chemotherapies</td>
<td></td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (9%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td>87</td>
</tr>
</tbody>
</table>

Cefotetan

• 2\textsuperscript{nd} Most common drug to cause DIIHA

• Hemolytic anemia presents 1-13 days after first dose of cefotetan

• Most patients present with signs of intravascular hemolysis e.g. hemoglobinuria

• \~20\% of cases are fatal

• \~20\% of cases associated with renal failure
Cefotetan

- DAT is always positive
  - 100% +IgG, 86% +C3

- Often misdiagnosed as postop bleeding or sepsis → prompting second dose of drug

- Cefotetan remains RBC-bound for a median of 67.5 days → slow recovery
Cefotetan

- May also appear after 1\textsuperscript{st} dose of drug due to environmental exposure (antibiotics used for livestock)

\textbf{Table 5.} Percentage of agglutinins reacting with drug-treated red blood cells found in our laboratory when screening blood donors' and random patients' sera*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood donors</th>
<th>Random patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin (unpublished results)</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Cephalothin\textsuperscript{59}</td>
<td>39%</td>
<td>NT</td>
</tr>
<tr>
<td>Ticarcillin\textsuperscript{66}</td>
<td>33%</td>
<td>NT</td>
</tr>
<tr>
<td>Cefotetan\textsuperscript{59} (and unpublished results)</td>
<td>80%</td>
<td>78%</td>
</tr>
<tr>
<td>Piperacillin\textsuperscript{72}</td>
<td>91%</td>
<td>49%</td>
</tr>
<tr>
<td>Oxaliplatin\textsuperscript{73}</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Cisplatin\textsuperscript{73}</td>
<td>7%</td>
<td>NT</td>
</tr>
<tr>
<td>Meropenem\textsuperscript{74}</td>
<td>93%</td>
<td>60%</td>
</tr>
</tbody>
</table>

\textsuperscript{*}It is interesting to note that, for some drugs, fewer patients than donors have antibodies.

NT = not tested.

Ceftriaxone

- 3rd most common drug to cause DILIHA
- More severe in children
- Fatal hemolytic anemia in 38% of cases (75% of these were children)
- Positive DAT
- In-vitro diagnosis → mixing serum + drug + RBCs
Piperacillin

• Most common drug to cause DIIHA

• Complement-mediated intravascular hemolysis

• Positive DAT (IgG and C3)

• May be misdiagnosed as AIHA, as in-vitro reactions seen without adding drug
  – Reactivity disappears within 48h of stopping drug (whereas reactivity persists in AIHA)
DIIIHA Mechanisms
DIIHA Mechanisms

DIIHA Mechanisms

(antibody to drug)

Drug-independent, methyldopa, fludarabine

(cytoxic drug, penicillin, cefotetan)

Drug-dependent, ceftriaxone, piperacillin

Antibody to (mainly) membrane components

Red cell membrane

DIIHA Mechanisms

• Drug adsorption
  – Penicillin
    – Drug binds to RBC membrane, antibody reacts to RBC-bound drug
    – DAT positive for IgG +/- C3
    – In vitro testing of serum and eluate with drug-coated RBCs is positive
Drug Adsorption
Drug Adsorption
Drug Adsorption

\[ \alpha - pcn \]
Ceftraixone and Piperacillin
Ceftraixone and Piperacillin

\[ \text{\text wholly contained in} \]

\[ \alpha\text{-piperacillin} \]
Ceftraixone and Piperacillin

α-piperacillin
Ceftraixone and Piperacillin
Piperacillin in vitro
Piperacillin in vitro

\[ \gamma \rightarrow \alpha\text{-piperacillin} \]
DIIHA Mechanisms

• Nonimmunologic protein adsorption (NIPA)
  – Cefotetan
  
  – Drug modifies RBC membrane (also called “membrane modification mechanism”)

  – DAT positive for IgG +/- C3

  – In vitro, drug-coated RBCs incubated with plasma become coated with proteins

  – RBCs incubated with eluate are nonreactive
Non-immune Protein Adsorption
Nonimmune Protein Adsorption
Nonimmune Protein Adsorption

albumin

fibrinogen
Nonimmune Protein Adsorption
Nonimmune Protein Adsorption
DIIHA Mechanisms

• Drug-independent (AIHA)
  – Methyldopa, fludarabine

  – Drug induces an alloantibody (IgG) similar to warm AIHA

  – DAT can last up to 2 years
Drug-independent (AIHA)
Drug-independent (AIHA)
Drug-independent (AIHA)
Drug-independent (AIHA)
Back to our case...
Ms. A – Hospital Course

- Required 1 unit phenotypically matched RBCs every ~48h x 1 week (goal Hct > 21)

- Cr peaked at ~9.8 after 1.5 weeks, then began to trend down

- Discharged home to follow-up with PCP

- Cephalosporins added to allergy list
DIIHA Summary

• Extremely rare but potentially fatal cause of hemolysis

• Always consider in patient with hemolytic anemia, panreactive antibody screen, and negative eluate

• Most common drugs are cefotetan, piperacillin and ceftriaxone (more common in kids)

• Management is withdrawal of offending drug and supportive care, unclear if steroids beneficial

• Re-exposure can be lethal (many case reports of lethal 2nd or 3rd cefotetan dose!)
References


Thanks!

Dr. Bimpe Adesina

Dr. Ryan Metcalf

Dr. Tejas Dhawale