Platelet Disorders

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INTRODUCTION

• QUANTITATIVE DISORDERS
  Thrombocytopenia
  Thrombocytosis

• QUALITATIVE DISORDERS
THROMBOCYTOPENIA

- Thrombocytopenia is defined as a count below 150,000/μL.
- Platelet-type bleeding typically involves skin or mucous membranes, including petechiae, purpura, ecchymosis, epistaxis, menorrhagia, and GI hemorrhage.
- Deep muscle hematomas and hemarthrosis are typically seen with defects in fluid hemostatic system.
- Clinical bleeding varies.
THROMBOCYTOPENIA

• Symptoms depend on the degree of thrombocytopenia
• At counts above 50,000/µL there are usually NO Symptoms
• At counts of 20,000 to 50,000/µL the patient may report EASY BRUISABILITY but no spontaneous bleeding is seen
• At counts <20,000/µL patients are AT HIGH RISK FOR SPONTANEOUS BLEEDING (GI bleeds, Mucous Membranes, Petechiae)
Thrombocytopenia: CAUSE?

Four Mechanisms

1. Decreased Bone Marrow Production
2. Sequestration
3. Accelerated Destruction in the periphery
4. Pseudo-Thrombocytopenia!!
# DRUGS AND PLATELETS

<table>
<thead>
<tr>
<th>Decreased platelet production</th>
<th>Increased platelet destruction</th>
<th>Altered platelet function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>Sulfonamides</td>
<td>Aspirin</td>
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<tr>
<td><strong>Alcohol</strong></td>
<td>Carbamazepine</td>
<td>Dipyridamole</td>
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<tr>
<td>Chloramphenicol</td>
<td>Heparin</td>
<td>SSRI</td>
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<tr>
<td>Interferon therapy</td>
<td>Quinidine/Quinine</td>
<td>Clopidogrel</td>
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<tr>
<td>Thiazide diuretics</td>
<td>Valproic acid</td>
<td></td>
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<tr>
<td>Estrogens</td>
<td>Digoxin</td>
<td></td>
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<tr>
<td>Ionizing radiation</td>
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<tr>
<td>Anticonvulsants</td>
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SEQUESTRATION

- Kasabach-Merritt syndrome – giant cavernous hemangioma and consumptive coagulopathy

- Hypersplenism (including liver disease)
  - Splenomegaly
  - Peripheral blood shows anemia, leukopenia, thrombocytopenia
  - Normo- or hypercellular bone marrow
  - Counts normalize after splenectomy
ACCELERATED DESTRUCTION

• IMMUNE
  Neonatal alloimmune thrombocytopenia (NAIT)
  Posttransfusion purpura (PTP)
  Immune Thrombocytopenia (ITP) and neonatal autoimmune thrombocytopenia

Drugs
  HIV
  Sepsis

• NONIMMUNE (mechanical damage or consumption)
  TTP/HUS
  DIC
ITP (Immune Thrombocytopenia)

• One of the most common acquired bleeding disorders encountered by the Hematologist

• Also the most common autoimmune disorder affecting a blood element
DIAGNOSIS

• Diagnosis of exclusion
• Antecedent infectious illness ~ 60%
• Physical exam remarkable only for purpura
• Negative family history
• Peripheral blood smear reveals thrombocytopenia and normal to large platelets
Primary versus Secondary ITP

ITP Diagnosis

- Thrombocytopenia without obvious etiology
- Exclude: HIV, HepC, HepB, H. pylori, Lymphoma, common variable hypogammaglobulinemia
- Bone marrow shows megakaryocyte production
- May have increased IgG/IgM on platelets
TREAT THE PATIENT, NOT THE COUNTS!

• Steroids: prednisone vs dexamethasone
• IV Immunoglobulin
• Anti-D antigen therapy
• Splenectomy
• Anti-CD20 therapy (Rituximab)
• Thrombopoietin analogs
  • Romiplostin
  • Eltrombopag
• Immunosuppressive agents
## Compare and Contrast Acute versus Chronic ITP

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>2-6 years</td>
<td>20-50 years</td>
</tr>
<tr>
<td>Sex predilection</td>
<td>None</td>
<td>Female over male, 3:1</td>
</tr>
<tr>
<td>Prior infection</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Onset of bleeding</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt;20,000/uL</td>
<td>30,000-80,000/uL</td>
</tr>
<tr>
<td>Duration</td>
<td>2-6 weeks</td>
<td>Months to years</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>90% of patients</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Seasonal pattern</td>
<td>Higher incidence in winter and spring</td>
<td>None</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>70% response rate</td>
<td>30% response rate</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Rare</td>
<td>&lt;45 yrs, 90% response; &gt;45 yrs, 40% response</td>
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Heparin-Induced Thrombocytopenia & Thrombosis Syndrome (HITTS)

• Occurs in 1-2% of patients getting unfractionated heparin and 0.5-1% patients getting low molecular weight heparin.

• Defined as a 50% drop in platelet count anywhere from 3-30 days after heparin administration.

• First manifestation is thrombocytopenia; 70% or more patients get venous or arterial thrombosis.

• Most are subclinical and thus need to be searched for by objective testing like venous doppler studies.
Pathogenesis of HITTS
Clinical-pathologic Criteria for Diagnosis of HIT

Clinical
(1) One or more of the following:
   Thrombocytopenia
   Thrombosis (venous, arterial, or microvascular)
   Necrotizing skin lesions at injection sites
   Acute anaphylactoid reactions
(2) Appropriate timing of heparin exposure
(3) Absence of a more compelling explanation

Pathologic
(1) Positive platelet activation assay
(2) Positive anti-PF4/heparin IgG assay

Warkentin TE
Agents for the treatment of heparin-induced thrombocytopenia.
Diagnosis & Management of HIT/HITTS

• Diagnosis
  - High index of clinical suspicion
  - Elisa for PF4 antibodies with heparin suppression
  - Platelet serotonin release assay with patient serum

• Management
  - Stop heparin, low molecular weight heparin
  - Warfarin is CONTRAINDIATED!
  - Anticoagulate with a direct thrombin inhibitor
  - Determine if occult thrombosis to ascertain duration of anticoagulation
Thrombotic Thrombocytopenia Purpura (TTP) (Moschcowizt Syndrome)

- TTP and HUS (hemolytic uremic syndrome) are both acute syndromes with abnormalities in multiple organ systems
- Evidence of MAHA and thrombocytopenia
- Presenting features are essentially the same in most adult patients
- Pathologic changes and Initial treatment is same
Definitions and Diagnosis

• The Classic Pentad of TTP
  – Microangiopathic hemolytic anemia
  – Thrombocytopenia
  – Renal insufficiency or abnormalities
  – Neurologic abnormalities that can be fluctuating
  – Fever

• Most common symptoms at presentation are nonspecific and include abdominal pain, nausea, vomiting and weakness.

• Male: female = 1:2
Mechanism of TTP

**ADAMTS13:** a disintegrin and metallo-protease with thrombospondin-like motifs-13
Pathogenesis of idiopathic thrombotic thrombocytopenic purpura (TTP) caused by ADAMTS13 deficiency
Thrombotic Thrombocytopenia Purpura (TTP) (Moschcowitz Syndrome)

- Clinical Presentations
- Congenital (Upshaw-Schulman Syndrome)
- Idiopathic acquired
  - Associated with medication such as clopidogrel, ticlopidine, quinine, cyclosporine, gemcitabine, mitomycin C
- BM transplant-associated (TMA-thrombocytopenic microangiopathy)
Other Thrombocytopenias & MAHA

Hemolytic Uremic Syndrome (HUS) (mostly children)

Present with bloody diarrhea and frank renal failure
Verocytotoxin-producing *E. coli* 0157:H7, 0104:H4 & Shigella toxin
Food contamination: hamburger meat, spinach, fruit
*E coli* LPS & Stx toxin from Shigella stimulate cytokines
Renal inflammation and injury

Atypical HUS – Complement proteins defects

Factor H, I, membrane complement protein (MCP), thrombomodulin, C3, factor B, diacylglycerol kinase ε (DGKE)
Microangiopathic Hemolysis
### Differential Diagnosis of Acquired Destructive Thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>APTT</th>
<th>Platelets</th>
<th>Schistocytes</th>
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<tbody>
<tr>
<td>DIC</td>
<td>Long</td>
<td>Long</td>
<td>Low</td>
<td>+/-</td>
</tr>
<tr>
<td>ITP</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>-</td>
</tr>
<tr>
<td>TTP</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>+++</td>
</tr>
<tr>
<td>HUS</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>+++</td>
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Case 1

- JB is a 64 year old AAF, with no significant PMH, admitted for chest pain with mildly elevated troponin (1.12)
- Wbc 10.8, H/H 9.2/27.2, plt 19
- CMP normal except for BUN 48, Creat 2, AST 93, ALT 61, T bil. 3.3
- Patient has a seizure shortly after admission
• LDH 1400, Haptoglobin <8
• Reticulocytes 4%
• Coagulation screen and fibrinogen WNL
Case 2

- SR is a 51 yr old AAF who presents with a rash on her arms and blisters in her oral cavity.
- PMH of sarcoidosis, COPD, HTN
- Denies fevers, chills, change in medications.
- Wbc 5.7 (normal Diff), Hb 12.6, Plts 1
• PT/aPTT normal range
• LDH, haptoglobin normal
• BUN 19, creat 1.2 (baseline)
Case 3

• CF is a 28 yr male, with not significant PMH.
• CBC on routine annual examination reveals platelet count of 70K, rest cbc within normal limits.
• No bleeding history
• No FH of blood disorders
• No medications
• P/E within normal limits
Case 4

• AE is a 66 yr old male with a neuroendocrine duodenal mass. Underwent Whipple procedure.
• 8 days post op, wbc 12.2, H/H 9.1/27.7, plts 27 (250-309 previously)
• BUN 24, creat 3.4 (previously normal)
• Slightly drowsy
• Routine CT abd day prior show non-occlusive splanchnic vein thrombus
• AST 792, ALT 253, Bil normal
• LDH 981, Hapto 166
• Coags: PT 17.6, aPTT normal
• Argatroban initiated for suspected HIT
• 4 limb usg - right femoral vein clot
• Repeat abd imaging – hepatic vein thrombus
• PF4 Ab strongly positive
• SRA confirmed diagnosis