Thrombotic Microangiopathies

ASH/San Antonio Breast Cancer Symposium Review

James N. George
March 14, 2015
Thrombotic Microangiopathies (TMA): Everything you need to know from 5 patient stories

- Thrombotic thrombocytopenic purpura (TTP)
  - Role of ADAMTS13 measurements
  - Role of rituximab
  - Risk of pregnancy
  - Role of bone marrow biopsy

- Drug-induced TMA
  - Don’t miss the diagnosis!
Patient 1 (2001)

• 20 yo previously healthy BF, BMI 41
  • Uncomplicated first pregnancy, C-section
  • 4 days pp: Hct 29, Plt 329
  • 8 days pp: routine post-op. SOB, weak, dark urine, no neurologic signs. Hct 18, Plt 9, Cr 0.8, LDH 2316, red cell fragments

• PEX + steroids: 6 days → Plt 199; stop PEX → 56; resume → 167; stop → 97; resume → 268 (26 PEX, 33 days)
  • ADAMTS13 <10% (+ inhibitor)
Patient 1

- 2003, 2005: uncomplicated pregnancies
- 2004: remission ADAMTS13 100%
- 2006-2014: 8 remission ADAMTS13 measurements, all <10% (+ inhibitor); no symptoms, normal CBC
- 2015: She has remained normal since recovery from her initial TTP episode
Patient 1: Lessons

- Typical demographic features, typical presentation, typical clinical course
- Rituximab can (almost always) prevent prolonged requirement for PEX
- Subsequent pregnancies usually without complications, and without relapse
- Clinical importance of severe ADAMTS13 deficiency during remission is unknown
Patient 2 (1998)

- 41 yo previously healthy BM
  - 3 days of abdominal pain, nausea, vomiting, diarrhea, weakness. Transient aphasia and numbness of his left face and arm.
  - Hct 19, Plt 7, Cr 1.2, LDH 1946, red cell fragments
- Recovered with 6 PEX, no corticosteroids
- HIV positive
**Patient 2**

<table>
<thead>
<tr>
<th>Episode</th>
<th>ADAMTS13 Activity</th>
<th>ADAMTS13 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IB</td>
<td>FRETS</td>
</tr>
<tr>
<td>1 (1998)</td>
<td>60 %</td>
<td>53 %</td>
</tr>
<tr>
<td>2 (2000)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 (2000)</td>
<td>50 %</td>
<td>15 %</td>
</tr>
<tr>
<td>4 (2001)</td>
<td>6 %</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>5 (2003)</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>6 (2008)</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

*Haematologica 2012; 97: 297*
Patient 2: Lessons

- Normal ADAMTS13 activity does not exclude the diagnosis of TTP
- Diagnosis of TTP and initiation of PEX are clinical decisions (This is not oncology, where diagnosis and treatment require pathology)
Patient 3 (2008)

- 55 yo previously healthy WF
  - 3 days of chest pain, dyspnea, then right-side weakness, aphasia
  - Hct 33, Plt 33, Cr 1.6, LDH 1084, red cell fragments, neg DAT, normal coagulation tests
  - EKG, chemistries: MI; MRI: left MCA infarct, multiple cerebellar infarcts; TEE: aortic valve vegetation and regurgitation
  - Blood cultures: Enterococcus
Patient 3

- Diagnoses: Bacterial endocarditis (+ TTP)
- Treatment: Antibiotics, PEX, steroids
- Recovery to normal Plt, Cr, and LDH
- 3 months later: aortic valve replacement
## Patient 3

<table>
<thead>
<tr>
<th>Assay</th>
<th>ADAMTS13 Activity</th>
<th>ADAMTS13 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IB</td>
<td>FRETS</td>
</tr>
<tr>
<td>Before PEX</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2009</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>2010</td>
<td>50%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Patient 3: Lesson

- Severe ADAMTS13 deficiency supports (but does not confirm) the diagnosis of TTP or exclude alternative diagnoses

- 52 yo woman, sudden abdominal pain and syncope, suspected cholecystitis
- 3 years previously: breast cancer, + axillary nodes, chemotherapy
- Hct 25, Plt 17, Cr 1.0, bilirubin 5.5 (direct, 1.6), LDH 1431, red cell fragments, INR/PTT 1.2/23, Fibrinogen 424, DAT neg. Chest x-ray, abdomen ultrasound, chest/abdomen CT: normal
Patient 4

- **PEX**: no response over 3 days
- Day 3: Severe tachypnea, hypoxemia, bilateral pulmonary emboli
- Day 4: died
- Autopsy:
  - No cause of death apparent
  - No pulmonary thromboembolism
- Diagnosis: TTP
Patient 4

- Autopsy microscopic report:
  - Hyaline thrombi in brain, lungs, kidney
  - Microscopic metastatic carcinoma in brain, lungs, kidneys, heart, liver, esophagus, adrenals, thyroid, spleen, marrow
Brain: Metastatic Carcinoma
Lung: Hyaline Thrombus
Lung: Metastatic Carcinoma
Patient 4: Lessons

• Systemic malignancies can mimic all clinical features of TTP

• Consider a bone marrow biopsy in puzzling patients with atypical features (e.g., pulmonary symptoms, bone pain) – especially patients with a history of malignancy
Patient 5 (2009)

- 35 yo previously healthy WF
  - Sudden onset of nausea, vomiting, diarrhea, chills, fever, abdominal and back pain
  - ER (Day 2): Hct 39, Plt 132, no chemistries, IV hydration, antiemetics
  - ER (Day 4): Symptoms, except back pain, improved but continued anuria
  - Hct 30, Plt 42, Cr 10.7, LDH 2402, AST/ALT 350/274, red cell fragments
Patient 5

Additional history

• Vodka and tonic at an employee recognition party about 1-2 hours preceding symptoms (“I only had a little sip…..”)

• Previous tonic water exposure 15 months before: sudden onset of severe headache, nausea, vomiting, chills, fever

• ER: ? Meningitis; LP, CT head normal. Hct 35%, Plt 257, Cr 1.7 (subsequently 0.7)
Patient 5

- Stop PEX after 13 days: Plt 150, Hct 27, Cr 7.9, LDH 370
- Quinine-dependent antibodies reactive with platelets and neutrophils
- ADAMTS13 100%
- Hemodialysis continued for 2 months
- 2014: Cr 1.25, eGFR 54, hypertension
Flow Cytometry Detection of Drug-Dependent Antibodies

A. Normal serum/Normal platelets
B. Patient serum/Normal platelets
C. Normal serum/Drug/Normal platelets
D. Patient serum/Drug/Normal platelets
Patient 5: Lesson

• Do NOT miss the diagnosis of quinine-induced TMA!