ABNORMAL HEMOSTASIS

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Lecture Outline

I. Pathology of Platelets
II. Vascular Disorders
III. Bleeding Disorders due to Coagulation Factor Abnormalities (Hemophlias)
IV. Bleeding Disorders due to Abnormalities of the Fibrinolytic System
V. Drug Induced Bleeding Disorders
VI. HIV Associated Bleeding Disorders
VII. Diagnosis of Bleeding Disorders
**Introduction**

- Thrombotic and bleeding disorders can result from abnormalities of platelets, endothelial function and coagulation abnormalities.
- Both acquired and congenital factors contribute to these disorders.

**Illustration of the Cellular Contents of a Platelet**

1. Granular content
2. Surface receptors
3. Thromboxane formation

**Pathology of Platelets**

- Both quantitative and qualitative disorders of platelets result in bleeding and thrombotic disorders.
- These disorders may be acquired or congenital.
Role of Platelets in Hemostasis
Primary hemostatic plug, platelet factor 3 availability in the microvascular region.

Quantitative Disorders

• A number of diseases result in a decrease or increase in the number of platelets.
• A decreased platelet count results in bleeding and is known as thrombocytopenia.
• An increased platelet count results in thrombocytosis when it is benign and thrombocythemia when it is a clonal proliferation (neoplastic). Both bleeding and thrombosis may occur.
Thrombocytopenia
Decreased number of circulating platelets

• Alterations in bone marrow
  – Marrow hypoplasia, aplasia, replacement by neoplastic cells, marrow fibrosis, radiation injury, leukemia, paroxysmal nocturnal hemoglobinuria (PNH).

• Hereditary thrombocytopenia
  – May Hegglin anomaly (autosomal dominant), Wiskott-Aldrich syndrome, absent radius syndrome, Fanconi’s anemia

Thrombocytopenia
Decreased number of circulating platelets

• Abnormal hematopoiesis (acquired)
  – B12/Folate deficiency, pre-leukemia

• Drug Induced thrombocytopenia
  – Heparin, gold, quinine, quinidine, sulfonamides, GP IIb/IIIa Inhibitors

• Dilutional
  – hemodialysis, heart lung machine

Generation of Multiple Antibodies with Heparin

- Heparin
- PF-4
- Heparin-PF-4 Complex
Digital ischemia in HIT

Thrombocytopenia
Decreased number of circulating platelets

- ITP and TTP
  - ITP: Immune thrombocytopenic purpura (IgG mediated)
  - TTP: Thrombotic thrombocytopenic purpura (abnormal VWF multimers), arterial thrombi (platelet-rich)
- HUS: Hemolytic Uremic Syndrome
Thrombocytosis
Increased number of circulating platelets

- **Splenectomy** - platelets function is normal.
- **Reactive thrombocytosis** - due to cancer, infection, drugs.
- **Autonomous thrombocytosis** (thrombocythemia) clonal disorder.

Platelets ↑ (> 1,000,000/µl): clusters of platelets in circulation. Bleeding may occur.
Qualitative Disorders
Platelet numbers are usually normal, however, platelet function is impaired

- **Disease induced platelet defects**
  Liver disorders, paraproteinemia (abnormal proteins)

- **Drug induced platelet defects**
  Aspirin, NSAIDS (non-steroidal anti-inflammatory drugs)

- **Diet induced platelet defects**
  Omega 3 fatty acids (ocean fish)
Inherited Disorders of Platelets
Congenital disorders resulting in bleeding diathesis

• **Glanzmann’s thrombasthenia**
  – Autosomal recessive, GPIIb/IIIa defect, aggregation defect, bleeding time ↑

• **Bernard-Soulier disease**
  – Autosomal recessive, GP Ib defect, adhesion defect, bleeding time ↑

Inherited Disorders of Platelets
Congenital disorders resulting in bleeding diathesis

• **Storage pool disease**
  – decrease dense granule content, no aggregation

• **Other disorders**
  – Purpura of unknown origin - gray platelet syndrome, lack of alpha granules
Other Acquired Disorders of Platelets

- Metabolic disorders - uremia (bleeding)
- Myeloproliferative disorders - polycythemia vera, granulocytic leukemia, myelofibrosis.

Vascular Disorders

- These disorders are usually called non-thrombocytopenic purpuras.
- Although common, these disorders do not result in severe bleeding diathesis.
- Platelet function and coagulation are normal.
- Easy bruising, bleeding from mucosa, purpura, vasculitis.

Subendothelial Disorders

- Congenital- Ehler Danlos Syndrome-Hypermobile joints. Hyperflexible skin, osteogenesis imperfecta, drugs, infections, amyloidosis
- Acquired- Purpura simplex, amyloids, drugs, steroid purpura (prednisone), Cushing’s syndrome (steroid excess), Henoch-Schonlin purpura (usually drug induced).
Endothelial Disorders

- **Congenital**: Most common, hereditary hemorrhagic, telangiectasia (HHT), arteriovenous malformation; giant hemangioma (Kasaback-Merritt syndrome)
- **Acquired**: Inflammation, vasculitis (drugs, viruses, Rickettsia)
Mechanical Disorders

- Orthostatic purpura (standing or sitting for a long time)
- Mechanical purpura (moving too fast, i.e. elevator going really high, increased pressure)
- Increased transluminal pressure

Nutritional Disorders

- Scurvy (vitamin C deficiency)
Bleeding Disorders due to Coagulation Factor Abnormalities
Intrinsic Pathway

**Hemophilia A (Factor VIII)** and **Hemophilia B (Factor IX)** are the most common coagulation defects.

Extrinsic Pathway

Uncommon to have a congenital defect of Factor VII

Common Pathway

Molecular variants of fibrinogen are found.
Introduction

• Specific defects in clotting factors VIII, IX, etc.

Laboratory Diagnosis

• PT (extrinsic) II, V, VII, X and fibrinogen
• APTT (intrinsic) VIII, IX, XI and XII (actually measures all factors but FVII, FXIII, protein C and S).
The Hemophilias (Hemophilia A & B)

- Most defects due to coagulation factors result in bleeding.
- Hemophilia A (Classical) Factor VIII coagulant deficiency
- Hemophilia B (Christmas Disease) Factor IX deficiency
- Both are transmitted as sex linked recessive; APTT is elevated, no effect on platelets.
Von Willebrand’s Disease

- Hemostatic defect due to von Willebrand factor (ristocetin co-factor, factor VIII antigen) defect.
- vWF factor binds to platelet receptor (glycoprotein Ib) and to collagen and subendothelium.

Von Willebrand’s Disease (continued)

1. Type-1 and Type-3 von Willebrand’s diseases are characterized by a decrease in the circulating level of the factor.
2. Type-2 von Willebrand’s disease is characterized by a qualitative defect in the protein.
Hemophilias vs. Von Willebrand’s Disease

**Hemophilias**
- APTT prolongation
- Platelet function-normal
- Bleeding time - no effect

**Von Willebrand’s Disease**
- APTT slightly elevated due to mild reduction in factor VIIIc
- Hemostatic function impaired due to impaired adhesion of platelets to collagen in-vivo.
- Bleeding time elevated.

Bleeding Disorders Due to Abnormalities of the Fibrinolytic System
Introduction

• Excessive activation of the fibrinolytic system can cause bleeding.

• A decrease in the fibrinogen concentration and an increase in degradation product formation contribute to bleeding.

Primary Fibrinolysis

• In primary fibrinolysis, only fibrinogen is converted into fibrinogen degradation products.

• This condition is seen in dead fetus syndrome (Abruptio Placenta).

  plasmin

• Fibrinogen $\rightarrow$ Fibrinogen degradation products

Primary Fibrinolysis

• Excessive fibrinolysis can result in bleeding due to decreased fibrinogen levels.

• Fibrinogen degradation products can also produce anticoagulant effects.

• Overdosage of thrombolytic agents can result in a primary fibrinolytic state and cause bleeding.
Secondary Fibrinolysis
(Disseminated intravascular coagulation)

• In secondary fibrinolysis both fibrin and fibrinogen are digested by plasmin. Secondary fibrinolysis is also associated with digestion of clotting factors and consumption of platelets.

Pathogenesis of Sepsis Associated DIC

Complex syndrome/consumption coagulopathy
Deficiency of α₂-Antiplasmin

- Results in increased fibrinolysis (Bleeding)
  - Excessive plasmin digests circulating fibrinogen
Inhibition of Plasmin by $\alpha_2$ Antiplasmin ($\alpha_2$-AP)

Drug Induced Bleeding Disorders

- Bleeding with thrombolytic drugs.
- Bleeding with anticoagulants (Heparin)
- Bleeding with drugs
  - Anti-platelet drugs
  - Thrombolytic drugs
- Drug induced thrombocytopenia
- Heparin induced thrombocytopenia (HIT)

HIV Associated Bleeding Disorders

Mostly due to thrombocytopenia
Diagnosis of Bleeding Disorders

• Bleeding time
• Platelet count
• Platelet function studies
  – Adhesion
  – Aggregation
  – Activation

Which of the blood clotting tests is commonly used for the diagnosis of Hemophilias?

A. Activated partial thromboplastin time
B. Prothrombin time/INR
C. Thrombin time
D. Bleeding time
E. Fibrinogen levels

A patient was admitted to the hospital with an urinary tract infection. Two days later he developed fever and his coagulation parameters and platelet count became abnormal. Additional test showed D-dimer positive and positive blood cultures for *E. Coli*. What is the likely diagnosis of this patient?

A. DIC
B. Hemophilia
C. Hypercoagulable state
D. APC Resistance
E. Von Willebrand disease