A Case of a Late Bleeder

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Learning Objectives

1. Recognize Plasminogen Activator Inhibitor-1 deficiency as a rare bleeding disorder associated with delayed postoperative bleeding.
2. Be able to diagnose the common and rare causes of bleeding diathesis.

Case Report

"Ms. Y" is a 79-year-old Caucasian woman with degenerative arthritis and right knee pain for 15 years. On September 11, 2014, she received two intra-articular injections of 2% lidocaine/40mg Kenalog, with reduced pain. On September 29, 2014, she presented with two days of 10/10 right knee pain with edema but without redness, warmth, or fever. She denied any recent traumatic injury. MRI of the right knee showed hemorrhagic effusion with purpura extending to the pelvis and feet (FIG 1), and was admitted for medical workup. Past medical history was notable for heavy menses since menarche. Even as a toddler, however, she had mild anemia. She suffers from frequent migraines with associated epistaxis. Past work ups had led to no identified bleeding disorder. Surgical history was notable for hysterectomy at 39 for uncontrolled uterine bleeding secondary to fibroids and endometriosis, as well as significant post-operative bleeding after tonsillectomy and wisdom tooth extraction. She is not allergic to any medications, and has not used aspirin nor NSAIDs since age 60. She takes estrogen replacement. Family history is negative for bleeding disorders. She has no history of drinking, smoking, or illicit drugs. Her physical exam besides her purpura was unremarkable.

Labs showed normal prothrombin time (PT) and normal partial thromboplastin time (aPTT). Factor VIII activity, factor IX activity, and von Willebrand panel were normal, as were complements levels. Factor XIII, α_2-antiplasmin, fibrinogen by clotting method, thrombin time, and von Willebrand 2N were all within normal limits. The patient's DNA, however, was PAI-1 Locus heterozygous for the 4G/5G deletion/insertion allele. This suggests intermediate PAI-1 activity (FIG 2,4). Ms. Y was diagnosed with plasminogen activator inhibitor-1 deficiency.

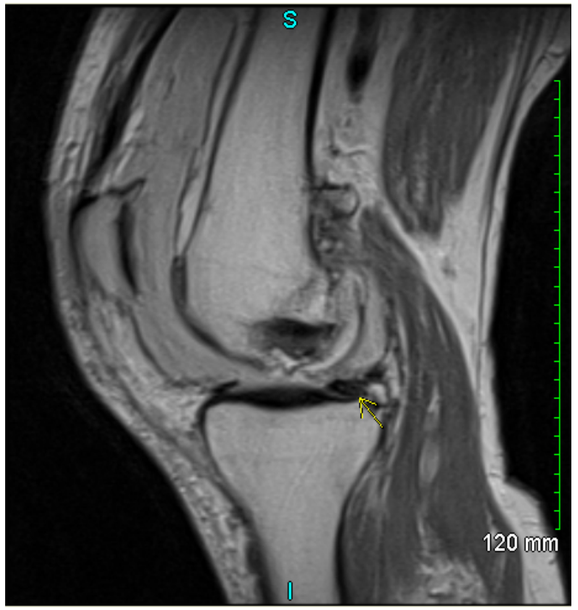

FIG 1. MRI of the right knee showed hemorrhagic effusion 2 weeks after intra-articular injections

Tests	Results	Reference
PT	10.5s	10.3-12.8s
aPTT	33s	26-36s
Factor VIII	97%	55-200%
Factor IX	105%	65-140%
von Willebrand	90%	55-200%
Factor XIII	No Lysis	No Lysis
α_2-antiplasmin	104%	80-140%
Fibrinogen	296mg/dL	200-430mg/dL
von Willebrand 2N	Negative	Negative
PAI-1	Deficient	Normal

FIG 2. Summary of lab workup for coagulopathy

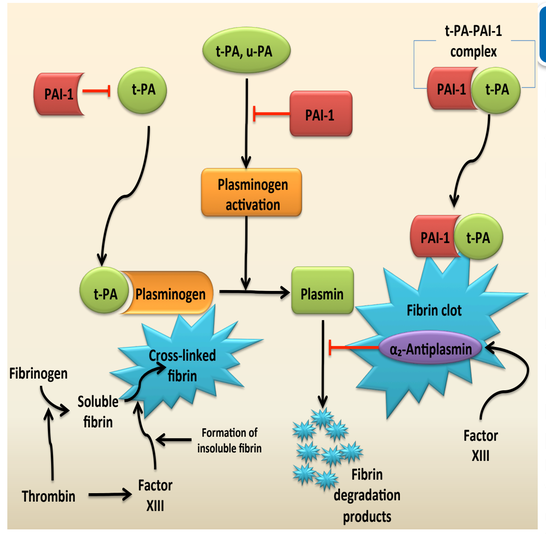

FIG 3. Activation and Inhibition of the Fibrinolytic Pathway

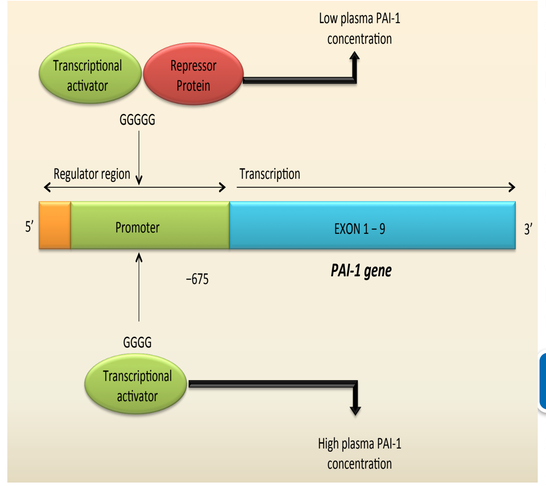

FIG 4. Structure of the Gene for Plasminogen-Activator Inhibitor Type 1 (PAI-1)

Discussion

PAI-1 is an important down regulator of the fibrinolytic system (FIG 3). Plasmin, the primary protease responsible for fibrinolysis, is formed from the cleavage of the zyomogen plasminogen. Plasminogen activator inhibitors control this process, with the primary inhibitor being PAI-1. PAI-1 is a 47-kDa protein that binds to plasminogen activators with rapid and irreversible inhibition. PAI-1 is mainly produced by the endothelium, but can also be secreted by other tissue types such as adipose tissues. PAI-1 inhibits the serine proteases t-PA and u-PA, therefore inhibiting fibrinolysis. Clear reports of PAI-1 deficiency are rare, with a first case reported in the 1980s. Affected patients express mild to moderate bleeding symptoms ranging from epistaxis to delayed bleeding after surgical procedures. Complete deficiency, however, is linked to life threatening hemorrhage and prolonged wound healing.

Ms. Y had an extensive history of bleeding, including anemia, heavy menses, postsurgical bleeding, and the presenting episode of hemarthrosis. Classically, mucosal bleeding is associated with problems of platelet quality or quantity; vasculitis; or connective tissue disease. Ms. Y's platelet function testing (PFA-100) was normal, and her platelet numbers sufficient. She had no obvious blood vessel issues, nor findings pointing to Osler-Weber-Rendu. Importantly, her history showed delayed bleeding, very similar to factor deficiencies.

Ms. Y had a normal aPTT, mildly low PT, and normal platelet count. Therefore, one must think of other reasons for her bleeding (FIG 3). Factor VIII and factor IX activity could be responsible, but their levels and activities were normal. The panel of tests for von Willebrand deficiency, another common cause of bleeding with normal PT/aPTT, was ordered and was normal (FIG 2).

At this point, differential would include rarer disorders such as factor XIII deficiency, dys- or hypo-fibrinogenemia, von Willebrand disease type 2N (Normandy), α_2-antiplasmin deficiency, and plasminogen activator inhibitor deficiency (Fig 2,3). PAI-1 deficiency is a rare bleeding disorder whose diagnosis is a challenge but not impossible. It is our hope that this case report will add to a future database of clinical manifestations of intermediate activity of PAI-1 deficiency, which can help define the wide spectrum of a disease not yet fully understood.

References

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