Qualitative and Quantitative Platelet Disorders

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<table>
<thead>
<tr>
<th>Platelet vs. Coagulation Bleeding</th>
<th>Findings</th>
<th>Coagulation</th>
<th>Platelet</th>
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<tr>
<td>Petechiae</td>
<td>Rare</td>
<td>Common</td>
<td></td>
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<tr>
<td>Hematomas and Hemarthroses</td>
<td>Common</td>
<td>Rare</td>
<td></td>
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<tr>
<td>Delayed Bleeding</td>
<td>Common</td>
<td>Rare</td>
<td></td>
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<tr>
<td>Bleeding cuts</td>
<td>Minimal</td>
<td>Persistent</td>
<td></td>
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<tr>
<td>Gender</td>
<td>Male</td>
<td>Women</td>
<td></td>
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<tr>
<td>Mucosal</td>
<td>Minimal</td>
<td>Typical</td>
<td></td>
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</tbody>
</table>

N.B. Some platelet disorders are associated with thrombosis (HIT, TTP)

Laboratory Tests

- Automated Cell Counter
  - Platelet Count
  - Mean Platelet Volume
  - Platelet Distribution
- Smear morphology
- Coagulation
  - PT, aPTT, Fib, TT
- Bleeding Time
- Aggregometry
- vWD
  - Ristocetin Cofactor
  - vWF:Ag
  - FVIII:C
  - Multimers

Platelet Signaling

EDTA

Forward Scatter: Size
Side Scatter: Complexity
Case

22 year old student athlete undergoes a routine preoperative physical exam and laboratory studies prior to right knee arthroscopy; he has no significant past medical history; no bleeding or family bleeding history; he takes no medications; physical exam is unremarkable

WBC 5.0, Hct 45%, Plt 20K, smear next slide

Pseudothrombocytopenia
Anti-coagulant dependent agglutinins associated with EDTA
Re-rerun with citrate or heparin tube

Platelet Morphology

Bernard-Soulier
Gray Platelet Syndrome

Real or Spurious Platelet Count: Schistocytes

Platelets 200K, but platelets rarely seen on smear

- To screen for inherited platelet dysfunction (e.g. vWD)
- Done under standardized conditions
  - 40 mmHg
  - Two small punctures on volar surface
  - Absorbed every 30 sec
  - Measured by time in minutes
  - Should not be done if plt<50K, anemia or uremia
- Mainly affected by platelet number and function, hematocrit
- There is no evidence that the bleeding time predicts bleeding
- no correlation between bleeding time and visceral bleeding
Bleeding Time Prolonged

- Congenital
- Drugs (e.g. antiplatelet drugs +/- ASA)
- Alcohol
- Uremia
- Hyperglobulinemias
- Fibrin/fibrinogen split products
- Thrombocythemia
- Cardiac Surgery

Interpretation

- Evaluate the slope of aggregation; both primary and secondary wave
- Evaluate the extent of aggregation
- Low dose ADP: two waves; high dose a single wave
- Epi biphasic in 80% of normal
- Collagen acts by releasing ADP so only a single wave
- Ristocetin antibiotic that makes vWF bind platelets and induces aggregation; normal tracing does not exclude vWD

Aggregometry

- Purpose: used to detect abnormalities in platelet function
- Principle: an aggregating agent is added to platelet rich plasma in a cuvette; as the platelets aggregate, the light transmission increases
- Specimen: platelet rich plasma prepared from citrate whole blood with test completed within 3 hours of the collection
- Procedure: soft spin to prepare platelet rich plasma prepared; hard spin to prepare platelet poor plasma (blank)

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Accumetrics

- Fibrinogen coated beads
- Agonist (e.g. ADP)
**Evaluate as two groups**

- **Quantitative**
  - Production, Destruction, Sequestration

- **OR**

- **Qualitative**
  - Adhesion, Aggregation, Secretion, Other

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**Quantitative**

- **Production**
  - Reduced
    - Megakaryocytes
    - Infiltration (e.g. tumor)
    - Aplasia (e.g. chemicals)
    - Congenital (e.g. WAS)

- **Ineffective**

  - Megaloblastic anemia, myelodysplasia, ETOH

- **Destruction**
  - Immune
    - Autoantibody e.g. ITP
    - Alloantibody
    - NAT, HIT
  - Consumption
    - DIC
    - TTP
    - Mechanical

- **Sequestration**
- **Hemodilution**
- **Real or Spurious?**

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**Case**

- 75 year-old man with no significant past medical history s/p bowel resection for carcinoma. He spiked a temperature of 103. Blood and urine cultures are positive for GNR. He is noted to have petechiae on his legs. His venipuncture sites are oozing. No organomegaly.

- Data: WBC 25K with left shift, Hct 30%, Plts 20K. PT 21s, PTT 120s, Fib 80, D-Dimer>20, schistocytes

- DDX: ITP, TTP/HUS, DIC, HIT

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**Case**

- 35 year-old F previously in good health, developed URI sx's 1 wk PTA. A few days later, felt "hot" with headache, and developed bruising on ant shins. Went to urgicare, sent home. Then was called back for admission in the evening, due to PLT 5

- PE: T 99, VS stable, marked ecchymosis on B/L extremities, especially LE, a few on body.

- Lab:
  - PLT 5, WBC 7.7, H/H=11.3/34.3
  - PT/PTT 12.4/30.7, fib 327
  - TB/DB 2.6/0.4, AST/ALT 65/13
  - BUN 11, Cr 0.5
  - Urine: hemoglobin 2+, RBC 15, WBC 0-2, Prot. neg
  - PB smear: schistocytes > 5/HPF
  - ANA, Speckled nuclearplasmic patterns

- DDX: ITP, HELLP, HUS, DIC, HITetc.

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**TTP In Brief**

**Pentad**

- Microangiopathic hemolytic anemia ( vesel narrowing) with schistocytes (mechanical injury to RBCs)
- Severe Thrombocytopenia
- (systemic PLT aggregation)
- Neurologic abnormalities
- (CNS ischemia)
- Acute renal insufficiency
- (renal ischemia)
- Fever
- Associated with thrombosis
- Plasmapheresis w FFP infusion
- Prednisone
Qualitative

- Inherited
  - Bernard-Soulier
  - Glanzmann’s
  - Storage pool disease (Chediak-Higashi, Wiscott-Aldrich, Hermansky-Pudlak, Gray Platelet Syndrome)

- Acquired
  - Drugs (e.g. ASA, ADP, Iib/IIa)
  - Uremia, Post-bypass
  - Primary marrow disorders; MDS, Dysproteinemias

Inherited

- Adhesion
  - Bernard-Soulier

- Aggregation
  - Glanzmann’s

- Secretion
  - E.g. Gray Platelet Syndrome

Glanzmann’s Thrombasthenia

- Rare Condition
- Inherited absence of GPIIb/IIIa (AR)
- Severe Bleeding manifestations
  - GPIIb/IIIa a key platelet glycoprotein required for aggregation
- Absence of aggregation with ADP, Epi, Collagen
- Normal ristocetin
Bernard-Soulier

- Rare inherited bleeding disorder
- Lack of GPIb which is necessary for the formation of the hemostatic plug by binding to subendothelial von Willebrand factor
- Aggregation with ADP, Epi and collagen; absent ristocetin

von Willebrand’s Disease

- Inherited bleeding disorders
- Absent or decreased levels of vWF or lack of large and medium sized multimers
- Work up includes vWF:Ag level, FVIII:C activity, Ristocetin Cofactor Activity, Platelet Aggregation studies

Thrombocytopenias

- Common
- Abnormality in the release reaction
- Storage Pool Disease (no ADP in granules)
- Release defect (defects in mechanism of release)
- Resembles same pattern as aspirin

Hermansky-Pudlak

- 21 month old male with bruisability and bleeding
- Albino features
- Oculomotor nystagmus
- Delayed development
- Tyrosinase-positive oculocutaneous albinism (Ty-pos OCA), bleeding diathesis, and systemic complications associated to ceroid-lipofuscin–like lysosomal storage disease.

Case

- 33 year old woman with menorrhagia
- History of epistaxis since childhood
- Cousin with similar problems
- Aspirin for headaches; no other meds
- PT, PTT, TT, Platelets normal count
- Blood smear platelet morphology normal
Differential Diagnosis

• Inherited
  – Bernard-Soulier
  – Glanzmann’s
  – Storage Pool Defect
  – vWD
• Acquired
  – DIC, MDS, uremia, drugs, dysproteinemia

Type I vWD

• Most frequently encountered
• All polymeric forms are present, but to a decreased level
• Bleeding time usually prolonged; can be normal if mild deficiency

vWD Lab Workup

• Bleeding Time
• Ristocetin Cofactor (functional)
• Ristocetin Aggregation
• vWF Ag (quantitative)
• Factor VIII:C
• Multimeric Analysis

Type II vWD

• Type IIA
  • Amount synthesized may be normal
  • Failure to form intermediate or large multimers
  • BT usually prolonged
  • FVIII decreased or normal
• Type IIB
  • Less common
  • May not respond to DDAVP
  • Largest multimers are absent
  • Concentration too low to induce aggregation

Type III

• Severe bleeding disorder
• Very low levels of all multimers; low vWF:Ag, FVIII:C, Ristocetin Cofactor activity
<table>
<thead>
<tr>
<th>Test</th>
<th>IA</th>
<th>IIA</th>
<th>IIB</th>
<th>III</th>
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<tbody>
<tr>
<td>BT</td>
<td>V</td>
<td>V</td>
<td>V</td>
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<tr>
<td>FVIII</td>
<td>D</td>
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<tr>
<td>vWAg</td>
<td>D</td>
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<td>Rist Cof</td>
<td>D</td>
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<td>D or N</td>
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<tr>
<td>Rist Aggr</td>
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<tr>
<td>Multimer</td>
<td>N</td>
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