Out-of-Group Platelet Transfusion

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Case Presentation

Child presents to Emergency Department with symptomatic anemia

- Hb = 6.1 g/dL and Hct = 16.2%
- Recent history of dark urine
- Recent transfusion

Blood Bank: Initial Testing

<table>
<thead>
<tr>
<th>ABO and Rh Typing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward</td>
</tr>
<tr>
<td>Anti-A</td>
</tr>
<tr>
<td>2+</td>
</tr>
</tbody>
</table>

Antibody Screen Results
3 out of 3 screening cells NEGATIVE
DAT (ordered separately by clinical team)
IgG 2+; C3 NEGATIVE; ELUATE NEGATIVE
Additional History

- "Brown" urine and serum
- Transfused the week of presentation at "someplace 3 hours away"
- History of Acute Myeloid Leukemia (AML)

Additional History

- Cord blood transplant 6 months prior
  - A-to-O major ABO mismatch
- Chronic Graft-versus-Host Disease (cGVHD)
- Multiple Medications
  - Prophylactic antimicrobials (penicillin)
  - Immunosuppressants

Additional Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count (175-475 x10³/uL)</td>
<td>126x10³</td>
</tr>
<tr>
<td>Reticulocyte Count (0.5-3.5%)</td>
<td>7.9</td>
</tr>
<tr>
<td>Reticulocyte Production Index (0.5-1.5 %)</td>
<td>1.3</td>
</tr>
<tr>
<td>Total Bilirubin (0-2.0 mg/dL)</td>
<td>0.3</td>
</tr>
<tr>
<td>Direct Bilirubin (0-0.3 mg/dL)</td>
<td>2.6</td>
</tr>
<tr>
<td>Haptoglobin (30-200 mg/dL)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>BUN (7-22 mg/dL)</td>
<td>40</td>
</tr>
<tr>
<td>Creatinine (0.3-1.0 mg/dL)</td>
<td>0.7</td>
</tr>
<tr>
<td>Urine: hemoglobin, urobilinogen, coarse granular casts</td>
<td></td>
</tr>
</tbody>
</table>
Peripheral Smear: Low Power

Peripheral Smear: High Power

Hemolytic Anemia: Immune Mediated

- Alloimmune Hemolytic Anemia
  - No identifiable antibody specificity on RBC panel
- Warm AIHA
  - DAT positive with IgG on RBCs
  - No identifiable antibody specificity on screen and no panagglutinin
  - Eluate negative

Hb = 4.5 g/dL
Hemolytic Anemia: Immune Mediated

- Drug-induced Hemolytic Anemia
  - Penicillin
    - 3% of pts on high-dose IV therapy with positive DAT
    - <1% hemolyze, usually EXTRAVASCULAR (IgG)

Patient needs blood...

- Patient is A-positive by initial testing with no discrepancy between front and back type
- Crossmatch with A RBC units: INCOMPATIBLE
- Crossmatch with O RBC units: COMPATIBLE

Patient needs blood...

- More transfusion history
  - Outside blood bank gives recent transfusion history
    - 11/16: A+ PLT, A+ RBC
    - 11/23: A+ PLT
    - 12/1: A+ RBC
    - 12/2: O- PLT
  - VSS and asymptomatic during recent transfusion
Immunohematology Reference Lab Results

- Anti-A IgG identified at 37/AHG
- No IgM identified
- Repeat reverse type with A cells
  - Immediate spin: NEGATIVE
  - 37/AHG: 2+
- Patient receives 1 O RBC unit and responds well

Anti-A: Donor or Recipient

- Passively-acquired from O Platelet unit
  - Minor mismatch
  - Donor with "high titer" anti-A, anti-B, and/or anti-A,B
  - Finite amount of antibody, undetectable in a few days
  - Often not clinically significant

Anti-A: Donor or Recipient

- Posttransplant immune hemolysis
  - Major mismatch (A-to-O)
  - Typically see a mixed-field of donor and recipient RBCs
  - Hemolysis can be chronic if chimerism develops
  - Continuous production of antibody as long as immune stimulus is present
**Anti-A: Donor or Recipient**

- Patient has fully converted to cord blood donor type (group A)
- Blood Center has retained a sample from apheresis-derived platelet (SDP) unit for QC testing
- Anti-A titer on group O SDP sample (donor)
  - IgM: 256
  - IgG: 4096
- Titer on recipient sample
  - IgM: 2
  - IgG: 32
- DAT NEGATIVE at 1-week follow-up

**Hgb and Bilirubin: Hospitalization and Follow-up**

<table>
<thead>
<tr>
<th>HD#1</th>
<th>HD#2</th>
<th>HD#3</th>
<th>HD#4</th>
<th>HD#5 (DIC)</th>
<th>D#1</th>
<th>D#2 (FUA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Case Evaluation**

- What clinical factors contributed to hemolysis?
  - Recipient is blood group A
  - Platelet shortage
    - Only O units available on a Friday afternoon for outpatient transfusion
    - Entire SDP unit transfused (~300 mL)
  - Platelet unit not volume reduced
Case Evaluation

- What clinical factors contributed to hemolysis?
  - Recipient with small plasma volume
  - “High titer” platelet unit
  - History of A-to-O HSCT, decreased anti-A neutralization due to lack of A antigen on tissues

Diagnostic Challenges

- What factors complicated the identification of the anti-A?
  - Only the IgG isotype was detected
    - Immediate spin ABO type routinely performed, which detects IgM
  - Delay in presentation
    - IgM-bound cells are more rapidly cleared
  - Positive DAT but negative eluate
    - Eluate is tested with panel of group O cells
  - Initial lack of an adequate transfusion history
    - No knowledge of group O SDP transfusion

Diagnostic Challenges

- Why was there a delay in signs and symptoms?
  - Recipient did not report symptoms to staff but complained to mother about transient back pain
  - Medications masked s/sx of AHTR (cytokine storm)
  - Dark urine was noticed by mother the next morning but may have been present earlier
Platelet Transfusion: Minor ABO Mismatch

- Passively transfused donor anti-A, anti-B, or anti-A,B that bind to recipient antigens
- Apheresis-derived Platelets (SDP)
  - 300 mL plasma per unit
  - Antibodies from a single donor
- Whole blood-derived Platelets (RDP)
  - 50 mL plasma per unit
  - Pool dilutes each donor's antibodies

Platelet Transfusion: Minor ABO Mismatch

- AABB Standards
  - A plasma unit should be ABO compatible with recipient's RBCs (volume ~ 300 mL)
  - No ABO compatibility requirement for platelet units
- ABO-matched platelet products are considered first-line therapy

Platelet Transfusion: Minor ABO Mismatch

- Limitations to providing ABO-matched platelets
  - Limited supply of Platelets
  - Crossmatch-compatible and HLA-matched requirements may necessitate out-of-group transfusion
  - Frequency of donor blood groups
  - Encourage group O donors to donate during shortage
How big is this problem?

### Platelet Transfusions: 13 Reported HTR in Adults

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Age</th>
<th>ABO</th>
<th>Ph Type</th>
<th>PltABO</th>
<th>Saline Titer</th>
<th>AHG Titer</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoes, 1977</td>
<td>44</td>
<td>AB</td>
<td>RDP</td>
<td>0</td>
<td>256</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>McLeod, 1982</td>
<td>45</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>1280</td>
<td>12,240</td>
<td>S</td>
</tr>
<tr>
<td>Pierce, 1985</td>
<td>58</td>
<td>B</td>
<td>RDP</td>
<td>0</td>
<td>912</td>
<td>32,090</td>
<td>S</td>
</tr>
<tr>
<td>Ferguson, 1988</td>
<td>66</td>
<td>A</td>
<td>RDP</td>
<td>0</td>
<td>256</td>
<td>&gt;4,000</td>
<td>S</td>
</tr>
<tr>
<td>Reis, 1989</td>
<td>56</td>
<td>B</td>
<td>SDP</td>
<td>0</td>
<td>NR</td>
<td>6,098</td>
<td>S</td>
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<tr>
<td>Murphy, 1989</td>
<td>50</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>236</td>
<td>1,024</td>
<td>NR</td>
</tr>
<tr>
<td>MacManigal, 1999</td>
<td>28</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>912</td>
<td>NR</td>
<td>S</td>
</tr>
<tr>
<td>MacManigal, 1999</td>
<td>72</td>
<td>AB</td>
<td>SDP</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Larsson, 2000</td>
<td>44</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>16,384</td>
<td>NR</td>
<td>S</td>
</tr>
<tr>
<td>Valbonesi, 2000</td>
<td>51</td>
<td>A</td>
<td>SDP (dry)</td>
<td>0</td>
<td>&gt;6,500</td>
<td>NR</td>
<td>S</td>
</tr>
<tr>
<td>Ozturk, 2003</td>
<td>21</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Josephson, 2004</td>
<td>8</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>NR</td>
<td>5,122</td>
<td>S</td>
</tr>
</tbody>
</table>

### Platelet Transfusions: 7 Reported HTR in Children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Age</th>
<th>ABO</th>
<th>Ph Type</th>
<th>PltABO</th>
<th>Saline Titer</th>
<th>AHG Titer</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conway, 1984</td>
<td>15</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>8,192</td>
<td>NR</td>
<td>D</td>
</tr>
<tr>
<td>Pierce, 1985</td>
<td>15</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>912</td>
<td>32,000</td>
<td>S</td>
</tr>
<tr>
<td>Chow, 1991</td>
<td>15</td>
<td>AB</td>
<td>SDP, RDP</td>
<td>0</td>
<td>1,024</td>
<td>NR</td>
<td>S</td>
</tr>
<tr>
<td>Valbonesi, 2000</td>
<td>18</td>
<td>A</td>
<td>SDP (dry)</td>
<td>0</td>
<td>&gt;6,500</td>
<td>NR</td>
<td>D</td>
</tr>
<tr>
<td>Duprat, 1999</td>
<td>5</td>
<td>A</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>S</td>
</tr>
<tr>
<td>Angiulli, 2004</td>
<td>8 m</td>
<td>A</td>
<td>SDP</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>D</td>
</tr>
</tbody>
</table>
Platelet Transfusion: Minor ABO Mismatch and Hemolysis


* Retrospective review (7 month period) N = 16
* Inclusion: Non-group O Auto-BMT ADULTS who received ABO-identical and non-identical SDP in 24 hrs.
* Exclusion: RBC transfusion during the 24 hr period.
* 1 AHTR in 6,000 ABO-mismatched platelet transfusions

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Mean Change Hb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO-identical</td>
<td>24</td>
<td>-0.50</td>
<td>-0.72-0.29</td>
</tr>
<tr>
<td>Plasma-incompatible</td>
<td>24</td>
<td>-0.11</td>
<td>-0.36-0.15</td>
</tr>
</tbody>
</table>

*p = 0.193

Minor ABO Mismatch and Hemolysis: Mitigating Factors

* Antibody Dilution
  - Antibodies in plasma product are diluted in recipient plasma volume
    * Issue
      - Small-volume recipients have less dilutional capacity
      - "High-titer" anti-A or anti-B may not be effectively diluted (e.g. SDPs)

Minor ABO Mismatch and Hemolysis: Mitigating Factors

* Antibody Neutralization
  - Infused donor ABO antibodies are neutralized by soluble and tissue-expressed ABO substances
    * Issue
      - Some individuals do not have soluble ABO substances
      - ABO mismatched HSCT patients (ABO tissue expression different from RBC expression)
"High Titer" Donors: UK Policy

"Platelet recovery of both major and minor ABO incompatible platelet transfusions may be impaired to some extent, but this is not usually clinically significant. A more important consideration concerning donor ABO antibodies is the avoidance of acute haemolysis, which may occur after ABO-incompatible platelet transfusions, typically with transfusions of high titre anti-A to A1 recipients. This problem has been particularly apparent in small children receiving apheresis platelet concentrates, which contain large volumes of plasma from single donors. Group O platelets should only be used for group A, B and AB patients if they have been tested and labelled as negative for high titre anti-A and anti-B. Consider anti-A titer ≥ 128 as "high titer."

Critical Titer: "Dangerous Universal Donor"

- "Dangerous Universal Donor" termed in 1923
  - Blood from some Group O donors caused AHTR
  - Required minor crossmatch to be performed
- A critical antibody titer was attempted to be defined
  - Methods not standardized
  - High prevalence of "dangerous universal donors" relative to number of passive AHTRs

Critical Titer: "Dangerous Universal Donor"

<table>
<thead>
<tr>
<th>Reference</th>
<th>Date</th>
<th>Titer</th>
<th>Medium</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruzin</td>
<td>1950</td>
<td>200</td>
<td>Saline</td>
<td>6% anti-A</td>
</tr>
<tr>
<td>Groen</td>
<td>1950</td>
<td>200</td>
<td>Saline</td>
<td>2% anti-B</td>
</tr>
<tr>
<td>Crick</td>
<td>1952</td>
<td>200</td>
<td>AGS serum</td>
<td>15% anti-A</td>
</tr>
<tr>
<td>Grove-Rasmussen</td>
<td>1956</td>
<td>20</td>
<td>AGS serum</td>
<td>42%</td>
</tr>
<tr>
<td>Gardner and Tovey</td>
<td>1954</td>
<td>Strong</td>
<td>Saline</td>
<td>8.1% anti-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36% anti-B</td>
</tr>
<tr>
<td>Grove-Rasmussen</td>
<td>1953</td>
<td>20</td>
<td>AGS serum</td>
<td>10.2%</td>
</tr>
<tr>
<td>Groen-Rasmussen</td>
<td>1956</td>
<td>20</td>
<td>Saline</td>
<td>15% A</td>
</tr>
<tr>
<td>Todd</td>
<td>1946</td>
<td>500</td>
<td>Saline</td>
<td>3.5% B</td>
</tr>
<tr>
<td>Ebert</td>
<td>1942</td>
<td>512</td>
<td>Saline</td>
<td>40% A</td>
</tr>
<tr>
<td>Aubert</td>
<td>1942</td>
<td>512</td>
<td>Saline</td>
<td>9% B</td>
</tr>
</tbody>
</table>

Significant numbers of apheresis-derived group O platelet units have "high-titer" anti-A/Bi implications for transfusion policy.

Transfusion. 2004;44:805-808

N=100 Critical Titer: IgG ≥ 256 and IgM ≥ 64

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>IgG (1:32)</th>
<th>IgM (1:32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>53</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>123</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>1024</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Prevalence of "high titer" donors: 30 – 40%

Out-of-Group Platelet Transfusion: Other Concerns

- Platelet Refractoriness
- Immune Complex Formation
- Increased Morbidity and Mortality in Acute Leukemia and BMT Patients
- Stem Cell Transplant Population
  - Limited studies on safety and efficacy out-of-group platelet transfusions

Out-of-Group Platelet Transfusion: Other Concerns

- Platelet Refractoriness
- Immune Complex Formation
- Increased Morbidity and Mortality in Acute Leukemia and BMT Patients
- Stem Cell Transplant Population
  - Limited studies on safety and efficacy out-of-group platelet transfusions

Table 3 Suggested approach to transfusion therapy in stem cell transplant recipients and other patients receiving multiple transfusions

- Transfuse only leukoreduced blood components
- Transfuse only ABO identical blood components
- When this is not possible because of ABO nonidentical transplants, or shortages of ABO blood group identical components
- Use cord cell and platelet transfusions lacking subject ABO antigens to which the recipient has antibodies (usually group O red cells and platelets)
- Remove supernatant plasma containing antibody to recipient or donor ABO antigens before transfusion, by washing or centrifugation
- Except when serious shortages occur, do not transfuse ABO nonidentical components merely for purposes of blood bank inventory control (i.e. to prevent wastage)

What would Karl Landsteiner do? The ABO blood group and stem cell transplantation

Transfusion therapy in stem cell transplant recipients and other patients receiving multiple transfusions

- Transfuse only leukoreduced blood components
- Transfuse only ABO identical blood components
- When this is not possible because of ABO nonidentical transplants, or shortages of ABO blood group identical components
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- Except when serious shortages occur, do not transfuse ABO nonidentical components merely for purposes of blood bank inventory control (i.e. to prevent wastage)

Bone Marrow Transplantation 2005;30:747-755
Table 4: Select transfusions in ABO nonidentical stem cell transplants

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Transfused RBC</th>
<th>Transfused platelets</th>
<th>Transfused plasma/serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>AB</td>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>O</td>
<td>A, B, AB</td>
<td>Washed O</td>
<td>Washed O</td>
<td>AB</td>
</tr>
<tr>
<td>A</td>
<td>AB</td>
<td>Washed A</td>
<td>Washed A</td>
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<td>Washed O</td>
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</tr>
<tr>
<td>AB</td>
<td>B</td>
<td>Washed B</td>
<td>Washed B</td>
<td>AB</td>
</tr>
</tbody>
</table>

Platelet Transfusion:
Minor ABO Mismatch and Hemolysis

- **Possible Preventive Measures**
  - Avoid ABO-mismatched platelet transfusions
    - Limited general platelet supply
    - Limited B and AB products
  - Avoid transfusing group O platelets to non-group O recipients
    - Limited platelet supply
    - Group O donors are prevalent and encouraged to donate

Platelet Transfusion:
Minor ABO Mismatch and Hemolysis

- **Possible Preventive Measures**
  - Avoid transfusing ABO-mismatched platelet transfusions to children and neonates
    - Limited platelet supply
  - Volume-reduce ABO-mismatched platelets
    - Loss of some platelets in processing
    - Delay in platelet transfusion
  - Screen group O donors/products for high titer anti-A
    - "Critical" titer difficult to define
    - Increased fiscal cost
    - Requires time and technical resources
Platelet Transfusion: Minor ABO Mismatch and Hemolysis

- Screen group O donors/products for high titer anti-A
  - "Critical" titer difficult to define
  - Increased fiscal cost
  - Requires time and technical resources

- Pre-pooled RDPs
  - Potential to improve platelet supply
  - Increase supply from group A whole blood donors
  - Dilutes a "high titer" unit among 5-6 other units
  - Exposes to multiple donors (HLA alloimmunization)

Summary

- Minor ABO mismatched platelet transfusion can result in severe hemolytic reactions

- High-titer group O SDP products appear to be of greatest risk

- Consider vulnerable populations
  - Children and neonates
  - Stem cell transplant patients
Summary

- Prevention strategies include:
  - Avoid transfusing group O platelets to non-group O recipients, if possible
  - Volume reduce group O platelets designated for non-group O recipients
  - Titer group O units and avoid transfusing those with high titer
  - Increase awareness about group O platelets and HTR
- Pre-pooled RDPs