If you prick us, do we not bleed?
The story of a Factor VIII inhibitor.

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Case presentation

- HPI: 65-year-old woman with history of rheumatoid arthritis, and recent total left ankle arthroplasty who was admitted to orthopedics from 4/16-4/18 for wound dehiscence with wound vac placement.
- She went for a planned debridement and reconstruction of the left ankle on 4/29.
- Past Medical History: Rheumatoid arthritis, HTN, Hyperlipidemia.
- Medications: Enoxaparin SQ ppx, folate, leflunomide, metoprolol, omeprazole, prednisone 5 QAM, 1 QPM, triamterene/HCTZ.
Pre-operative labs

- Unfortunately, coags and CBC were not performed on the day before surgery, but were checked intraoperatively...

- Operative note:
  - “It was noted that the patient was significantly oozy, despite attempts to obtain hemostasis… the left ankle and thigh wounds continued to ooze significantly. Therefore, labs were drawn.”
Intraoperative labs

1:1 Mixing study results:
- PTT Patient 90 s
- PTT 1:1 Mix Immediate 39 s
- PTT 1:1 Mix Incubated 61 s

What is/are the potential diagnosis(s)? Which test do you perform next?

8.25 188
21

INR 1
PTT 90 s
PT 12.9 s

Fibrinogen 323 mg/dL
Further testing

• Factor VIII Inhibitor testing – an overview

  – When to suspect the diagnosis:

    • Prolonged aPTT and normal PT

    • aPTT does not correct with normal plasma after a 2 hour incubation

    • Reduced factor VIII level
Factor VIII: its role in the coagulation cascade

• Factor VIII: functions as a cofactor to factor IXa – a deficiency results in
  – Reduced generation of thrombin on the surface of activated platelets

• Factor VIII inhibitors
  – Congenital hemophilia A – alloantibodies to FVIII in 20-40% of patients
  – Acquired factor VIII inhibitor in nonhemophiliacs – rare; approximately 1 case per million per year

Kinetics of Factor VIII inhibitors

• In contrast to hemophilia A patients, in acquired hemophilia, autoantibodies are:
  • Nonprecipitating immunoglobulins from IgG family
  • Bind FVIII in time- and temperature-dependent fashion
  • Exhibit non-linear activation pattern (see left).

Ma et al. ASH Education Book Jan 2006
Factor VIII activity levels

• If testing reveals a low FVIII activity level, the titer of the antibody inhibitor is ascertained:
  
  – Inhibitor strength: measured in BU (Bethesda Units)
  
  – Bethesda Assay: measures residual FVIII activity after incubation of normal plasma with serial dilutions of patient plasma for 2 hours at 37°C
  
  – Inhibitor titer in BU represents reciprocal dilution of the patient’s plasma that leads to 50% inhibition
  
  – Actual value of titer less relevant; useful for following treatment efficacy

Ma et al. ASH Education Book Jan 2006
Initial inhibitor assay results for our patient

- Factor 8 Inhibitor was initially 5 BU during surgery (immediately following elevated aPTT result), and factor VIII activity level was 16%.

- Patient moved to ICU post-op; continued oozing from graft site, went back to OR later for hematoma evacuation.

- Blood loss at that point – average 150 cc/hr; patient required 5 units pRBC’s overnight and 1 unit frozen plasma
Initial management

• For titers < 5 BU:
  – Start recombinant FVIII infusion (Advate®)
  – Goal: FVIII activity level of 30-50%
  – Check FVIII activity level 30 min after bolus
  – Starting dose: 100 units/kg for significant bleeding
Initial management

• In this patient, treatment was started immediately with the following:

  – FVIII IV, 200 unit/kg bolus with increase in her FVIII activity levels from 16 → 50% the evening after surgery, followed by continuous infusion at 5 units/kg/hr.

  – In AM, went to OR again; post-op, FVIII activity level had dropped to 19%

  – Started IV solumedrol, 20 mg IV Q8H as stress-dose steroids
What happened next

• For the next 7 days, she required uptitration of the rFVIII infusion, with multiple boluses.

• Continued to exhibit slow oozing from the graft site, with intermittent transfusional support needed.

• On the 6\textsuperscript{th} day of Advate\textregistered infusion, FVIII activity level was checked and was 173; however, pan-lupus inhibitor present (activity assay less precise).

• Ultimately the FVIII infusion was uptitrated to 27 units/kg/hr before a different approach was taken.
Management of patients refractory to recombinant FVIII

• General approach – use of bypassing agents.

  – What are ‘bypassing agents’?

  – Agents that can promote hemostasis through mechanisms alternate to the FVIII-Xa complex

  – 2 preparations used in clinical practice:

    • aPCC

    • Recombinant activated factor VII

Franchini et al. Semin Thromb Hemost 2013
Bypass agents: aPCC

• aPCC’s
  
  – Activated Prothrombin Complex Concentrates
  
  – Composed of activated FII, FIX, FX, and small amounts of FVII
  
  – Mechanism of action: likely involves helping thrombin generation on the surface of platelets
  
  – Dose: 50 to 100 IU/kg every 8 to 24 hours (NTE 200 IU/kg/day)

Franchini et al. Semin Thromb Hemost 2013
Factors II and Xa in FEIBA NF can generate thrombin downstream from the inhibitor blockade.
Bypass agents: recombinant activated factor VII

• Recombinant activated factor VII:
  – Also known as rFVIIa
  – Mechanism of action: binds to surface of activated platelets, supports thrombin generation, bypassing need for FVIII
  – Initially developed to treat bleeds in patients with congenital hemophilia and inhibitors
  – Dose: 90-120 µg/kg every 2-3 hour; single dose of 270 µg/kg

Ma et al. ASH Education Book Jan 2006
Franchini et al. Semin Thromb Hemost 2013
What was our next step in managing the patient?

- Discontinued rFVIII infusion, given ongoing oozing from left thigh wound site despite increasing doses of rFVIII

- FVIII activity level had decreased from 9 to 8 after increase in infusion to 27 units/kg/hr and 6,000 unit bolus.

- aPCC started, at dose of 50 units/kg IV every 8 hours

- Shortly after starting aPCC, her bleeding abated considerably with no signs of graft compromise
aPCC’s – Evidence for use in acquired hemophilia

- Few data for acquired hemophilia are available

- 1 Retrospective analysis, Sallah Haemophilia 2004
  - Efficacy of aPCC in patients with acquired hemophilia
  - Median inhibitor titer: 128 BU for severe, 34 BU for moderate
  - Majority received dose of 75 units/kg Q8-12 hours
  - Total CR rate of 86%
    - 76% CR rate for severe
    - 100% CR rate for moderate
aPCC – Evidence from congenital hemophilia inhibitor cohorts

  - Multicenter, retrospective study
  - 433 bleeding episodes in 60 patients, from 15 hemophilia centers
  - Efficacy:
    - Good/excellent in 81.3% of episodes
    - Poor in 16.9% of episodes
    - Non-existent in 1.8% of episodes
- Safety – Dimichele et al, Haemophilia 2006
  - <0.4% adverse events
  - No thrombotic complications occurred
rFVIIa – evidence for use in acquired hemophilia

  - 38 patients, acquired hemophilia in rFVIIa compassionate use program
  - Median FVIII inhibitor titer – 43 BU
  - Median starting dose of 90.4 µg/kg, median of 28 doses given
  - 14 patients received as 1st line – 100% response rate
  - 60 salvage bleeds:
    - Good in 75%, Partial in 17%, and Poor in 8%
  - 1 patient developed DIC during treatment
rFVIIa compared with aPCC, Part 1

• Astermark et al, Blood 2007
  – Randomized trial
  – Population: 48 hemophilia A patients with joint bleeds
  – Interventions:
    • aPCC at 85 IU/kg
    • rFVIIa at 105 µg/kg x 2 doses
  – Results
    • aPCC’s and rFVIIa showed similar effect on joint bleeds (effective in 81.3% and 78.1% of recipients, respectively)
    • High rate of discordant responses
rFVIIa compared with aPCC, Part 2

- Young et al, Haemophilia, 2008
  - Randomized trial
  - Population: 42 patients with hemophilia A
  - Interventions:
    - aPCC at 75 IU/kg
    - rFVIIa at 90 µg/kg x 3 doses or 270 µg/kg
  - Results:
    - Similar effects on joint pain & mobility within 9 hours
    - The requirement for additional hemostatic agents lower for rFVIIa at 270 µg/kg compared with aPCC
Clinical course on aPCC’s

- She did well on aPCC at 50 units/kg Q8 hours, and was eventually titrated down to Q12H dosing.

- Prior to discharge, was transitioned to Q other day dosing, without any worsening bleeding.

- FVIII assay performed on 5/31 (1 month after initial diagnosis) – elevated at 173 BU.

- Following discharge, continued on thrice weekly aPCC infusions at Group Health.
Later, aPCC’s were discontinued

- Patient noted increasing episodes of spontaneous bruising.

- Seen in Plastics clinic, who noted concerns regarding discontinuation of aPCC’s and her wound healing, noting “would ask the patient’s outpatient hematologist to consider this… potentially reinitiating factor VIII treatments (sic) or immunomodulation that would suppress factor VIII antibody with such agents as rituxan, cytoxan…”
Disease associations

- Possible associated illnesses – present in 50% of patients
  - Autoimmune most common association; 2 largest case series show association in 17-18%
  - SLE, Rheumatoid arthritis, or Sjogren’s syndrome
  - Solid tumors, lymphoproliferative disorders

Ma et al. ASH Education Book Jan 2006
Treatment of underlying immune disorder

- Goal – inhibitor eradication

- Approaches:
  - Prednisolone 1 mg/kg/day
  - Cytoxan addition – can improve response rates to 60-70%
  - Other options – azathioprine, vincristine, mycophenylate, 2-CDA.
Other therapies

- IVIG: useful as second line therapy; response rate of ~30%.

- Cyclosporine A: used with/without corticosteroids; effective in patients with underlying SLE

- Biologics: Rituximab at 375 mg/m² IV weekly x 4 doses
  - Consider when intolerant or resistant to first line therapy.

Schwartz RS et al Blood 1995
Schulman S et al Thomb Hemost 1996
Summary

- Factor VIII inhibitors – rare, but keep in the differential
- Initial treatment is with recombinant factor VIII
- Refractory treatment – either aPCC’s or rFVIIa
- Treat the underlying disorder with prednisolone, cytoxan, or rituximab