DIAGNOSIS AND MANAGEMENT OF THROMBOTIC MICROANGIOPATHY

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CASE

- 44 yo AAF with 3 days of h/o headache, heavy menstrual bleeding.
- She had an episode of syncope with involuntary defecation.
- She had headache and heavy menstrual bleeding.
- Also, she complained chest pain, sore throat, and fever, treated with amoxicillin x10 days at PCP office.



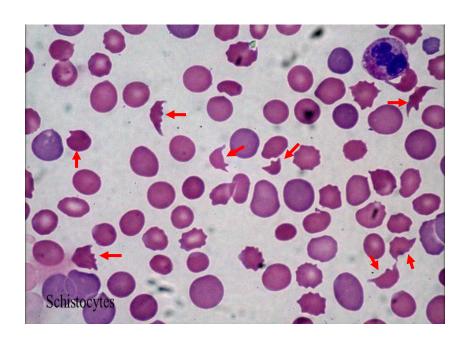
CASE (CONT.)

- At ED, labs showed: H/H 6.7/20, platelet count 13, LDH 718, fibrinogen 320, D-dimer 6,644, DAT (+) for IgG, HIV rapid test (+), HBSAg (+).
- PT 13.7, PTT 30, troponin < 0.01
- AST/ALT: 46/31
- Cr, 0.5



PERIPHERAL BLOOD SMEAR:

Numerous schistocytes and helmet cells.



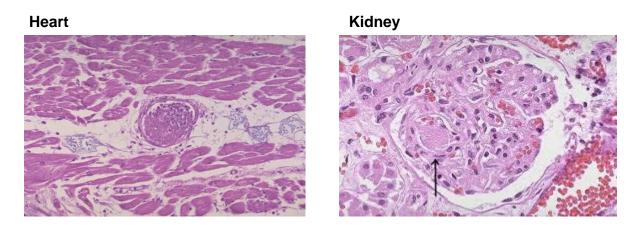
WHAT COULD BE THE DIAGNOSIS?

TMA, TTP and HUS?



DEFINITION OF TMA

 A pathology term, describing the presence of thrombosis in capillaries and arterioles, due to an endothelial injury



Seen in various conditions



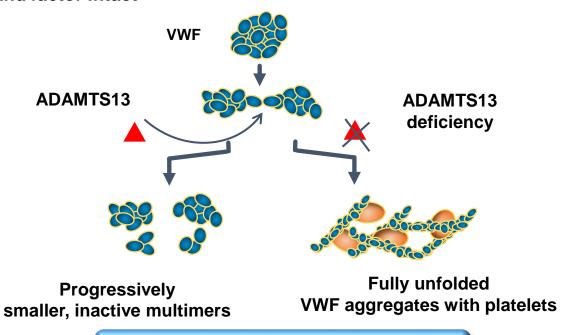
TMA MAY BE ASSOCIATED WITH THE FOLLOWING CONDITIONS:

- TTP
- STEC-HUS
- aHUS
- DIC
- Malignant hypertension
- <u>Hemolysis</u>, <u>Elevated Liver enzymes</u>, <u>Low Platelet count</u>) (HELLP) syndrome
- Antiphospholipid antibody syndrome
- Drug toxicities (e.g. calcineurin inhibitor)



Mechanism of TTP

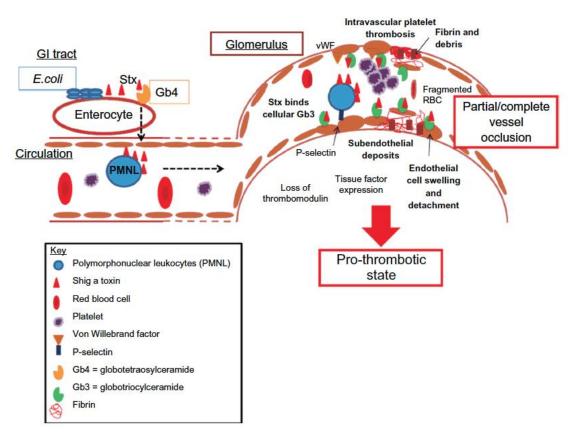
Insufficient ADAMTS13 activity (<5%) leaves von Willebrand factor intact



Suppress/remove inhibitor autoantibody; replace ADAMTS13



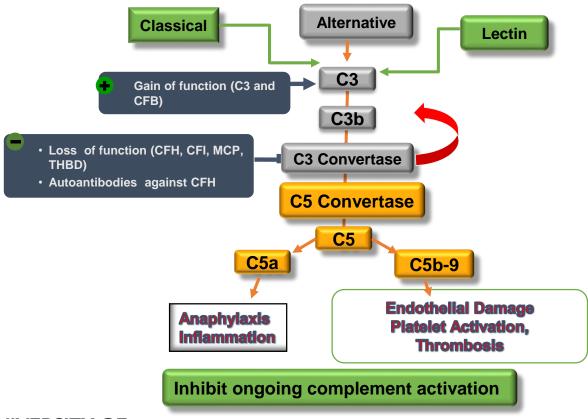
MECHANISM OF STEC-HUS





MECHANISM OF ATYPICAL HUS

Genetic defects lead to chronic uncontrolled activation of the complement system





CLINICAL DIFFERENTIAL DIAGNOSIS

Thrombocytopenia

Platelet count <150,000/μL or >25% decrease from baseline

AND

Microangiopathic hemolysis

Schistocytes, elevated LDH, decreased haptoglobin, decreased hemoglobin

Plus 1 or more of the following:

Neurological symptoms

Renal impairment

Gastrointestinal symptoms

Cardiovascular symptoms

Pulmonary symptoms

Visual symptoms

Evaluate ADAMTS13 activity and Shiga-toxin/EHEC test

While ADAMTS13 results are awaited, a platelet count >30,000/µL or serum creatinine >1.7-2.3 mg/dL almost eliminates the possibility of severe ADAMTS13 deficiency (TTP)

ADAMTS13 activity (<10%)

ADAMTS13 activity (Usually>20%)

Shiga toxin/EHEC positive

TTP

aHUS

STEC-HUS

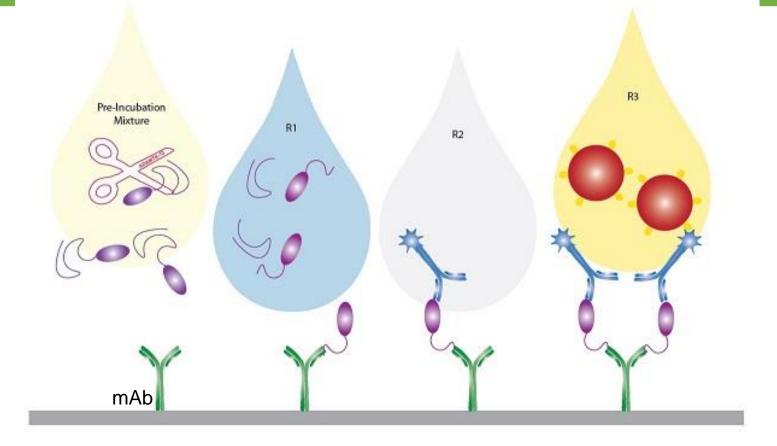


HOW TO TEST ADAMTS13 ACTIVITY?

- Screening activity assay
- FRETS-VWF73 activity assay
- Chromogenic ELISA activity assay
- Fluorogenic activity assay
- ADAMTS13 antigen assay
- Anti-ADAMTS13 IgG assay



TECHNOSCREEN® ADAMTS-13 ACTIVITY



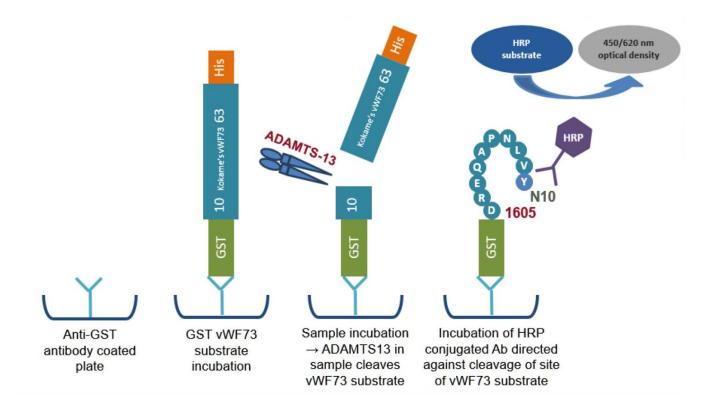


FLUORESCENT ENERGY RESONANCE TRANSFER (FRET) ASSAY

Quencher that suppresses Fluorescent tag fluorescent emission Recombinant peptide encompassing the cleavage site Active ADAMTS13 from patient plasma Peptide bond is cleaved separating the quencher from the fluorescent tag Fluorescence emission is quantitated by a fluorometer



CHROMOGENIC ELISA-BASED ADAMTS13 ACTIVITY ASSAY





HOW TO INTERPRET THE RESULTS?

 ADAMTS13 activity <10% or 10 U/dL Inhibitor >0.4 U/mL (positive)



Immune-mediated TTP (iTTP)

 ADAMTS13 activity <10% or 10 U/dL Inhibitor <0.4 U/mL (Negative), but Anti-ADAMTS13 IgG > 15 U/mL



Immune-mediated TTP (iTTP)

 ADAMTS13 activity <10% or 10 U/dL Inhibitor <0.4 U/mL (Negative)
Anti-ADAMTS13 IgG < 15 U/mL or ADAMTS13 mutation test (positive)



Hereditary or congenital TTP (cTTP)



MANAGEMENT OF TMA

cTTP: Plasma infusion,

Factor VIII concentrate

Recombinant ADAMTS13

Gene therapy

iTTP: Therapeutic plasma exchange

Corticosteroids/Vincristine/Cytoxan

Rituximab

Caplacizumab

Recombinant ADAMTS13

aHUS: Eculizumab



TAKE HOME MESSAGE

- TTP and aHUS are two distinct prototypes of TMA.
- Clinical parameters + ADAMTS13 are essential for differential diagnosis
- Plasma exchange, steroids, rituximab, and caplacizumab are for iTTP, but eculizumab for aHUS.
- Further investigation is necessary to understand the pathogenesis of other types of TMA.

