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: 12.1 sec/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

INTRINSIC PATHWAY

Damaged surface

Kininogen Kallikrein

XII → XIIa

XI → XIa

IX → IXa

VIIIa

VIIIa

VIIa → VII

EXTRINSIC PATHWAY

Trauma

Tissue factor

Trauma

X → Xa

V → Va

Prothrombin (II)

Thrombin (IIa)

Fibrinogen (I)

Fibrin (Ia)

XIIIa

FINAL COMMON PATHWAY

Cross-linked fibrin clot

Courtesy of NIH website
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

• 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‡

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

‡Usually associated with clotting
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 ameliorate 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 patients 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
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…

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But wait…there’s still more!
In the tradition of Drs. Riblet, Pelausa and Ramirez...