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Acquired Bleeding Disorders

M2 Hematology/Oncology Sequence
Steven Pipe, MD

Winter 2009
Acquired Bleeding Disorders

• Can be a recognized manifestation of a known disorder

• Can prompt a differential diagnosis to identify an underlying disease
Promoters and Inhibitors of Coagulation

• Coagulation cascade
  – Tissue factor (Extrinsic) Pathway
  – Intrinsic Pathway
  – Fibrinogen, Factor XIII and Fibrinolysis

• Inhibitors
  – Physiologic
  – Acquired
  – Therapeutic
Mechanisms In Hematology Israel
Protein C - Protein S System
Mechanisms in Hematology Israel
Acquired Bleeding Disorders associated with PT and aPTT

- Various Medical Conditions
  - Anticoagulation
  - Disseminated Intravascular Coagulation
  - Vitamin K Deficiency
  - Liver Disease
  - Massive Transfusion

- Dysfibrinogenemias

- Acquired Inhibitors to Factors V, II & X
Disseminated Intravascular Coagulation (DIC)

- DIC is evidence for the simultaneous presence of:
  - thrombin (procoagulation)
  - plasmin (fibrinolysis)

- Presentations:
  - an acute hemorrhagic disorder
  - an indolent, subacute thrombotic disorder
Primary Events in DIC

Underlying Disorder

Systemic Activation of Coagulation

Widespread Intravascular Fibrin Deposition

Consumption of Platelets and Clotting Factors

Thrombosis

Bleeding

Pathophysiology of DIC

Blue (dotted) indicates inhibitors of coagulation
Etiology of DIC

• Acute DIC
  – **Infection:** Gram -ve sepsis, viremia, parasitic
  – **Obstetric:** Abruption, amniotic fluid embolism, eclampsia
  – **Malignancy:** Acute promyelocytic leukemia
  – **Trauma:** Crush injury, freshwater drowning, heat stroke, snakebite
  – **Other:** Homozygous protein C and S deficiency (infants), severe liver disease, HIT

• Subacute DIC
  – **Malignancy:** mucinous adenocarcinoma (Trousseau syndrome)
  – **Obstetric:** retained dead fetus
  – **Vascular:** hemangioendothelioma (Kasabach-Merritt), venous thromboembolic disease, chronic renal failure
Post-varicella purpura fulminans
Diagnosis of DIC

• Screening tests:
  – Activated partial thromboplastin time (prolonged)
  – Prothrombin time (prolonged)
  – Fibrinogen (decreased)
  – Platelet count (decreased)

• Confirmatory tests:
  – D-dimer (elevated)
  – Fibrin degradation products (elevated)
Value of the D-dimer

• Measure of D-dimers liberated from fibrin by action of plasmin
  – Evidence of prior thrombin activity followed by fibrinolysis
• Should be part of evaluation of DIC
• Also now an important screening and prognostic tool in venous thromboembolic disease
  – Good positive predictive value for DVT and PE
  – Very high negative predictive value

Source: Wells et al., NEJM, 2003;349:1227-1235
Eichinger et al., JAMA, 2003;290:1071-1074
Treatment of DIC

• Treat the underlying condition first!
  – Antibiotics, surgery, chemotherapy, embolization
  – disease-specific therapy
    • APML - all trans-retinoic acid (ATRA)

• Replacement therapy
  – Platelets, FFP, cryoprecipitate

• Heparin
  – May be useful in certain situations
    • Acral cyanosis and digital ischemia, purpura fulminans, retained dead fetus, migratory thrombophlebitis
Microangiopathic Hemolytic Anemia

1. Shistocyte
2. Microcyte

* Note absence of platelets
Microangiopathic Hemolytic Anemias

Pathophysiology

• Hallmarks are red cell fragmentation (shistocytes, microcytes) on peripheral blood smear, often accompanied by thrombocytopenia

• Intravascular hemolysis as red cells are damaged traversing small blood vessels with fibrin deposition or platelet aggregates
  – Can also occur in areas of high turbulence (e.g. Aortic stenosis)

• Red cell fragments are targeted for destruction in the reticuloendothelial system (e.g. spleen)
Microangiopathic Hemolytic Anemias
Differential Diagnosis

- Disseminated intravascular coagulation (DIC)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)
- Malignant hypertension
- Aortic stenosis
- HELLP syndrome and eclampsia
- Heparin-induced thrombocytopenia
- Severe glomerulonephritis
Thrombotic Thrombocytopenic Purpura

• Classic pentad:
  – Microangiopathic hemolytic anemia
  – Thrombocytopenia
  – Renal involvement
  – Neurologic signs
  – Fever

• Most cases in adults are caused by acquired autoantibodies that inhibit ADAMTS13, a metalloprotease that cleaves vWF within platelet-rich thrombi
  – Congenital form (Upshaw-Schulman syndrome) is the result of a deficiency of ADAMTS13

• Treatment is plasma exchange +/- immunosuppression
Pathogenesis of Idiopathic TTP caused by ADAMTS13 Deficiency

Sadler, J. E. *Blood* 2008;112:11-18
## DIC vs TTP

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>DIC</th>
<th>TTP</th>
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<tbody>
<tr>
<td>Abnormal PT/PTT</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Abnormal Renal Tests</td>
<td>N</td>
<td>Y</td>
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</tbody>
</table>
Acquired Bleeding Disorders associated with PT and aPTT

- Various Medical Conditions
  - Anticoagulation
  - Disseminated Intravascular Coagulation
  - Vitamin K Deficiency
  - Liver Disease
  - Massive Transfusion

- Dysfibrinogenemias

- Acquired Inhibitors to Factors V, II & X
Vitamin K deficiency

• Vitamin K cycle
• Mechanisms of Vitamin K deficiency
• Warfarin action
Mechanisms of Vitamin K deficiency

• Nutritional depletion
  – Alcoholics, long-term IV nutrition

• Antibiotic administration
  – Interfere with bacteria synthesis and absorption

• Warfarin
  – Inhibition of epoxide reductase and (to a lesser degree) quinone reductase
Liver Disease

- Liver synthesizes and clears both procoagulants and inhibitors
- Paradoxically factor VIII is often elevated
  - Likely due to decreased clearance
- Reduced factor V helps distinguish liver synthetic dysfunction from vitamin K deficiency
- Fibrinogen the last to fall
- Structural manifestations of liver disease contribute to bleeding
  - Portal hypertension, varices, gastritis, hemorrhoids
Massive Transfusion

- Defined as transfusion of more than 1.5 times the patient’s blood volume in 24 h
- Acquired coagulopathy results from dilution of plasma and platelets and excess anticoagulant
  - 10% of transfusion is anticoagulant
- Prevention:
  - Administer 1 unit FFP and calcium chloride for every 4-6 units PRBC’s
Other uncommon acquired coagulation protein defects

- Dysfibrinogenemia
  - Acquired liver disease (EtOH, immunologic, toxic, viral)
- Inhibitors to X, V, II and fibrinogen
- Hypergammaglobulinemia
  - Multiple myeloma (IgG)
  - Waldenstrom macroglobulinemia (IgM)
- Systemic amyloidosis
  - Decreased factor X or IX
- Heparinoids
  - Heparin-like anticoagulants produced in patients with an underlying malignancy
- Factitious
  - Self-administered heparin/warfarin
Acquired bleeding disorders associated with prolonged aPTT only

- Inhibitors to factor VIII
  - Elderly, post-partum, connective tissue disorder, B cell malignancy
  - Prolonged aPTT but normal PT
  - Skin ecchymoses and tissue hematomas
  - Respond to immunosuppressive therapy
  - “bypassing agents” to treat bleeding
    - Activated prothrombin complex concentrates
    - Recombinant factor VIIa (Novoseven)
  - Prognosis generally favorable