Qualitative and Quantitative Platelet Disorders

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Platelet Signaling

Platelet vs. Coagulation Bleeding

<table>
<thead>
<tr>
<th>Findings</th>
<th>Coagulation</th>
<th>Platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Hematomas and Hemarthroses</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Delayed Bleeding</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding cuts</td>
<td>Minimal</td>
<td>Persistent</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Women</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Minimal</td>
<td>Typical</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
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
Real or Spurious Platelet Count: Schistocytes

Platelets 200K, but platelets rarely seen on smear

NORMAL

+Schistocytes

Hct 43.5
PLTs 184
MPV 9.6
MCV 96.7

Hct 40
PLTs 850
MPV --
MCV 70.4
Platelet Morphology

- Bernard-Soulier
- Gray Platelet Syndrome

- 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

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)
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
Accumetrics

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

• Quantitative
  – Production, Destruction, Sequestration

• OR

• Qualitative
  – Adhesion, Aggregation, Secretion, Other

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
      – NAIT, HIT
  – Consumption
    • DIC
    • TTP
    • Mechanical

• Sequestration
• Hemodilution
• Real or Spurious?
Thrombocytopenia on Automated Counter

Rerun with Heparin Anticoagulant

Clumping? NO

Obvious Reason? YES

Bone Marrow Megakaryocytes

Decreased Normal

MDS, Infiltrate

DIC, TTP, ITP, HIT, drugs, SLE

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
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, HIT etc.

TTP In Brief

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

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

• Acquired
  – Drugs (e.g. ASA, ADP, Iib/IIIa)
  – 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

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.

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
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

vWD Lab Workup

• Bleeding Time
• Ristocetin Cofactor (functional)
• Ristocetin Aggregation
• vWF Ag (quantitative)
• Factor VIII:C
• Multimeric Analysis
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
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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</thead>
<tbody>
<tr>
<td>BT</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>FVIII</td>
<td>D</td>
<td>D or N</td>
<td>D or N</td>
<td>D</td>
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<tr>
<td>vWAg</td>
<td>D</td>
<td>N or D</td>
<td>N or D</td>
<td>D</td>
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<td>Rist Cof</td>
<td>D</td>
<td>D</td>
<td>D or N</td>
<td>D</td>
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<tr>
<td>Rist Aggr</td>
<td>D or N</td>
<td>D</td>
<td>I</td>
<td>D</td>
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<tr>
<td>Multimer</td>
<td>N</td>
<td>A</td>
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