Transfusion Related Acute Lung Injury (TRALI)

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Outline

• Case Presentation
• Criteria for Diagnosis
• Epidemiology
• Pathogenesis
• Management & Prognosis
• Summary
50 year old man with Marfan syndrome and valvular cardiomyopathy

Admitted for orthotopic heart transplantation (OHT)

Blood type: AB negative

Multiple transfusions in the past for multiple surgical procedures
Event

- INR 2.9 -- Surgical team requested 2 (to 4) units of FFP
- 1 unit of FFP issued
- 1 hr 15 mins (275 mL volume transfused):
  - Feeling badly and shivering – transfusion stopped

- Pre-transfusion: T 36.3 C, BP 125/72, pulse 64, RR 18
- Post-transfusion: T 35.8 C, BP 166/79, pulse 76, RR 18
Event

- Benadryl and Tylenol given
- Patient reported shortness of breath $\rightarrow$ 87% O2 sat room air
- Placed on 4L of oxygen on nasal cannula $\rightarrow$ 96% O2 sat NC $\rightarrow$ later placed on BiPap
- Patient looked anxious and continued to have shortness of breath
- Repeated administration of Lasix iv $\rightarrow$ no improvement
Event

- Blood Bank notified of reaction 6 hours afterwards (work-up)
  - Clerical check – pass
  - Visual hemolysis check – pass
  - DAT – negative

- Patient brought to OR for transplant but given the continued hypoxemia → procedure discontinued

- CXR ordered
CXR$_s$

PRE-TRANSFUSION

POST-TRANSFUSION
Taken together...

- Acute onset (<6 hours post-transfusion)
- Hypertension
- Shortness of breath
- Hypoxemia
- Post-transfusion CXR findings
- Lack of response to repeated diuretic administration

TRALI
Diagnosis & Epidemiology
Criteria for Diagnosis of TRALI

- A. Acute lung injury (ALI)
  - I. Acute onset
  - II. Hypoxemia
    - PaO2/FiO2 ≤ 300, or SpO2 < 90% RA or other clinical e/o hypoxemia
  - III. Bilateral infiltrates on frontal CXR
  - IV. No e/o left atrial hypertension (i.e. circulatory overload)
- B. No preexisting ALI before transfusion
- C. During or within 6 hours of transfusion
- D. No temporal relationship to an alternative risk factor for ALI

Kleinman et al. Transfusion 2004;44:1774-89.
Learning Points:
1. Clinicians don’t recognize cases as potential TRALI → usually no BB transfusion work-up initiated
2. Respiratory symptoms are mild → no CXR performed
3. Cases may not fit strict definition of TRALI (may underestimate TRALI incidence)
4. Transfusions were not indicated

Davis et al. Transfusion 2008;48:541-545.
TRALI – Femme Fatale?

- Incidence 1:3300 to 1:7900 in U.K. and U.S.
- #1 cause of transfusion mortality in U.S.
- Current mortality rates vary ~5-10%

- Blood products w/ large amounts of plasma
- Female donor
- Female donor with at least 1 pregnancy

Popovskv M, Davenport RD. Transfusion 2002;41:312-315.
### TRALI: Leading Cause of Transfusion-related Fatalities by Complications, FY2005-2010

<table>
<thead>
<tr>
<th></th>
<th>Number of Fatalities</th>
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<tbody>
<tr>
<td>TRALI</td>
<td>FY05: 29 FY06: 35 FY07: 34 FY08: 16 FY09: 13 FY10: 18</td>
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<tr>
<td>HTR (non-ABO)</td>
<td>FY05: 16 FY06: 9 FY07: 2 FY08: 7 FY09: 8 FY10: 5</td>
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<tr>
<td>HTR (ABO)</td>
<td>FY05: 6 FY06: 3 FY07: 3 FY08: 10 FY09: 4 FY10: 2</td>
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<tr>
<td>Microbial Infection</td>
<td>FY05: 8 FY06: 7 FY07: 6 FY08: 7 FY09: 5 FY10: 2</td>
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<tr>
<td>TACO</td>
<td>FY05: 1 FY06: 8 FY07: 5 FY08: 3 FY09: 12 FY10: 8</td>
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<tr>
<td>Anaphylaxis</td>
<td>FY05: 0 FY06: 1 FY07: 2 FY08: 3 FY09: 1 FY10: 4</td>
</tr>
<tr>
<td>Other</td>
<td>FY05: 2 FY06: 0 FY07: 0 FY08: 0 FY09: 1 FY10: 1</td>
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Reports of TRALI Cases by Implicated Blood Products, FY2005-2010

<table>
<thead>
<tr>
<th>Blood Product</th>
<th>FY05</th>
<th>FY06</th>
<th>FY07</th>
<th>FY08</th>
<th>FY09</th>
<th>FY10</th>
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<tr>
<td>FFP</td>
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<td>22</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td>4</td>
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<tr>
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<td>5</td>
<td>12</td>
<td>5</td>
<td>6</td>
<td>8</td>
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<tr>
<td>Plasma</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Platelets Pheresis</td>
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<td>2</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Pooled Platelets</td>
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<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Multiple Products</td>
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<td>5</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
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Red Cross estimated risk of fatal TRALI per component:

- Plasma: 1:202,673
- Apheresis platelets: 1:320,572
- RBCs: 1:2,527,437

Leading theories

- Anti-neutrophil antibodies:
  - Antibodies in donor plasma react with antigens on recipient’s neutrophils → initiate inflammatory response in lung microvasculature (less commonly recipient plasma reacts to donor granulocytes)

- Neutrophil priming:
  - Lipids and cytokines contained in transfusions have ability to prime the activity of neutrophils → increased vessel permeability

- Two-event hypothesis (composite theory):
  - Recipient neutrophils are primed (by transfused active substances or by patient’s underlying illness)
  - Transfused antibodies then “activate” hyperactive neutrophils
Neutrophil activation and extravasation

Direct antibody-mediated TRALI

Supportive studies:

- 65-90% of TRALI cases → implicated donors have leukocyte Abs (HLA & HNA Ab)
- Incidence of Ab increase with # of pregnancies

TRALI lookback studies:

- 103 recipients of donor w/ multiple HLA class I & II Abs → only 1 TRALI case, even though 54/55 patients had cognate antigens
- TTP pt developed TRALI after RBC transfusion from a donor w/ multiple anti-neutrophil Abs → 0/21 previous donations resulted in txf reaction
“Two-hit” hypothesis (composite theory): TRALI mouse model w/ cognate antigens

- TRALI induced with both LPS + MHC Ab, but not with LPS or MHC Ab alone

Data not shown:
- Mice in pathogen-free barrier room + MHC Ab = no TRALI
- Introduce mice to LPS (pathogen) + MHC Ab = TRALI

Proposed factors influencing clinical severity

Host genetic susceptibility
- C3 regulation
- Antigen expression on vessels & WBCs
- Cytokine responsiveness

Clinical comorbidities
- Impaired hemostasis
- LVEDP
- Pulm infxn
- Preexisting hypoxia
- Capillary leak

Mild

Moderate to severe

FATAL

Donor factors inducing TRALI
- Antibody titer, subclass, affinity, specificity, dose, rate of infusion

Davis et al. Transfusion 2008;48:541-545.
Management & Prognosis

- Prompt response is necessary to quarantine units and avoid additional patient exposure to donor

- Supportive ventilatory therapy
  - Mechanical ventilation, supplemental oxygen

- Usually resolves in ~72 hours

- Can receive additional blood products in the future

- Spectrum from mild to severe

- Can lead to death in ~5-10% of cases
Prevention

- Avoid unnecessary transfusions
- Produce FFP only from male donors
- Screen previously pregnant and previously transfused apheresis donors for HLA antibodies
- Exclude donors with high HLA antibody titers
TRALI Summary

• TRALI should be considered whenever shortness of breath, hypoxemia, pulmonary infiltrates, within six hours of transfusion

• Typically occurs with blood products with high plasma volume & from donors with anti-leukocyte antibodies (i.e. multiparous women)

• Leading cause of transfusion-related mortality

• Two-hit hypothesis:
  • #1 Recipient neutrophils are primed
  • #2 Preformed anti-leukocyte antibodies in donor product “activate” hyperactive neutrophils

• Management of patients: supportive therapy

• Minimizing use of plasma and platelet products from donors with leukocyte antibodies can decrease incidence of TRALI


Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies.


HLA antigen type (pt E.S.)

**MHC Class I**
- HLA-A Loci IR1-2
- HLA-A Loci IR1-29
- HLA-B Loci IR1-44
- HLA-B Loci IR2-44
- HLA-BW Loci IR1-4
- HLA-BW Loci IR2-4

**MHC Class II**
- HLA-DRB1 Loci IR1-4
- HLA-DRB1 Loci IR2-7
- HLA-DQB1 Loci IR1-2
- HLA-DQB1 Loci IR2-7
- HLA-DRB4 Loci IR1-53
- HLA-DRB4 Loci IR2-53