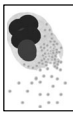
Slide 1



Platelets:
Purpose, Pictures
plus
Problems

Slide 2

Objectives

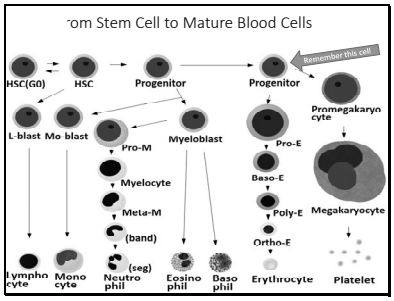
1. **Review the basic function of platelets**
2. **Exam the 3 stages of platelet function**
3. **Take an in depth look at several disease states involving platelets**
4. **Review case studies involving platelet abnormalities**

Slide 3

Platelets – The Basics

- Also called thrombocytes
- Biconvex discoid shaped
- Cytoplasmic fragments of a megakaryocyte
- 1/3 the size of a normal erythrocyte with a ratio of platelet to red blood cell approx. 1:15
- Shed in the bone marrow and found in the peripheral blood

Slide 4



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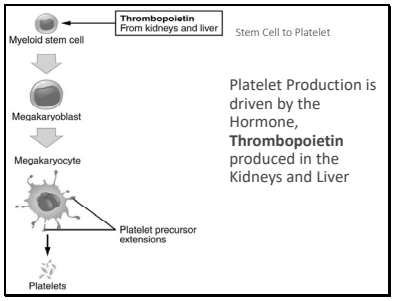


Stem Cell to Platelet

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

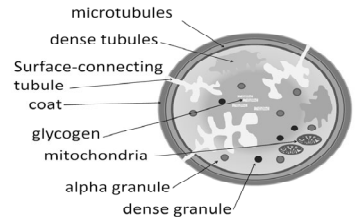
Slide 6

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

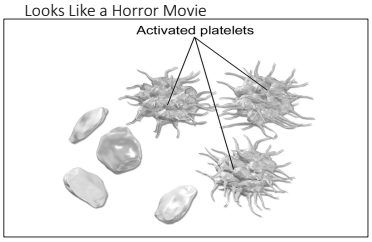
Slide 7

Let's Take a Look



Slide 8

Looks Like a Horror Movie



Slide 9

Platelet Kinetics

- Production regulated by thrombopoietin, a hormone produced in the kidneys and liver
- Each megakaryocyte produces 1,000 – 3,000 platelets
- Approx. 10 billion platelets are produced daily in healthy adults
- Average life span is 6-8 days
- Old platelets are destroyed by phagocytosis in the spleen and liver

Slide 10

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!!

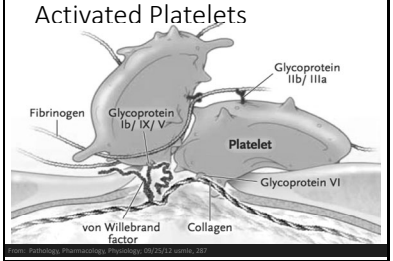
Slide 11

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 & secret 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

Slide 12

Activated Platelets



Elsm. Pathology, Pharmacology, Physiology, 09/25/12 comb. 287

Slide 13

Platelet Disorders

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

Slide 14

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**

Slide 15

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

Slide 16

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)

Slide 17

Drugs and Platelets

Different drugs affect platelet function in various ways

Some Drugs
- **Suppress Platelet Function**
  - Aspirin
  - Clopidogrel (Plavix)
  - Cilostazol

Some Drugs
- **Stimulate Platelet Production**
  - Thrombopoietin mimetics
  - Desmopressin
  - Factor VIIa

Slide 18

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 which is needed in order for platelets to aggregate
- 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

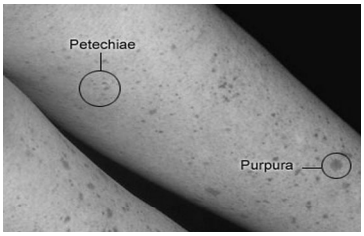
Slide 19

Symptoms of Platelet Disorders

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

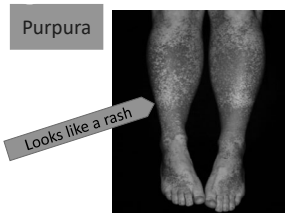
Slide 20

Pictures to Ponder



Slide 21

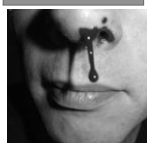
Pictures to Ponder

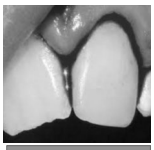


Slide 22

Pictures to Ponder

Nose Bleed

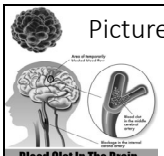




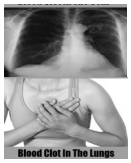
Bleeding Gums

Slide 23

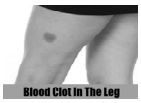
Pictures to Ponder



Blood Clot In The Brain



Blood Clot In The Lungs



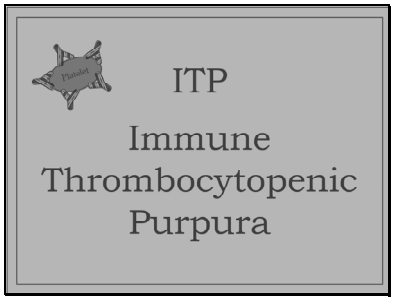
Blood Clot In The Leg

Slide 24

Disorders 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**

Slide 25



Slide 26

Taking a Closer Look at ITP

- Immune (Idiopathic) Thrombocytopenic Purpura
  - Autoimmune disorder resulting in thrombocytopenia
  - Etiology unknown
    - Acute infection may trigger

Slide 27

In Addition with ITP

- Increased prevalence in people with systemic autoimmune diseases such as Rheumatoid arthritis and systemic lupus (SLE)
- Genetic component suspected to predispose

Slide 28

ITP – The Mechanism

- Complex, unbalanced immune response
- Antibodies attach to platelet surface-membrane glycoproteins
- Macrophages are highly stimulated which adds to the efficient binding of the coated platelets

Slide 29

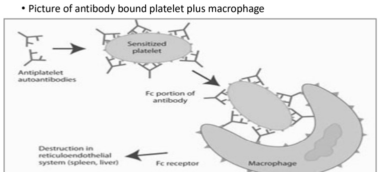
ITP – The Mechanism

- Platelets bound by these antibodies contain the FC region of the antibody
- Platelets are cleared by FcyR-bearing macrophages
- Occurs in the reticuloendothelial system, specifically the monocytic - phagocytic cells in the spleen

Slide 30

A Picture Tells the Story

- Picture of antibody bound platelet plus macrophage



- Platelet opsonization occurs = decreased platelets
- And an interesting aside, platelet production may also be decreased in some cases

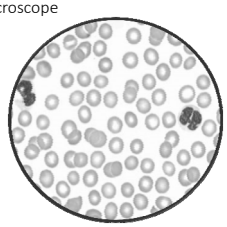
From: Fikri Abdullah Zawawi, Kathryn Kaniasan; Health and Medicine 11-13-16

Slide 31

ITP Under the Microscope

Very Rare Platelet Noted on Peripheral Smear

RBCs are normal



Slide 32

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

Slide 33

Other Options for ITP Treatment

- Anti-D (must be Rh positive to be a candidate)
- Immunosuppressant Therapy
- Vincristine
- IVIg
- N plate (Romiplostim)
- Splenectomy

Slide 34

TTP

Thrombotic Thrombocytopenic Purpura

Slide 35

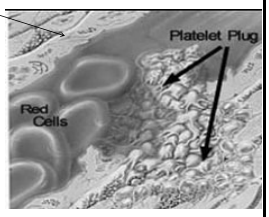
TTP – What's the Difference

- Thombotic 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
      ADAMTS13 = **A** **D**isintegrin **A**nd **M**etalloproteinase with **T**hrombospondin type 1 motifs, member **13**
  - 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

Slide 36

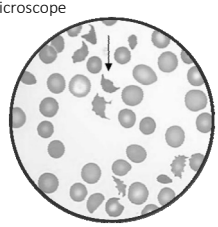
RBCs Forced to Travel in Narrowed Vessel
Red Cells may **BURST** going through



Slide 37

TTP Under the Microscope

Very Rare Platelet Noted on Peripheral Smear Plus Schistocytes



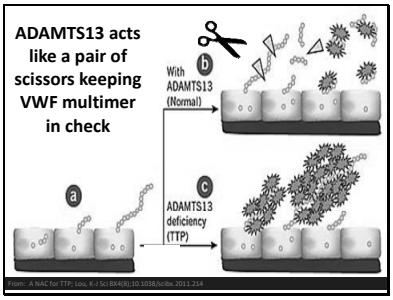
Slide 38

TTP in Layman's Terms

- VWF (VonWillebrand's Factor) is a multimeric plasma glycoprotein. It recruits platelets to the site of vessel injury.
- VWF multimeric **size** directly **relates** to its **hemostatical activity**
  - **The larger 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

Slide 39

ADAMTS13 acts like a pair of scissors keeping VWF multimer in check



Slide 40

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

Slide 41

Treatment for TTP

- ADAMTS13
  - No natural inhibitor
  - Long plasma half-life
  - Relatively low levels required to keep VWF multimers in check
- Immunosuppression drugs
  - Used to combat autoimmune aspect of the disease
  - Stops immune system from making more antibodies !

Slide 42

CIT

Chemotherapy Induced Thrombocytopenia

Slide 43

Chemotherapy Induced Thrombocytopenia

- Chemotherapy-induced thrombocytopenia (CIT) is a common hematologic side effect of both myelosuppressive and ablative therapy
- Runs the risk of life-threatening spontaneous hemorrhage
- CIT necessitates reduction or delays in chemo treatment

However

- **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**

Slide 44

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 myeloablation of the marrow stroma
  - Megakaryocytes cannot be produced until the hematopoietic tissue bed repairs and reconstitutes

Slide 45

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)

Slide 46

Thrombocytosis in Iron Deficiency

Slide 47

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

Slide 48

Thrombocytosis in Iron Deficiency

- 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

But what does this have to do with platelets ?

Slide 49

Thrombocytosis in Fe Deficiency

Side effects of Erythropoietin in bone marrow

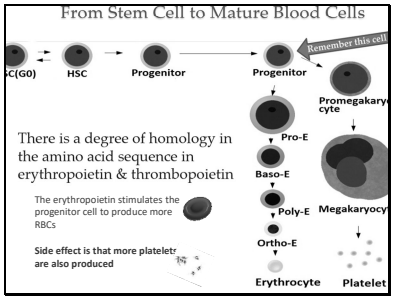
- There is a degree of homology in the amino acid sequence in erythropoietin and thrombopoietin (the hormone that stimulates platelets)
- This results in stimulation of the megakaryoblasts by the erythropoietin resulting in an increased production of platelets

Slide 50

Thrombocytosis in Fe Deficiency

- 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, reduces the chance of a thromboembolic event

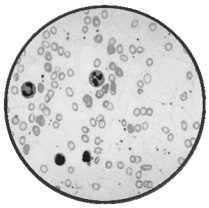
Slide 51



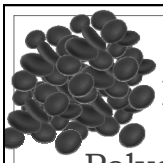
Slide 52

Under the Microscope in Iron Def.

Microcytic - Hypochromic RBCs with Increased Platelets



Slide 53



PCV

Polycythemia Vera

Slide 54

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

Slide 55

Signs of PCV

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

More severe PCVcan result in:

- Heart attack
- Stroke
- DVT's

Slide 56

PCV Mechanism

- Results from a mutation occurring in tyrosine kinase
  - Janus Kinase family – JAK2 (V617F)
- Erythroid precursors become hypersensitive to erythropoietin

  Very little erythropoietin causes mass production of RBCs. Also results in over production of platelets!

Slide 57

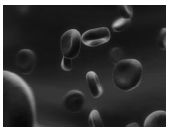
PCV Mechanism

- Results from a mutation occurring in tyrosine kinase
  - Janus Kinase family – JAK2 (V617F)
- Results in erythroid precursors being hypersensitive to erythropoietin
  - Very little erythropoietin causes mass production of RBCs. Also results in over production of platelets.
- Essential thrombocythemia
  - Increase in platelet "stickiness "
  - Tiny blood clots in vessels of extremities
  - High volume of blood causes sluggish flow – giving more time for platelets to get "stuck"

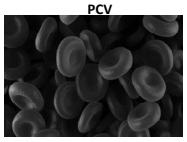
Slide 58

High number of RBCs makes travel slow

Normal Number of RBCs



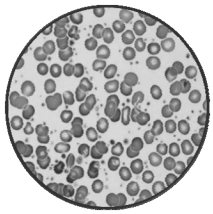
Abnormal high number of RBCs in PCV



Slide 59

Polycythemia Vera Under the Microscope

Lots and lots of RBCs and lots and lots of Platelets

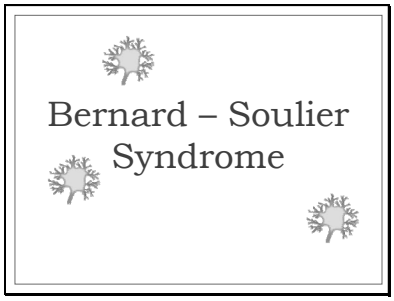


Slide 60

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)

Slide 61



Slide 62

Bernard – Soulier Syndrome

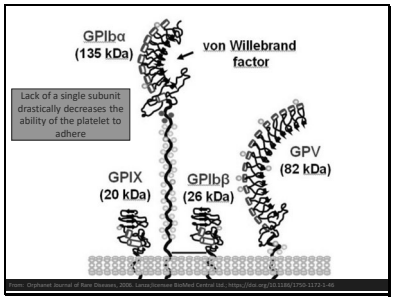
- Hemorrhagiparous thrombocytic dystrophy
- Rare autosomal recessive coagulapathy
  - Less than 1 case per million
- Deficiency or dysfunction of glycoprotein complex
  - GPIb/V/IX - the receptor for von Willebrand factor

Slide 63

Bernard – Soulier Syndrome

- Decreased platelet survival
- Increase in megakaryocytes and large/giant platelets
- Inability of platelets to bind and aggregate at the sites of vascular endothelial injury

Slide 64



Slide 65

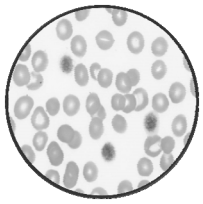
Signs /Symptoms in Bernard-Soulier

- 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**

Slide 66

Bernard-Soulier Under the Microscope

Low number of Platelets and Platelets are large in size



Slide 67

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

Slide 68

Treatment for BSS

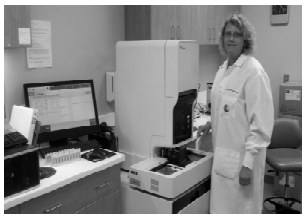
- Blood and platelet transfusions used when severe bleeding occurs
- Desmopressin found to decrease bleeding times
- Bone marrow or stem cell transplantation in extreme cases

Slide 69

Platelet Count Testing

Slide 70

At CHC we use Sysmex XN-1000



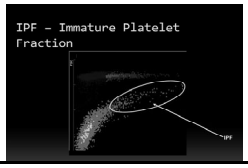
Slide 71

Expanded Platelet Count Testing

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)**

IPF CPT CODE 85055



Slide 72

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)**

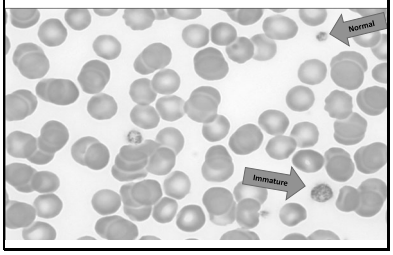
Slide 73

Immature Platelet Fraction (IPF)

- Monitor marrow recovery post chemotherapy
- Platelets are killed off by chemotherapy drugs
- 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**

Slide 74

Normal and Immature Platelets



Slide 75

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

Slide 76

Case Studies

Finally,
What You've Been Waiting For
!

Slide 77

Fall in Michigan

Slide 78

Case #1 Fall in Platelets

48 year old married man with twin 14 year old sons is diagnosed with Pancreatic Cancer – DX 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 recheck of scans and CA19-9 tumor marker.

Note: A cycle is three weeks long. Chemotherapy drug is given on day one and on 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 CBC's are drawn to make sure blood counts are within range so drug can be given safely.

Baseline CBC obtained: Cycle 1 –Day 1

WBC, RBC, and PLT all within normal range, the HGB is slightly decreased

COMPLETE BLOOD COUNT - Final Ordered by: 001

WBC		5.3	x10^3ul	4.0 - 11.0
RBC		4.48	x10^6ul	4.20 - 6.00
HGB		13.1 *Low*	g/dL	13.5 - 18.0
HCT		37.7 *Low*	%	40.0 - 52.0
MCV		84.2	fL	82.0 - 97.0
MCH		29.2	pg	27.0 - 33.4
MCHC		34.7	g/dL	32.5 - 35.5
Plat		205	x10^3ul	130 - 400

First and second cycles go smoothly- no issues or complications.

Slide 79

Cycle 3 – Day 1

- Platelet count has dropped to 92,000
- RBC and HGB are also slightly decreased
- WBC is within normal range

COMPLETE BLOOD COUNT - Final edit *Ordered by: 017*

WBC	4.0	x10^3ul	4.0 - 11.0
RBC	4.06 Low	x10^6ul	4.20 - 6.00
HGB	12.6 Low	g/dL	13.5 - 18.0
HCT	36.3 Low	%	40.0 - 52.0
MCV	84.0	fL	82.0 - 97.0
MCH	28.9	pg	27.0 - 33.4
MCHC	34.2	g/dL	32.5 - 35.5
Plat	92 Low	x10^3ul	130 - 400

Slide 80

Cycle 3 – Day 8

- Platelet count has dropped to 42,000
- Fluorescent platelet is reflexed
- IPF is 0
- WBC, RBC and HGB are also low

COMPLETE BLOOD COUNT - Final edit *Ordered by: 017*

WBC	2.8 Low	x10^3ul	4.0 - 11.0
RBC	3.97 Low	x10^6ul	4.20 - 6.00
HGB	10.9 Low	g/dL	13.5 - 18.0
HCT	30.6 Low	%	40.0 - 52.0
MCV	83.9	fL	82.0 - 97.0
MCH	28.6	pg	27.0 - 33.4
MCHC	33.4	g/dL	32.5 - 35.5
Plat	42 Low	x10^3ul	130 - 400

plt count obtained by Fluorescent Flow Cytometry which is specific for platelet mitochondria, the most accurate enumeration methodology

IMMATURE PLATELET FRACTION TEST - Final edit *Ordered by: 017*

IMMATURE PLATELET FRACTION	0.0 Low	%	0.9 - 7.0

Slide 81

Action Taken

- Patient's nurse reports the IPF of 0 to the physician
- Physician orders a repeat platelet count for the next day
- Patient is given instructions not to shave and to call if he has a nose, gum or any other type of bleed
- Patient returns in the morning for the repeat CBC; platelet count is 6 and IPF is still 0
- Patient receives 2 units of platelets

Slide 82

Summary - CIT

- Without the IPF parameter, patient may not have had his platelet count checked the next day
- Patient may have experienced serious bleeding after hours or on the weekend prompting an ED visit
- By running the IPF, the extreme drop in platelets was anticipated and proactively followed and treated

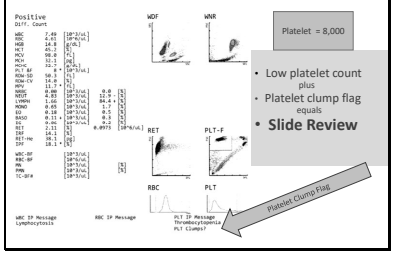
Slide 83

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

Slide 84

Results from the Analyzer

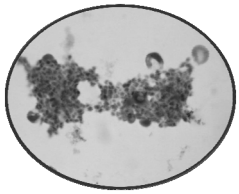


Platelet = 8,000

- Low platelet count
  plus
- Platelet clump flag
  equals
- **Slide Review**

Slide 85

Marked Platelet Clumping on Slide Review

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

Slide 86

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
- Primary causes for this phenomenon
  - EDTA anticoagulant
  - Cold Agglutinins
  - Multiple Myeloma

Slide 87

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 therapy & blood transfusions due to anemia
- Full hematology work up done in office including CBC, Ferritin and Iron/Iron binding

Slide 88

CBC Results

COMPLETE BLOOD COUNT - ***Final*** edit *Ordered by: 017*

WBC	5.07	x10^3ul	4.0 - 11.0
RBC	3.73 Low	x10^6ul	3.90 - 5.20
HGB	5.8 Panic Low		12.0 - 16.0
HCT	24.2 Low	%	36.0 - 47.0
MCV	62.9 Low	fL	82.0 - 97.0
MCH	18.8 Low	pg	27.0 - 33.4
MCHC	28.9 Low	g/dL	32.5 - 35.5
Plat	646 High		130 - 400
Neut%	52.7	%	38 - 70
Lymph%	33.1	%	20 - 45
MONO%	8.9	%	2 - 14
EOS%	3.9	%	0 - 5
BASO%	1.2	%	0 - 2
Immature Gran %	0.2	%	
Nucleated RBC %	0.0	%	<1

WOW – That's Low!

But what's up with this?

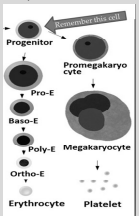
Slide 89

Result	Value (Previous)	Units	Range
FERRITIN - ***Final*** *Ordered by: 030*			
Ferritin	<5.0 Low	Ng/mL	10 - 120
IRON/IRON BINDING - ***Final*** *Ordered by: 030*			
IRON	12 Low	ug/dl	37 - 145
TIBC	441 High	ug/dl	250 - 400
Iron Sat Percent	3 Low	%	15 - 50
VITAMIN B12 / FOLATE - ***Final*** *Ordered by: 030*			
B12	452	pg/ml	200 - 1100
Folate	10.1	Ng/mL	0 - 20

Slide 90

Cross Over Stimulation

- So, remember me?



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

Slide 91

Follow Up

- Significant anemia consistent with iron deficiency
- 2 units of PRBCs given
- Strongly recommend a GYN consultation for possible hysterectomy
- Injectafer® to be given in 1 week
- Recheck CBC in 2 weeks
- Note: IPF is normal at 2.4%

Slide 92

Two Weeks Later

Hemoglobin goes up and platelet count goes down

COMPLETE BLOOD COUNT W/MANUAL DIFF - *Final* *Ordered By: 030*

WBC	5.1	x10^3ul	4.0 - 11.0
Segs	59	%	
Bands	0	%	
RBC	3.69 Low	x10^6ul	3.90 - 5.20
HGB	6.9 Low ← Hgb going up		12.0 - 16.0
RESULTS GIVEN TO DR WONG			
Lymphocytes	30	%	
Monocytes	6	%	
HCT	24.0 Low	%	36.0 - 47.0
MCV	65.0 Low	fL	82.0 - 97.0
Basophils	2	%	
Eosinophils	3	%	
MCH	18.7 Low	pg	27.0 - 33.4
MCHC	28.8 Low	g/dL	32.5 - 35.5
Atypical Lymphs	0	%	
Metamyelocytes	0	%	
Plat	520 High ← Platelets going down		130 - 400

Slide 93

Case #4 Unexplained Thrombocytopenia

- A 29 year old woman presents with bruising and petechiae
- Patient states recent viral illness
- Past history of thrombocytopenia, age 2, attributed to ITP
- LDH is slightly elevated at 420 U/L
- Initial CBC reveals platelet count of 14,000 and IPF of 46%
- IPF indicates bone marrow is working – not a production problem

Slide 94

The Results

COMPLETE BLOOD COUNT - *Final* edit *Ordered by: 017*

WBC	12.7 High	x10^3ul	4.0 - 11.0
RBC	3.33 Low	x10^6ul	3.90 - 5.20
HGB	10.1 Low	g/dL	12.0 - 16.0
HCT	33.0 Low	%	36.0 - 47.0
MCV	99.1 High	fL	82.0 - 97.0
MCH	30.3	pg	27.0 - 33.4
MCHC	30.6 Low	g/dL	32.5 - 35.5
Plat	14 Alert-Low	x10^3ul	130 - 400

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

Neut%	81.5 High	%	38 - 70
Lymph%	0.16 Low	%	20 - 45
MONO%	0.02 Low	%	2 - 14
EOS%	0.01	%	0 - 5
BASO%	0.00	%	0 - 2
Immature Gran %	0.00	%	
Nucleated RBC %	0.0	%	<1

IMMATURE PLATELET FRACTION TEST - *Final* edit *Ordered by: 017*

IMMATURE PLATELET FRACTION	46 High	%	0.9 - 7.0

AN ELEVATED IMMATURE PLATELET FRACTION INDICATES PLATELETS ARE BEING PRODUCED

Way too low

But working hard to make more

Slide 95

Diagnosis and Treatment

- Recurrence of ITP
- Critically low platelet count along with very high IPF – common findings in ITP
- Initial therapy was 1 mg/kg dosing of prednisone
- After no significant improvement in 48 hours, IVIG was added with a 1g/kg x2 day course
- Platelet count responded appropriately and count increased to 114,000
- Patient to continue on 90 mg prednisone and weekly CBC checks

Slide 96

5 Days Later - Following Treatment

COMPLETE BLOOD COUNT - *Final* edit *Ordered by: 017*

WBC	6.56	x10^3ul	4.0 - 11.0
RBC	3.86 Low	x10^6ul	3.90 - 5.20
HGB	10.9 Low	g/dL	12.0 - 16.0
HCT	34.3 Low	%	36.0 - 47.0
MCV	98.7 High	fL	82.0 - 97.0
MCH	31.2	pg	27.0 - 33.4
MCHC	32.0 Low	g/dL	32.5 - 35.5
Plat	114 Low	x10^3ul	130 - 400
Neut%	6.27 Low	%	38 - 70
Lymph%	0.15 Low	%	20 - 45
MONO%	0.09 Low	%	2 - 14
EOS%	0.01	%	0 - 5
BASO%	0.00	%	0 - 2
Immature Gran %	0.03	%	
Nucleated RBC %	0.00	%	<1

IMMATURE PLATELET FRACTION TEST - *Final* edit *Ordered by: 017*

IMMATURE PLATELET FRACTION	17 High	%	0.9 - 7.0

Much Better

Still working but not as hard

Slide 97

Case # 5 Low Hemoglobin – High Platelets

- 41 year old male presented to the clinic with splenomegaly related to his history of severe anemia due to pyruvate kinase deficiency

PK deficiency 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 & 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

Slide 98

- Additional symptom includes abdominal pain due to splenic infarcts
- Hgb low at 6.3 and platelet count high at 489
- Remember the cross over effect of erythropoietin?

COMPLETE BLOOD COUNT *-Final* edit *Ordered by: 02.*

WBC	6.1
RBC	1.98 *Low*
HGB	6.3 *Low*
HCT	19.4 *Low*
MCV	110.6 *High*
MCH	34.8 *High*
MCHC	31.0 *Low*
Plat	489 *High*

Note the high platelet count

Slide 99

- Patient receives two units of packed RBCs and is scheduled for follow up care and weekly CBCs
- CBC repeated at return visit: Hgb is 8.5 but platelets are crazy high – **over a million**

Result	7/9/2015 11:24:00 AM	6/22/2015 10:31:00 AM	6/19/2015 8:06:00 AM
*** Hematology ***			
WBC	14.8	6.1	6.3
ANC	10.2	4.1	4.1
RBC	2.71	2.66	2.03
HGB	8.5	9.0	7.0
HCT	26.0	27.3	22.3
MCV	95.9	102.6	109.9
MCH	31.4	33.8	34.5
MCHC	32.7	33.0	31.4
Plat	1325	433	466

WOW

Slide 100

What are Those High Platelets From?

- Critical high platelet count reported to physician
- Physician informs the tech that the patient had a splenectomy the previous week
- The spleen plays a major role in platelet regulation as the primary site of destruction of platelets
- Reactive thrombocytosis is a predicatable finding after a splenectomy with platelet counts peaking at 1- 3 weeks and returning to normal after approx. one month

Slide 101

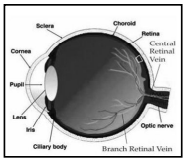
Case #6 Tooth Extraction Complication?

- 48 year old women reports to the ED with complaints of generalized weakness with increased intensity over the past week
- Patient states she has visual changes in her right eye
- History includes recent tooth extraction (two weeks prior) followed by antibiotic therapy to ward off infection
- Patient has increased bruising, bloody nose and persistent blood clots along with bleeding in her mouth
- Complains of dyspnea on exertion and chills on and off for the past month

Slide 102

Ultrasound and Lab Work Done

- Ultrasound shows blood clot in her retinal vein



- Lab work done including a CBC

From: Addenbrookes Hospital. Cambridge 2011 Genetics Panel

Slide 103

Pancytopenia
Bone Marrow Production Problem

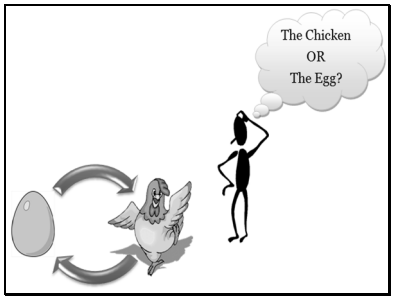
WBC	1.7 Low	10*3/uL	4-11
ANC	0.3 Low	10x3/mm3	1.5-7.7
RBC	1.84 Low	10x9/uL	3.9-5.2
HGB	3.3 Low	g/dL	12-16
HCT	10.1 Low	%	36-47
MCV	64 Low	fL	82-97
MCH	17.9 Low	g/dL	27-33.4
MCHC	32.6	g/dL	32.5-35.5
Plat	1 Low	varies	130-400
IMMATURE PLATELET FRACTION	0.0	Indicates Bone Marrow Production Problem	

Slide 104

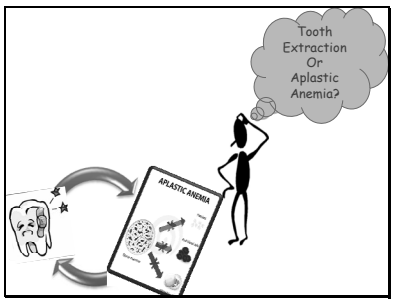
The Follow-up

- Patient was transfused with both RBCs and Platelets
- Hematology consultation ordered, including bone marrow biopsy
- Bone marrow result 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?*

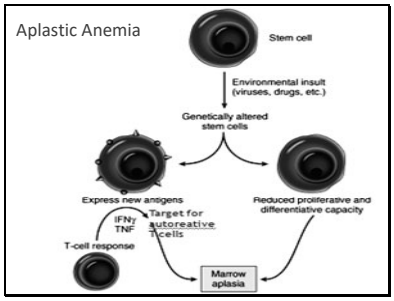
Slide 105



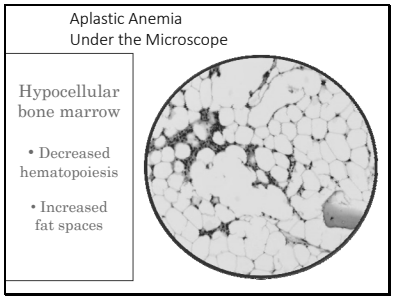
Slide 106



Slide 107



Slide 108



Slide 109

Summary and Conclusion

- Retinal clot most likely due to complications from the tooth extraction
- Shortness of breath & chills were present for over a month but dental work occurred only two weeks before ED visit

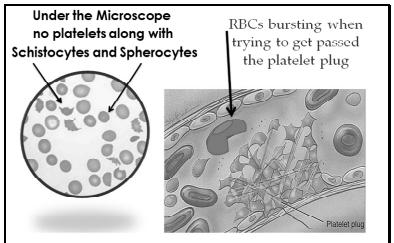
  Aplastic anemia was likely already present
- The aplastic anemia resulted in decreased platelet production, making it difficult for healing at the site of the tooth extraction

Slide 110

Case #7 Blast from the past - 2009

- 19 year old female presents to the ED with a headache, nausea, vomiting, fatigue and confusion
- CBC reveals 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
- Clinical diagnosis of TTP

Slide 111

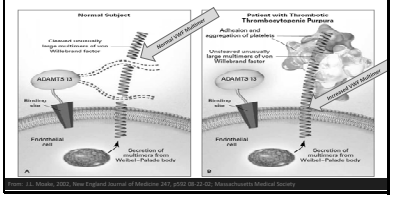


Presence of schistocytes suggest thrombotic microangiopathy

Slide 112

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



Slide 113

Treatment

Patient was treated with plasma exchange, steroids and PRBC transfusions

- Plasma exchange 3 times a day for 1st week
- Plasma exchange once a week for 10 additional weeks
- Steroids – Solu-Medrol 250 mg IV
- 2 units of PRBCs
- Lab support included daily CBCs until normal platelet count, then weekly for a year

Slide 114

Fast Forward to 2019

- Symptomatic 29 year old female seen for in the office for thrombocytopenia, platelet count = 9,000 with an IPF of 19%
- Microangiopathic hemolytic anemia, Hgb = 6.4 and elevated LDH =1138
- Peripheral smear compatible with the diagnosis of recurrent TTP – many schistocytes noted
- Patient has history of TTP – 2009 – treated successfully with plasmapheresis
- Complicating factor – patient is 20 weeks pregnant

Slide 115

Here We Go Again

COMPLETE BLOOD COUNT - *Final* edit — *Ordered by: 017*

WBC	5.1	x10^3ul	4.0 - 11.0
RBC	2.17 Low	x10^6ul	3.90 - 5.20
HGB	6.4 Low	g/dL	12.0 - 16.0
HCT	20.1 Low	%	36.0 - 47.0
MCV	92.6		82.0 - 97.0
MCH	29.4	pg	27.0 - 33.4
MCHC	31.8 Low	g/dL	32.5 - 35.5
Plat	9 Alert-Low	x10^3ul	130 - 400
Platelet count obtained by Fluorescent Flow Cytometry methodology which is specific for Platelet Mitochondria, providing the most accurate enumeration.			
Neut%	49.5	%	38 - 70
Lymph%	36.0	%	20 - 45
MONO%	12.3	%	2 - 14
EOS%	1.8	%	0 - 5
BASO%	0.2	%	0 - 2
Immature Gran %	0.2	%	
Nucleated RBC %	0.0		<1

IMMATURE PLATELET FRACTION TEST - *Final* edit — *Ordered by: 017*

IMMATURE PLATELET FRACTION	19 High	%	0.9 - 7.0
AN ELEVATED IMMATURE PLATELET FRACTION INDICATES PLATELETS ARE BEING PRODUCED			

Very Low Hgb

Very Low Platelet

High IPF

Slide 116

Moving Too Fast

- Patient begins daily plasmapheresis x2/day
- TTP is a high risk factor in pregnancy (patient has already had two miscarriages)
- Due to complications, baby is delivered by cesarean section at 24 weeks
- Baby boy is born measuring 11" long and weighing only 1lb 6oz. Baby is admitted to NICU.
- Mom continues to have plasmapheresis after delivery as her life is still in danger. Tapered down to 3 times weekly once platelet count started to recover.
- Mom's platelet count returns to normal, Platelet = 296,000
- At 5 weeks, baby boy is stable and up to1lb 12oz

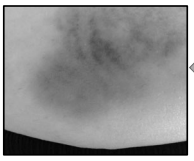
Slide 117

Happy Ending

Slide 118

Slide 119

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

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Summing it Up

- Platelets play a vital role in the clotting cascade
- Platelet dynamics are complicated
- Platelets have three functions; adhesion, activation and aggregation
- Issues can occur when there are too few, too many or dysfunctional platelet
- Platelet disorders are numerous and can be serious, even life-threatening
- Case studies involving platelet abnormalities provide a good source for education

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