Catastrophic Thrombosis Syndromes

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Catastrophic Thrombosis Syndromes

--Systemic vascular disorders that result in arterial thrombosis and tissue infarction/organ failure

-Venous thromboembolism can be increased in these disorders but do not qualify as “catastrophic”

-Primary Hematologic Disorders can increase risk of arterial thrombosis but are not considered in this topic (PNH, P VERA, E Thrombocytosis)

Case #1

-Previously healthy 34 yo male presents to ED with sudden onset RUE weakness

-Physical Exam notable only for focal neurologic deficit

-Brain MRI c/w left hemispheric infarct

-CBC and MetC are normal

Case #1

What testing do you order?

Thrombotic Risk Profile

- Free Protein S → Reflex to Protein S Ag
- Protein C
- Antithrombin III
- Factor V Leiden
- Prothrombin gene mutation
- Homocystine
- Factor VIII
- PTT and Lupus anticoagulant
- Cardiolipin antibodies

Antiphospholipid Antibody Syndrome (APS)

Autoimmune disorder characterized by one (or more) of the following laboratory abnormalities:

-Lupus Anticoagulant (LA)*
(artifactual prolongation of PTT)

*Sydney Criteria

Antiphospholipid Antibody Syndrome (APS)

Autoimmune disorder characterized by:

-antibodies to cardiolipin (false + VDRL) (>40 GPL or MPL)*

-antibodies to ß2-glycoprotein 1 (>99%ile)*

*Sydney Criteria

Antiphospholipid Antibody Syndrome (APS)

And characterized by one of the following obstetrical complications:

-one spontaneous abortion of morphologically normal fetus post-10 weeks gestation or;

-one premature delivery (<34 weeks) due to eclampsia/preeclampsia or placental insufficiency or;

-3 or more spontaneous abortions before 10 weeks gestation with other causes excluded

*Sydney Criteria OR

Antiphospholipid Antibody Syndrome (APS)

Or characterized by vascular thrombosis:

-One or more events of venous or arterial thrombosis

-If histology is performed, there can be no evidence of vasculitis

*Sydney Criteria

Antiphospholipid Antibody Syndrome (APS)

Autoimmune disorder characterized by vascular thrombosis:

-In a case-control study LA was associated with a 3.6-fold increased risk of venous thrombosis

-In patients < 50 yo, LA associated with a 43-fold increase risk of stroke

(risk increases to 200-fold with concurrent OCP use and 80-fold with concurrent smoking)

Case #1

-Recommended treatment:

Life-long anticoagulation due to 43-fold increased risk of stroke associated with LA.

(Note: There is NO data to support the use of NOACs in APS and until this data is available, this is not recommended)

Case #2

-Healthy 21 yo diagnosed with APS following spontaneous abortion in presence of a low titer LA (normal PTT, mild prolongation of DRVVT)

-Four years later delivered a healthy baby boy with lovenox administered 40 mg SQ throughout the pregnancy

Case #2

Presents to ED one week post-partum c/o urticarial rash on buttocks and face;

pain in upper abdomen and thighs

Meds:

lovenox 40 mg SQ

ASA and ibuprofen prn

Augmentin

Case #2

Exam:

-small violaceous, tender lesions on ears and buttocks

-abdomen mildy tender, but not acute

-muscular tenderness in thighs

(Doppler U/S without evidence of clots)

Case #2

Labs:

-PTT 73.7

-platelets 202K

-anti-Cardiolipin IgG >1/100

Treatment:

- Lovenox at full anti-coagulation dosing and transitioned to coumadin with resolution of sxs

Case #2

-3 years, due to a desire to become pregnant, transitioned to lovenox (full-dose)

-1 week later with c/o nausea, diarrhea and chest pain

Case #2

	8/4	8/11	8/14	8/15
Hgb	13.9	13.2	11.9	10.7
platelets	281	199	154	146
AST	nl	85	121	
Anti-Xa		0.86		
Radiology		CTPA (-)	CT AP (-)	

Case #2

-Switched to coumadin the following day (bridging with lovenox)

-Admitted to hospital 3 days later with persistent symptoms

-Fluid overload with EF 30% & troponin 30

-Treated for MI/CHF, improved and remains stable on anti-coagulation with coumadin

Case #2

Did this patient fail on heparin therapy or have “autoimmune” HIT?

Heparin-induced thrombocytopenia

A thrombotic disorder (venous and arterial) that occurs following exposure to heparin

Heparin-induced thrombocytopenia (HIT)

4 "T" scoring system to assess probability of HIT

-Timing (5-10 days post-exposure)

-Thrombocytopenia (> 50% reduction in platelet count)

-Thrombocytopenia (without other explanation)

-Thrombosis

0-2 points accorded for each T

0-3 low risk, 4-5 intermediate, 6-8 high risk

Pathogenesis of HIT & APS

	HIT	APS	Result
Antigen	PF4 bound to anion (heparin)	ß2GP1	
Platelet Target	PF4 FcR	Glycoprotein IB ApoE receptor 2	Platelet aggregation and activation→ Thrombin
Vascular Target	PF4/Heparan	Annexin A2* ApoE receptor 2	Increased TF expression→ Thrombin
2° factors	Increased tissue damage	Inflammation	-PF4 generation -Endothelial activation

Heparin-induced thrombocytopenia (HIT)

Treatment:

-inhibit thrombin

-Argatroban (direct thrombin inhibitor)

Decrease thrombin generation

-Do not start coumadin until plt > 140 K

Case #3

-52 yo female presents with abdominal pain and diarrhea

-One week later admitted to hospital with following labs:

creatinine 3.2, plts 68K, Hgb 8.5, LDH 442, Tbili 2.1

Case #3

What do you order to establish Dx?

Shiga Toxin-Mediated Hemolytic Uremic Syndrome

- A subset of thrombotic disorders characterized by MicroAngiopathic Hemolytic Anemia (MAHA)
  - Hemolytic Uremic Syndrome (HUS)
  - Thrombotic Thrombocytopenic Purpura (TTP)
  - Complement-Mediated Thrombotic Microangiopathy

    (Atypical HUS)

Clinical features of MAHA

- MicroAngiopathic Hemolytic Anemia (MAHA)
  - Elevated LDH and Bilirubin
  - Schistocytes
- Thrombocytopenia
- Absence of coagulapathy (DIC)
- Organ failure
  - Somewhat variable depending on cause
    - HUS and aHUS– renal
    - TTP – CNS, others, rarely significant renal failure

Specific Lab testing for MAHA

- TTP – decreased ADAMTS13 activity
  - auto-antibodies to ADAMTS13
  - ADAMTS13 Deficiency (Congenital)
- HUS – E.Coli O157:H7
- Complement-mediated (atypical HUS) exclusion of above two causes
  - May be acquired, due to auto-antibodies to CFH or
  - Inherited due to defects in proteins that downregulate complement activation

Pathology of MAHA

- TTP – failure to cleave large von Willebrand multimers (deficiency of ADAMTS13
- HUS – binding of Shiga toxin to CD77 on endothelial cells results in apoptosis
- aHUS – complement-deposition results in damage to endothelial cells and activation of platelets

Pathology of MAHA

- Platelet adherence to wall of small arterioles
- Due to increased platelet aggregation (TTP), vessel wall damage (HUS) or both (aHUS).
- Occlusion of small arterioles leads to shearing of RBCs

Alternate Causes of MAHA

- Drug-mediated
  - –Immune-mediated
    - »Quinine, quetiapine, gemcitbine
  - –Toxic
    - »VEGF inhibitors (avastin, et al)
    - »Calcineurin inhibitors (cyclosporine, tacrolimus)

Alternate Causes of MAHA

- DIC (elevated PT, decreased fibrinogen)
- Valve hemolysis (no thrombosis)
- Vascular malformations (Kasabach-Merritt)

Treatment of MAHA

- TTP – plasmapheresis to remove antibodies + immunosuppresive therapy
- HUS – hydration and supportive care
- aHUS – eculizumab
- Drug-induced – remove offending drug and supportive care

Catastrophic Thrombosis Syndromes

--Systemic vascular disorders that result in arterial thrombosis and tissue infarction/organ failure

--Coagulation testing is rarely helpful (except to exclude DIC), since the primary defect is endothelial in most cases

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Suggested References:

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