Case Study 1

• 75 year old is referred to you for recurrent gastrointestinal bleeding.
• Past History- HTN, Hyperlipidemia
• Surgical History- Hysterectomy, Tooth extraction
• Medications- Amlodipine, Atorvastatin, Prilosec, Multivitamin, Iron, Folic acid

Case Study 1

• Exam- No petechiae, bruises.
• Labs- WBC 12,000, Hct 31%, Pts 231K, PT 10, aPTT 28, Fibrinogen 288

Case Study 1

• Which of the following bleeding disorders should be investigated?
  – A. Hemophilia A
  – B. Surreptitious warfarin poisoning
  – C. Disseminated intravascular coagulation
  – D. von Willebrand Disease
Questions?

Case 2

- 65 year old woman who presents to the ED with bleeding after tooth extraction
- Meds: None
- Labs: WBC 6,000, Hgb 10 (12.4), Plt 1.5 million, PT 10.5, aPTT 30.

Case 2

- What other labs would you order?
  - A. Factor XIII activity
  - B. Euglobulin lysis time
  - C. MTHFR genotype
  - D. Ristocetin cofactor
Acquired von Willebrand disease

- Previously negative bleeding history
- Mechanism- antibody-mediated, adsorption, decreased synthesis, increased destruction
- vWD w/u, vWF propeptide level
- Humate-P, DDAVP, IVIG, treat underlying disorder

Associated disorders
- Lymphoproliferative diseases
- Plasma cell dyscrasias
- Myeloproliferative disorders
- Neoplasms
- Autoimmune disease
- Hypothyroidism
- Cardiac valve disease
- Angiodysplasia
- Idiopathic

Case 3

- 40 y.o. Iranian engineer
- Hx/o epistaxis, ecchymoses, surgical bleeding
- PEX: Ecchymosis
- Lab: WBC 6K, Hct 42%, Platelet 200K, PT 11, aPTT-28
- What other tests should be ordered?
  - A. Factor VIII
  - B. Factor VII
  - C. Platelet aggregation
  - D. Factor XII

Case 4

- You are called to see a 68 year old patient in the CICU who had excessive intra-operative bleeding after CABX4, MVR.
- No previous history of bleeding
- Meds- ASA, LMWH
- Labs- Hgb 7.8 (10.5), Plts 60K (185K), SCr 2.8
- What is the likely cause of this patient's coagulopathy?
  - A. Aspirin
  - B. von Willebrand disease
  - C. LMWH
  - D. Uremic platelet defect
Case 5

• 72y.o. truck driver
  S/P CABG X 2 2 weeks ago.
• No bleeding
• Exam: No bleeding
• Normal pre-op labs
• Lab: CBC - nl, PT 78 sec, aPTT 146 sec

Case 5

• What tests would you order?
  – A. Mixing study, factor VIII, factor IX
  – B. Mixing study, factor II, factor V
  – C. Mixing study, Factor XI, Factor XII
  – D. Factor V Leiden DNA

Case 6

• 29 y.o. transferred for coagulopathy
• Meds: None
• Exam: ecchymoses
• Lab: PT >120sec, aPTT 51 sec
Case 6

• What tests would you send?
  – A. Mixing study, Factor 8, 9
  – B. Mixing study, factor 7, 9
  – C. Mixing study, factor 2, factor 10

Questions?

Case 7

• 82 year old male with a history of coronary artery disease status post recent stent placement transferred from an outside hospital with epistaxis requiring nasal packing. Of note, he was currently receiving dual antiplatelet therapy with aspirin and clopidogrel.

• Admission Labs:
  • Hgb 8.9 g/dl
  • Platelet count 174,000
  • PT 14.9 sec (10.8 – 13.1)
  • INR 1.26
  • APTT 140.7 sec (25 – 39)
  • Hepzyme APTT 160 sec
Case 7 Lupus Anticoagulant Testing

Case 7 Question
What is the most likely diagnosis in this case?
1. Factor Deficiency
2. Specific Factor Inhibitor i.e. Acquired Factor VIII inhibitor
3. Lupus Anticoagulant / Antiphospholipid Syndrome
4. Interfering substance i.e. C-reactive protein
5. Other

Case 7 Question
Which of the following should be excluded from the differential diagnoses of an acquired FVIII inhibitor?
1. Lupus anticoagulant
2. Factor XII deficiency
3. Acquired von Willebrand disease
4. Factor XI deficiency
False Positive LA Results

- CRP is an acute phase reactant with known affinity for phospholipids, especially phosphatidylcholine (PC)
- While PC is the principal CRP ligand, CRP also interferes with other PL such as phosphatidylethanolamine

Case 7 ECAT Proficiency Testing

Case 8

- 53 year old white male with no significant past medical history until
- 11/1/11: presented to OSH complaining of left sided weakness, diagnosed with possible CVA and multiple myeloma
- 11/9/11: underwent biopsy of a right sided pulmonary nodule at OSH which was complicated by extensive right hemothorax, which did not resolve with chest tube or thoractomy, and extensive bleeding requiring PRBC transfusion
- 11/22/11: readmitted to OSH with MRSA empyema
- 12/1/11: transferred to Emory for thoracic surgery consultation for surgical decortication
- 12/2/11: CT scan at EUH demonstrates multiloculated right empyema and left pulmonary artery non-occlusive PE
  - Therapeutic LMWH started
Case 8

- 12/5/11: Patient develops respiratory distress and requires intubation. EKG shows characteristic S1V3T3 findings of a massive PE and echocardiogram demonstrates right heart strain
- Patient too unstable to obtain repeat imaging
- Systemic thrombolytics given in ICU
- Unfractionated heparin drip was started
  - High standard protocol with goal anti-Xa activity 0.5-0.7 u/ml

Part I: Heparin Resistance

- Patient most likely heparin resistant
- Rebolused with 1000 U, heparin gtt increased to 3000 U/hr, and heparin levels drawn every 4 hours
Part II: Hypofibrinogenemia

- Patient was scheduled to go to the OR for decortication
- How do we manage the patient peri and intra-operatively?

<table>
<thead>
<tr>
<th>Case 8 Labs</th>
<th>Test Result</th>
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<tbody>
<tr>
<td>TT</td>
<td>Not performed</td>
</tr>
<tr>
<td>RT</td>
<td>56.7 sec (&lt;22 sec)</td>
</tr>
<tr>
<td>Fibrinogen Ag</td>
<td>681 mg/dl (150-450)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>14,838 ng/ml DDU</td>
</tr>
<tr>
<td>ELT</td>
<td>&gt;120 min (&gt;120 min)</td>
</tr>
<tr>
<td>SPEP/IFIX</td>
<td>IgG lambda paraprotein 5.13 grams</td>
</tr>
</tbody>
</table>

Case 8 Question

What test would you order next?

1. Thrombin Time
2. Reptilase Time
3. Euglobulin Lysis Time
4. No further testing required

Case 8 Labs

- TT Not performed
- RT 56.7 sec (<22 sec)
- Fibrinogen Ag 681 mg/dl (150-450)
- D-dimer 14,838 ng/ml DDU
- ELT >120 min (>120 min)
- SPEP/IFIX
  - IgG lambda paraprotein 5.13 grams
Case 8 Questions

What’s the most likely diagnosis?

1. Hypofibrinogenemia
2. Dysfibrinogenemia
3. Acquired Factor VIII inhibitor
4. Supratherapeutic anticoagulation
5. Disseminated intravascular coagulation

Coagulation and Multiple Myeloma

- Thrombosis
  - It is well known that patients with MM are at increased risk of VTE
    - Treatment associated (thalidomide/lenalidomide + dex and chemo)
    - Other mechanisms proposed include acquired APCR, increased levels of vWF and FVIII, increased blood viscosity, and platelet activation
- Bleeding
  - Associated with an acquired dysfibrinogenemia
    - Paraprotein impairs fibrin formation/fibrin polymerization by
      - Antigen-antibody interactions
      - Non-specific interactions
      - Increasing plasma viscosity
    - Fibrin networks formed in the presence of paraprotein have been described to have abnormal viscoelastic properties
Case 9

- 84 year old female presented to the Emory ED complaining of progressive shortness of breath, non-productive cough, diffuse arthralgias, and lower extremity edema
- PMH: hypertension and hyperlipidemia
- PSH: left total hip arthroplasty 2003
- Physical Exam
  - O$_2$ saturation 97% on RA
  - However, patient was unable to speak in full sentences with accessory muscle use and expiratory wheezes
  - In addition, she was noted to have axillary and inguinal lymphadenopathy

Case 9

- A CT scan was performed, which demonstrated extensive bronchiectasis in the right middle and lower lobes with extensive mediastinal adenopathy resulting in narrowing of the right lower lobe bronchus
- Due to the concern for malignancy, a surgery consult and request for lymph node biopsy were obtained
- Pre-operative labs were ordered and a coagulation consult was requested...

Pre-Operative Coags

- PT 51.5 sec (10.8-13.1)
- INR 4.84
- APTT 109.1 sec (25.0-39.0)
Case 9 Question

What test would you order next?

1. Repeat PT/APTT
2. PT and APTT Mixing Studies
3. Factor Activity Assays
4. Lupus Anticoagulant Profile

Case 9 Labs

- PT and APTT Mixing Study Results

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>1 Hour</th>
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<tbody>
<tr>
<td></td>
<td>PT</td>
<td>PTT</td>
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<tr>
<td>Control</td>
<td>12.1</td>
<td>34.4</td>
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<tr>
<td>Patient</td>
<td>51.1</td>
<td>113.9</td>
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<tr>
<td>Control+ Patient Mix</td>
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<td>51.0</td>
</tr>
</tbody>
</table>

- Factor II Activity 58% (50-150)
- Factor V Activity < 5% (50-150)
- Factor X Activity 67% (50-150)

Case 9

- The patient was subsequently diagnosed with an acquired factor V inhibitor
- She was taken to the OR for a right axillary lymph node biopsy, which was consistent with dermatopathic lymphadenitis
- The patient was given inhaled corticosteroids and her respiratory status improved
- In addition, the etiology of her arthralgias and edema remained unknown and continued to improve without intervention
- One month after admission, the following labs were obtained
  - PT 36.1 sec
  - INR 1.38
  - APTT 31.3 sec
Factor V Inhibitors

- Antibodies directed against factor V are rare
  - The first cases of an acquired inhibitor of factor V were reported in 1955
  - Since 1955, 126 cases have been documented
- Spontaneous factor V inhibitors occur without any clearly identifiable cause
  - However, common clinical events that preceded inhibitor development included surgical procedures, infections, exposure to antibiotics, namely aminoglycosides, or blood transfusions
- A second group of factor V inhibitors occur after exposure to exogenous human or bovine factor V
  - The source of bovine factor V is typically from bovine thrombin preparations used to make fibrin glue

Clinical Features of Factor V Inhibitors

- Factor V inhibitors can produce clinically significant bleeding
  - 72% of reported cases of spontaneous FV inhibitors suffered bleeding complications
    - 17% of these were fatal
  - In contrast, 33% of bovine thrombin induced inhibitor patients developed bleeding with 6% being fatal
- Spontaneous inhibitors persist an average of 5.1 months after diagnosis, whereas bovine thrombin associated inhibitors emerge a mean of 8.3 days after exposure and persist for 2.3 months
- Although routine coagulation tests are useful to identify FV inhibitors, there is no way to identify patients who are at likely to bleed
  - However, spontaneous inhibitors more often present with spontaneous, non-traumatic bleeding

Laboratory Features of Factor V Inhibitors

- Unlike spontaneous factor V inhibitors, bovine thrombin associated antibodies are often accompanied by antibodies to other coagulation factors including prothrombin, thrombin, and fibrinogen
- In addition, antibody titers are much higher and persist much longer against bovine coagulation proteins
- Lupus anticoagulant assays including platelet neutralization procedures may be positive in patients with factor V inhibitors