Acquired Von Willebrand’s Syndrome

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Case Presentation

• 78-year-old man with refractory IgA lambda myeloma
• ARRY 520 Research protocol
• H/o LE DVT on Coumadin
• Fell at home, sustained a L rib fracture. Admitted to OSH for management of L flank hematoma. Taken off of coumadin
• Readmitted after having syncopal episode. Worsening hematoma, HCT of 16.5, transfused 6 U pRBCs.
• Admitted to UWMC ...
Case Presentation

Unsuccessful attempts at embolization, CT surgery consult.

• Required 11 U PRBCs. Platelet count maintained at 100K, Vitamin K given for a persistent INR of 1.3-1.5.
Case Presentation

• Social history:
  – Originally from Germany, works as baker/caterer on Camano Island
  – No tobacco, etoh or illicit drug use
• Family history: father died at 53yo 2/2 myeloma. Brother died of oropharyngeal CA. No family h/o bleeding.
• Physical exam:
  – GEN: very pleasant male, NAD
  – HENT: mmm, o/p clear, tongue appears to have normal geography.
  – LUNGS: clear on R, decreased BS on L
  – CV: RRR 2/6 systolic murmur heard best at LUSB
  – ABD: ntnd, nl BT, no HSM
  – SKIN: very large hematoma over left flank extending up to the shoulder.
  – NEURO: AAO x 3, nl speech.
  – MSK: no joint swelling or erythema. No pain to palpation of spine. No LE edema.
Case presentation (cont.)...

- Hematology Consulted...
  - PTT was 50 (22-35), corrected on the 1:1 mix to 29 and then mildly prolonged with incubation to 36.
  - PT was 16.4 (10.7-15.6) and corrected with 1:1 mix.
  - TT was normal.
  - Impression was a vitamin K factor deficiency and a likely weak lupus inhibitor.
- Given a calculated dose of FFP dose to correct his INR.
- Initially treated with DDAVP (possible VWD) and Amicar.
- Sent additional testing PFA, VWD screen to start
Von Willebrand’s Factor

- Present in plasma and subendothelial matrix
- Damaged endothelium → exposure of subendothelial VWF and collagen to circulating VWF and platelet Gp1b receptors which allows platelet tethering to the site of injury.
- Platelet to platelet and platelet to vessel wall adhesion are mediated through the IIb-IIIa receptor.
- Serves as a carrier for Factor VIII in circulation, preventing clearance.

(Picture NEJM 351;7 . 683-694)
**Congenital/Inherited vW Disease**

- **Type 1 (75%-80%):** Partial quantitative deficiency of VWF (AD)
- **Type 2:** Qualitative defects in VWF
  - **A:** (10-15%) → leads to increased proteolysis of VWF
    - Decreased HMWM
    - Decreased VWF activity compared with antigen
  - **B:** (5%) → abnormal structure of binding site for platelet GPIb receptor which leads to spontaneous binding of platelets in the circulation
    - Thrombocytopenia, some decrease in HMWM, increased platelet aggregation with low concentrations of ristocetin
  - **N:** (rare) decreased ability to bind FVIII and protect from clearance
  - **M:** (extremely rare) decreased ability of VWF to bind platelets due to a different mutation in A1 domain.
- **Type 3 (rare):** FVIII low (~5%), undetectable VWF levels
- **Platelet-type (pseudo vWD):** similar to 2B but defect is on platelet Gp1b.
Diagnosis of vW Disease

- Classic: low levels of FVIII and prolonged bleeding time.
- Today:
  - VWF antigen (presence of VWF in the plasma)
  - Ristocetin cofactor activity (ability to promote platelet aggregation)
  - VWF activity
  - VWF: collagen binding assay
  - VWF:RCo / VWF: Ag ratio; VWF: CBA/ VWF: Ag ratio
  - Factor VIII activity
  - Multimer analysis: presence of large multimers in serum
  - VWF: platelet binding assay
  - VWF: FVIII binding assay
Acquired vW Syndrome

• Structural or functional defects of VWF that are not inherited and that lead to an increased risk of bleeding.
• Often occurs in the setting of an underlying disorder
• Mechanisms
  – Ab binding to VWF $\rightarrow$ increased clearance
  – Ab mediated functional interference with VWF activity
  – Adsorption of VWF to the surface of transformed cells or platelets
  – Increased sheer stress and enhanced proteolysis
  – Decreased production of VWF
Epidemiology of a vWS

• Reports to registries and case series
  – 266 cases 1968-1999
  – 186 cases reported by the ISTH 2000
  – Budde et al: 187/5014 blood samples from patients with bleeding d/o collected over 2 years in German case series.

• More common in the elderly (median age 62 @ diagnosis).
Associated Conditions

• ISTH registry:
  – lymphoproliferative d/o (48%)
  – Cardiovascular conditions (21%)
  – Myeloproliferative (15%)
  – Other neoplastic (5%)
  – Autoimmune disorders (2%)
  – Thyroid d/o 2%
  – Drug effect
Lymphoproliferative & Autoimmune disorders

- CLL, Lymphomas, Multiple myeloma, MGUS
- SLE, Mixed Connective tissue disease, GVHD
- Mechanism is thought to be antibody production against VWF → increased clearance or adsorption to malignant cells/paraproteins
- Management: short term improvements with DDAVP or VWF-concentrates due to increased clearance.
- IVIG has been shown to be effective in patients with IgG MGUS/paraprotein (effect observed 1-4 days after administration).
- Plasmapheresis combined with VWF concentrates for IgM paraproteinemia.
- Antifibrinolytic therapy for mucocutaneous bleeding
- Treatment of underlying condition (difficult with MGUS)
  - Chemo for lymphoma/MM
  - Steroids and immunosuppressants for autoimmune d/o
Myeloproliferative Disorders

- Essential thrombocythemia (ET) and polycythemia vera > CML, primary myelofibrosis, AML
- Primary mechanism is adsorption to malignant cells or platelets in ET.
- Risk factors:
  - Higher platelet counts (> 1500 nL)
  - Platelet function defects may contribute
- Management (difficult due to concurrent thrombotic risk):
  - Cytoreductive therapy (hydrea, chemotherapy, platelet pheresis)
  - Consider holding on ASA initiation until platelet count < 1 million
  - DDAVP 21% response rate
  - VWF-containing concentrates at higher doses
  - Recombinant factor VIIa
Association with Cardiovascular Disorders

- Increased association with cardiovascular disorders, suggesting increasing awareness of d/o amongst cardiologist and surgeons
- Mechanism thought to be secondary to high sheer stress leading to increased proteolysis of VWF multimers
Cardiovascular disease

• Characteristics:
  – Decreased HMW multimers
  – Antigen, activity and collagen binding may be normal or increased
  – Ratios may be decreased

• Aortic Valve Stenosis:
  – “Heydes Syndrome”
  • Association between AS and GI bleeding first identified in 1958 by Dr. Edward J. Heyde
  • Chronic bleeding from angiodysplastic lesions in the GI tract of AS patients promoted by an acquired type 2A VWS
  • Other clinically significant bleeding (skin/mucosal) reported in up to 21% of patients with AVS.
  • Demonstrated inverse association between the number of circulating HMW multimers and increasing Ao valve gradient.
Cardiovascular disorders (cont.)

• LVAD dependence:
  – Use is increasing (> 3000 implants in 2009).
  – Bleeding rates as high as 65% in 1st year after placement
  – Majority are GI / nasal mucosal bleeds
  – Complicated by anticoagulation

• HOCM, PDA, MV stenosis, replacement
Cardiovascular disorders (cont.)

• Management
  – Correction of cardiac defect
  – Poor response to DDAVP, vWF concentrates w/ high risk
  – Antifibrinolytic agents may aid in the acute setting
  – Particularly difficult due to concurrent need for anticoagulation in many patients
Thyroid disorders

• Decreased production and secretion of VWF → VWD type 1.
• May also be some association w/ autoimmunity.
• *In vitro* studies show a relationship between T3 exposure and up regulation of mRNA expression and protein synthesis of VWF.
• Franchini et al. 2005. 8/131 patients with low VWF levels on coagulation screening tests showed concomitant evidence of subclinical hypothyroidism.
  – Only three patients had bleeding.
  – Coagulation abnormalities normalized after thyroid replacement.

• Management:
  – DDAVP has been shown to immediately reduce bleeding time, increase platelet adhesion and increase plasma VWF and FVIII concentrations in the serum.
  – Thyroid replacement therapy has been shown to lead to normalization of FVIII and VWF concentrations after 4 months.
When to consider avWS or an associated condition?

- Patients with conditions associated w/ high rates of avWS who are contemplating procedures associated with high risk of bleeding.
- Bleeding patients with lab abnormalities suggestive of a defect in vWF function.
Case presentation (cont.)

• PFA was prolonged for col/EPI and col/ADP (>300, and 205)

• VWF screen: antigen of 52% (nl), activity level of 69% (nl), CBA 36% (L) and factor VIII activity 36% (L), multimer analysis showed decrease in the high molecular weight multimers. These were drawn after initiation of DDAVP.

• Given Humate P™ at 50U/kg which calculated to a correction to 100%:
  • Pre:  54
  4 hours post  93
  6 hours post  92
  8 hours post  71
  • Assuming an in vivo half-life of 10-12 hours for vWF, these appeared to a slightly increased clearance time.

• Tests for the presence of an inhibitor on a blood sample obtained before Humate P (vWF ag 52, CBA straight 46,: CBA 1:5=45, CBA 1:10=50, CBA 1:20 = 45 – not suggestive of an inhibitor).
VON WILLEBRAND DISEASE PANEL

Patient Name: [Redacted]
Hospital: [Redacted]
Lab. Acc. #: [Redacted]

Clinical History: Age 78 Sex m

Date sample drawn: 11/14/11
Ordering Loc.: [Redacted]
Ordering Dr.: [Redacted]

P.T. 13.1
A.P.T.T. 45
T.T. 20
FIBRINOGEN: 219

OTHER TEST(S)

Factor VIII Activity 36% F8/VWFAG ratio 0.69
Von Willebrand Factor Antigen 52% ACT/AG ratio 1.33
Von Willebrand Factor Activity 16% CB/AG ratio 0.69
Collagen Binding Assay 36% 

MULTIMER ANALYSIS

Date 11/15/11
Gel position 1 1:10

HIGH MOLECULAR WEIGHT MULTIMERS Decreased
INTERMEDIATE WEIGHT MULTIMERS Present
LOW MOLECULAR WEIGHT MULTIMERS Present

INTERPRETATION: acquired vWD
Case presentation (cont)

- Recommendation was to target a normal collagen binding assay with Humate P™ infusion (but this took several hours to return) so alternately, we targeted a normal Factor VIII level as the two were well correlated.
- DDAVP stopped after 4 doses.
- Amicar continued, platelets>100, HCT >30%
- Stopped FFP infusions as factors were obviously replete.
- Patient stopped dropping his HCT was able to be discharged to a SNF.
References

- Cuker et al. A Bloody Mystery. NEJM 361;19 November 5, 2009