A 60 year old woman with altered mental status and thrombotic microangiopathy

Josh Veatch
Previously healthy 60 year old woman

• 2-3 months of fatigue following a URI, transient episodes being “out of it”
• 1/21 presented with transient left sided weakness
• Hct 22%, Plt 141, LDH 573, negative Coombs, normal creatinine
• 2/7 again presented with TIA symptoms, negative extensive brain imaging, normal carotid US, started on prednisone 80mg QD
A second opinion

• Referral for “Coombs negative hemolytic anemia”
More labs

• Creatinine 1.02, Bilirubin 2.5, hct 24, plt 121, retic 16.5%, AST 65, Epo 46, LDH 767
• ADAMTS-13 level >100%
• Fibrinogen 379
TTP/HUS

• Thrombotic Thrombocytopenic Purpura
  – Classic pentad of MAHA, thrombocytopenia, fever, altered mental status, and renal failure
  – Classical- defect in ADAMTS-13, usually respond to plasma exchange

• Hemolytic uremic syndrome- shiga toxin

• “Atypical” HUS – inherited or acquired defects in complement activation
She gets worse

- 2/26 altered mental status, expressive aphasia, intermittent myoclonic jerking
- CT chest, CT head, abdominal ultrasound, transthoracic echo all within normal limits
- EEG with diffuse generalized slowing
- Transfer to UWMC 3/1
She gets worse

- WBC 11.66, Plt 63K, Hct 25
- LDH 923, AST 80, ALT 44, Bili 3.1
- Creatinine 0.85, UA with 1+ protein
- INR 1.1, Fibrinogen 276
- C3 94, C4 15
- Stool cultures negative for pathogens
Plasma exchange does not help

- Patient does not improve in terms of hemolysis and continues to deteriorate with progressive encephalopathy despite 6 plasma exchanges and continued steroids
- Repeat MRI brain unchanged, LP with elevated protein to 80 but otherwise normal, CTA of the aorta normal
- CT pelvis with subtle possible sclerotic lesions
Bone marrow biopsy 3/5
Cancer associated MAHA

- Thrombotic microangiopathy secondary to disseminated cancer
- ER+PR+H2N- lobular breast cancer
Cancer-Related Microangiopathic Hemolytic Anemia
Clinical and Laboratory Features in 168 Reported Cases
Klaus Lechner, MD, and Hanna Lena Obermeier
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- 81% (90/111) patients with bone marrow biopsy had involvement
- Only 36% had fibrinogen <200mg/dL
- 49/154 patients had lung involvement
- Relatively few presented like TTP/HUS
- The VAST majority of cancer metastatic to bone do not do this...

*Medicine (Baltimore)*, 2012 Jul;91(4):195-205
Cancer-Related Microangiopathic Hemolytic Anemia
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Disseminated Malignancy Misdiagnosed as Thrombotic Thrombocytopenic Purpura: A Report of 10 Patients and a Systematic Review of Published Cases

Kristin K. Francis, Nalini Kalyanam, Deirdra R. Terrell, Sara K. Vesely and James N. George

• 10/351 patients treated with plasmapheresis for presumed TTP were diagnosed with cancer
• 7/10 had confusion/focal neurological signs
• 3/10 had normal renal function
• Plasmapheresis not effective
• Median survival 2 weeks

Thrombotic Thrombocytopenic Purpura Associated with Bone Marrow Metastasis and Secondary Myelofibrosis in Cancer

• 6/7 patients with malignancy associated had bone marrow involvement
• “Severe anemia and thrombocytopenia with leukoerythroblastosis were prominent clinical features in all six patients. Four patients had neurological (mental) changes and three developed fever, but none had significant renal dysfunction.”
• Several improvements with effective chemo
Mechanism?

- In some lymphoma associated cases, there were ADAMTS-13 antibodies
- Widespread tumor emboli at autopsy
- Mucin-producing adenocarcinoma
- A rare manifestation of common cancers
- Could complement play a role?
A model of the role of UL-VWF and ADAMTS12 in TTP

Proc Natl Acad Sci USA 2002;99:11552-11554
The complement system

- A proteolytic cascade that responds to antibody/antigen complexes leading to phagocytosis, inflammation, direct lysis
- Classical pathway- Initiated by C1 and C4 and antibody conjugate
- Alternative pathway- Mediated by spontaneous C3 turnover
Complement in TMAs?

- TTP- ADAMTS-13 deficiency
- HUS- Shiga toxin
- Atypical HUS- does not respond to plasma exchange as well, associated with defects in down-regulation of complement- benefit to eculizumab
Mechanism

• Widespread microvascular invasion and tumor thrombi leading to mechanical shearing and thrombosis
• Could complement activation be playing a role?
• Crude measure of activation of complement-C3 and C4 were at the low end of normal on admission
Cancer associated thrombotic microangiopathy

• Patient transfers to Green medicine, starts aromatase inhibitor and paclitaxel
• One week later, with continued hemolysis, LDH 1500+, continued deterioration in mental status