The Pre-Operative Evaluation of the Patient with Abnormal Clotting Studies

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Case Presentation: #1

- 52 y.o. man referred to the office for evaluation of abnormal PTT prior to planned total knee replacement
- Had undergone prior limited procedures to knee without unusual bleeding complications
- No other prior major surgery
- No history of abnormal bleeding
- No family history of bleeding
- No prior clotting studies could be found

Initial Laboratory Values

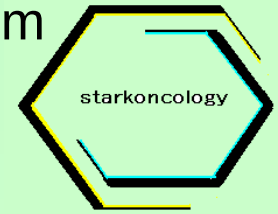
- CBC normal
- PT/INR: 12.1sec/1.0
- PTT: 42 sec (normal up to 37)
- Additional studies ordered
- But first…on to case number 2

Case Number 2

- 66 year-old lady pre-operative total hip replacement with possible coagulopathy
  - CBC: minimal anemia with no obvious cause
  - PT/INR normal
  - PTT abnormal at 52 seconds
  - Additional lab studies ordered….
  - But first…some information about clotting

Blood Clotting 101

- Platelets: form initial hemostatic plug
  - Can be quantitatively or qualitatively abnormal
- Quantitatively
  - Thrombocytopenia
    - Typically not a surgical problem unless platelets < 50,000; depends on amount of tissue trauma
    - Patients with immune thrombocytopenia (ITP or ITP-like illnesses) will have normal hemostasis down to very low platelet counts
    - If platelets are low secondary to bone-marrow failure usually there will be a hemostatic defect
    - Template bleeding time if properly performed can assess in vivo platelet effectiveness
  - Thrombocytosis, if secondary to myeloproliferative disorder
    - Post-splenectomy thrombocytosis usually not a problem



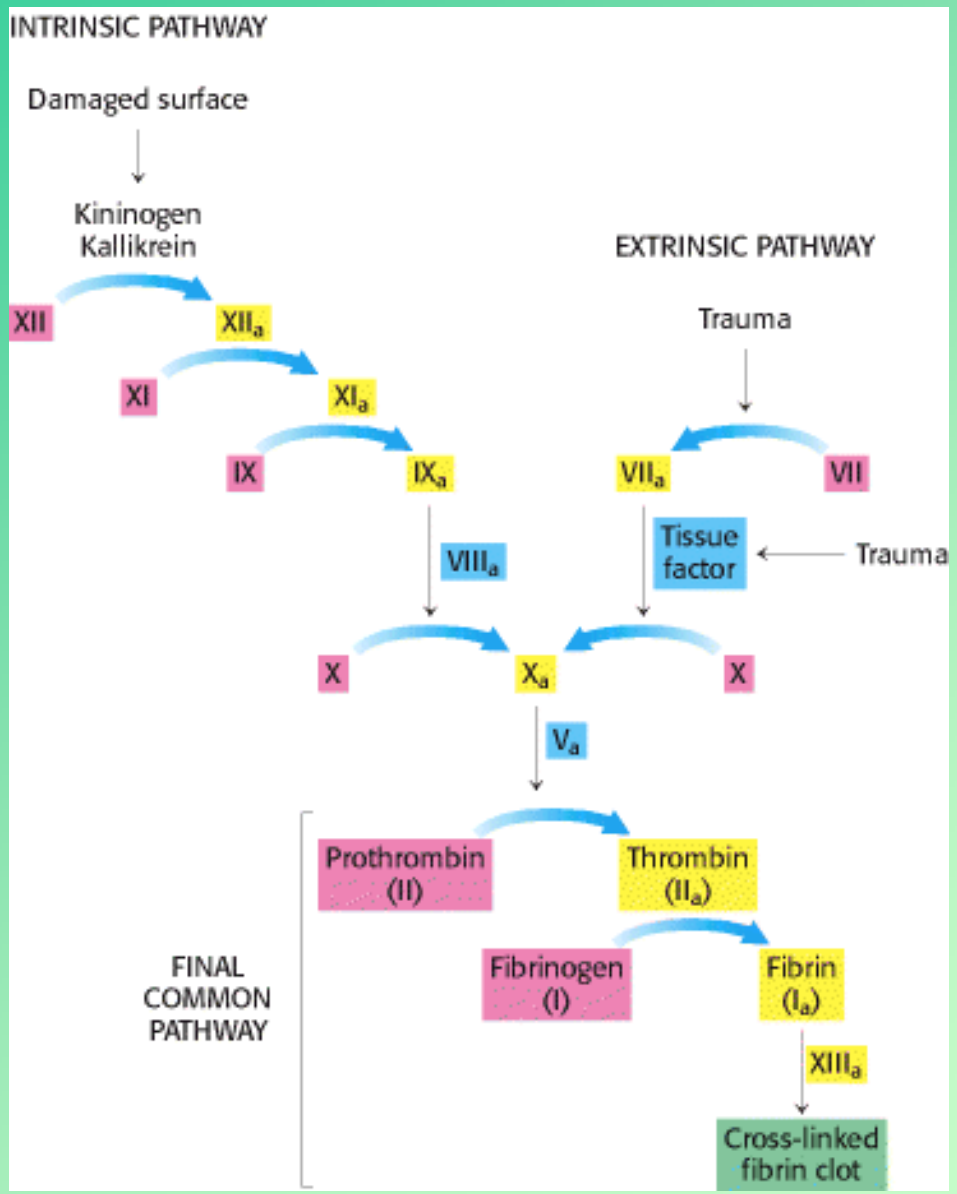
Platelet abnormalities, cont.

- Qualitatively abnormal platelets
  - Most common cause is drugs, usually aspirin
  - Can be qualitatively abnormal in myeloproliferative disorders even when normal in number
  - Rare primary disorders of platelet morphology and function
  - Platelet aggregometry and adhesiveness tests can screen for subtle defects; no point in doing if aspirin taken in the previous ten days
  - Von Willebrand Disease…stay tuned

Soluble Clotting Factors

- Complex subject, constantly undergoing conceptual revision
- Old models of intrinsic and extrinsic pathways probably gross oversimplification
- Nonetheless for understanding how to cope with abnormal lab tests and bleeding tendency the old model usually suffices

Conventional (Simplified) View of Clotting



Courtesy of NIH website

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Clotting Cascade

- Useful in interpreting laboratory tests even though an oversimplification
  - Vitamin K dependent factors: II, VII, IX and X
    - Levels of those factors depressed with naturally occurring vitamin K deficiency or with Warfarin (Coumadin)
  - These factors are assayed by the PT/INR
  - PTT test is affected by those clotting factors in the intrinsic pathway (XII, XI, IX, VIII)

Causes of Abnormal Clotting Tests

- Abnormal PT only
  - Vitamin K deficiency
  - Factor VII deficiency
  - Inhibitor of Factor VII
  - Warfarin administration
  - Liver Disease

*XII deficiency usually associated no clinical sequelae, rarely with clotting

‡Usually associated with clotting

- Abnormal PTT only
  - Deficiencies of factors VIII, IX, XI, and XII*
  - Inhibitors of above factors
  - Inherited Von Willebrand Disease
  - Acquired Von Willebrand Disease
  - Heparin Administration
  - Lupus-like anticoagulant‡

Causes of Simultaneously Abnormal PT and PTT

- DIC
- Severe Liver Disease (source of all clotting factors except Von Willebrand Factor)
- Supratherapeutic doses of Warfarin or Heparin
- Combined Heparin and Warfarin administration
- Combined Argatroban and Warfarin administration
- Inhibitors of factors I, II V or X
- Factor X deficiency associated with amyloidosis

Last two quite rare

Why is any of this important?

- Surgery represents a huge hemostatic insult to the patient
- Only exceeded by blunt trauma such as seen in battlefield injuries
- Patients with subtle coagulation defects and no previously history of bruising or bleeding can bleed excessively at surgery, threatening their intravascular volume and risking the integrity of the surgical procedure – especially joint-replacement surgery

Back to Our First Patient

- Additional studies ordered:
  - Mixing study (looking for circulating anticoagulant)
  - Factors VIII, IX, XI, XII
  - Von Willebrand factor

Results of Studies

- Mixing of patient's plasma with normal plasma at 1:1 dilution corrected the prolongation of PTT
  - Therefore, the prolongation was not caused by an inhibitor (rules out lupus anticoagulant with associated anti-phospholipid syndrome which can cause catastrophic clotting)

Results, continued

- Factors XI and IX normal
- Factor XII 47% of predicted
- Factor VIII 43 % of predicted
- Von Willebrand antigen 40% of predicted

Conclusion Regarding Patient #1

- Patient has mild factor XII deficiency
- Patient has mild Von Willebrand disease

- Co-incidence of these two abnormalities in the same patient is of unknown frequency
  - May occur more often than by chance alone
  - Some authors report that these patients bleed less than patients with equally severe VWD alone

Von Willebrand Disease

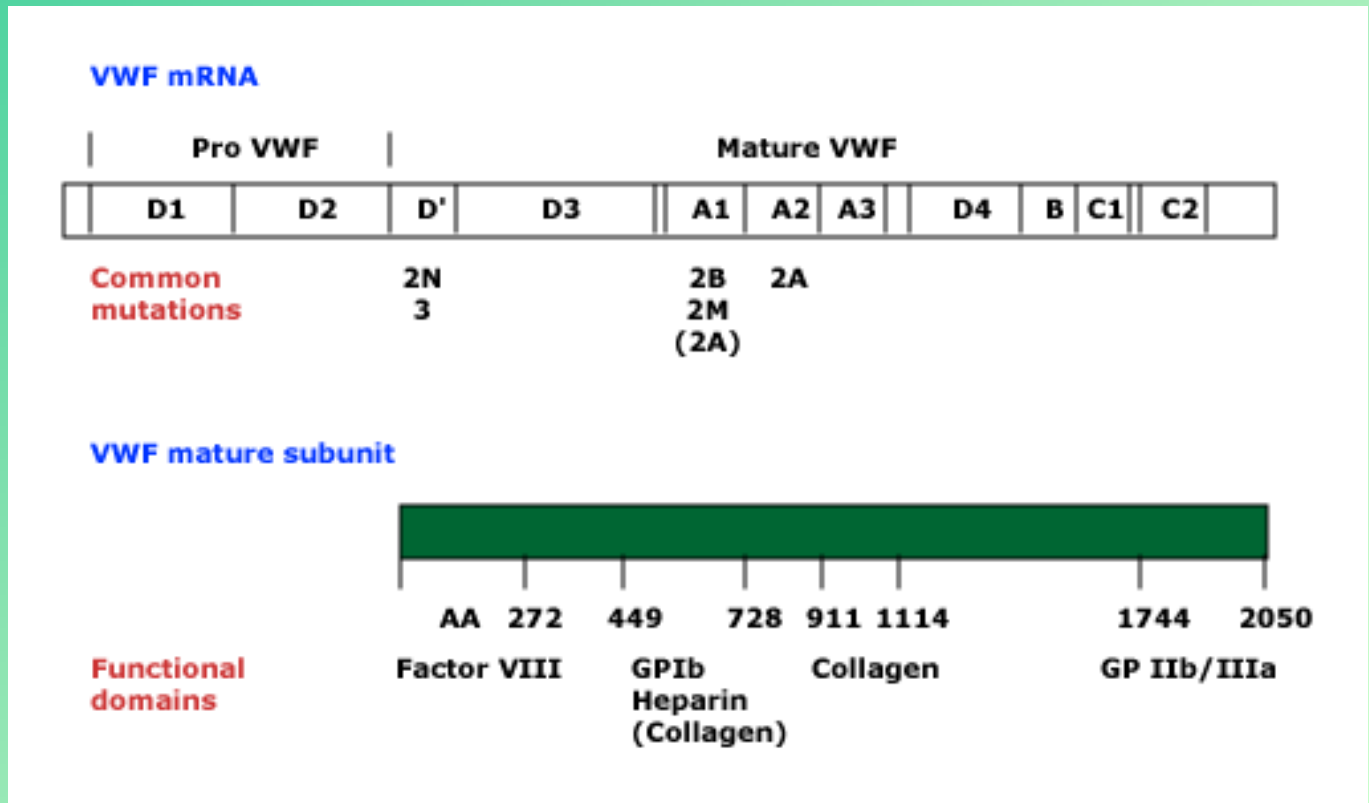
- Exceedingly complex subject, many variants
- In general:
  - Caused by mutations leading to impaired concentration or function of Von Willebrand factor
  - VW factor present in many physiologic forms (dimers, multimers)
  - Synthesized by megakaryocytes and endothelial cells and involved in platelet and endothelial interactions

Von Willebrand Disease, cont.

- Can demonstrate biochemical evidence of VWD in 1% of population but only a 1% of these people actually have a clinical bleeding disorder (i.e., 0.01% incidence of symptomatic VWD)
- Also present in an acquired form
- Results in reduced factor VIII levels because VW factor acts as a carrier of factor VIII; no basic abnormality of factor VIII *per se* but PTT is prolonged – as a clue to presence of disease

Von Willebrand Disease, cont.

- Many subtypes depending on the locus of the mutation…



Von Willebrand, cont.

- Treatment depends on the clinical severity and the subtype…subject for another discussion
  - Includes cryoprecipitates and dDAVP
  - Recombinant VWF is in development but not generally available
  - Many patients with biochemical evidence of VWD do not need treatment

Acquired VWD

- Antibodies to VWF can occur with connective tissue diseases and can mimic native VWD; won't correct with mixing studies
- Non-immune adsorption of VWF can also occur which leads to decreased functioning VWF; will correct with replacement or treatment of underlying disease, e.g., myeloma, hypothyroidism

Factor XII deficiency

- Autosomal recessive, i.e., severe deficiency requires both parents to carry one copy of mutation
- Incidence of severe (double dose of gene) deficiency 1:1,000,000
- Unassociated with bleeding
- May be associated with thrombophilia; index case died of thrombotic complications in 1968
- Usually diagnosed because of increased PTT in an era when factor assays are available

Association of VWD and Factor XII deficiency: chance alone?

- Among patients with VWD between 0.4% and 10% are XII deficient depending on which study one relies on
- Either figure is higher than that seen in the general population
- At least one study suggests that XII deficiency may ameliiorate the bleeding tendency seen with VWD
- Pathophysiologic and/or genetic mechanism linking two diseases is unknown but suspected
- May be epiphenomenon: routine use of PTT may pick up previously unsuspected patients with XII deficiency and mild VWD in whom the PTT would not otherwise be prolonged

Plans for Patient #1

- Will undergo knee replacement without pre-operative factor replacement
- Anticipate no difficulties
- Could have done dDAVP and/or cryoprecipitate “dry run” but seemed like overkill
- I will be standing by in the event of trouble

Results for Patient #2

- Mixing study 1:1 with normal plasma failed to correct
- Anti-phospholipid and anti-cardiolipin antibodies weakly positive
- Asymptomatic but at some risk for developing Anti-Phospholipid Syndrome
- Patient underwent uneventful surgery with prompt anti-coagulation post op and never developed any clotting or bleeding problems
- Is convalescing from the surgery as of this talk with progressive return of function
- No further evidence of APS
- Follow-up advisable

What about other patients with other problems?

- Patients with elevated PT/INR secondary to liver disease represent a hemostatic challenge
  - Many fail to correct adequately with infusions of vitamin K and fresh frozen plasma; worth a dry run if PT sufficiently prolonged and surgery sufficiently bloody
  - For them decision ré surgery weighs risks and benefits
  - Other patients with elevated PT/INR without liver disease require further study and individualized approach – very rare conditions include abnormal fibrinogens, require referral to clotting center
- Some patients with prolonged PT/INR are vitamin K deficient secondary to starvation or prolonged use of antibiotics – will respond to exogenous vitamin K

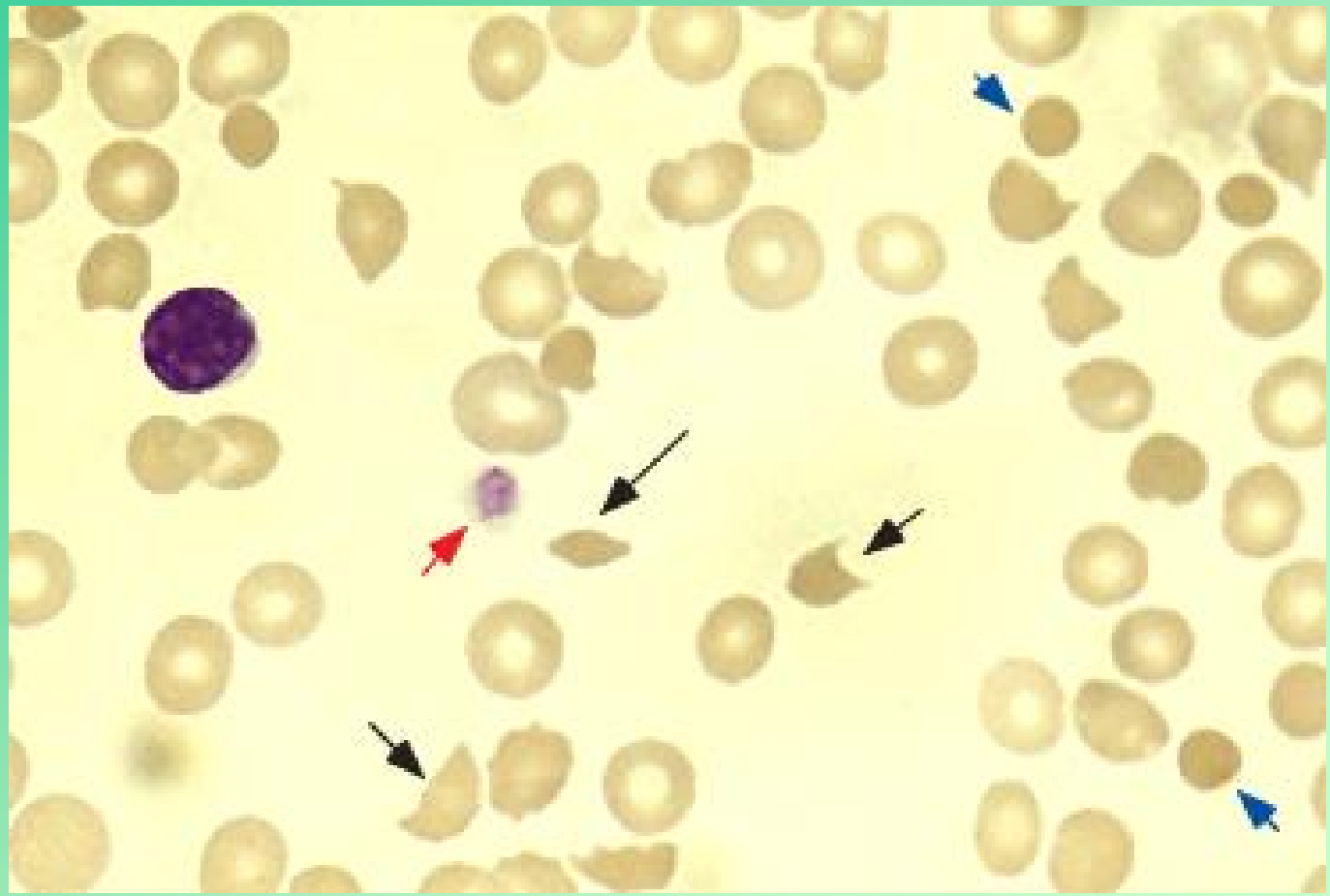
Other patients with Elevated PTT

- Big group to segregate out are those with circulating anticoagulants who do not correct with mixing studies
- A significant proportion will have clinical or sub-clinical anti-phospholipid syndrome and can have DVT/PE post-op
  - These patient are candidates for aggressive post-op anticoagulation in conjunction with advice and consent of surgeon

Patients with Elevated PT *and* PTT

- These patients may have profound hemostatic defects and must be individualized to assess hemostatic risk and ability to correct defect pre-operatively
- Must always worry about acute or chronic DIC – if chronic may be subtle
  - Seen in patients with disseminated cancer as pre-terminal event
  - Also seen with endothelial disruption, e.g., abdominal aortic aneurysm, giant hemangioma (Kasabach-Merritt syndrome)
  - If body overcompensates for consumption of clotting factors, thrombosis can dominate clinically ("thrombotic DIC")

Peripheral Blood in Chronic DIC – Microangiopathic Hemolytic Anemia



Very bad news; patients usually obviously ill

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Conclusions

- Surgery represents hemostatic stress and clotting ability must be assessed ahead of time
- Routine studies can uncover many different esoteric conditions only some of which need to be treated
- Difficult field – not for amateurs!

For a copy of this talk…

- Visit us on the web (www.StarkOncology.com) or at the office…

But wait…there's still more!

In the tradition of Drs. Riblet, Pelausa and Ramirez…