Disclosure

• I am receiving an honorarium from Sysmex for today's presentation.

Platelets – The Basics

• Platelets are also called thrombocytes
• Biconvex discoid in shape
• Cytoplasmic fragments of a megakaryocyte
• Platelets do not have a nucleus
• Shed in the bone marrow and found in the peripheral blood
• 1/3 the size of a normal erythrocyte with a ratio of platelet to red blood cell approx. 1:15
• Four zones
  1) Peripheral  2) Sol-gel  3) Organelle  4) Membranous
From Stem Cell to Mature Blood Cells

- From stem cell to platelet

**Platelet Production is driven by the Hormone, Thrombopoietin produced in the Kidneys and Liver**

Breaking it Down

- **Peripheral Zone**
  - Rich in glycoproteins required for adhesion, activation and aggregation
- **Sol-gel Zone**
  - Rich in microtubules and microfilaments allowing platelets to maintain the discoid shape
- **Organelle Zone**
  - Rich in platelet granules
    - Alpha - contain clotting mediators, Factors V, VIII, Fibrinogen
    - Delta - also called "dense bodies" contain ADP, calcium & serotonin
- **Membranous Zone**
  - Endoplasmic reticulum-derived membranes organized into a dense tubular system responsible for thromboxane A2 synthesis
Let’s Take a Look

- microtubules
- dense tubules
- Surface-connecting tubule coat
- glycogen
- mitochondria
- alpha granule
- dense granule

Looks Like a Horror Movie

Platelet Kinetics

- Megakaryocyte and platelet production is regulated by thrombopoietin, a hormone produced in the kidneys and liver
- Each megakaryocyte produces between 1,000 and 3,000 platelets during its lifetime
- An average of 10 billion platelets are produced daily in healthy adults
- Reserve platelets are stored in the spleen and released when needed by splenic contraction
- Average life span of a circulating platelet is 6-8 days
- Old platelets are destroyed by phagocytosis in the spleen and liver
Platelet Dynamics

**IT'S COMPLICATED**

- **193** proteins and **301** interactions are involved
- Three stages – Adhesion, Activation, Aggregation
- These stages occur in rapid succession and each continues until the trigger for that stage is no longer present – lots of overlap!!

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Super Simplified

- **Adhesion** - Platelets attach to the outside of the interrupted endothelium
  - When an endothelial layer is disrupted, collagen and vWF anchor platelets to the sub-endothelium.
  - Platelet GP1b-IX-V receptor binds with vWF and GPVI receptor binds with collagen
- **Activation** - Platelets change shape, turn on receptors & secrete chemical messages
  - Occurs seconds after adhesion starts
  - Activated platelets secrete the contents of their granules through their canalicular systems to the exterior
  - Morphology of platelet changes and becomes "sticky"
- **Aggregation** - Platelets connect to each other through receptor bridges
  - Occurs minutes after activation starts
  - Shape changes from curled to straight and becomes capable of binding

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Come Together

-**Fibrinogen**
-**Glycoprotein Iib/IIia**
-**von Willebrand factor**
-**Collagen**
-**Glycoprotein VI**

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Platelet Disorders

• There are several things that can cause problems
  • **Thrombocytopenia** - Not enough
  • **Thrombocytosis** - Too many
  • **Dysfunctional** - Not working correctly

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Thrombocytopenia – Not Enough

• Immune Thrombocytopenic purpura (ITP)
• Thrombotic Thrombocytopenic purpura (TTP)
• Chemotherapy induced
• Splenomegaly
• Drug induced
• Aplastic anemia
• Pregnancy associated
• Babesiosis
• Pseudothrombocytopenia

• **And it goes on and on and on**

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Thrombocytosis – Too Many

**Reactive**
  • Chronic infection
  • Chronic inflammation
  • Malignancy
  • Post splenectomy
  • Iron deficiency
  • Acute blood loss

**Myeloproliferative neoplasms** (platelets elevated and dysfunctional)
  • Essential thrombocytosis
  • Polycythemia vera
  • Congenital
  • Associated with other myeloid neoplasms
Dysfunctional – Not Working

**Congenital**
- Bernard-Soulier Syndrome – adhesion disorder
- Hermansky-Pudlak Syndrome – activation disorder
- Wiskott-Aldrich Syndrome – aggregation disorder
- Plus many, many more …
  - Granule amount and release disorder
  - ADP receptor defect
  - Storage pool defects

**Acquired**
- PNH (Paroxysmal Nocturnal Hemoglobinuria)
- Asthma
- Cancer
- Samter’s Triad (aspirin exacerbated respiratory disease)

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Drugs – Just Say “NO”

- Different drugs can affect platelet function in various ways.
  - **Suppress Platelet Function**
    - Aspirin
    - Clopidogrel
    - Cilostazol
  - **Stimulate Platelet Production**
    - Thrombopoietin mimetics
    - Desmopressin
    - Factor VIIa

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Aspirin – Just for a Minute

- Aspirin irreversibly disrupts platelet function by inhibiting cyclooxygenase -1 (COX-1) thus preventing normal hemostasis
- Platelets in the presence of aspirin are unable to produce new cyclooxygenase
- Normal platelet function will not return until the use of aspirin has ceased and old platelets are replaced with new ones that haven’t been exposed to aspirin
- Time to return to normal function after discontinuing use of aspirin is about one week
Symptoms of Platelet Disorders

- Excessive bleeding
- Spontaneous bleeding
- Petechiae
- Purpura
- Bleeding gums
- Nose bleed
- G.I. bleed
- Menorrhagia
- Intracranial bleeding
- Thrombosis

Pictures to Ponder

Purpura

That looks nasty
Pictures to Ponder

Nose Bleed
Bleeding Gums

Pictures to Ponder

Blood Clot In The Brain
Blood Clot In The Leg

A Few For Us to Review in More Detail

- ITP – Immune Thrombocytopenic Purpura
- TTP – Thrombotic Thrombocytopenic Purpura
- CIT – Chemotherapy Induced Thrombocytopenia
- Thrombocytosis in Iron Deficiency Anemia
- Polycythemia Vera
- Bernard-Soulier Syndrome
Taking a Closer Look at ITP

- Immune (Idiopathic) Thrombocytopenic Purpura
  - Autoimmune disorder resulting in thrombocytopenia
  - Etiology unknown
    - Acute infection may trigger
    - Increased prevalence in people with systemic autoimmune diseases such as Rheumatoid arthritis and systemic lupus (SLE)
  - Genetic component suspected to predispose

ITP – The Mechanism

- Complex, unbalanced immune response
- Antibodies attach to platelet surface-membrane glycoproteins
- Platelets bound by these antibodies contain the FC region of the antibody and are cleared by FcyR-bearing macrophages in the reticuloendothelial system (monocytic phagocytic cells in the spleen)
- Macrophages are highly stimulated which adds to the efficient binding of the coated platelets

A Picture Says 1000 Words

- Platelet opsonization occurs = decreased platelets
- And an interesting aside, platelet production also decreased
Treatment of ITP

- Treatment is based on severity of symptoms and not on platelet count.
- First line therapy for ITP is corticosteroids
  - These suppress the immune system (T and B cell reactivity)
  - Urgent situations require infusions of dexamethasone or methylprednisolone
  - Less severe cases are usually treated with oral prednisone
  - Steroid therapy is reduced as the platelet count increases and patient symptoms stabilize
  - Approx. 75% of patients will experience a relapse during dose reduction or cessation

Other Options for ITP Treatment

- Anti-D (must be Rh positive to be a candidate)
- Immunosuppressants
- Vincristine
- IVig
- N plate (Romiplostim)
- Splenectomy
TTP – What’s the Difference

- Thrombotic Thrombocytopenic Purpura
  - Thrombotic microangiopathy
  - Platelet consumption resulting in thrombocytopenia
  - Rare disease – only 6 cases per million per year – most acquired but rare congenital
  - Occurs when there is an ADAMTS13 deficiency
    - Autoimmune disease – development of inhibitory antibodies to ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombospondin type 1 motifs, member 13) (Now that’s a long name)
  - Acute, life threatening disease that is a medical emergency
- Symptoms
  - Thrombocytopenia
  - Hemolytic anemia
  - Confusion
  - Headaches
  - Visual problems
  - Renal impairment
  - Fever

Let’s talk about this

TTP Under the Microscope

Very Rare Platelet Noted on Peripheral Smear
  - Plus Schistocytes

TTP in Layman’s Terms

- VWF (VonWillebrand’s Factor) is a multimeric plasma glycoprotein that recruits platelets to the site of vessel injury
- VWF multimeric size directly relates to its hemostatic activity
  - The bigger it is the more hypercoagulability the VWF multimer
- Regulation of the VWF size is controlled by ADAMTS13
- Deficiency in ADAMTS13 allows VWF multimer to increase in size and in hyperactivity
- Results are unwanted platelet aggregation and platelet rich thrombus formation
## Treatment for TTP

**First line treatment for TTP is plasma exchange**
- Plasma exchange removes circulating ADAMTS13 autoantibodies and provides a fresh source of ADAMTS13.
- Decreases mortality from 90% down to 10%.
- During crisis, patient undergoes plasma exchange 2-3 times a day until stable and then once a day until the 2nd day after platelet count is back to normal.
- Continued exchange every 3-4 weeks to prevent relapse.

**ADAMTS13**
- No natural inhibitor
- Long plasma half-life
- Relatively low levels required to keep VWF multimers in check.

**Immunosuppression drugs are used to combat the autoimmune component of the disease.**

## Chemotherapy Induced Thrombocytopenia

**Chemotherapy-induced thrombocytopenia (CIT) is a common hematologic side effect of both myelosuppressive and ablative therapy.**

**CIT has the risk of life-threatening spontaneous hemorrhage.**

**CIT necessitates reduction and delays in chemotherapy treatment.**
- Dose and time schedule of chemo drug is scientifically derived to produce the best chance of survival or cure.
- When dose of therapy is reduced or treatment cycles prolonged, cure rates are lowered.

## What Causes CIT?

**Chemotherapy works by killing rapid growing cancer cells**
- Hematopoietic progenitor cells are also rapid growing cells
- Chemotherapy interferes with cell production in the bone marrow.

**Thrombopoietin is the primary regulator of thrombopoiesis**
- Promotes megakaryocyte differentiation from stem cells
- Works in conjunction with other cytokines including interleukin.

**Interaction between megakaryocytes and bone marrow stromal components are critical for platelet production**
- Chemotherapy results in myelosuppression of the marrow stroma.
- Megakaryocytes cannot be produced until the hematopoietic tissue bed repairs and reconstitutes.
Treatment for CIT

- Most common treatment is platelet transfusion
  - Transfusions are a temporary fix until the bone marrow can start producing platelets on its own
  - Dose reduction of chemotherapy or holding chemotherapy will allow the marrow to recover more quickly
- Growth factor drugs used to stimulate production
  - Romiplostim (Nplate)
  - Eltrombopag (Promacta)

Thrombocytosis in Iron Deficiency

- Iron Deficiency is the leading cause of anemia
- Microcytic-hypochromic iron deficiency anemia impairs oxygen delivery to the tissues
- Iron deficiency anemia has lower numbers of circulating red cells - less cells to carry the oxygen
- Receptor cells in the kidneys detect low O2 levels
- Kidneys respond by increased secretion of erythropoietin into the blood
- Erythropoietin causes the proerythroblasts in the bone marrow to mature more quickly
  
  Nice, but what does this have to do with platelets??????

Thrombocytosis in Fe Deficiency

- Side effects of Erythropoietin in the bone marrow
  - There is a degree of homology in the amino acid sequence in erythropoietin and thrombopoietin (the hormone that stimulates platelets)
  - The result is there is also stimulation of the megakaryoblasts by the erythropoietin resulting in an increased production of platelets
- Reactive Thrombocytosis occurs
  - The greater the degree of iron deficiency the greater the degree of thrombocytosis
  - Increased chance of thrombosis - can be life threatening
- Vice Versa
  - Treatment of the iron deficiency reduces the thrombocytosis and the chance of a thromboembolic event
Polycythemia Vera (PCV)

- Also known as erythremia
- Neoplasm in which bone marrow produces too many RBCs
- Also, results in overproduction of WBCs and Platelets
- Most common in the elderly
- May or may not be symptomatic

Signs of PCV

- Itching
- Pain in hands and feet
- Bluish coloration of skin
- Gout-like type of arthritis
- Peptic ulcers
- Headache

More severe PCV can result in:

- Heart attack
- Stroke
- DVTs
PCV Mechanism

- Results from a mutation occurring in tyrosine kinase
  - Janus Kinase family - J AK2 (V617F)
- Results in erythroid precursors being hypersensitive to erythropoietin
  - Very little erythropoietin causes massive production of RBCs. Also results in over production of platelets
- Essential thrombocytopenia
  - Increased platelet "stickiness"
  - Tiny blood clots in vessels of extremities
  - High volume of blood causes sluggish flow - giving more time for platelets to get "stuck"

Polycythemia Vera Under the Microscope

- Lots and lots of RBCs and lots and lots of Platelets

Treatment of PCV

- Chronic disease – no cure
- Untreated cases may be fatal
- Need to treat the symptoms
  - Therapeutic phlebotomy
    - Decreases the number of circulating RBCs
  - Aspirin therapy
    - Decreases the platelets ability to “stick”
  - Interferon
  - Chemotherapy
    - Hydroxyurea – with caution
      - Leads to increased risk of converting to Acute Myelogenous Leukemia (AML)
Bernard–Soulier Syndrome

- Hemorrhagiparous thrombocytic dystrophy
- Rare autosomal recessive coagulopathy
  - Deficiency or dysfunction of glycoprotein complex
    - GPIb/V/IX - the receptor for von Willebrand factor
- Decreased platelet survival
- Increase in megakaryocytes and large/giant platelets
- Inability of platelets to bind and aggregate at the sites of vascular endothelial injury

Signs /Symptoms in Bernard-Soulier

- Pre and postoperative bleeding
- Bleeding gums
- Easy bruising
- Heavy menstrual periods
- Nosebleeds
- Prolonged bleeding from small cuts
- Decreased platelet counts (20,000 – 100,000)
- Large and giant platelets on peripheral smear
- Often misdiagnosed
Low number of Platelets and Platelets are large in size

**Treatment for BSS**
- No cure - but can have quality of life
- Therapeutic approaches to general and specific treatment of bleeding episodes
- Patients should avoid aspirin products
- Blood and platelet transfusions used when severe bleeding occurs
- Desmopressin found to decrease bleeding times
- Bone marrow or stem cell transplantation in extreme cases

**Platelet Count Testing**
Platelet Count Testing

- Sysmex XN-1000
- Fluorescent Platelet Count
  - Done whenever platelet count is 50,000 or below or when specifically requested by the physician
  - Added benefit is
    - Immature Platelet Fraction (IPF)

Immature Platelet Fraction (IPF)

- IPF is a measure of immature platelets in the circulating blood
- An increased IPF with thrombocytopenia may indicate:
  - Peripheral destruction or consumption of platelets such as:
    - Idiopathic thrombocytopenia (ITP)
    - Thrombotic thrombocytopenic purpura (TTP)
    - Disseminated intravascular coagulation (DIC)
**Immature Platelet Fraction (IPF)**

- Another important use of the IPF - monitor marrow recovery post chemotherapy.
- Platelets are killed off by chemotherapy drugs
  - Some drugs such as Gemzar can destroy most of the circulating platelets and suppress production in the bone marrow.
- In bone marrow recovery, platelets are produced to resupply the peripheral blood.
- When platelets are needed in the blood, immature platelets are released early from the marrow.
- **A high IPF post chemotherapy is a good indication that platelets are being produced.**

**Normal and Immature Platelets**

**Examples of Canned Text Comments for Platelets and IPF**

**Fluorescent Platelets**
- Platelet count obtained by Fluorescent Flow Cytometry methodology which is specific for Platelet Mitochondria, providing the most accurate enumeration

**Immature Platelet Fraction**
- An elevated immature Platelet Fraction indicates platelets are being produced
- A low platelet and low IPF is consistent with a platelet production disorder
Case Studies

Finally, What You’ve Been Waiting For!

Fall in Michigan

Case #1 Fall in Platelets

46 year old married man with twin 14 year old sons is diagnosed with Pancreatic Cancer – CT 157.0. He has no family history of cancer of any kind. He presented with upper abdominal pain – like an ulcer. CT scan showed a mass on the head of the pancreas and biopsy confirmed adenocarcinoma. Patient is going through first line treatment with Gemcitabine (Gemzar). Treatment plan is 7 cycles of Gemzar and then a resection of tumor if possible.

Note: A cycle is three weeks long. Chemotherapy drug is given on day one and day eight. In addition, laboratory work, including a CBC is done on these days. No drug is given on day fifteen but the patient presents for lab tests and a nurse evaluation.

Weekly CBCs are done to make sure blood counts are within range so drug can be given safely.

Baseline CBC: Initials (Cycle 1 - Day 1)

<table>
<thead>
<tr>
<th>COMPLETE BLOOD COUNT</th>
<th>WBC</th>
<th>RBC</th>
<th>MCH</th>
<th>MCV</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected Range:</td>
<td>4.0 - 11.0</td>
<td>4.0 - 11.0</td>
<td>32.5 - 35.5</td>
<td>82.0 - 97.0</td>
<td>33.5 - 36.5</td>
</tr>
<tr>
<td>Measured Value:</td>
<td>3.3</td>
<td>4.48</td>
<td>33.3</td>
<td>86.2</td>
<td>39.2</td>
</tr>
<tr>
<td>Unit:</td>
<td>x10^12/L</td>
<td>x10^12/L</td>
<td>g/dL</td>
<td>fl</td>
<td>g/dL</td>
</tr>
<tr>
<td>Ordered By:</td>
<td>001</td>
<td>001</td>
<td>001</td>
<td>001</td>
<td>001</td>
</tr>
</tbody>
</table>
Action Taken

- Patient’s nurse is proactive and reports the IPF of zero to the physician.
- The physician holds that day’s scheduled chemotherapy treatment. The patient is then scheduled to return the very next day for a repeat CBC and nurse evaluation.
- Patient is also given instructions not to shave and to call if he has a nose, gum or any other type of bleed.
- The patient returns in the morning for the CBC. Platelet count is 6 and IPF is still 0. The patient receives 10 units of platelets.
- Patient able to attend his twins’ football game that night.
**Summary - CIT**

- Before having the ability to run and report the immature platelet fraction parameter, this patient may have been given his day 8 chemotherapy treatment.
- The patient’s platelet count would not have been scheduled to be rechecked until the following Monday, which would have been day 15 of cycle three.
- The patient may have experienced serious bleeding and would have reported to the Emergency Department resulting in a hospital admission and a platelet transfusion.
- By running the IPF, the extreme drop in platelets was not only anticipated but was proactively followed, giving the patient the required transfusion before an active bleed.
- Not only did the IPF improve the patient’s outcome, it greatly reduced medical dollars by eliminating an Emergency Room visit and a hospital stay.

**Case #2  New Consult for Thrombocytopenia**

- A 67 year old man presents for evaluation of low platelet level
- Patient has no history of bleeding problems but platelet count from routine physical before having a colon polyp removed reveals a platelet count of 8,000
- Surgery was postponed and patient was referred for a hematology consultation
- History of surgery: tonsillectomy as a child with no known complication or profuse bleeding
- Repeat CBC was done in the Hematologist’s office

**Results from the Analyzer**

- Low platelet count plus
- Platelet clump flag equals
- Slide review needed
But Not Really

- Platelet Count from analyzer = 8,000
- But look what is on the slide????

Summary - Pseudothrombocytopenia

- CBC was repeated with collection in a Na Citrate tube in place of the traditional EDTA tube.
- Platelet count from the Na Citrate tube = 278,000
- Pseudothrombocytopenia also called spurious thrombocytopenia
- Phenomenon caused by in vitro agglutination of platelets
- Analyzers cannot differentiate between platelet clumps and individual cells
- Primary causes for this phenomenon
  - EDTA anticoagulant
  - Cold Agglutinins
  - Multiple Myeloma

Case #3 - Unexplained Blood Clot

- A 39 year old female presents with a blood clot in her leg
- Patient has a history of iron deficiency due to heavy menorrhagia
- Patient also claims to have bleeding episodes between periods
- Patient takes a minimal dose of oral iron due to problems with constipation when taking increased dose of iron supplements
- History of iron infusions and blood transfusions due to anemia
- Full hematology work up done in office including CBC, Ferritin and Iron/Iron binding
CBC Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>5.07</td>
<td>x10^9/L</td>
</tr>
<tr>
<td>RBC</td>
<td>3.73</td>
<td>x10^12/L</td>
</tr>
<tr>
<td>MCHC</td>
<td>28.9</td>
<td>g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>80.0</td>
<td>fl</td>
</tr>
<tr>
<td>MPV</td>
<td>18.8</td>
<td>pg</td>
</tr>
<tr>
<td>HCT</td>
<td>36.3</td>
<td>%</td>
</tr>
<tr>
<td>HGB</td>
<td>12.9</td>
<td>g/dL</td>
</tr>
<tr>
<td>PLT</td>
<td>130.0</td>
<td>x10^9/L</td>
</tr>
</tbody>
</table>

This Supports Iron Deficiency

<table>
<thead>
<tr>
<th>Result</th>
<th>Value (Previous)</th>
<th>Units</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>&lt;5.0</td>
<td>ng/mL</td>
<td>10 - 120</td>
</tr>
<tr>
<td>ION / IRON BINDING</td>
<td>12.6</td>
<td>ug/dl</td>
<td>37 - 245</td>
</tr>
<tr>
<td>TIBC</td>
<td>441</td>
<td>ug/dl</td>
<td>250 - 400</td>
</tr>
<tr>
<td>Iron Sat Percent</td>
<td>3</td>
<td>%</td>
<td>15 - 50</td>
</tr>
<tr>
<td>Vitamin B12 / FOLATE</td>
<td>452</td>
<td>pg/ml</td>
<td>200 - 1100</td>
</tr>
<tr>
<td>Folate</td>
<td>10.1</td>
<td>ng/mL</td>
<td>0 - 20</td>
</tr>
</tbody>
</table>

Cross Over Stimulation

Stimulation of Megakaryoblasts by erythropoietin resulting in increased platelet production and increased chance of a thrombotic episode.
Follow Up

- Significant anemia consistent with iron deficiency
- In addition, fatigue, headaches and dyspnea
- 2 units of PRBC’s given
- Strongly recommend a GYN consultation for possible hysterectomy
- New FDA approved IV iron preparation called Injectafer will be given in one week
- Will recheck CBC in 2 weeks
- And if you’re wondering, IPF is normal at 2.4%

Two Weeks Later

- Hemoglobin goes up and platelet count goes down

<table>
<thead>
<tr>
<th>Complete Blood Count (CBC)</th>
<th>Platelet Count</th>
<th>IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cells (RBC)</td>
<td>4.4</td>
<td>14,000</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>110,000</td>
<td>46%</td>
</tr>
<tr>
<td>Hemoglobin (Hgb)</td>
<td>12.4</td>
<td>14,000</td>
</tr>
</tbody>
</table>

Two Weeks Later

Case #4

Unexplained Thrombocytopenia

- A 29 year old woman presents to her physician with unexplained bruising and petechiae
- Patient states recent viral illness (had the flu for 4 weeks)
- Past history of thrombocytopenia at age 2 that resolved spontaneously with no intervention and was attributed to ITP
- LDH is slightly elevated at 420 U/L
- Initial CBC reveals platelet count of 14,000 and IPF (immature platelet fraction) of 46%
- IPF indicates bone marrow is working – not a production problem!
- Are platelets being consumed or destroyed?????
The Results

### Diagnosis and Treatment

- Due to medical history and rapid onset of thrombocytopenia following a recent viral infection this is most likely recurrence of ITP
- Lack of evidence of end organ damage lowers the suspicion for TTP
- Extremely low platelet count along with very high IPF reflects common findings in ITP (IPF in TTP would not be as high)
- Initial therapy was 1 mg/kg dosing of prednisone. After no significant improvement in 48 hours of starting the corticosteroid, IVIG was added with a 1 g/kg X2 day course
- Platelet count responded appropriately and count increased to 114,000.
- Patient to continue on 90 mg prednisone and follow up with weekly CBC checks.

### 5 Days Later - Following Treatment

<table>
<thead>
<tr>
<th>WBC</th>
<th>12.7 x10^3</th>
<th>4.0 - 11.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB</td>
<td>10.9 g/dL</td>
<td>12.0 - 16.0</td>
</tr>
<tr>
<td>HCT</td>
<td>33.3 %</td>
<td>36.0 - 47.0</td>
</tr>
<tr>
<td>MCV</td>
<td>80.1 fl</td>
<td>82.0 - 97.0</td>
</tr>
<tr>
<td>MCH</td>
<td>27.0 pg</td>
<td>27.0 - 32.5</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.4 g/dL</td>
<td>32.4 - 32.8</td>
</tr>
<tr>
<td>Plat</td>
<td>114 x10^3</td>
<td>150 - 400</td>
</tr>
<tr>
<td>%</td>
<td>2.79 %</td>
<td>2.4 - 4.5</td>
</tr>
<tr>
<td>NYCT</td>
<td>0.15 %</td>
<td>0.03 - 0.8</td>
</tr>
<tr>
<td>RDW-CV</td>
<td>16 %</td>
<td>11.9 - 14.8</td>
</tr>
<tr>
<td>IMMATURE PLATELET FRACTION</td>
<td>17 %</td>
<td>0.0 - 7.0</td>
</tr>
</tbody>
</table>

The results show a significant improvement in platelet count following treatment.
Case #5  Low Hemoglobin – High Platelets

- A 41-year-old male presented to the clinic with splenomegaly related to his history of severe anemia due to pyruvate kinase deficiency (PKU)
  - PKU is an inherited metabolic disorder of the enzyme pyruvate kinase. This enzyme is essential in glycolysis for ATP production in the RBC.
  - Without pyruvate kinase, RBCs cannot synthesize ATP and cellular death occurs by dehydration at the cellular level.
- The patient routinely has Hgb levels of 6-7g/dl.
- He has not been under the care of a physician for several years.

- Additional symptoms include abdominal pain due to splenic infarcts.
- CBC was drawn with the following results:
  - Hgb low at 6.3 and platelet count high at 489 – remember the cross-over effect of erythropoietin?

<table>
<thead>
<tr>
<th>COMPLETE BLOOD COUNT</th>
<th>Final</th>
<th>Ordered by: 02</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>1.98</td>
<td>low</td>
</tr>
<tr>
<td>Hgb</td>
<td>6.3</td>
<td>low</td>
</tr>
<tr>
<td>HCT</td>
<td>19.4</td>
<td>low</td>
</tr>
<tr>
<td>MCV</td>
<td>110.6</td>
<td>high</td>
</tr>
<tr>
<td>MCH</td>
<td>34.8</td>
<td>high</td>
</tr>
<tr>
<td>MCHC</td>
<td>31.0</td>
<td>low</td>
</tr>
<tr>
<td>Plat</td>
<td>489</td>
<td>high</td>
</tr>
</tbody>
</table>

- Patient receives two units of packed RBCs and returns for weekly CBCs and follow up care.
- When patient comes in on 7/9, Hgb is 8.5 but platelets are crazy high - over a million.

<table>
<thead>
<tr>
<th>Result</th>
<th>7/9/2015 11:24 PM</th>
<th>8/22/2015 10:31 PM</th>
<th>8/19/2015 8:06 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>14.8</td>
<td>6.1</td>
<td>6.3</td>
</tr>
<tr>
<td>ANC</td>
<td>10.2</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>RBC</td>
<td>3.71</td>
<td>2.66</td>
<td>2.03</td>
</tr>
<tr>
<td>Hgb</td>
<td>6.5</td>
<td>9.0</td>
<td>7.0</td>
</tr>
<tr>
<td>HCT</td>
<td>26.0</td>
<td>27.3</td>
<td>22.3</td>
</tr>
<tr>
<td>MCV</td>
<td>95.9</td>
<td>102.6</td>
<td>109.9</td>
</tr>
<tr>
<td>MCH</td>
<td>31.4</td>
<td>33.8</td>
<td>34.5</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.7</td>
<td>33.0</td>
<td>31.4</td>
</tr>
<tr>
<td>Plat</td>
<td>WOW</td>
<td>1325</td>
<td>433</td>
</tr>
</tbody>
</table>
What are Those High Platelets From?

- The medical technologist takes the report with the critical high 1,325 platelet count to the physician.
- The physician informs the tech that the patient had a splenectomy the previous week due to the splenic infarcts which were the cause of the patient's abdominal pain.
- The spleen plays a major role in platelet regulation as the primary site of destruction of platelets.
- Reactive thrombocytosis is a predictable finding after a splenectomy with platelet counts peaking at 1 to 3 weeks and returning to normal levels after about a month but can take a year or even longer.

Case #6 Tooth Extraction Complication?

- 48 year old woman reports to the Emergency Dept. with complaints of generalized weakness with increased intensity over the past week.
- States visual changes in her right eye – very difficult to see.
- History includes recent tooth extraction (two weeks prior) followed by antibiotic therapy to ward off infection.
- Patient has increased bruising & bloody nose. Also shares she has persistent blood clots and bleeding in her mouth.
- She states that she has had dyspnea on exertion and chills on and off for the past month.

Ultra-sound and Lab work done

- Ultra-sound shows blood clot in her retinal vein.
- Lab test shows a CBC with a WBC of 1.7, Hgb 3.3 and platelet count of 1.

Pancytopenia
Bone Marrow Production Problem

<table>
<thead>
<tr>
<th>WBC</th>
<th>1.7 ×10^9/L</th>
<th>10^9/L</th>
<th>4-11</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>0.3 ×10^9/L</td>
<td>1000/mm^3</td>
<td>1.5-7.7</td>
</tr>
<tr>
<td>RBC</td>
<td>1.84 ×10^12/L</td>
<td>10^12/L</td>
<td>3.9-5.2</td>
</tr>
<tr>
<td>HGB</td>
<td>3.3 g/dL</td>
<td>g/dL</td>
<td>12-15</td>
</tr>
<tr>
<td>HCT</td>
<td>10.1 %</td>
<td>%</td>
<td>36-47</td>
</tr>
<tr>
<td>MCV</td>
<td>64 fl</td>
<td>fl</td>
<td>82-97</td>
</tr>
<tr>
<td>MCH</td>
<td>17.9 g/dL</td>
<td>g/dL</td>
<td>27-33.4</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.6 g/dL</td>
<td>g/dL</td>
<td>32.5-35.5</td>
</tr>
<tr>
<td>Plat</td>
<td>1 ×10^9/L</td>
<td>×10^9/L</td>
<td>varies</td>
</tr>
<tr>
<td>IMMATURE PLATELET FRACTION</td>
<td>0.0 %</td>
<td>%</td>
<td>Indicates Bone Marrow Production Problem</td>
</tr>
</tbody>
</table>

The Follow-up

- Patient was admitted to the hospital and transfused in order to get her hemoglobin above 7 & platelets above 15
- Hematology consultation was ordered which included a bone marrow biopsy to determine the cause of the pancytopenia
- Bone marrow was notable for Aplastic anemia
- Multiple blood and platelet transfusions did not improve her blood counts
- Patient was put on cyclosporine (immunosuppressive therapy) along with prednisone (steroid therapy)
- Did the complications and medication from the tooth extraction cause the Aplastic anemia?
Tooth Extraction Or Aplastic Anemia?

Aplastic Anemia

Under the Microscope

Hypocellular bone marrow

- Decreased hematopoiesis
- Increased fat spaces
Summary and Conclusion

- Retinal clot was most likely due to complications from the tooth extraction – clot formed at site of extraction and traveled to retinal vein
- Although the onset of the Aplastic anemia could be the result of the exposure to the antibiotics it is more likely that the tooth extraction brought an underlying problem to the surface
- Because the patient states she had shortness of breath and chills for over a month and the dental work was only two weeks before her hospital admission, the conclusion would be the Aplastic anemia was already present
- The Aplastic anemia resulted in decreased platelet production thus making it difficult for healing at the site of the tooth extraction

Case #7 Blast from the past - 2005

- 19 year old female presents to the Emergency Department with a headache - states for over a week
- In addition, nausea, vomiting, fatigue and confusion
- CBC reveals a HGB=5.8g/dl and platelet count = 1,000
- Patient was jaundiced and bilirubin was 4.4 mg/dl
- Blood smear showed microspherocytes and schistocytes
- Coombs test was negative
- Bone Marrow biopsy was performed and peripheral smear sent to pathologist for review. Results consistent with consumption and a clinical diagnosis of TTP

The Test Confirms TTP

- ADAMTS13 Activity Test <5 L % (normal range >67)
- This range of ADAMTS13 is high risk and associated with an increased risk for recurrent clinical episodes of TTP
Treatment

• Patient was treated with plasma exchange, steroids and was given PRBC’s
  • Plasma exchange 3 times a day for the first week
  • Then plasma exchange 1 time a week for ten weeks
  • Steroids – Solu-Medrol 250 mg IV
  • 2 units of PRBC’s
  • Daily CBC’s until normal and then 1x week for 1 year

Fast Forward to 2015

• 29 year old female seen for thrombocytopenia, platelet count at initial visit = 9,000 with an IPF =19%
• Microangiopathic hemolytic anemia, Hgb=6.4 and elevated LDH (LDH =1138)
• Peripheral smear compatible with the diagnosis of recurrent TTP
• Patient has history of TTP – 2005 – treated successfully with plasmapheresis
• Complicating factor – patient is 19 weeks pregnant
• Patient has had two miscarriages in the past, possibly related to her TTP

Here We Go Again
Moving Too Fast

- Patient begins daily plasmapheresis X2
- TTP is a high risk factor in pregnancy
- Due to complications, baby is delivered by cesarean section at 24 weeks
- Baby boy is born and is only 11” long and weighs 1 lb, 6 oz. He is admitted to neonatal intensive care unit
- Mom continued to have plasmapheresis after delivery but is tapered down to 3 times weekly
- Mom’s platelet count is stable at 296,000
- At 5 weeks, baby boy stable & up to 1 lbs, 12 oz. He will remain in NICU for several months, but he is making good progress

Happy Ending

www.nichw.com
My Embarrassing Bruise

Fell off the step stool looking for the previous picture

At least I didn't break my neck – and I did find the picture

www.drew.com