**Disclosures for Michele P. Lambert, MD, MTR**

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

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Presentation includes discussion of the following off-label use of a drug or medical device:

\(<N/A>\)
What do you do?

- A 20 yo woman with ITP diagnosed at 13 months of age with average of platelet count of 60-80K but significant bleeding symptoms requiring frequent interventions and no response to platelet raising therapies.

- A 4 yo male with normal platelet count and life threatening tonsillar bleeding from eating a potato chip with abnormal platelet aggregation to ADP, epinephrine and collagen but normal secretion (and aggregation responses showing significant delayed responses).

- An 11 yo male patient with nystagmus since infancy, “asthma” and GI bleeding.
What do you do?

- A 34 yo pregnant woman with a platelet count of 70K in the first trimester. Her father was hard of hearing and died of complications of renal disease in his late 50s.

- A neonate with a platelet count of 10K and intracranial hemorrhage at birth.

- A 2 yo female with a history of neuroblastoma who had a total resection and as a result of her abdominal surgery requires a bowel and liver transplant and is TPN dependent. She now has hemolytic anemia and macrothrombocytopenia with an unmeasurable MPV and her platelets are larger than her red blood cells.
Case 1:
- A 20 yo woman with chronic refractory ITP
- She was diagnosed at 13 months of age
- Her average of platelet count is about 60K
- She has had 3 significant bleeding events:
  - during splenectomy,
  - a tonsillar bleed at 3 yo with “bad tonsillitis”
  - menorrhagia that resulted in anemia and IDA
Case 1:

- Two episodes of significant bleeding required platelet transfusions and stopped reasonably quickly with transfusion

- She has always had bruising, petechiae and oral bleeding

- Has never had significant change in platelet count with IVIG, steroids or anti-D immunoglobulin

- Her parents are healthy and so is her 15 yo brother.
Case 1: Exam and Laboratory studies

- Normal examination with the exception of palpable bruising, petechiae and significant bruising.
- CBC showed platelet count 78K and MPV of 13.1
- Hemoglobin and WBC count were normal.
Case 1: Further Laboratory Testing

GP Ibα

GP IX

GP V

NORMAL ➤

AGONISTS ➤

RISTOCETIN ➤

BERNARD SOULIER SYNDROME ➤

Cell Number

Log Fluorescence Intensity

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Case 1: Bernard Soulier Syndrome

- Defective (or absent) GPIb/IX/V complex on the surface of the platelet – vonWillebrand factor receptor

- Mild-moderate thrombocytopenia with giant platelets

- Significant bleeding diathesis

- Heterozygosity for mutations in this complex can cause thrombocytopenia and decreased expression of GPIb/IX on platelets (22q deletion)
Bernard Soulier Syndrome

**Major ligand-binding domain of GPIb-IX-V**
- von Willebrand factor
- Thrombospondin
- P-selectin
- $\alpha_m\beta_2$
- Thrombin
- Factor XI, XII
- HMW kininogen

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Michael C. Berndt, and Robert K. Andrews Haematologica
2011;96:355-359
Bernard Soulier Syndrome


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Bernard Soulier Syndrome

- Mutation analysis is available on a clinical basis

- She was confirmed to be homozygous variants in GPIX
  - Asn61Ser
Case 2

- A 4 yo male life threatening tonsillar bleeding from eating a potato chip
- No family history of bleeding
- Prior history of easy bruising, petechiae, and bleeding gums with brushing teeth
Case 2

- Normal platelet count and CBC only significant for microcytic anemia
- Iron studies consistent with iron deficiency with a ferritin of 2
- Platelet function abnormal platelet aggregation to ADP, epinephrine and collagen (significantly delayed response) but normal secretion
Case 2

- Normal expression of GP1b/IX and GPIIb/IIIa on surface of platelets

- EM of platelets showed:

- Whole exome sequencing performed which revealed two variants (one each inherited from one parent) in RASGRP2 (codes for CalDAGGEF1)
Case 2

Signaling Defects

- Variable bleeding diathesis

- In this patient severe, life-threatening hemorrhage but some patients have only mild bleeding

- Normal platelet count usually
Case 3

- An 11 yo male patient with nystagmus since infancy, “asthma” and GI bleeding.
- Nystagmus diagnosed at birth
- “Pale” per mother since birth
- Intermittent BRBPR for the past 6 months associated with diarrhea, abdominal pain
- “asthma” with shortness of breath and chest pain with exercise
Case 3


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Hermansky Pudlack Syndrome

- Microdeletion of HPS6 on one chromosome and variant on other chromosome
- Absent dense granules on platelet EM
- Normal platelet function on LTA and abnormal serotonin release and uptake as well as abnormal ATP:ADP ratio
- Endoscopy showed:
Hermansky-Pudlak Syndrome

- Autosomal recessive granule assembly defect
- 9 HPS genes identified (HPS1-6, AP3B1, DTNBP1 and BLOC1S3)
- Founder effect in Puerto Rican population but don’t need to be Puerto Rican to have HPS
- Oculocutaneous albinism, nystagmus, some variants are associated with pulmonary fibrosis and Crohn’s like GI illness
- Bleeding varies but dense granule deficiency
Hermansky-Pudlak Syndrome

HPS Proteins in the Pathways of Biogenesis of Lysosome-Related Organelles

Adapted from Li W, et al. *BioEssays*, 2004; 26: 616-628
Case 4

- A 34 yo pregnant woman with a platelet count of 70K in the first trimester.

- No previous blood work (first pregnancy)

- Her father was hard of hearing and died of complications of renal disease in his late 50s.

- Paternal aunt with low platelet counts in pregnancy that were thought to be “ITP”
Case 4

- CBC shows platelet count of 63K.
- Manual review of smear shows some very large platelets and platelet count closer to 80K
- Inclusions in neutrophils are seen on the smear as well.
MYH9-RD

- Formerly May-Hegglin anomaly, Sebastian Syndrome, Epstein syndrome, Fechtner syndrome
- Mutations in non-muscle myosin heavy chain 9
- Mutations in head of MYH9 may have more severe phenotype than mutations in tail
- Platelet count generally 60-90K with variability in this
- Large platelets on smear (may be counted as RBC)
MYH9-RD

- Mild to no bleeding diathesis

- No clear genotype-phenotype correlation and all patients are at risk for:
  - Renal disease (nephropathy)
  - Cataracts
  - Hearing loss

- Mutation analysis available on a clinical basis
MYH9-RD

- Generally do not need treatment as risk of bleeding is pretty low

- For particularly at risk procedures would consider platelets on hold for bleeding (?T&A)

- Some patients with very low platelet counts and bleeding: anti-fibrinolytics, platelet transfusions

- Some patients can have severe bleeding!!!
MYH9-RD: Genotype/Phenotype

Generally more severe phenotype

More likely hematologic only
Case 5

- A 2 yo female with a history of neuroblastoma who had a total resection and as a result of her abdominal surgery requires a bowel and liver transplant and is TPN dependent.

- She now has hemolytic anemia and macrothrombocytopenia with an unmeasurable MPV and her platelets are larger than her red blood cells.
Case 5
Sitosterolemia

- Measurement of serum plant sterols revealed marked elevation
- Testing for genetic variants in ABCG-5 and ABCG-8 negative
- Transporter is in liver and small bowel but this patient had no small bowel that was functional and was in liver failure
- TPN contains significant plant sterols
Take home points

- Inherited disorders and acquired disorders can occur in combination or look like each other

- While each individual platelet disorder may be relatively rare, in aggregate, they are not at all uncommon

- Be on the look out for platelet disorders in your patients with bleeding, thrombocytopenia or combination
Thank you