Case Summary

• 29 old male, heavy smoker no other known risk factors presents with inferior STEMI.
• Gives a history of repeated minor bleeds, diagnosed since age 6 as Glanzmann’s thrombasthenia by multiple hematologists at the Maadi armed forces hospital by leasing experts using state of the art tests.
• Patient taken to cath lab after heparin, no aspirin or Plavix given, angio via radial approach
Findings

• RCA full of thrombus, distally occluded, receiving faint collaterals from a normal left system.
• Pain resolved, LV normal except for small area of inferior hypokinesia.
• Patient treated conservatively, fully heparinized guided by AcT for 5 days then discharged, 3 month follow up excellent, quit smoking, on ACE and Statins, no aspirin or Plavix.

Process of Hemostasis

■ Vascular injury
■ Platelet adhesion and activation
■ Platelet aggregation (1° hemostatic plug)
■ Fibrin formation via cascade (2° hemostasis)
■ Clot retraction (thrombasthenin)
■ Fibrinolysis and healing
Role of Platelets

- Surveillance for vascular integrity
- Formation of 1º hemostatic plug
- Activation of 2º hemostasis
- Healing

Platelet Formation

- Megakaryoblast undergoes endomitosis
- Intermediate stage promegakaryocyte without granules
- Megakaryocyte (2N to 64N) with over 100µ diameter
- IL3, GM-CSF, thrombopoietin
- 20% of platelet stored in spleen
Platelet

- 2 - 4μ diameter
- Round or oval
- Hyalomere - clear peripheral zone
- Granulomere - highly stained area with granules
Platelet Anatomy

- Peripheral zone with glycoprotein receptors
- Structural zone with contractile microtubules (thrombasthenin)
- Organelle zone with granules
- Membrane with open canicular and tubule systems for increased surface area and rapid release

Electron micrograph of a platelet x 25,000

Longitudinal peripheral microtubule (brown), endoplasmic reticulum (blue), mitochondria (green), glycogen (black)
Primary Hemostasis: The Platelet

- Anuclear discoid cell (3-5 microns) arising from megakaryocytes in bone marrow
- 4-5 day maturation, 9-10 day life span
- Bilamellar membrane contains multiple invaginations with an open canalicular system:
  - Attached to intracellular dense tubular system, forming an interconnecting network (membrane complex) throughout the cell
  - Facilitates secretion of granules
Platelet morphology

• Numerous G-protein receptors or adhesion receptors (integrins) are present on the cell surface
  – transmembrane heterodimers composed of alpha and beta subunits, responsible for adhesion and signal transduction
  – Glycoproteins are designated I (large) to IX (small); a and b were added when electrophoretic techniques allowed for resolution of single bands to separate bands

Glycoprotein receptors

• GP Ib-V-IX; complex of four gene products, serves as a receptor for vWF; adhesion; Bernard-Soulier
• GP IIb-IIIa; most abundant, recognizes four adhesive receptors: fibrinogen, fibronectin, vitronectin, and vWF; aggregation; Glanzmann’s
• Others:
  – GP Ia, IIa; GP VI: collagen receptors
Primary hemostasis

- Extremely dynamic, complicated, and continuous interaction between vessel, platelet, and plasma components

- Adhesion, Activation (Secretion), Aggregation

Adhesion

- Vascular injury exposes the pro-coagulant components of the sub-endothelial extracellular matrix: collagen, proteoglycans, and fibronectin
- Platelets are exposed to these components in a rolling fashion
- vWF acts as an adhesion bridge between the platelet GP Ib-V-IX complex and exposed collagen; platelets also adhere to fibronectin
- However, vWF-GPIb bridge is the only association strong enough to overcome blood flow shearing force
Secretion

• Shape change via cytoskeletal activation: spherical with extending pseudopods
• Platelet granules are released thru canalicular system
• Cytoplasmic activation of eicosanoid pathway (TXA2), decreased cAMP, and mobilization of Ca++
• Phospholipids are translocated to cell surface membrane (phosphatidylserine)
  – Binding surface for factor Va and Xa (along with Ca++) forms prothrombinase complex; secondary hemostasis
Aggregation

- Promoted by ADP and TXA2 release
- ADP induces a conformational change of the IIbIIIa receptor, allowing fibrinogen binding
- Platelets aggregate via fibrinogen bound to IIbIIIa receptors
- Auto-catalytic reaction activating other platelets
- Formation of primary hemostatic plug
Qualitative Platelet Disorders

- Berhard-Soulier: GP-Ib deficiency, adhesion problem
- Von Willebrand’s: vWF deficiency, adhesion problem
- Glanzmann’s thrombasthenia: GP-IIb/IIIa deficiency, aggregation problem -- cannot bind vWF and Fib
- Storage pool disease: dense body defect, secretion problem
Bernard-Soulier Syndrome

- First described in 1948 by Jean Bernard and Jean-Pierre Soulier; French hematologists
- AR; characterized by moderate to severe thrombocytopenia, giant platelets, and perfuse/spontaneous bleeding
- Basis for the disease is deficiency or dysfunction of the GP Ib-V-IX complex

Glanzmann’s Thrombasthenia

Eduard Glanzmann (1887-1959), Swiss pediatrician

Reported a case of a bleeding disorder starting immediately after birth

Jahrbuch für Kinderheilkunde, 1918; 88: 1-42, 113-141.
Glanzmann’s

- IIbIIIa most abundant platelet surface receptor (80,000 per platelet)
- IIbIIIa complex is a Ca++ dependent heterodimer
- Genes for both subunits are found on Chromosome 17
- Disease is caused by mutations (substitution, insertion, deletion, splicing abnormalities) in genes encoding for IIb or IIIa resulting in qualitative or quantitative abnormalities of the proteins
• AR inheritance
• Patients present with wide spectrum of disease
• Like thrombocytopenic bleeding: skin, mucous membrane (petechiae, echymoses), recurrent epistaxis, GI hemorrhage, menorrhagia, and immediate bleeding after trauma/surgery
• ICH, joint, muscle bleeding uncommon
Glanzmann’s patients are stratified into three groups based on complex expression:
- Type I less than 5 percent GPIIbIIa, absent alpha granule fibrinogen
  - Usually as a result of IIb gene mutation
- Type II <20 percent, fibrinogen present
- Type III >50 percent; “variant” thrombasthenia; qualitative disorder

Diagnosis

- Platelet count and morphology are normal
- Bleeding time prolonged
- The hallmark of the disease is severely reduced or absent platelet aggregation in response to multiple agonists ie ADP, thrombin, or collagen (except Ristocetin)
- Flow cytometry: decreased mAb expression of CD41 (GPIIb) and CD61 (GPIIIa)
Aggregation Studies

- ADP
  - reversible 1° wave
  - if ADP is released, then 2° wave
  - abnormal with aggregation and release problems
- Epinephrin
  - similar to ADP
- Collagen
  - direct release so only one wave of aggregation
- Ristocetin
  - antibiotic
  - aggregation only with vWF and GP-Ib
Dr. Coller went on to present his initial studies of platelet function and how it led to his current work in platelet assays and pharmacologic treatment of coronary artery thrombosis. In some of his early work Dr. Coller studied Glanzmann thrombasthenia and polymorphisms in the genes encoding glycoprotein αIIbβ3 (formerly known as GPIIbIIIa) which are responsible for this disease. He then went on to discuss mechanisms of thrombosis, including the role of fibrinogen, von Willebrand’s factor, and finally, his cell of interest, the platelet. αIIbβ3 plays a central role in platelet aggregation as a polyvalent transmembrane platelet surface protein that allows platelets to bind one another. He described his translation research approach, using the benefits of small molecules and drug discovery that led to the development of a chimeric monoclonal antibody, now marketed as abciximab. When added to normal platelets, abciximab produces platelet aggregation identical to that observed in patients with Glanzmann thrombasthenia.
Conclusion

• The rare disorder Glanzmann’s Thrombathenia (300 reported cases) with congenital absence of platelet 2b3a receptors has led to the discovery of the drugs 2b3a receptor blockers in a most fascinating piece of translational research.

• Facing an adult with Glanzmann’s thrombasthenia and STEMI poses real challenges in bleeding/access/revascularization/adjunctive therapy, in our case we were lucky just to anticoagulate.