Atypical HUS?

Case Presentation – HMC
Erin Currin
Case Presentation

**Presentation:** 66 yo woman, 1-2 wk nausea, vomiting, weight gain, low urine output, brown urine, epistaxis

**PMH:** DM2, HTN, HLD, gout, Asthma

**Family History:** Brother req kidney transplant, not known why

**Meds:** Glimepiride, Metformin, Amlodipine, Simvastatin, Allopurinol

**Physical Exam**

Wt 88.5 kg, T 36.5 HR 98 RR 16 O2 Sat 98% Room Air

**Skin:** Abdominal ecchymosis below umbilicus

**GI:** liver and spleen edge not palpable, moderate ascites

**CN:** CN 2-12 intact, strength symmetric and 5/5
Basic Labs *Day 1*

UA
2+ protein
3+ occult blood
1+ WBC
3+ RBC

AST 89
ALT 43
Alk Phos 117
T bili 0.9
Albumin 2.7

PT 15.8
PTT 41
INR 1.3
CK 1652
Case Day 1-2

• Admit MICU

• Renal Consult: oliguric renal failure
  • ATN, pre-renal?, Glomerulonephritis
  • Medications– recently started on Bactrim
  • NS given, minimal improvement

• Abdominal US
  • Kidneys: normal in size, increased echo texture
  • Liver: small, nodular and course echo texture, sluggish flow
  • Spleen: “normal in size”
### More Labs Day 2

#### Peripheral Smear
- Rare helmet cells and Schistocytes < 1 hpf
- Basophillic stippling
- Essentially nl

- **DIFF:** normal

#### DIC? Hemolysis?
- Fibrinogen 238
- D Dimer 1.84
- LDH 307
- Thrombin Time 20
- ADAMTS-13 protease activity > 100%

#### Iron Studies
- Iron 103
- TIBC 291 R
- Ferritin 130
- Sat 30 %

#### Absolute Reticulocyte count
- 62

#### Reticulocyte count
- 2.2

#### Haptoglobin
- 27

#### DAT Coombs negative

#### MCV
- 84
Clinical Course *Day 2-4*

- Not responding to fluids
- Heparin SQ Days 1-4
- Steroids Solu-Medrol 500 mg IV x 3 days
- Dialysis started
- Plan for renal biopsy
More Labs *Day 4*

HIV negative
EBV negative
Hepatitis A neg
Hepatitis B
Hepatitis C neg
CMV 37 IU/ml

Ceruloplasmin neg
AMA neg
Anti SMA neg
RF neg
B12 normal
Folate normal

Anti-Cardiolipin IgM < 9
Anti-Cardiolipin IgA <9
Anti Cardiolipin IgG 13
Anti Beta 2 glycoprotein IgM <1
Anti Beta 2 glycoprotein IgG 14
Lupus Inhibitor negative
Complement C3 <10L
Complement C4 6L

SPEP hypogammaglobulinemia polyclonal
UPEP negative
Clinical Course *Day 5*

Day 5: plts 69K, hct 26% = Heme Consult

**Anemia:**
- hypoproliferation, renal insufficiency, low epo
- Not thought to be hemolysis
- Lead

**Thrombocytopenia**
- HIT
- Drug Related: statin, bactrim?
Clinical Course Day 6-14

Day 6: plt30K, renal biopsy cancelled
- Renal team: low complement, low plt
  - Atypical HUS?
  - Antibody to Complement Factor H
- Day 7: plasmapheresis started x 5 doses
- No biopsy until r/o marrow process
  AND platelets > 70K without transfusion

- Day 10: platelets 10K
  - no improvement with plasmapheresis

- Day 14 Bone marrow biopsy
Bone Marrow Aspirate 40x
Bone Marrow Aspirate 20x
Bone Marrow Biopsy
Clinical Course: *Day 15 - death*

**Day 15:** Eculizumab approved
- Transient improvement: Plt 115K, then to 14K

**Day 21:** 2\(^{nd}\) dose Eculizumab
- Hypotensive
- Low fibrinogen (89), D-Dimer 9.6, INR 2.0, PTT 38 PT 22.5
- Transferred to MICU
- CT scan concerning for intra abdominal abscess

**Day 24:** not a surgical candidate
- Died of sepsis/fungemia
aHUS
Diagnosis and Work Up
aHUS Diagnosis

• Key Clinical Features
  – Thrombotic Microangiopathy (TMA)
  – Thrombocytopenia
  – Renal Failure
  – Progression to multi organ failure
    • Cardiac Failure
    • Severe HTN
    • Neurologic impairment

• Labs:
  – Low C3, normal C4
  – Genetic testing

Sadler et al, Blood, 4 June 2015; Gavrifilaki et al, Blood 4 June 2015
Diagnostic Challenge

• Diagnosis of Exclusion
  – Typical HUS: Shiga toxin producing *E.Coli*
    • Less commonly *Shigella dysenteriae type 1*
  – TTP
    • ADAMTS -13 < 5%-10% (severe)
    • More prominent neurologic disease than aHUS

• Diagnostic Challenge
  – ADAMTS -13 can also be low in aHUS
  – Complement is not always low in aHUS
  – *NO RELIABLE TEST!*
ADAMTS-13 to differentiate?

Reported rates of severely deficient ADAMTS13 activity in patients clinically diagnosed with aHUS or TTP across different studies.

<table>
<thead>
<tr>
<th>Clinical categorization</th>
<th>Number of patients</th>
<th>Patients with severe ADAMTS13 deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHUS/TTP</td>
<td></td>
</tr>
<tr>
<td>Veyradier et al. [2]</td>
<td>45/66</td>
<td>13%</td>
</tr>
<tr>
<td>Remuzzi et al. [23]</td>
<td>9/12</td>
<td>55%</td>
</tr>
<tr>
<td>Tsai et al. [3,4]</td>
<td>NA/127</td>
<td>NA</td>
</tr>
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<td></td>
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<td></td>
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<td>TTP</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veyradier et al. [2]</td>
<td></td>
<td>89%</td>
</tr>
<tr>
<td>Remuzzi et al. [23]</td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>Tsai et al. [3,4]</td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Cataland et al, Eur Journal Internal Medicine, 2013
Differential Diagnosis aHUS

Other etiologies to consider:

- DIC
- Scleroderma associated renal crisis
- Drugs
- Malignancy
- APL antibody syndrome
- HIV
- SLE
Pathophysiology aHUS

• Activation Alternative Pathway of Complement
  – Complement deposition on renal vasculature
  – Low C3 and/or C4
• ~70 % inherited or genetic defect
  – Genes encoding for complement regulators
    • Factor H (20-30%), Factor I, CD46 (MCP)
    • Thrombomodulin gene
  – Genes encoding for complement activators
    • C3, Factor B
• Acquired
  • Antibody to Factor H (10%)

1 Frimat et al, Blood, 2013 122(2)
2 Loirat et al, Semin Thromb Hemostat, 2010
Complement Pathways
Complement C5a, C5b-C9

• Retrospective analysis
  – 19 pts with aHUS (plt <100K, A13 >10%, Cr >2.25)
  – 38 pts TTP (A13 < 10%)

• Complement levels
  – C3a, C5a, C5b-9 higher levels in aHUS than TTP

• However
  – Reti et al, Wu et al
  – Complement C3a, C5b-C9 elevated in TTP

Cataland et al, Blood June 2014
Treatment
Plasma Exchange (PEX)

• Standard of care prior to Eculizumab
• Initiate when TMA suspected
  – Sort out aHUS vs. TTP later
• Plasma Exchange in aHUS
  – Removes mutant complement and Antibodies to complement
    • Brings in new CFH, CFI, CFB, C3

Cataland et al, European Journal Internal Medicine 2013
Outcomes of PEX in aHUS

- 8% mortality during 1st episode
- May transiently normalize LDH/plt
- Complement dysfunction may persist
  - Ongoing TMA, renal failure despite PEX
  - Within 1yr of PE, >50% pts progress to ESRD
- 65% aHUS patients treated with PEX patients die or develop in 1st year
- ESRD 60-90% graft failure in transplanted kidneys

Loirat et al, Plasmatherapy in Atypical HUS, Semin Thromb Hemost 2010
Caprioli, Genetics of aHUS, Blood 2006
Response to PEX by mutation

• CFH 30%
  – 93% PEX, 67% response
  – 6 kidney transplants, 6 graft failures

• MCP 12%
  – Response 91% in PEX, 100% non PEX
  – 5 kidney transplants, intact grafts (failure 10yrs)

• CFI 4.5%
  – Similar to CFH

Caprioli et al, Blood, 2006
• Terminal Complement inhibitor
  – High affinity to human C5 complement protein
  – Blocks generation pro-inflammatory C5a & C5b-9
  – Approved for PNH

• Case reports suggested efficacy in aHUS
Study Design

• 37 patients, prospective RCT
• > age 12, diagnosis of aHUS
• Divided into 2 trial arms
  – Arm 1: low plt count and renal damage
  – Arm 2: renal damage, plt decrease no more than 25% over 8 weeks during PEX
• Received Eculizumab median 62-64 weeks
Clinical diagnosis of atypical HUS

Trial 1
- Progressing TMA measured by low platelet count (<150x10^9/liter) at screening and a decrease of >25% lower than the average of 3 platelet count measures before the most recent TMA complication
- ≥4 PE/PI sessions in the wk before screening
- Evidence of hemolysis: LDH ≥ULN, haptoglobin <LLN, or schistocytes
- Impaired renal function (creatinine ≥ULN)
- ADAMTS13 activity >5% in plasma, no STEC infection
- No requirement for an identified genetic mutation

17 Patients were screened
17 Were treated

Trial 2
- No platelet count decrease >25% during the 8-wk observation period
- ≥1 PE/PI sessions every 2 wk, but ≤3 times per wk for ≥8 wk
- Evidence of hemolysis: LDH ≥ULN, haptoglobin <LLN, or schistocytes
- Impaired renal function (creatinine ≥ULN)
- ADAMTS13 activity >5% in plasma, no STEC infection
- No requirement for an identified genetic mutation

23 Patients were screened
2 Were ineligible
1 Withdraw consent
20 Were treated
End Points *Legendre et al*

- **Trial 1**
  - Inhibition of complement mediated TMA
    - Indicated by: change in platelet count
- **Trial 2**
  - Event Free Status for 12 weeks
    - No $\downarrow$ > 25% platelets
    - No PEX or infusion
    - No initiation of dialysis
## Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Median Duration</td>
<td>64 weeks</td>
<td>62 weeks</td>
</tr>
<tr>
<td>Mean increase platelet count to week 26</td>
<td>$73 \times 10^9$</td>
<td></td>
</tr>
<tr>
<td>HD discontinued</td>
<td>4/5 patients</td>
<td>NA * no new HD</td>
</tr>
<tr>
<td>TMA Event Free status</td>
<td>88% (15/17) at 26 wks</td>
<td>80% at 26 weeks</td>
</tr>
<tr>
<td></td>
<td>76% (13/17) at 62 wks (secondary end point)</td>
<td>85% at 62 weeks</td>
</tr>
<tr>
<td>Normalization platelets, LDH</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>Improvement QOL</td>
<td>87%</td>
<td>73%</td>
</tr>
</tbody>
</table>
eGFR
Inhibition of Complement
Eculizmab

• Side Effects
• Need for Meningococcal vaccine
• COST!
• Is there any better way to determine who should get this drug?
If giving Eculizumb

• Remember to give VACCINES!

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

• Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.

• Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. (See Serious Meningococcal Infections for additional guidance on the management of the risk of meningococcal infection.)

• Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.
MenB Vaccine

• Use of Seroroup B Meningococcal Vaccine
  – Preliminary approval for patients with complement deficiencies

“Persistent (ie: genetic) deficiencies in the complement pathway (e.g. C3, properdin, Factor D, Factor H or C5-C9)”

MacNeil, Advisory Committee on Immunization practices, 2015 CDC
Novel Assay?

Modified Ham test for atypical hemolytic uremic syndrome

Eleni Gavriilaki,¹ Xuan Yuan,¹ Zhaohui Ye,¹ Alexander J. Ambinder,¹ Satish P. Shanbhag,¹ Michael B. Streiff,¹ Thomas S. Kickler,² Alison R. Moliterno,¹ C. John Sperati,³ and Robert A. Brodsky¹

How to distinguish aHUS from other TMAs?
Modified Ham Test

Low in PNH:
CD 55: regulates C3 convertase
CD 59: prevents C9 into MAC
→ Leads to hemolysis

TF-1 cell:
Engineered to lack CD 55, CD59
Results
Autopsy Results

• Bowel perforation:
  – 2\textsuperscript{nd} part duodenum, colon

• Disseminated CMV
  – Histologically visible and confirmed in epiglottis with ulcer, bilateral lungs, small bowel, large bowel, kidneys

• Disseminated Fungemia

• Cirrhosis

• Evidence of chronic thrombotic microangiopathy
Chronic Renal Microangiopathy
The End