Abnormalities in the Fibrinolysis Pathway and Clinical Implications

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Introduction

The fibrinolytic system, also known as the plasminogen-plasmin (PP) system, is composed of plasminogen activators (PAs) which converts plasminogen to the proteolytic enzyme plasmin. It is maintained in a state of balance by inhibitors of PAs and of plasmin (Fig. 1). There are four known PA inhibitors (PAIs): PAI-1, PAI-2, activated protein C inhibitor (also known as PAI-3), and thrombin activatable fibrinolytic inhibitor (TAFI), of which PAI-1 has the most influence on many physiologic and pathologic functions.

A major function of the PP system is the lysis of excessive fibrin formed during hemostasis. Thus, excess fibrinolysis will result in unstable clot formation and bleeding. Conversely, abnormally decreased fibrinolysis will increase the risk of thrombosis (Collen 1999; Kwaan 1992). As plasmin is also involved in many other physiologic and pathologic processes such as breakdown of extracellular matrix and activation of latent growth factors, abnormalities of the PP system are implicated in a variety of disorders such as atherosclerosis and carcinogenesis (Kwaan and Mazar 2013), but they do not directly increase the risk of thrombosis or bleeding. On the other hand, abnormal bleeding as well as thrombotic manifestations, though not common, does occur when there is dysregulation of the fibrinolytic system. The Q and A in this chapter is limited to discussion of the fibrinolytic pathway affecting hemostasis.

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Case 1: Review of Fibrinolytic Bleeding

Seventeen-year-old female presented with a 3-day history of spontaneous bruising of the left thigh. Three weeks earlier, after completing a 25 km bicycle ride, she had diffuse myalgias, fever, and mild but transient pharyngitis. There was no relief after 5 days of amoxicillin. Past history revealed a bilateral malar rash for 6 months treated with topical steroids by her general practitioner. There was no history of spontaneous bruising or bleeding, nor family history of a bleeding diathesis. Her parents are not related. Laboratory findings include hemoglobin of 11.5 g/dl; WBC, $7{,}200 \times 10^6$/l with normal differential; platelets 190×10^9/l; prothrombin time, 20 s (control 13 s); PTT, 41 s (control 30 s); mixing test, both PT and PTT corrected by mixing with 1:1 volume/volume (v/v) normal plasma; D-dimer >5,000; TT, 26 s (control: 10 s); clotting factor assays Factors II 55 %, V 60 %, VII 124 %, VIII 17 %, IX 80 %, X 72 %, XI 52 %, and XII 36 %; and VWF:Ag, VWF:CB, and VWF:RCo all >150 %. There was no evidence of anti-VWF antibody. Lupus

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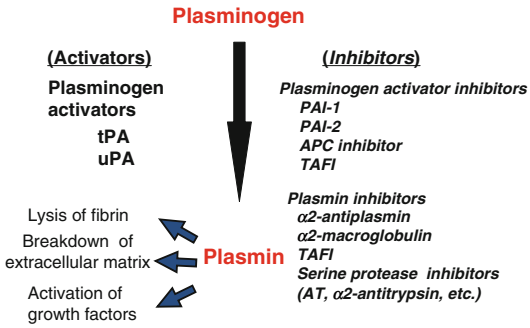

Fig. 1 The plasminogen-plasmin system

anticoagulant (LA) and anticardiolipin (aCL) were negative. Peripheral blood smear showed normal red cell, white cell, and platelet morphology, with no schistocytes.

Within 12 h, the bruises rapidly spread to both buttocks, hips, and right thigh. The hemoglobin fell to 6.2 g/dl. WBC count was $12{,}000 \times 10^6$/l with normal differential, platelets 180×10^9/l, prothrombin time >30 s (control 13 s), PTT >120 s (control 30 s), and fibrinogen <60 mg/dl.

Question 1. Which of the following is likely the cause of her bleeding?

A. Abnormal platelet function
B. Acquired F VIII inhibitor
C. Acquired F VII inhibitor
D. Disseminated intravascular coagulation (DIC) or abnormal fibrinolysis.

Expert Perspective This patient's bleeding can be due to any of the above causes; one significant laboratory finding was the severe hypofibrinogenemia, pointing to either severe DIC or abnormally excessive fibrinolysis. Severe reduction of fibrinogen level occurs when there is impairment of hepatic synthesis, such as in acute liver failure or during L-asparaginase therapy, or, more commonly, when there is a rapid consumption of fibrinogen that overwhelms the replacement by hepatic synthesis. This happens in acute severe DIC or when there is excessive fibrinogenolysis. In this scenario, further tests are needed to differentiate between DIC and abnormal fibrinolysis.

Question 2. Which of these are *not* likely to produce meaningful results to differentiate between DIC and abnormal fibrinolysis?

A. Mixing tests
B. D-dimer
C. Euglobulin lysis time
D. Thromboelastography

Expert Perspective Correction of the prolonged PT/PTT with mixing tests would be most helpful to rule out the presence of inhibitors while at the same time will indicate whether there is consumption of coagulation factors as in DIC. An increased D-dimer is nonspecific and is likely increased due to the internal hematoma. On the other hand, both the euglobulin lysis time and thromboelastography are most helpful in the diagnosis of excessive fibrinolysis. Even with both of these tests, it may not be possible to distinguish between primary fibrinolysis and fibrinolysis secondary to DIC.

Question 3. Results showed a euglobulin lysis time of 6 min (normal: >1 h) and TEG (decreased maximum amplitude; 100 % clot lysis at 30 min), both indicating increased fibrinolysis. As she had recent bilateral malar flush, tests for systemic lupus erythematosus (SLE) were obtained and results were positive. What are the possible causes of her excessive fibrinolysis?

A. Strenuous exercise (patient had participated in competitive bicycle race)
B. Cellulitis in her lower extremities
C. Complication of SLE
D. Hereditary deficiency of one of the fibrinolytic inhibitors

Expert Perspective While strenuous exercise has long been shown to increase fibrinolytic activity (Biggs et al. 1947), it does not lead to the excessive bleeding seen in this patient. Likewise, her cellulitis was limited and effectively treated by antibiotics. On the other hand, she did have active SLE, in which a known complication is the presence of autoimmune antibody to PAI-1 (Bates et al. 2003). A low PAI-1 activity can lead

to the failure to inhibit any increased antifibrinolytic activity induced by exercise.

Likewise, if there is an inherited deficiency of one of the other inhibitors of fibrinolysis, a similar effect can be seen. Verification of these possibilities will require assay of PAI-1 activity, as well as those of antiplasmin.

Case 2: Impairment of Antifibrinolytic Pathways: Inherited Disorder

A 42-year-old woman presented in preoperative consultation prior to cholecystectomy. She reported easy bruising throughout her life, as well as menorrhagia. She had postpartum hemorrhage requiring multiple units of packed red blood cells approximately 10 years previously. She eventually underwent total abdominal hysterectomy at age 38, with excessive bleeding beginning on postoperative day 1. Most recently, she developed a hematoma following biopsy of a benign breast lesion. She denied spontaneous bleeding symptoms and was unaware of bleeding problems in her family.

Workup revealed a normal platelet count, platelet aggregation studies, von Willebrand antigen and activity, prothrombin time, partial thromboplastin time, fibrinogen, and FXIII activity. Thromboelastography demonstrated 100 % clot lysis at 30 min. Additional testing was notable for normal α2 antiplasmin but an undetectable PAI-1 activity.

Question 4. Which of the following would also be expected laboratory findings?

A. Normal total tissue plasminogen activator (t-PA) antigen
B. Elevated free tissue plasminogen activator antigen
C. Reduced t-PA/PAI-1 complexes
D. All of the above

Expert Perspective This woman had severe plasminogen activator inhibitor-1 (PAI-1) deficiency. PAI-1 is a main regulator of fibrinolysis, through inhibition of both urokinase and tissue-type plasminogen activators. In the circulation, it is present in both plasma and in platelets (Erickson et al. 1985). Under normal circumstances, PAI-1 forms complexes with both t-PA and u-PA, thereby inhibiting fibrinolytic activity. Adverse thrombotic events including myocardial infarction and deep vein thrombosis have been seen with abnormally high levels of PAI-1 (Hamsten et al. 1985; Wiman et al. 1985). Conversely, severe deficiency of functional PAI-1 results in bleeding due to heightened fibrinolysis (Dieval et al. 1991; Lee et al. 1993; Schleef et al. 1989). The reduction in PAI-1, and therefore reduced t-PA/PAI-complexes, allow for increases in the amount of free, unopposed t-PA activity. The total amount of t-PA, however, is normal. Bleeding is typically observed only after trauma or surgery, although severe menstrual bleeding and bruising can also be seen. The use of antifibrinolytic agents including ε-aminocaproic acid and tranexamic acid in the perioperative period can reduce bleeding complications.

Question 5. She inquired as to whether her daughter could be affected. Is this a possibility?

A. Yes.
B. No.

Expert Perspective This patient's daughter could theoretically also have inherited PAI-1 deficiency. The PAI-1 gene resides on chromosome 7 and consists of 9 exons, corresponding to a protein of 379 amino acids (Bosma et al. 1988; Ginsburg et al. 1986). A severe deficiency of PAI-1 activity has been described to result from homozygous inheritance of a frame-shift mutation in exon 4 of the PAI-1 gene (Fay et al. 1992, 1997). A dinucleotide insertion within exon 4 shifts the PAI-1 reading frame, causing a premature stop codon and therefore synthesis of a nonfunctional PAI-1 protein. Homozygosity is required for development of clinical manifestations of bleeding. Heterozygous individuals are not affected by abnormal bleeding even after surgery or trauma (Fay et al. 1997; Lee et al. 1993). If the daughter's father has a normal genetic complement, she would not be expected to have a clinically significant bleeding phenotype.

Case 3: Impairment of Fibrinolytic Pathways, Iatrogenic Causes

A 24-year-old woman presented at the emergency department with swelling of her left leg and shortness of breath for 24 h. She was on oral contraceptive, Desogen™ (containing 30 μg ethinyl estradiol and 150 μg desogestrel), daily. She has no past history of thrombosis. She has had menorrhagia due to uterine fibroids, well controlled by tranexamic acid, 3.9 g daily orally for first 5 days of menstruation. There is no family history of thrombosis. Her height is 6 ft and weight is 250 lbs (BMI = 33.9). The CBC, PT, and PTT are normal. Pulse oxygen is 87 % on room air. The fibrinogen is 420 mg/dl (normal), and D-dimer is 300 μg/L (normal).

Question 6. In view of this history, the diagnosis of pulmonary embolism (PE) is:

A. Likely
B. Not likely

Expert Perspective The history indicates the presence of a number of risk factors for venous thromboembolism (VTE), including use of combined oral contraceptive (COC). Such risk was noted soon after its introduction in the USA in 1960 (Jordan 1961). The estrogen component is believed to be responsible for the thrombogenicity. Thus, the thrombosis risk varies with the type and dosage of estrogen in different COCs (van Hylckama Vlieg et al. 2009). The specific type of COC (estradiol combined with desogestrel) that this patient was taking carries risk for thrombosis of 19.0 % with odds ratio 7.3 (95 % CI = 5.3–10.0).

She was also taking the antifibrinolytic agent, tranexamic acid, for her menorrhagia. Thrombotic complications with tranexamic acid administered for this indication (Goshtasebi et al. 2013; Peitsidis and Koukoulomati 2014) have been reported in the literature, though uncommon. The antifibrinolytic agents, epsilon aminocaproic acid and tranexamic acid, are derived from hexanoic acids and have been extensively used for control of bleeding when excessive fibrinolysis is believed to be a major factor. In addition to these two risk factors, she was also obese. Thus, with this clinical presentation of shortness of breath, the diagnosis of acute pulmonary embolism should be suspected. A key diagnostic test for VTE/PE, an increased D-dimer level, (Anderson and Wells 2000; Michiels et al. 2000; Perrier et al. 1999) was normal in this patient.

Question 7. On the basis of these available laboratory findings, would you continue to pursue the likely diagnosis of VTE and order further tests?

A. Yes.
B. No.

Expert Perspective Yes: she had clinical manifestations consistent with pulmonary embolism, despite a negative D-dimer. D-dimer is the breakdown product of cross-linked fibrin monomer and is elevated when there is fibrin formation, initiated by the cleavage of thrombin on fibrinogen, producing fibrin monomers. The cross-linked monomers are broken down by plasmin, yielding D-dimer. The sensitivity depends on the various methods used (Anderson and Wells 2000). In a cohort of 1,177 patients with suspected pulmonary embolism, the overall negative predictive value was 96 % (Ginsberg et al. 1998).

However, the formation of D-dimer requires the prior breakdown of the monomers by plasmin. Our patient was taking the antifibrinolytic tranexamic acid for her menorrhagia so her D-dimer is expected to be false negative. The dependence of a positive D-dimer test on the presence of fibrinolytic activity is underrecognized (Mihalache and Ames 2012).

Case 4: Failure of Removal of Fibrinolytic Factors

A patient undergoing orthotopic liver transplantation for a solitary metastatic lesion in his left lobe of liver develops excessive bleeding. The

primary tumor was carcinoma of the colon, resected 6 months ago.

Question 8. Which factor is the most likely to affect hemostasis in this setting?

A. Deficiency of clotting factors as shown by prolonged PT/PTT
.B. Impaired thrombopoietin resulting in thrombocytopenia
C. Dysregulation of the fibrinolytic balance
D. Hypercoagulable state due to cancer

Expert Perspective During the anhepatic phase of transplant procedure, the normal hepatic clearance of t-PA stops, leading to its rapid accumulation in the circulation (Porte et al. 1989; Segal et al. 1997). This happens concomitantly with other hemostatic changes in orthotopic liver transplantation, including the release of tissue factor and activated clotting factors with reperfusion of the graft, and with the cessation of hepatic clearance of these procoagulants which commonly results in DIC and leads to secondary fibrinolysis. Fibrinolytic bleeding is common unless counterbalanced by treatment with fibrinolytic inhibitors such as tranexamic acid or epsilon aminocaproic acid. Another antifibrinolytic agent, aprotinin, had been used in the past for massive bleeding in cardiac surgery and in liver transplantation (Massicotte et al. 2011); but its use had been discontinued since 2008 due to the finding of excessive 30-day mortality rate (Fergusson et al. 2008).

Question 9. Which is the best way to monitor the abnormal fibrinolysis during liver transplantation?

A. PT/PTT
B. Platelet count
C. Platelet function assay
D. Thromboelastography

Expert Perspective Standard PT and PTT tests are nonspecific and are excessively prolonged with deficiency of liver-synthesized coagulation factors and thus, in that setting, may not reflect the degree of fibrinolysis. In healthy subjects or in patients with mild fibrinolysis, the whole blood clot lysis time or the euglobulin clot lysis time are slow due to the presence of the natural inhibitors of fibrinolysis. To circumvent this problem, this test is modified by diluting samples tenfold. Such dilution also dilutes the fibrinolytic factors and their inhibitors. As a result, these tests provide only a partial picture of the fibrinolytic balance in the body. On the other hand, viscoelastic measurements such as thromboelastography (TEG®) or ROTEM®, a more global measure of coagulation, use whole blood to monitor hemostasis from the initiation of clotting to the lysis of the clot (Kitchen et al. 2010) and have been used in liver transplantation (Yang Lu et al. 2014).

Case 5: Review of Pathologic Fibrinolysis

A previously healthy 32-year-old male had a 4-day history of excessive bruising, mild epistaxis, and bleeding of the buccal mucosa. He had a fever of 39.5 °C. There was no general malaise nor bone pain. On the fifth day, he presented to the emergency room with generalized headache but no visual symptoms nor neurologic deficits. There was no past history nor family history of bleeding. Physical examination revealed the presence of ecchymoses of the trunk and extremities. There was no lymphadenopathy. The spleen tip was palpable. The hemoglobin was 9 g/dl, WBC was 19×10^{6}/l, differential showed 35 % "blasts," and the platelet count was 14×10^{9}/l. The coagulation profile showed PT 28.0 s (control: 12 s), PTT 98 s (control: 30 s), and fibrinogen <50 mg/dl.

Question 10. Which of the following diagnosis most likely fit this clinical presentation?

A. Acute myeloblastic leukemia
B. Acute myelomonocytic leukemia
C. Acute promyelocytic leukemia
D. Acute lymphoblastic leukemia

Expert Perspective The presence of blasts in the peripheral blood with anemia, leukocytosis, and thrombocytopenia suggests the presence of acute leukemia. When this is associated with a severe coagulopathy, the diagnosis of acute promyelocytic leukemia (APL) is highly probable. Over 90 % of APL patients present with severe coagulopathy, while this is rare in acute myelomonocytic leukemia.

Question 11. Which of the following is a risk factor for bleeding in APL?

A. Thrombocytopenia
B. Hypofibrinogenemia
C. Excessive fibrinolysis
D. High white blood cell count
E. All of the above

Expert Perspective The risk factors for bleeding include WBC over 10×10^6/l, peripheral blast count over 30×10^6/l, age over 60 years, impaired renal function, and increased fibrinolysis as reflected by fibrinogen <100 mg/dl (Choudhry and DeLoughery 2012; de la Serna et al. 2008; Kwaan and Cull 2014). Severe thrombocytopenia is generally considered to be a bleeding risk, although platelet count may not correlate with bleeding. Increased fibrinolytic activity has long been recognized to be a major hemostatic dysfunction in APL (Kwaan 2007, 2014; Kwaan and Cull 2014). Abnormalities include increased tissue plasminogen activator (t-PA) (Menell et al. 1999; Tallman et al. 2004) and uPA and an increase in two receptors of t-PA, annexin A2 (Menell et al. 1999) and the S100-binding protein A4 (S100A10) (Kwaan 2014; Kwaan and Cull 2014; O'Connell et al. 2011). Excessive fibrinolysis is also due to a reduced PAI-1 activity (Sakata et al. 1991) and to a low thrombin activatable fibrinolysis inhibitor (TAFI) (Meijers et al. 2000). In addition, increased annexin A2 has been found to be constitutively expressed in microvascular endothelial cells in the brain (Kwaan et al. 2004), leading to preferential binding of circulating t-PA to this organ, which may account for the excessively high incidence of intracerebral hemorrhage in APL.

Question 12. Which agent is the currently recommended treatment for bleeding in APL?

A. Antifibrinolytic agents
B. All-trans-retinoic acid (ATRA)
C. Heparin
D. Cryoprecipitate,
E. Platelet transfusion
F. B, D, and E

Expert Perspective The DIC in APL is associated with both primary and secondary fibrinolysis. The role of heparin, though helpful in anecdotal reports, is of no benefit (Rodeghiero et al. 1990) and not recommended. Antifibrinolytic agents likewise have also been shown in clinical trials to be of no benefit. The early initiation of chemotherapy, all-trans-retinoic acid (ATRA), is the currently recommended treatment for APL (Sanz et al. 2009). Delay in initiation of ATRA therapy by as little as 24 h is associated with poorer outcome (Altman et al. 2013; Roldan et al. 2013). Thus, ATRA should be initiated at clinical diagnosis of APL, even before genetic confirmation (t(15,17)). Additional supportive measures should include platelet transfusions to maintain platelets $>100 \times 10^9$/l and cryoprecipitate to maintain fibrinogen >150 mg/dl.

Controversies

- Is there a diagnostic test for increased fibrinolytic activity in blood with better sensitivity and specificity?
- In patients with autoantibodies against PAI-1, such as those seen in systemic lupus erythematosus, when is immunosuppressive therapy needed?
- How safe is the use of antifibrinolytic agents at the recommended doses and

how much is the risk of thrombotic complications with these agents?
- How much provocation is needed, i.e., how strenuous is the exercise, to precipitate bleeding in patients with hereditary deficiencies of fibrinolytic inhibitors?
- Despite evidence of increased fibrinolytic activity in acute promyelocytic leukemia, why is there a lack of benefit of antifibrinolytic agents in reducing the bleeding complications?
- What is the best way of titrating the doses of antifibrinolytic agents during the anhepatic phase of liver transplantation?

Answers

Question 1. D
Question 2. B
Question 3. C or D
Question 4. D
Question 5. A
Question 6. A
Question 7. A
Question 8. C
Question 9. D
Question 10. C
Question 11. E
Question 12. F

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