The Antiphospholipid Antibody Syndrome: The Spectrum of Thrombophilia

James J. Stark, MD, FACP
Medical Director Cancer Program
Maryview Medical Center

Professor of Medicine
Eastern Virginia Medical School

www.StarkOncology.com
Case Presentation: LF

• 23 y.o. WF presented to ER with personality change and difficulty speaking
  – Headache for a week prior to visit to ER
• 4 mos post-partum uneventful pregnancy and delivery
• Started oral contraceptives after delivery
• No history of illicit drug use
• Exam: aphasic, deaf
Case Presentation

LF, continued

- Emergency CT scan of the head....

- MRI of head next morning....

- Diagnosis multiple brain infarcts, etiology unknown
LF evaluation

- Echocardiogram negative for vegetation or patent foramen ovale
- Hypercoagulable workup:
  - Factor V Leiden negative
  - Protein S, Protein C normal
  - Homocysteine level normal
  - Prothrombin gene mutation: absent
  - Phospholipid antibody panel…
## LF workup, continued

<table>
<thead>
<tr>
<th></th>
<th>IgM</th>
<th>IgG</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiolipin**</td>
<td>neg</td>
<td>40 (+)</td>
<td>neg</td>
</tr>
<tr>
<td>Phosphatidyl Inositol</td>
<td>neg</td>
<td>43 (+)</td>
<td>neg</td>
</tr>
<tr>
<td>Phosphatidyl Glycerol</td>
<td>neg</td>
<td>36 (+)</td>
<td>neg</td>
</tr>
<tr>
<td>Phosphatidyl Serine</td>
<td>neg</td>
<td>26 (+)</td>
<td>neg</td>
</tr>
<tr>
<td>Phosphatidyl Ethanolamine</td>
<td>neg</td>
<td>21 (+)</td>
<td>neg</td>
</tr>
</tbody>
</table>

**Strikingly positive

**Only antibody currently required for diagnosis (see criteria)**
LF, continued

• Oral contraceptives stopped
• Heparinized, switched to warfarin
• Slowly improved with gradual return of hearing and speech
• Remains mildly impaired to this date
• INR kept between 3 and 4
• Plan to keep anticoagulated indefinitely
Thrombophilia or Hypercoagulability: various definitions

- Second thrombotic event (in someone with prior history of venous thrombosis)
- First thrombotic/embolic event if no antecedent history of relevance obtained
  - Catastrophic consequences steers in direction of calling patient *thrombophilic*
- No agreement among authorities as to which definition to accept or when workup is called for
One author’s approach…

**Recommended Screening in Thrombophilia**

The following recommendations concerning which conditions should be tested for are based on a characterization of the patient as either "strongly" or "weakly" thrombophilic:

**Strongly thrombophilic:**
- First idiopathic venous thrombosis before 50 years of age **OR**
- History of recurrent thrombotic episodes **OR**
- First-degree relative(s) with documented thromboembolism before age 50

**Weakly thrombophilic:**
- First episode of idiopathic venous thromboembolism at age ≥50 years **AND**
- Negative family history of thromboembolism

<table>
<thead>
<tr>
<th>Condition tested for:</th>
<th>Strongly thrombophilic</th>
<th>Weakly thrombophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated protein C resistance</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>


Let’s look at this problem etiologically…
Thrombophilia: looking at by cause: the inherited clotting disorders

(Can be arterial, venous or both)

- Factor V Leiden mutation
- Protein S or C deficiency
- Prothrombin gene mutation
- Anti-thrombin deficiency
- And what is new: Elevated factor levels: perhaps hereditary; not completely clear
  - II, VIII, IX, XI
  - Quality of the evidence…
Kaplan-Meier Estimates of the Risk of Recurrent Venous Thromboembolism According to the Plasma Level of Factor VIII

Case Presentation

Pathophysiology

Relative Risk of Recurrent Venous Thromboembolism According to the Plasma Level of Factor VIII

<table>
<thead>
<tr>
<th>FACTOR VIII (IU/dl)</th>
<th>PERCENTILE</th>
<th>NO. OF PATIENTS</th>
<th>NO. OF RECURRENCES</th>
<th>UNIVARIATE RELATIVE RISK (95% CI)</th>
<th>MULTIVARIATE RELATIVE RISK (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;25th</td>
<td>94</td>
<td>6</td>
<td>1.0 (0.0–5.0)</td>
<td>1.0 (0.0–5.0)</td>
</tr>
<tr>
<td>120–150</td>
<td>25th–50th</td>
<td>90</td>
<td>11</td>
<td>1.6 (0.5–4.5)</td>
<td>1.6 (0.5–4.4)</td>
</tr>
<tr>
<td>151–192</td>
<td>51st–75th</td>
<td>88</td>
<td>8</td>
<td>1.7 (0.6–4.8)</td>
<td>1.5 (0.5–4.6)</td>
</tr>
<tr>
<td>193–234</td>
<td>76th–90th</td>
<td>52</td>
<td>3</td>
<td>0.9 (0.2–3.7)</td>
<td>0.9 (0.2–4.3)</td>
</tr>
<tr>
<td>&gt;234</td>
<td>&gt;90th</td>
<td>36</td>
<td>10</td>
<td>6.6 (2.4–18.4)</td>
<td>11.4 (3.1–42.5)</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.
†Multivariate relative risks were calculated with adjustment for age, sex, the presence or absence of factor V Leiden, the presence or absence of the G20210A prothrombin mutation, and the duration of anticoagulation.

Risk of Thrombosis According to Factor XI Level: same issue as for Factor VIII

Odds Ratio for Thrombosis According to the Factor XI Level

O.R. 1.7-3.3 (95% C.I.)

Those conditions which create clots by accident:

- Post-operative state, especially orthopedic
- Heart rhythm disturbances
- Mural thrombus/Hypertrophic cardiomyopathy
- Patent foramen ovale (can be clinically unsuspected)
Evaluation of the Hypercoagulable State, cont.

Those entities which produce clots through an alteration of the intravascular milieu and/or the balance between thrombosis and thrombolysis:

- Lipid abnormalities
- Malignancy: occult or obvious
- Recent heparin therapy/falling platelet count (HIT)
- Pregnancy
- Drugs, e.g., oral contraceptives, tamoxifen
- Hyperhomocysteinemia
- Paroxysmal Nocturnal Hemoglobinuria
- Myeloproliferative Disorder (P. vera, essential thrombocythemia)

- And…the Anti-Phospholipid Antibody Syndrome
Odds Ratio for Thrombosis According to Plasma Homocysteine Level

![Graph showing odds ratio for thrombosis at different plasma homocysteine levels.](image)

---

The Antiphospholipid Syndrome: Criteria

• Clinical Criteria:
  – Vascular thrombosis: arterial or venous
  – Complications of pregnancy
    • Death of morphologically normal fetus after week 10; or
    • Premature (<34 weeks) labor and delivery; or
    • Three or more consecutive miscarriages before tenth week of pregnancy

  AND...

• Laboratory criteria
  – Anticardiolipin antibodies (IgG or IgM) present on 2 occasions 6 weeks apart; or
  – Lupus anticoagulant antibodies on 2 occasions 6 weeks apart
Antiphospholipid Antibodies: Historical Perspective

• First detected in 1906 in patients with syphilis: basis for VDRL test
• Relevant antigen later identified as cardiolipin
• Discovered to be positive in patients with lupus ("false + VDRL")
• In 1983 test for anticardiolipin antibodies developed: 2 orders of magnitude more sensitive than classic VDRL
The “Lupus Anticoagulant”

• Suspected in patients with prolonged PTT and paradoxical thrombosis (may be lab value only without clinical events)

• Circulating anticoagulant test positive but not against any particular clotting factor
  – Mixing of patient’s plasma with normal plasma at 1:1 dilution fails to correct elevated PTT
    • Mixing test corrects prolonged PTT when single clotting factor is deficient (e.g., hemophilia)

• Concordance with, but not identical to, anticardiolipin antibodies

• Part of Antiphospholipid Antibody Syndrome
Proposed Mechanisms of How Antiphospholipid Antibodies Lead to Thrombosis:

- Inhibition of Protein C pathway
- Inhibition of antithrombin III activity
- Inhibition of fibrinolysis
- Potentiation of platelet activation

- …i.e., no one really knows
Antiphospholipid Syndrome: Primary versus Secondary

• Primary: no clinical evidence of other autoimmune phenomena

• Secondary: in association with clinical lupus or rheumatoid arthritis

• Our patient had no other clinical evidence of a connective tissue disorder
Antiphospholipid Syndrome: The “Second Hit” Hypothesis

- Patients with antiphospholipid antibodies can have normal hemostasis for years
- Second event or “hit” comes along which then triggers thrombosis
  - Oral contraceptives in our patient thought highly significant in this regard
Clinical Manifestations of the Antiphospholipid Syndrome

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Thrombosis of the aorta or axillary, carotid, hepatic, ileofemoral, mesenteric, pancreatic, popliteal, splenic, or subclavian artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Angina, myocardial infarction, cardiac valvular vegetations, valvular abnormalities, intracardiac thrombi, nonbacterial thrombotic (Libman–Sacks) endocarditis, peripheral embolization, or atherosclerosis</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Superficial thrombophlebitis, splinter hemorrhages, leg ulcers, distal cutaneous ischemia, infarcts of the skin, blue toe syndrome, or acrocyanosis</td>
</tr>
<tr>
<td>Endocrine or reproductive</td>
<td>Adrenal infarction, adrenal failure, testicular infarction, prostate infarction, necrosis of the pituitary gland, or pituitary failure</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Budd–Chiari syndrome, hepatic infarction, intestinal infarction, splenic infarction, esophageal perforation, ischemic colitis, infarction of the gall bladder not attributable to gallstones, pancreatitis, or ascites</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Thrombocytopenia, hemolytic anemia, or hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Perforation of the nasal septum or avascular necrosis of bone</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Transient ischemic attack, cerebrovascular accident (thrombotic or embolic), chorea, seizures, multi-infarct dementia, transverse myelitis, encephalopathy, migraines, pseudotumor cerebri, cerebral venous thrombosis, mononeuritis multiplex, or amaurosis fugax</td>
</tr>
<tr>
<td>Obstetrical</td>
<td>Pregnancy loss, intrauterine growth retardation, HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count in association with preeclampsia), oligohydramnios, uteroplacental insufficiency, or preeclampsia</td>
</tr>
<tr>
<td>Ophthalmologic Pulmonary</td>
<td>Thrombosis of the retinal artery, thrombosis of the retinal vein, or amaurosis fugax Pulmonary emboli, pulmonary hypertension, pulmonary arterial thrombosis, or alveolar hemorrhage</td>
</tr>
<tr>
<td>Renal</td>
<td>Thrombosis of the renal vein, thrombosis of the renal artery, renal infarction, hypertension, acute renal failure, chronic renal failure, proteinuria, hematuria, or the nephrotic syndrome</td>
</tr>
<tr>
<td>Venous</td>
<td>Deep venous thrombosis of the legs or thrombosis of the adrenal, hepatic, mesenteric, portal, or splenic vein or of the inferior vena cava</td>
</tr>
</tbody>
</table>

**Bewildering array of end-organ damages; easy to confuse with other entities**

Spectrum of Clinical Manifestations of the Antiphospholipid Syndrome, Simplified

- DVT large veins of legs most common
  - One half of these patients have PE
  - Associated with lupus anticoagulant
- Arterial occlusions much less common:
  - 50% in brain
  - 25% in coronary arteries
  - 25% all else: e.g., renal, retinal, pedal, subclavian
  - Associated with anti-cardiolipin Ab’s
- Recurrent miscarriages
- Recurrent thromboses true to form, i.e., arterial occlusions recur as arterial
Catastrophic Antiphospholipid Syndrome

• Multiple simultaneous occlusions throughout the body
• Often results in death
• Usually smaller vessels involved
• Can be associated with DIC
• Usual organs involved:
  – Kidneys
  – Skin
  – Brain
  – Lungs
  – Heart
Catastrophic APS, continued

• Precipitating events:
  – Withdrawal of anticoagulants
  – Oral contraceptives
  – Infections

• Initial thrombosis can precipitate cascade of additional thromboses

• Mortality high
Treatment of APS

- In people with anti-cardiolipin antibodies and no history of thrombosis aspirin may be sufficient treatment in women; does not work in men (reasons unknown)
- After first thrombosis only full dose warfarin (INR ≥ 2) protects against further episodes
- Discontinuation of warfarin especially hazardous in people with prior thrombosis and APS
Conclusions

• Thrombophilia can be caused by:
  – Inherited predilection to clot
  – Mechanical predisposition to clotting
  – Acquired coagulation abnormality
    • Combinations of the above make pathologic clotting much more likely
Conclusions, continued

• APS is uncommon but potentially catastrophic syndrome associated with a variety of antibodies
• Index of suspicion required to make diagnosis; can be easily confused with other entities
• Thrombophilia is final common path with many different etiologies
• For a copy of this talk and other information, turn to....