A clot (possibly) due to loss of TNF α suppression

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Case Presentation

34-year-old African American female

PMH of multiple DVT’s, miscarriages & reported Crohn’s
Noncompliant with TNF α inhibitor & lovenox ~6 mths

Presented with shortness of breath and pleuritic chest pain
Case Presentation

Vital Signs
T: 98.1 BP: 124/98 HR: 87 Pulse Ox: 94%

PT: 15.1
INR: 1.18
PTT: 227

ESR: 22
CRP: 55.4

UPT negative
HIV (Ant/Ab) negative

CTA Thorax. Acute pulmonary thromboembolism involving the main, lobar, and segmental pulmonary arteries bilaterally
Case Presentation

Develops severe abdominal pain

CTA reveals thrombosis of infra-renal abdominal aorta, proximal left common iliac artery, and right renal artery.

Loses sensation and pulses of left lower extremity.

Emergent vascular surgery to restore blood flow.
Case Presentation

CTA Abd/Pelvis. Partially occlusive thrombus in the infrarenal abdominal aorta & proximal left common iliac artery
Case Presentation

Working differential diagnosis for venous and arterial thrombosis:

1. Antiphospholipid Syndrome
   • Highly suspicious on first glance

2. Heparin Induced Thrombocytopenia and Thrombosis
   • Immune-mediated disorder that typically occurs 4-10 days after exposure to heparin and has life- and limb-threatening thrombotic complications

3. Paroxysmal Nocturnal Hemoglobinuria
   • Rare, acquired, nonmalignant disorder of hematopoietic stem cells characterized by hemolysis, diminished hematopoiesis, and thrombophilia

4. Malignancy
   • 34 yo with no overt symptoms or risk factors (non-smoker, no family history)
Antiphospholipid Syndrome

Sydney Criteria 2006

• Must meet at least one of the clinical and one of the laboratory criteria

• Clinical criteria
  • Vascular thrombosis
  • Pregnancy morbidity

• Laboratory criteria (two or more occasions at least 12 weeks apart)
  • Lupus anticoagulant
  • Anticardiolipin antibody
  • Anti-β2 glycoprotein-I antibody
Case Presentation

Post surgery, anticoagulated & treated for APS:
4 days of plasma exchange and high dose steroids

Anti-β2 glycoprotein I antibody negative
Lupus anticoagulant negative
Anti-cardiolipin negative
Phosphatidylserine IgM/IgG/IgA negative
Case Presentation

• Patient ultimately discharged on lifelong anticoagulation due to life threatening clot; however, reason for her clot remained undetermined

• Speculations of Antiphospholipid Syndrome were unable to be confirmed, and outpatient flow cytometry was negative for Paroxysmal Nocturnal Hemoglobinuria
Could this be a clot due to loss of TNF α suppression?
Endothelium

1628: Harvey - Description of blood

17th century: Malphigi - Network of vessels which blood flows through

17th century: Von Recklinghausen - Vessels are lined by cells

18th century: Palade & Gowan - Endothelium interacts with lymphocytes

Endothelial cells are dynamic, heterogeneous and make up a disseminated organ that possess vital secretory, synthetic, metabolic, and immunologic functions

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A crucial function of endothelium is to facilitate blood flow by providing an antithrombotic surface that inhibits platelets and clotting.

VASODILATION (leukocyte inhibition, platelet disaggregation)

VASOCONSTRICTION (promotes leukocyte adhesion)

PAF

Endothelin

PGI₂

Pivotal step in transforming the endothelial surface from an anticoagulant to a procoagulant surface is the induction of tissue factor.

Surface results in its transformation into a thrombotic surface.
Inflammation Activates Endothelium

- Thrombosis and inflammation have been closely associated
- Endothelial cells express membrane bound pro-inflammatory molecules, leukocyte-endothelial cell adhesion molecules (CAM)
  - Tethering and rolling and ultimate recruitment of more WBC’s and platelets
  - “Cytokine milieu” including TNF α
- Inflammation results in an activated endothelium → PROTHROMBOTIC
Tumor Necrosis Factor α

- TNF-α is a low molecular weight peptide with a broad range of biological and immunologic effects

- “Potent inducer of pro-coagulant activity”
Tumor Necrosis Factor α

MODULATION OF ENDOTHELIAL CELL HEMOSTATIC PROPERTIES BY TUMOR NECROSIS FACTOR

BY PETER P. NAWROTH AND DAVID M. STERN

From the Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104

TNF-α → Tissue Factor Expression → CLOT
• Anti-TNF α agents are being increasingly used in Behcet’s syndrome
  • Used in situations of pulmonary artery involvement - most lethal complication
Experimental data has proven that low molecular weight heparin has ability to decrease TNF $\alpha$. 

“Take-Away” Points

• The endothelium is a heterogeneous organ that functions in concert with local factors resulting in either an anticoagulant or procoagulant state.

• TNF α plays a crucial role in the activation of procoagulant state, likely through its ability to enhance tissue factor expression.

• Suppression of TNF α through monoclonal antibody therapy, may act to down regulate the inflammatory state of endothelial cells that results in clot formation.
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Resources


