THROMBOCYTOPENIA IN THE ICU

MAZYAR SHADMAN

FACULTY DISCUSSANT: TERRY GERNSHEIMER, M.D.

Hematology Fellows Conference
August 10th, 2012
34 year-old female; 36 weeks pregnant

Presentation to the OSH with:

- Abdominal Pain
- Nausea and Vomiting
- WBC 14.0, HCT 32%, PLT 211,000
- Hemolysis labs: LDH 220, ?
- PT 28, PTT 50, Fibrinogen ?
- Elevated LFTs (AST 330; ALT 190, ALK 200)
- GFR 55% (baseline normal)

Concerning for HELLP => Cesarean Section => Hypotension => Intubation => transfer to the UWMC
DAY 1

- WBC 32,000; HCT 32% => 28%, PLT: 211,000 => 81,000
- GFR 17 (baseline normal)
- LFTs in 400s
- Hemolysis: Haptoglobin 45, LDH 250, Retic 3%, DAT neg
- Febrile, Intubated, on pressors

Hematology consult

- ? TTP/HUS or HELLP vs. Medications vs. DIC vs. Sepsis
- No fragments
- PT 29, PTT 57, Fibrinogen 42

Recommendations:
- Factor replacement
- Treat infection
- ? Retained pregnancy products/placenta
Day 7

- Taken off the consult list 😊
- Page from SICU re: Ms. MJ 😞
- PLT 75,000 => 4,000 !!!
- WBC 25,000, HCT 31%
- Renal and Hepatic functions improving

- ? DIC (normal PT and PTT, Fibrinogen 440)
- ? PTP (HPA-1a negative)
- ?? HIT (low clinical probability, negative PF-4)
- ?TTP/HUS/HELLP (no fragments)
- ?Infection/sepsis: Toxic granulations, Döhle bodies
- ?Immune thrombocytopenia (why now?)
- ?Drugs

Recommendations:
- Treat the infection
- Transfuse for PLT goal of 10,000
DAY 8

- Response to transfusion: 4,000 => 10,000 => 7,000
- Hemolysis labs: Haptoglobin 45, DAT weakly positive, LDH 300, Retic :3%

- Immune thrombocytopenia/Hemolytic Anemia
  - Active infection => no steroid
  - Renal and Hepatic issues - ? IVIG
  - IVIG 500 mg/kg x2
  - Plt 7,000 => 69,000 => 248,000 (in 7 days)
  - ...
  - Still on the list 😊
DAY 16

- Platelet count: 248,000 => 29,000
  - No RBC fragments
  - No DIC
  - Hemolytic anemia -- ? Evan’s syndrome
  - Infected wound

- Repeat IVIG 500 mg/kg x 2 doses
- Platelet count: 29,000 => 143,000 => 278,000

- Discharged home on day 19
PREGNANCY-ASSOCIATED THROMBOCYTOPENIA

- **Isolated**
  - Incidental (Gestational)
  - Immune (ITP)
  - Drug-induced
    - HIT
  - Congenital
  - Type IIb vWD

- **Systemic Disorders**
  - Preeclampsia
  - HELLP syndrome
  - Thrombotic microangiopathies
    - TTP, HUS
  - Acute fatty liver
  - SLE / Antiphospholipid antibodies
  - DIC
  - Viral infection (HIV, EBV, CMV)
  - Nutritional deficiencies
  - Hypersplenism
  - Bone marrow dysfunction
CAUSES OF MATERNAL THROMBOCYTOPENIA

- Hypertensive: 74%
- Incidental: 21%
- Immune: 4%
- Other: 1%

Burrows et al, NEJM, 1993
PLATELET COUNT AND ETIOLOGY

Platelet Count <150 X10⁹/L (n=262)
- 81% gestational
- 16% preeclampsia
- 3% ITP

Platelet Count <123 X10⁹/L (n=96)
- 33% gestational
- 29% preeclampsia
- 38% ITP

Platelet Count <100 X10⁹/L (n=23)
- 46% gestational
- 27% preeclampsia
- 27% ITP

Platelet Count <70 X10⁹/L (n=8)
- 38% gestational
- 37% preeclampsia
- 25% ITP

DRUG-INDUCED THROMBOCYTOPENIA (DITP)
DRUG-INDUCED THROMBOCYTOPENIA (DITP)

- Idiosyncratic immune-mediated

- Antibodies bind firmly to specific epitopes on platelet surface glycoproteins only in the presence of the sensitizing drug

- GP IIb-IIIa and/or GP Ib-V-IX

- Typically occur after exposure to a new drug for 1 to 2 weeks

George, et al. Hematology, 2009
# DRUG-INDUCED THROMBOCYTOPENIA (DITP)

<table>
<thead>
<tr>
<th>Drug (brand name)</th>
<th>Number of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Definite evidence</td>
</tr>
<tr>
<td>Abciximab (ReoPro)</td>
<td>6</td>
</tr>
<tr>
<td>Acetaminophen (Tylenol, Panadol, and others)</td>
<td>3</td>
</tr>
<tr>
<td>Carbamezapine (Tegretol)</td>
<td>0</td>
</tr>
<tr>
<td>Chlorpropamide (Diabinese)</td>
<td>0</td>
</tr>
<tr>
<td>Cimetidine (Tagamet)</td>
<td>1</td>
</tr>
<tr>
<td>Danazol (Danocrine)</td>
<td>3</td>
</tr>
<tr>
<td>Diclofenac (Cataflam and Voltaren)</td>
<td>2</td>
</tr>
<tr>
<td>Efluzumab (Raptiva)</td>
<td>0</td>
</tr>
<tr>
<td>Eptifibatide (Integrilin)</td>
<td>2</td>
</tr>
<tr>
<td>Gold (Ridaura, Solganal, and others)</td>
<td>0</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>(Aquazide-H, Esicrix, and others)</td>
<td>0</td>
</tr>
<tr>
<td>Interferon-α (Roferon-A and Intron A)</td>
<td>1</td>
</tr>
<tr>
<td>Methyldopa (Aldomet)</td>
<td>3</td>
</tr>
<tr>
<td>Nalidixic Acid (NegGram)</td>
<td>1</td>
</tr>
<tr>
<td>Quinidine (Quinaglut, Cardioquin, and others)</td>
<td>26</td>
</tr>
<tr>
<td>Quinine (Quinamm, Quindan, and others)</td>
<td>14</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>0</td>
</tr>
<tr>
<td>Rifampin (Rifadin, Rimactane)</td>
<td>5</td>
</tr>
<tr>
<td>Tirofiban (Aggrastat)</td>
<td>2</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>(Bactrim, Septra, and others)</td>
<td>3</td>
</tr>
<tr>
<td>Vancomycin (Vancoled)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Data from www.ouhsc.edu/platelets. Drugs were selected for this table because they had 5 or more published reports of individual patient data or group data with definite or probable evidence for a causal relation to thrombocytopenia.*

George, et al. Hematology, 2009
Vancomycin-Dependent Antibodies Associated with Thrombocytopenia and Refractoriness to Platelet Transfusion in Patients with Leukemia

By Douglas J. Christie, Nancy van Buren, Shari S. Lennon, and Janice L. Putnam

Two patients with leukemia experienced profound thrombocytopenia and refractoriness to platelet transfusion during vancomycin treatment. In one patient, withdrawal of drug and administration of platelet transfusions restored platelet counts to near normal levels (~100 x 10⁹/L), however, subsequent challenge with vancomycin due to recurring infection again precipitated severe thrombocytopenia (platelets <10 x 10⁹/L) and life-threatening hemorrhagic symptoms. Potent vancomycin-dependent antiplatelet antibodies were detected in the serum of both patients during the refractory period using staphylococcal protein A rosette formation. Employing a monoclonal antibody-antigen capture enzyme-linked immunosorbent assay (ELISA), the patients were found to have vancomycin-dependent IgG antibodies that bound specifically to platelet glycoproteins (GP) IIb and/or IIIa. One of these antibodies failed to react with platelets deficient in GPIIb/IIIa obtained from an individual with Glanzmann’s thrombasthenia. These findings provide the first major evidence for drug-dependent antibodies in association with severe thrombocytopenia and refractoriness to platelet transfusion in alloimmunized leukemia patients and, further, provide the first demonstration of vancomycin-dependent antibodies reactive with platelets. © 1990 by The American Society of Hematology.
Christie et al., Blood, 1990
## STAPHYLOCOCCAL PROTEIN A ROSETTE ASSAY

- Semi-quantification of the percentage surface area of each protein A bead coated with adherent platelets
- Rosette score

### Detection of Vancomycin-Dependent Antibodies by Protein A Rosette Formation

<table>
<thead>
<tr>
<th>Patient</th>
<th>+ Vancomycin</th>
<th>+ PBS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KW</td>
<td>39 ± 6</td>
<td>4 ± 3</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>DA</td>
<td>61 ± 6</td>
<td>29 ± 7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>DA*</td>
<td>40 ± 3</td>
<td>11 ± 7</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Control†</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Monoclonal Antibody-Specific Immobilization of Platelet (MAIPA)

Fig 2. Identification of platelet binding site(s) for the vancomycin-dependent antibodies from DA(A) and KW(B) as determined by MAIPA assay. Experiments were performed with normal platelets and monoclonal antibodies directed against the following platelet glycoproteins: GP Ib (6D1), GP Ix (FMC25), GP IIla (AP3), and GP IIlb (10E5). Final concentration of vancomycin was 300 μmol/L. Significant positive reactions were only observed with 10E5 and AP3, indicating that the binding sites for the vancomycin-dependent antibodies reside on GP IIlb and/or GP IIla.
Rosette Formation

<table>
<thead>
<tr>
<th>Platelets</th>
<th>KW Serum</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ Vancomycin</td>
<td>+ PBS</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Normal</td>
<td>66 ± 2</td>
<td>12 ± 11</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Glanzmann’s thrombasthenic</td>
<td>43 ± 10</td>
<td>47 ± 10</td>
<td>&gt;.65†</td>
</tr>
<tr>
<td></td>
<td>(12 ± 8)*</td>
<td>(15 ± 11)*</td>
<td></td>
</tr>
</tbody>
</table>
Vancomycin-Induced Immune Thrombocytopenia


- 2001-2005
- BloodCenter of Wisconsin
- Vancomycin-induced thrombocytopenia
- Clinical data from primary physicians

Von Drygalski, et al. NEJM, 2007
METHODOLOGY:

- Patient samples ± Vancomycin 0.3 mg/ml
- Fluorescein-labeled anti-immunoglobulin reagent
- Positive if fluorescence intensity was at least twice compared to controls
RESULTS

- Positive in 39 patients (20% of the samples)

- type I Glanzmann’s thrombasthenia platelet
  - 12/22: no reaction
  - 6/22: weaker reaction
  - 4/22: equally strong reaction

- Other antigens are also involved

Von Drygalski, et al. NEJM, 2007
Von Drygalski, et al. NEJM, 2007
1 of 451 normal subjects had positive antibody
Von Drygalski, et al. NEJM, 2007
- Prior exposure => Earlier drop
- Renal Failure => Longer count recovery

Von Drygalski, et al. NEJM, 2007
COMPLICATIONS

- **Severe bleeding** 10
  - GI bleeding 2
  - Gross hematuria 1
  - Bleeding from IV sites 2
  - Intrapulmonary Hemorrhage 2
  - Mucosal/skin bleeding 3

- **Petechiae/Purpura** 10

- **No bleeding** 9

- **Mortality=> ?**
  - 3 patients, platelet <10,000, 2 with IPH, ? Contribution

Von Drygalski, et al. NEJM, 2007
## TREATMENTS

<table>
<thead>
<tr>
<th>Treatment</th>
<th># received treatment</th>
<th># responded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Transfusion</td>
<td>14</td>
<td>0/11 ; 3 unknown</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>IVIG</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Plasma Exchange</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anti-Rh immune globulin</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Von Drygalski, et al. NEJM, 2007
STUDY SUMMARY:

- It is real!
- Bleeding occurs more than other DITPs
- Antibodies can persist for months
- Drop after a single dose is possible (1/451)
- ? Incidence

Von Drygalski, et al. NEJM, 2007
ANAMNESTIC RESPONSE:

- 61 year-old male
- Lower extremity wet gangrene

Kenney, et al., Platelets, 2008
PRE VS. POST

Kenney, et al., Platelets, 2008

Table I. Serologic assessment for drug-dependent platelet antibodies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pre-exposure</th>
<th>Post-exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- ? Titers
- ? Antibodies after discontinuation
- ? Role of IgM
- ? Prior exposure vs. naturally occurring
OUR PATIENT ...

[ PATIENT'S SERUM WITHOUT DRUG: IgG: POSITIVE, IgM: Negative].

[ PATIENT'S SERUM WITH DRUG (Vancomycin): IgG: POSITIVE, IgM: Negative].

Positive reactions detected by flow cytometry in the absence of drug which were potentiated in the presence of vancomycin. These results indicate the presence of vancomycin-dependent and non-drug dependent platelet-reactive antibodies.

These results support a diagnosis of Vancomycin-Induced Immune Thrombocytopenia.
5 TAKE HOME POINTS:
THANKS TO:

- Dr. Terry Gernsheimer
- Dr. Tony Blau
- Dr. Roland Walter