BLEEDING DIATHESIS \(2^0\) TO PLATELETS DISORDERS

(DISORDERS OF PRIMARY HEMOSTASIS)

DISORDERS OF PLATELETS AND BLOOD VESSELS

- Questions to address:
  - Is a bleeding tendency present?
  - Is the condition familial or acquired?
  - Is the disorder one affecting
    - Primary hemostasis (platelet or blood vessel wall problems)
    - Secondary hemostasis (coagulation problems)
  - Is there another disorder present that could be the cause of or might exacerbate any bleeding tendency?
- Principal Presentations of bleeding disorders
  - Easy bruising
  - Spontaneous bleeding from mucous membranes
  - Menorrhagia – excessive bleeding during menstruation
  - Excessive bleeding after trauma

DIAGNOSIS OF BLEEDING PROBLEMS

EASY BRUISING

- Bruising with mild trauma
- Bruising without trauma
  - Petechiae
  - Ecchymoses
  - Hematoma

MUCOSAL BLEEDING & MENORRHAGIA

- Epistaxis - nosebleed
  - History of recurrence
- Gingival bleeding
- Hematuria, hemoptysis, hematemesis
  - Relatively uncommon presenting features
- Menorrhagia

EXCESSIVE BLEEDING AFTER TRAUMA

- Surgical trauma
- Dental extraction, tonsillectomy
- Delayed wound healing
- Postpartum hemorrhage
JOINT AND MUSCLE BLEEDS

- Hemarthroses (bleeding into joints) and spontaneous muscle hematomas
  - Characteristic of severe plasma protein deficiencies
  - Characteristic of Hemophilies
  - Rarely occur in other bleeding disorders
    - Except severe von Willebrand disease

TYPES OF BLEEDING DISORDERS

- Prothrombin Time (PT)
- Activated Partial Thromboplastin Time (APTT)
- Quantitative platelet count
- ( +/- ) Bleeding Time Test (BTT)
- ( +/- ) Thrombin Time

TYPICAL SCREENING TESTS FOR BLEEDING DISORDERS

<table>
<thead>
<tr>
<th></th>
<th>Platelet count</th>
<th>PT</th>
<th>APTT</th>
<th>Bleeding time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorder</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or abnormal</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Platlet Dysfunction</td>
<td>Usually Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or Abnormal</td>
</tr>
</tbody>
</table>

LAB TESTS IN DISORDERS OF PRIMARY HEMOSTASIS VASCULAR DISORDERS

- Most vascular diseases
  - Are not associated with platelet or plasma defects
  - Most common symptom
    - Abnormal bleeding into or under the skin due to increased permeability to blood
  - Laboratory tests are used to exclude
• Coagulation or platelet disorders
  – Majority of patients
  • Hemostatic testing is entirely normal, despite a history or physical examination that suggests substantial bleeding

**PLATELET DISORDERS**

• Quantitative
  – Thrombocytopenia
  – Thrombocytosis
• Qualitative
• Morphologic abnormalities
  – Macrothrombocytes
  – Microthrombocytes
  – Hypogranular or agranular platelets

**THROMBOCYTOPENIA**

• Platelet count
  – <150 x 10^9/L
  – Usually no ↑ risk of bleeding unless <50 x 10^9/L
  – Risk of severe and spontaneous bleeding when platelet count is <10 x 10^9/L
  – Petechiae
  – Bleeding from mucous membranes
    • GI, GU tract, etc
    • Bleeding into CNS
    • BT is related to the platelet count unless there is also a concurrent platelet dysfunction
• Thrombocytopenia may result from
  – Abnormal platelet distribution
  – Deficient platelet production
  – Increased platelet destruction

**PLATELET SEQUESTRATION (DISTRIBUTION DEFECT)**

• Normally ~30% of platelets held in spleen
• Splenomegaly/hypersplenism
  – Up to 90% sequestered
  – May occur in a wide variety of diseases
    • Infection
    • Inflammation
    • Hematologic diseases
    • Neoplasias

**DECREASED PRODUCTION**

• Failure of BM to deliver adequate platelets to the peripheral blood
Hypoplasia of megakaryocytes
- Drug or radiation therapy for malignant disease
  - Generalized marrow suppression
- Acquired aplastic anemia
- Replacement of normal marrow
  - Leukemias and lymphomas
  - MDS
  - Other neoplastic diseases
  - Fibrosis or granulomatous inflammation
- Ineffective thrombopoiesis
  - Megaloblastic anemia

DECREASED PRODUCTION
- Hereditary thrombocytopenias
  - Congenital aplastic anemia
  - Wiskott-Aldrich Syndrome (WAS)
  - X-Linked Thrombocytopenia (XLT)
  - Bernard-Soulier syndrome (BSS)
  - May-Hegglin anomaly (MHA)
  - Congenital amegakaryocytic thrombocytopenia (CAMT)
  - Congenital thrombocytopenia with radioulnar synostosis (CTRUS)
  - Thrombocytopenia with absent radii Syndrome (TAR)

INCREASED DESTRUCTION
- Immune destruction
  - Platelets are destroyed by antibodies
    - Platelets with bound antibody are removed by mononuclear phagocytes in the spleen
    - Anti-platelet antibody tests to identify antibodies on platelets are available

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)
- Caused by an autoreactive antibody to the patient’s platelets
  - Young children – acute and usually transient for 1-2 weeks with spontaneous remission
  - Adults – chronic and occurs more often in women
- Treatment
  - Corticosteroids
  - Splenectomy
  - Rituximab

ALLOIMMUNE THROMBOCYTOPENIAS
- Isoimmune neonatal thrombocytopenia
  - Maternal antibodies produced against paternal antigens on fetal platelets
– Similar to erythroblastosis fetalis
– HPA-1a
– Most serious risk: bleeding into CNS
• Posttransfusion purpura
  – More common in females
    • Previously sensitized, pregnancy or transfusion
  – Thrombocytopenia
    • Usually occurs 1 week after transfusion
    – Transfused and recipient’s and antigen-negative platelets are destroyed

**DRUG-INDUCED THROMBOCYTOPENIAS**

• Many drugs implicated
• Same mechanisms as described for drug induced destruction of RBCs
• Symptoms of excess bleeding
  – Usually appear suddenly and can be severe
• Removal of drug
  – Usually halts thrombocytopenia and bleeding symptoms

**HEPARIN & THROMBOCYTOPENIA.**

• Heparin associated thrombocytopenia (HAT)
  – Non-immune mediated mechanism
  – Develops early in treatment and is benign
  – Heparin causes direct platelet activation
    • Thrombocytopenia
  – Immune mediated destruction of platelets
    • Antibody develops against a platelet factor 4-heparin complex
      • Attaches to platelet surface
      • ↑ platelet clearance

**NON-IMMUNE MECHANISMS OF DESTRUCTION**

• Disseminated intravascular coagulation (DIC)
• Thrombotic thrombocytopenic purpura (TTP)
• Hemolytic Uremic Syndrome (HUS)
• PNH
• Mechanical destruction – artificial heart valves

**THROMBOCYTOSIS**

• ↑ platelet count above reference range
  – Peripheral blood smear
    • > 20 platelets per 100 x oil immersion field
  – Result of ↑ production by BM (not prolonged lifespan)
  – ↑ BM megakaryocytes
Primary
• Occurs in chronic myeloproliferative disorders and myelodysplasia

Secondary thrombocytosis
• Reactive thrombocytosis
• ↑ platelets caused by another disease or condition

Transient thrombocytosis

QUALITATIVE PLATELET DISORDERS

• Clinical symptoms vary
  – Asymptomatic → mild, easy bruisability → severe, life-threatening hemorrhaging

• Type of bleeding
  – Petechiae
  – Easy & spontaneous bruising
  – Bleeding from mucous membranes
  – Prolonged bleeding from trauma

INHERITED QUALITATIVE PLATELET DISORDERS

• Defects in platelet-vessel wall interaction
  – Disorders of adhesion
    • von Willebrand disease
      – Deficiency or defect in plasma VWF
    • Bernard-Soulier syndrome
      – Deficiency or defect in GPIb/IX/V
    • Defects in collagen receptors
      – GP-IcIIa; GPVI

• Defects in platelet-platelet interaction
  – Disorders of aggregation
    • Congenital afibrinogenemia - Deficiency of plasma fibrinogen
    • Glanzmann thrombasthenia
      – Deficiency or defect in GPIIb/IIIa

INHERITED QUALITATIVE PLATELET DISORDERS

• Defects of platelet secretion and signal transduction
  – Diverse group of disorders with impaired secretion of granule contents
  – Results in abnormal aggregation during platelet activation

• Abnormalities of platelet granules
  – Storage pool deficiency
• αSPD (grey platelet syndrome)
• δSPD
• αδSPD
• Defects in platelet coagulant activity
  – Decreased Va-Xa binding and VIIIa-IXa binding slows normal coagulant response.

VON WILLEBRAND DISEASE

ACQUIRED QUALITATIVE PLATELET DISORDERS
• Chronic renal failure
  – Platelet defects associated with uremic plasma
    • Dialysis corrects abnormal test results
• Cardiopulmonary bypass surgery
  – Thrombocytopenia
  – Abnormal platelet function
    • Correlates with duration of the bypass procedure
    – Platelet defect likely due to
      • Effects of platelet activation
      • Fragmentation in extracorporeal circulation
• Liver disease
  – Thrombocytopenia due to splenomegaly from portal hypertension
• Paraproteinemias
  – Clinical bleeding and platelet dysfunction are often seen

HEMATOLOGIC DISORDERS THAT AFFECT PLATELET FUNCTION
• Chronic Myeloproliferative Disorders
  – Can see either bleeding or thrombosis
  – Abnormal platelet function
• Leukemias & Myelodysplastic Syndromes
  – Bleeding usually due to thrombocytopenia
  – Abnormal platelet function
• Dysproteinemias
  – MM and Waldenström’s macroglobulinemia
  – Thrombocytopenia most likely cause of bleeding

**DRUGS THAT ALTER PLATELET FUNCTION**

• A variety of drugs alter platelet function
  – Some are used therapeutically for their antithrombotic activity
  – For others, abnormal platelet function is an unwanted side effect
  – Effect on platelet function
    • Defined by an abnormality of bleeding time or platelet aggregation
    • Aspirin is the only drug with a definitely established risk of excessive bleeding

**DRUGS THAT ALTER PLATELET FUNCTION**

• Aspirin
  – Inhibits platelet aggregation
  – Inhibits platelet secretion

**THANK YOU**