Thinking cAPS... a case-based approach

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1/30/15
clAPS, cAPS and snAPS…a journey through time

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1/30/15
23F with hx JRA, APS (dx 2007 with PE/LV thrombus, elevated aPLs, on indefinite AC), transferred to UWMC on 12/24/14, after prolonged hospitalization at Swedish, for further evaluation and treatment of persistent anemia/thrombocytopenia.

USOH until 11/2014 with URI sx, fevers, n/v at 17 weeks EGA (G1)

Presented to OSH and admitted for sx mgmt. Course notable for **progressive transaminitis** (AST 40→330, ALT 140→490) with worsening anemia (Hct 30→28→23) and **thrombocytopenia** (plt 94→70→50). Ab imaging neg (US and MRI), sx improved, dc home with MFM f/u

12/8/14: MFM f/u appt at Swedish, progressive RUQ pain, AST 1245, ALT 1445, Hct 22%, and plt 13K

Direct admit to Swedish for D&C in setting of **provisional dx of HELLP, chronic anticoag held**

Underwent D&C 12/9/14, gradual improvement in transaminitis, persistent anemia/thrombocytopenia

Concern for TTP (high LDH, schistos on PBS), underwent TPE x3 (12/14-12/16), ADAMTS13 returned at 77%

Concern for ITP, dex burst and IVIG x1 with minimal response (reduced plt transfusion req)

Concern for retained products of conception (persistent HELLP), repeat D&C 12/22 with no POC

Concern for underlying marrow process, BMBx 12/23:
Case 1: BP

BMBx 12/23/14:
Case 1: BP

- 12/24/14: transferred to UWMC for further evaluation
- On admission: Afebrile, VSS, Tearful and anxious, palmar-plantar rash noted.
- Admit labs notable for:
  - WBC 10 (nl diff), Hct 22%, plt 12K
  - AST/ALT 38/81, AP 132, Bili 0.8
  - LDH 939, hapto <10, retic 3.4%
  - PT 13.9\,/\, PTT 67, fibrinogen 417
  - DAT: 3+ positive for C3b, IgG neg
  - Recent aPL panel with aCL IgG 140, IgM 18, aB2GP1 IgM 7, IgG 25, LA—no recent report
Case 1: BP
Case 1: BP

- **HD2:**
  - I embark on a relaxing weekend getaway to Orcas Island...
  - Meanwhile...
    - Pt with progressive confusion, worsening HA...
    - MRI/MRA:
      - Punctate foci of diffusion restriction in the left frontal and parietal lobes, concerning for acute and subacute infarcts
      - Diffuse leptomeningeal and pachymeningeal exaggerated enhancement
    - CT venogram with acute sagittal sinus thrombosis
    - Palmar biopsy results: numerous small vessel thrombi
    - Vital sign instability, transferred to ICU
Case 2: MS

- 51F hx ESRD 2/2 FSGS and no other sig PMH admitted to UWMC for ddRT.
  - Transplant aborted due to donor issues, pt remained in house for new fevers/L ankle swelling
  - Admit labs notable for:
    - BUN/Cr 51/17, CBC: 13/30/294, PT/PTT 16.2/41 (ULN 15.6/35 resp)
    - Rheum consulted to eval new ankle pain/swelling
    - ANA neg, ds-DNA at 15 (ULN 14), anti-SSA/Ro positive
    - Ankle tapped HD#3, non-inflammatory effusion. Fevers resolved. Pt preparing for dc home...
Case 2: MS

- HD#5: MS with progressive confusion...
  - MRI brain: **foci of restricted diffusion involving the left parsagittal parietal lobe, temporal lobe, left basal ganglia, right insula, and temporal lobe** with associated FLAIR signal abnormality c/w acute/subacute infarction
  - TEE with “**Abnormal structure** seen at the left atrial side of the posterior lateral aspect of the **mitral valve**. Structure measures approximately **0.6 x 0.7 cm** as described above. The nature of this finding is not clear. **Differential includes thrombus and vegetation** although appearance is not typical for either.”
  - No anticoag initiated given concern for hemorrhagic conversion of cerebral infarcts
  - Repeat PT/PTT at 18.5/49, 1:1 mix with incomplete correction of PTT, **moderate positive lupus inhibitor**, aPL panel with **aCL IgM at 17**, otherwise unremarkable
Case 2: MS

- HD#10: acute onset abdominal pain
  - CT AP: **Multifocal splenic and left renal cortical infarcts**. Total lack of right renal cortical enhancement may be secondary to embolic or thrombotic disease. Cluster of extraluminal gas adjacent to small bowel in the right hemiabdomen is equivocal; as this finding could represent gas within small branches of the SMV secondary to bowel ischemia.
    - Rheum rally pack unrevealing
    - Hypercoag panel negative (prothrombin gene mutation, FVL mutation)
    - HIT ELISA negative
    - PNH flow negative
    - **Repeat lupus inhibitor and aCL IgM negative, aCL IgG and aB2GPI IgM and IgG remained negative**
    - PTT prolongation persisted with failure to correct on 1:1 mix, FVIII and FIX activity wnl
  - Taken emergently to OR for clinical dx of mesenteric ischemia...
Antiphospholipid antibody syndrome (APS)  
(Hughes syndrome)

- Graham R V Hughes (BMJ 1983):
  - "In some patients three apparently unrelated clinical features of systemic lupus erythematosus—recurrent venous thrombosis, central nervous system disease (including myelitis), and recurrent abortions—may, it seems, have common pathogenic mechanisms.

  - “For those of us hardened into nihilism by years of study of various autoantibodies in systemic lupus erythematosus, there is a rare sense of excitement at the implications of the associations now being reported.”
"An acquired thrombophilic disorder in which patients have vascular thrombosis and/or pregnancy complications attributable to placental insufficiency, accompanied by laboratory evidence for the presence of antiphospholipid antibodies in blood." (Williams Hematology, 8e)

Diagnosis: Sydney criteria/ revised Sapporo (Miyakis et al JTH 2006):

- Clinical:
  - Vascular thrombosis or pregnancy morbidity
    - Venous, arterial, small vessel thrombosis (LE DVT most common [~50%], arterial only in ~15%, venous only in ~60%, mixed venous and arterial in ~25%)
    - Fetal death ≥10 weeks EGA, fetal loss >3 times at <10 wks, ≥1 premature birth 2/2 enclampsia/placental insufficiency

- Laboratory:
  - The presence of aPL on two or more occasions at least 12 weeks apart
    - mod-high titer anti-cardiolipin IgM/IgG (>40 MPL units, or >99th percentile of reference lab)
    - anti-beta2-glycoprotein IgM/IgG (>99th percentile of reference lab)
    - LA activity with confirmatory testing

- Primary vs secondary APS: presence or absence of underlying rheumatologic disease (predominately SLE)
  - “The committee advises against using the term secondary APS. We could not find differences in the clinical consequences of aPL among patients in these two categories” (Miyakis, et al)
What exactly is an “anti-phospholipid antibody?”

1. 1952: Moore and Mohr report a “biologic false-positive” serologic test for syphilis, with a strong association with prolonged coagulation times, dubbed ‘aPTT inhibitor’

2. 1972: Feinstein and Rapaport describe phospholipid dependence of the ‘aPTT inhibitor’ and association with SLE, dubbed ‘lupus anticoagulant’ (despite growing body of evidence that patients were in fact prone to clotting, not bleeding)

3. 1983: Harris, et al use ELISA-based methods to define antibodies reacting against anionic phospholipids in patients with ‘lupus anticoagulant.’ Cardiolipin (a well described anionic phospholipid) was used in the assay as the target phospholipid, antibodies dubbed ‘anti-phospholipids’ or ‘anti-cardiolipins’
   - NB: cardiolipin (diphosphatidylglycerol), is the primary antigen in non-treponemal syphilis serological testing (RPR, VRDL)


5. 2006: Miyakis, et al update APS diagnostic criteria to include B2GPI
What exactly is an “anti-phospholipid antibody?”

“The accepted view is that antiphospholipid antibodies comprise a heterogeneous group of antibodies directed against neoepitopes on anionic phospholipids and proteins capable of binding to anionic phospholipids, of which b2GPI is the most common and seems most related to the risk of venous and arterial thrombosis and pregnancy loss” (Sandor Shapiro (1933-2007))
So then, what is a ‘lupus anticoagulant’?

- LAC assay: an indirect test for the presence of a heterogeneous group non-specific ‘aPLs’ (most often directed against B2GPI or prothrombin)
- Screen:
  - Prolongation of phospholipid-dependent clotting assays (aPTT, dRVVT, kaolin clotting time (KCT))
- Mix:
  - Inhibitor vs factor deficiency determined via 1:1 plasma mixing study
- Confirm:
  - Specific factor inhibitor vs PL-dependent aPL Ab determined via phospholipid ‘quench’ with addition of exogenous PL
APS: pathophysiology

- aPLs mediate thrombosis via:
  - Disruption of annexin A5 ‘anticoagulant shield’
  - Inhibition of fibrinolysis
    - B2GPI is a cofactor for plasminogen activation, anti-B2GPI→decreased plasmin generation
  - Acquired APC resistance
    - aPL blockage of thrombomodulin-thrombin complex activation of protein C
  - Direct injury to endothelial cells (aPL mediated)
  - Complement activation (→evolution of TF from mononuclear cells)
    - C3 convertase inhibition abrogates thrombosis in aPL mouse models
    - Eculizumab (?)
  - Platelet activation/adhesion
    - B2GPI binds directly to platelets, ‘dampening’ effect on plt interaction with vWF (inhibited by aB2GPI)
APS: pathophysiology

- Disruption of annexin A5 ‘shield’
Thrombocytopenia

- 20-40% prevalence in APS patients (Atsumi, et al)
- Etiology: concurrent ITP autoimmune phenomenon vs direct effect of aPLs on plt vs combination therein
  - Lipp et, al (1998): 70% of pt with ITP had concurrent aPLs (anti-cardiolipin, anti-phosphatidylinerine)
  - ITP pts with asymptomatic aPL (ie not APS) with increased clotting risk

Valvular heart disease

- 30-40% of APS patients have concurrent stereotypical valvulopathy; MV>AoV
- Valvular abnormalities include leaflet thickening, vegetations, regurgitation, and stenosis
- Histologically, lesions consist of fibrin deposition, vascular proliferation, calcification and aPL immune-complex deposition

Cutaneous manifestations

- ~25% prevalence in ‘asymptomatic’ aPL patients
- Livido reticularis most common feature, commonly due to underlying vasculitis

Liver disease, nephropathy, neurological manifestations, retinal disease, PAH, PAD, etc…
APS: ‘non-criteria’ clinical features

APS: ‘non-criteria’ clinical features

- Catastrophic antiphospholipid antibody syndrome (cAPS, Asherson’s syndrome)
- “Some patients with [APS], albeit a small minority, may present with or develop an acutely catastrophic or devastating syndrome characterized by multiple vascular occlusions and often resulting in death” (Ronald Asherson, J Rheumatology 1992)
Fulminant manifestation of APS with acute onset of multiorgan thromboses and failure, occurring in ~1% of APS patients with mortality on the order of 50% despite maximal intervention.

**Diagnosis** (Cervera, et al. Autoimmun Rev, 2014)

1. Evidence of involvement of 3 organs, systems, and/or tissues.
2. Development of manifestations simultaneously or in less than 1 week.
3. Laboratory confirmation of the presence of aPL (LAC and/or aCL and/or anti-2GPI antibodies) in titers higher than 40 UI/l.
4. Exclude other diagnoses.
Pathogenesis is well described and validated in several high impact, peer reviews journals.

Pathogenesis is largely unknown


- First hit is aPL and attendant thrombophilia
- Second hit is an ‘inflammatory environmental trigger’ (infection, trauma, malignancy, pregnancy complications [HELLP]) resulting in immune activation/dysregulation and resultant evolution of proinflammatory cytokines leading to increased microvascular inflammation and augmented prothrombotic state.
  - Further propagated by:
    - Microvascular thrombosis itself then leads to further evolution of inflammatory cytokines (IL-6, TNF, etc)
    - Rapidly evolving clots generate increasing amounts of thrombin and leading to consumption of natural anticoagulant proteins (APC,ATIII) (ie DIC)
    - Complement activation resulting in amplification of TF expression from mononuclear cells
cAPS: pathogenesis

- Asherson, et al.

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<thead>
<tr>
<th>Table 1. Precipitating factors</th>
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<tbody>
<tr>
<td>Unknown</td>
<td>100 (40.0%)</td>
</tr>
<tr>
<td>Infections</td>
<td>56 (22.0%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>28 (14.0%)</td>
</tr>
<tr>
<td>Anticoagulation problems</td>
<td>17 (7.2%)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>16 (16.8%)</td>
</tr>
<tr>
<td>Obstetric</td>
<td>11 (4.6%)</td>
</tr>
<tr>
<td>Lupus “flares”</td>
<td>7 (3.0%)</td>
</tr>
<tr>
<td>Others</td>
<td>11 (5.5%)</td>
</tr>
</tbody>
</table>

Diagram shows triggers for cAPS: Obstetric, Trauma, Infection, Drugs, A/C withdrawal (low INR), Malignancies, SLE “Flare”.
‘Seronegative’ APS

Definition (Hughes, et al 2003): Patients with clinical manifestations highly suggestive of APS but with persistently negative LA, aCL and aB2GPI testing.

‘Etiology:
- Misdiagnosis (ddx of other underlying acquired or congenital thrombophilia)
- Testing characteristics of available platforms
  - variability in detecting LAC, etc
- Transient autoantibodies missed on serial testing
  - consumption vs extinction
- Current range of testing is inadequate
  - What are we missing?
Non-criteria aPLs: Many other aPLs (that is, outside of aCL and aB2GPI) are known to exist, however their contribution to the thrombophilic state of APS remains undefined

Nayfe, et al (Rheumatology, 2013): mechanistic review of potential criteria candidates

- Phosphatidylethanolomine (PE)
  - Zwitterionic phospholipid, comprises 20-50% of total mammalian phospholipids
  - Enhances inhibitory activity of APC on FVa, inhibits Fxa-prothrombin complex (Smirnov, et al)
  - San Marco, et al: 369 pts with thrombosis; 15% positive for aPE (IgM) vs 3% in controls (sole aPL in 67% of positive cases)

- Phosphatidic acid (PA), phosphatidyserine (PS), phosphotidylinositol (PI)
  - Anionic phospholipids, fairly ubiquitous
  - Yetman, et al : 866 women with RPL: 87 positive for aPS/aPA/aPI as sole aPL (12% vs 3% of controls)
  - In vitro data for aPS inhibition of syncytiotrophoblast formation

- And many more!: vimentin/cardioliipin complex, anti-domain I of B2GPI, anti-prothrombin...
Conti et al 2014

- 24pt with ‘snAPS’ (from rheum clinic), 25pt with APS, 32 healthy subjects
  - TLC testing methods as well as interrogation for Vimentin/CL, aPT and anti-annexin V abs

### Table 2

<table>
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<tr>
<th>Autoantibodies</th>
<th>SN-APS (24) n (%)</th>
<th>APS (25) n (%)</th>
<th>SLE (18) n (%)</th>
<th>Healthy donors (32) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin by TLC-immunostaining</td>
<td>13 (54.2)</td>
<td>17 (68)</td>
<td>11/18 (61.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antivimentin/Cardiolipin</td>
<td>11 (45.8)</td>
<td>22 (88)</td>
<td>7/18 (38.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antiprothrombin</td>
<td>3 (12.5)</td>
<td>9 (36)</td>
<td>1/18 (5.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antiannexin V</td>
<td>1 (4.2)</td>
<td>14 (56)</td>
<td>4/18 (22.2)</td>
<td>0 (0)</td>
</tr>
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</table>
APS: therapy

- Asymptomatic aPL
  - Low dose ASA (APLASA study: no clear clinical benefit comprehensive thrombotic risk evaluation for identification of high risk individuals)

- cIAPS
  - Warfarin anticoagulation with INR goal of 2-3
  - Addition of plaquenil (esp in SLE patients)
    - Role of TSOACs (riva trial)

- cAPS
  - Anticoagulation and immunomodulation
    - Hep gtt -> warfarin
    - Corticosteroids, IVIG, plasmapheresis, cyclophosphimide
      - Rituxan, Eculizumab

- snAPS
  - Anticoagulation
    - Duration, agent, immunomodulation (plaquenil)
Back to the cases...

BP:

- Diagnosis?
  - cAPS ($\geq 3$ organ systems involved (brain, bone marrow, skin, likely liver), acute onset, known and reconfirmed aPL)
  - Trigger: infection (viral URI PTA), ?HELP, AC withdrawal at OSH

- Treatment:
  - Hep gtt, HDMP, IVIG, cyclophosphamide (1g/m2 x1), rituxan x4

- Course:
  - Mental status rapidly returned to baseline with above interventions, skin rash resolved, discharged home on warfarin and low pred taper.
Back to the cases...BP
Back to the cases...

- **MS**
  - **Diagnosis?**
    - snAPS (multiple thrombotic events, no viable competing dx (r/o hypercoag, PNH, HIIT, etc), cardiac valvular abnormalities, renal failure of unknown etiology, e/o inhibitor on aPTT, ‘transient’ aPL (aCL IgM/IgM neg on repeat testing, but s/p myriad thrombotic events (consumption) and IST (HDMP early in course for ‘autoimmune vasculitis’)
    - ?cAPS: less likely (clotting events likely cardioembolic in nature, recovery without IST (or AC!) intervention, no systemic sx of cytokine release/SIRS
  - **Treatment:**
    - Hep gtt → warfarin, plaquenil
  - **Course:**
    - Complicated (discharged HD#103). Home now! (on warfarin and plaquenil)
Summary and musings...

- aPLs are antibodies that recognize phospholipids, proteins that bind to phospholipids, complexes of proteins and phospholipids, or inhibit phospholipid-dependent coagulation reactions.

- APS is an acquired thrombophilic disorder with myriad clinical manifestations, mechanistically linked to aPL-mediated derangements of hemostasis.

- cAPS is a fulminant form of APS, requiring high index of suspicion and early intervention with multimodality therapy.

- snAPS is a provisional diagnosis with active research underway to define additional causative aPLs in patient with clinical manifestations of APS, but negative testing for criteria aPLs.
  - Defining ‘high risk’ groups within the category with ‘asymptomatic’ aPLs as well as in established ‘APS’ pts to help guide therapeutic decision making.
  - Functional vs phenomenological testing for APS (annexin A5 assay).
APS: pathophysiology

- Disruption of annexin A5 ‘shield’

Unshielded

+ Annexin A5

Normal plasma

Intact shield

Normal annexin A5
anticoagulant activity

Prolonged coagulation time

Unshielded

+ APS plasma

Disrupted shield

Resistance to annexin A5
anticoagulant activity

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References

Thank you

Questions?