Neurologic symptoms, Fever, Thrombocytopenia, Hemolytic anemia, Acquired TMA with two different etiologies
All resolved with drug cessation but no cause mentioned
Platelet count started to downtrend again
2 systematic reviews of total
Potential novel diagnostic entity
Labs:
Ab formation which binds with platelets, neutrophils and
Half life
hypertension, fatigue, weight loss, diarrhea,
Acquired Inhibitory Antibody (most common cause)
“Quinine (tonic water)
Side effects
7/977 patients experienced TMA mostly within 90 days
- All resolved with drug cessation but no cause mentioned
- No case reports so far
- Most common - hypertension, fatigue, weight loss, diarrhea, leukopenia and increased LFTs
- Half life – approximately 31 hours
- Many case reports of DITMA, drug induced TTP (DI-TTP), drug induced HUS (DI-HUS)
- 2 systematic reviews of total 442 cases – none showing a decreased ADAMTS13 activity as the identified mechanism
- DI-TTP has been disregarded as unique diagnostic entity

What is Drug Induced Thrombotic Microangiopathy (DITMA)?
- Acquired TMA with two different etiologies
  1. Immune mediated
     - Ab formation which binds with platelets, neutrophils and endothelial cells
     - Severity independent of dose
     - Example - Quinine (tonic water)
     - Happens in < 2-3 weeks after drug exposure
  2. Toxicity mediated
     - Direct tissue injury from agent
     - Severity dependent on dose and route
     - Example – Cancer therapies, immunosuppressants, illicit drugs
     - Happens over weeks to months

What is Thrombotic Thrombocytopenic Purpura (TTP)?
- Neurologic symptoms, Fever, Thrombocytopenia, Hemolytic anemia, Kidney Injury
  - “Nasty Fever Torched His Kidneys”
- Severe deficiency of ADAMTS13 activity (<10%) + clinical picture
  - ADAMTS13 cleaves Von Willebrand Factor (vWF) and is synthesized mostly by hepatic stellate cells
  - vWF is synthesized as large molecules by endothelial cells and accumulates platelets unless cleaved
- Two causes of TTP
  1. Acquired Inhibitory Antibody (most common cause)
     - Test = inhibitor with titer and antibody (Ab)
  2. Inherited gene mutations
     - Test = genetic testing

Figure 1 - Peripheral blood smear of the patient taken July 13th showing schistocytes (arrows)

Figure 2 - Platelet trend during PEX therapy

CASE DESCRIPTION
76 year old male with past medical history of grade 3 renal cell carcinoma (day 24 of pazopanib status post left radical nephrectomy), atrial fibrillation (apixaban 2.5mg twice daily), coronary artery disease (Aspirin 81mg daily), hyperlipidemia, obesity, obstructive sleep apnea who presented with fatigue, dyspnea, hematuria and confusion.

Day of admission
- Temperature 100˚ F on admission and 100.6˚ F on hospital day 3
- Exam: drowsy, irregularly irregular heart rhythm, below knee amputation on right, bilateral lower extremity venous stasis change
- Labs: acute thrombocytopenia (32k), anemia (Hgb 12.6), LDH 2001, Fibrinogen 652, normal INR/PTT, elevated LFTs (AST 113, ALT 147), acute kidney injury (creatinine 1.59 from baseline of 1.19), elevated bilirubin (2.2 – no diff obtained)
  - Scattered schistocytes on peripheral smear (figure 1)
  - Pazopanib held and started on dail, 1 volume plasma exchange (PEX) with rapid improvement in thrombocytopenia (figure 2)

- Further testing
  - ADAMTS13 activity undetectably low, no inhibitor
  - Plasmaspheresis continued for 19 days
    - Repeat ADAMTS13 activity level 2 days after plasmapheresis was stopped returned as normal.
  - Developed sepsisemia thought to be due to a line infection
    - Platelet count started to downtrend again
  - Placed on comfort care measures after discussion with his family
  - Autopsy listed the major cause of death as metastatic renal cell carcinoma

DISCUSSION
- Pazopanib (Votrient) is a tyrosine kinase inhibitor
  - Inhibits growth factors to halt angiogenesis
- Side effects
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  - All resolved with drug cessation but no cause mentioned
  - No case reports so far
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