Thrombotic Microangiopathies (TMA) / TTP/HUS/αHUS Pathology & Molecular Genetics

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TMA

• Affects 1-2%/million
• Most commonly involved organs: Kidney, CNS, GI tract
• 3 distinct clinical presentations
• TTP: Typically CNS (stroke-like symptoms) but it can affect primarily the Kidney (AKI)
• Classic HUS: D+ HUS (STEC-HUS)- Kidney (CNS) Atypical HUS - aHUS
Terminology for a systemic disease-multiorgan syndromes

- TTP
- Classic HUS
- Atypical HUS
- TMA: histopathological term
Typical clinical TMA symptoms

- AKI - ↑Scr
- Hemolysis
- ↑LDH
- ↓Platelets
- ↓Haptoglobin
- Schistocytes
- Diarrhea
- Anemia
- HTN
TTP

- Disease predominantly in adults
- Predominant CNS symptoms
- 50% of TTP have kidney involvement
- ADAMTS13 deficiency <5% of normal leading to generation of massive platelet thrombi
- Not all TTP have low ADAMTS13
TTP is due to decreased ADAMTS13 due to autoantibodies

- ADAMTS13 cleaves vWF in small units preventing clot formation
- ADAMPTS deficiency $\rightarrow$ large vWF multimers
- Most cases are acquired: bone marrow transplants, autoimmunity, cancer, drugs (oxymorphone, quinine, acyclovir, estrogens (contraceptives, etc)
- Rare cases are hereditary TTP (Upshaw-Schulman syndrome)
- Current therapy is supportive: Plasmapheresis
Normal Subject

Cleaved unusually large multimers of von Willebrand factor

Patient with Thrombotic Thrombocytopenic Purpura

Adhesion and aggregation of platelets

Uncleaved unusually large multimers of von Willebrand factor

Moake JL, NEJM 2002
Classic HUS

- *E Coli* producing Shiga toxin
- O157:H7 and other variants e.g., O104:H4
- Strep pneumonia
- Food contamination, swimming pools etc
- Symptoms: **Bloody diarrhea**, abdominal pain, confusion, HTN, AKI and hemolysis, ↓platelets
- Diagnosis: PCR and culture based assays for shiga toxin producing *E. coli* from stool or a rectal swab
- Therapy: dialysis, plasmapheresis, transfusions
Atypical HUS is a disease of the alternative complement pathway

- The most common TMA on renal biopsy
- AKI or subclinical onset
- Nephrotic Syndrome
- Hemolysis or thrombocytopenia frequently absent
- Numerous etiologies
The alternative complement pathway is always on as part of innate immunity protecting cells from injury.
Regulation of the alternative complement pathway
Diseases of Alternative complement abnormalities

• Have in common inability to control complement activation
• Includes aHUS
• Includes diseases known by other name (e.g., DDD, C3 glomerulopathy, antiphospholipid s.)
• ALL confer increased risk for thrombosis (TMA)
Alternative Complement pathway diseases

- Autoimmune diseases e.g., Lupus nephritis, antiphospholipid syndrome, rheumatoid arthritis, asthma
- C3 Glomerulopathy
- Dense Deposit Disease, MPGN type I
- Pregnancy related TMA, pre-eclampsia, post-partum, spontaneous fetal loss
- Malignant Hypertension
- Chemotherapy drugs (mitomycin, citarabin, cyclosporin)
- Monoclonal antibody drugs e.g., immune checkpoint inhibitors (CPIs)
- Elicit drugs (cocaine, ecstasy)
- Macular degeneration
Renal TMA = Endothelial Injury characterized by:

- Arteriolar intimal mucoid change/thrombosis
- Bloodless appearance of glomeruli
- Glomerular thrombosis / fibrinoid necrosis
- Mesangiolysis (mesangial matrix dissolution)
- GBM thickening, double contours
- Subendothelial edema and platelet thrombi
Mucoid intimal degeneration
Fibrinoid necrosis and bloodless glomerulus
Glomerular thrombi and segmental double contours
Mesangiolysis
Arteriolar thrombi
Fragmented RBCs in arteriolar walls
Subendothelial edema
Subendothelial arteriolar edema
Subendothelial edema and platelet thrombi

Arrow points to platelet aggregates

Normal GBM

Magnification 1800 x

10 μm
There are 3 ways microthrombi form

- Activation of endothelial cells e.g., Shiga toxin damages microvascular endothelial cells, presumably by pore formation in the cell membrane
- Decrease of inhibitory alternative complement pathway factors which keep complement pathway in check (hereditary, triggers in susceptible individuals)
- Local increase of pro-thrombotic agents
<table>
<thead>
<tr>
<th>Form of Disease</th>
<th>Complement Abnormalities</th>
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</thead>
<tbody>
<tr>
<td>Familial</td>
<td>Mutations in <em>CFH</em>, 40–45%; in <em>CFI</em>, 5–10%; in <em>C3</em>, 8–10%; in <em>MCP</em>, 7–15%; in <em>THBD</em>, 9%; and in <em>CFB</em>, 1–2%.</td>
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<tr>
<td>Sporadic</td>
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<tr>
<td>Idiopathic</td>
<td>Mutations in <em>CFH</em>, 15–20%; in <em>CFI</em>, 3–6%; in <em>C3</em>, 4–6%; in <em>MCP</em>, 6–10%; in <em>THBD</em>, 2%; and in <em>CFB</em>, 2 cases; anti-CFH antibodies: 6–10%</td>
</tr>
<tr>
<td>Pregnancy-associated</td>
<td>Mutations in <em>CFH</em>, 20%; in <em>CFI</em>, 15%</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Mutations in <em>CFH</em>, 10%; in <em>CFI</em>, 20%; and in <em>MCP</em>, 10%</td>
</tr>
<tr>
<td>Drugs</td>
<td>Rare <em>CFH</em> mutations (mostly unknown)</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>Mutations in <em>CFH</em>, 15%; in <em>CFI</em>, 16%</td>
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<tr>
<td>Human immunodeficiency virus infection</td>
<td>Unknown†</td>
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<tr>
<td>Cancer</td>
<td>Unknown†</td>
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</tbody>
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Genetic mutation cannot be identified in 30-50% of TMA

Norris: NEJM 2009
Mutations in ACP inhibitors

- Penetration of hereditary complement dysregulation is ~50%
- Other factors are likely required for aHUS to occur
- Infections and pregnancy itself are triggers (2nd hit)
- Irrespective of heredity early treatment with complement activation inhibitors seems to recover renal function

Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy.
20 year-old pregnant woman (26 weeks) with **nephrotic range** proteinuria. Serum creatinine is 0.7mg/dl, 7 grams proteinuria/24hours, HTN, no hemolysis
Subendothelial edema, closure of capillary loops

Normal glomerulus

Dx: Pregnancy induced TMA
Post-partum TMA

- 24-year-old Caucasian ♀ who delivered a child 5 days before, and now presents with acute renal failure, creatinine was 6.8 mg/dL (baseline of 0.6 mg/dL), proteinuria and clinical suspicion for TTP/HUS.
- The pregnancy was uneventful until 40 1/7 weeks when the patient was found to have mild hypertension and trace proteinuria.
- The delivery was uneventful and the patient was discharged home.
- Five days later, the patient returns with severe weakness, hemoglobin of 2.7 g/dL and platelets of 20,000. The LDH at that time was 2500 and the serum haptoglobin normal.
TMA in pregnancy presents with AKI

- 1:20,000 pregnancies in developed countries
- In developing countries incidence is unacceptably high ---10-15% of all pregnancies----
- This is due to poor care during and after pregnancy
- Septic abortions

George JN Hematology Am Soc Hematol Educ Program. 2015
74 year old woman with CKD4, sCr 2.91mg/dl, subnephrotic proteinuria and microscopic hematuria H/o ovarian cancer treated with multiple drugs 18 months prior to biopsy. Drugs including Gemcitabine and Cisplatin Platelets low normal at the time of the biopsy but known to have dropped recently.
Distinguishing TTP- aHUS clinically

- Is now possible through assays for ADAMTS13 and recognition of its importance in TTP pathogenesis
- Alternative complement pathway components are involved in hereditary or acquired aHUS
- These tests are now becoming increasingly available in diagnostic laboratories in ~48 hours - one week
- PCR and culture based assays for shiga toxin producing *E. coli* must be evaluated from stool or a rectal swab
TMA Diagnosis is a major challenge

1. Document hemolysis
2. Determine organ involvement, Kidney, CNS
3. Test for ADAMPTS13
4. Test for O157:H7 and other variants e.g., O104:H4 (1-2 days)
5. Test for Complement abnormalities (1-2 weeks)
6. A renal biopsy in the right clinical context, and in the absence of typical laboratory values (24 hrs)
7. Current treatment is diagnosis specific: TTP/STEC symptomatic
8. aHUS: complement inhibitors are most effective
Complement activation may occur in all 3 TMA groups.

**aHUS**
- Hereditary
- Amplifying trigger
  - Mal HTN
  - Pregnancy
  - Infection
  - Autoimmunity – SLE
  - Drugs
  - Cancer

**STEC - HUS**
- Shiga toxin

**TTP**
- Severe ADAMPTS 13 Deficiency
Missouri wild flowers: *windflower (bloodroot)*

Disclosure: Dr. Liapis serves on Alexion’s Speakers bureau