6 Excessive Bleeding with Normal Prothrombin Time, Partial Thromboplastin Time, and Platelet Count

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Introduction

The clinical evaluation of a patient with bleeding diathesis begins with a detailed history and physical exam, followed by laboratory testing. A comprehensive history should include the nature, frequency, duration, and severity of bleeding as well as common sites of bleeding such as oral mucosa, gastrointestinal, intramuscular, or intra-articular. In particular, a patient's response to hemostatic challenges in the past, especially surgical procedures and dental extractions, can be quite informative. Also, information regarding interventions performed to stop bleeding should be obtained. Patients with platelet function defects or von Willebrand disease (vWD) may present with bleeding involving the skin and mucous membranes. This usually involves ecchymoses, epistaxis, menorrhagia, gastrointestinal bleeding, as well as excessive bleeding after dental extractions or surgery. Musculoskeletal bleeding such as hemarthrosis is not usually observed. Typically, bleeding with invasive procedures is immediate and seldom life threatening. Severe intracranial or gastrointestinal bleeding is observed more commonly in patients with type-3 vWD. On the other hand, defects or deficiencies in coagulation factors lead to deep tissue bleeding such as intramuscular hematomas and hemarthrosis. They often present with delayed post-procedure bleeding that can be severe.

The platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) are general screening tests used for evaluation of hemostasis. While an abnormality in one of these tests can help delineate an underlying bleeding disorder, often these tests are normal making the diagnosis of a bleeding disorder challenging. A large prospective study in patients with mucocutaneous bleeding identified only about 41 % of patients with vWD, platelet function defects, or clotting factor deficiencies. The remainder had bleeding disorders without an identifiable cause (Quiroga et al. 2007). This usually results in exhaustive testing in an attempt to characterize accurately the bleeding disorder. More common disorders of hemostasis that may present with normal coagulation tests include qualitative platelet disorders, drug-induced platelet dysfunction, factor deficiencies, and abnormal vascular fragility. See Table 6.1 for a listing of such disorders. An algorithm to establish the diagnosis of these disorders is shown (Fig. 6.1).

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Table 6.1 Bleeding disorders with normal coagulation tests

Platelet function disorders
Inherited
Bernard–Soulier syndrome
Glanzmann thrombasthenia
Storage pool disease
Scott syndrome
Acquired
Uremia
Cirrhosis
Paraproteinemias
Drugs
Antiplatelet agents (aspirin, clopidogrel, prasugrel, abciximab, eptifibatide)
NSAIDs
SSRI
Valproic acid
Herbal supplements
Coagulation pathway defects
Factor XIII deficiency
von Willebrand disease
Alpha-2 antiplasmin deficiency
Plasminogen activator inhibitor-1 deficiency
Abnormal vascular fragility
Amyloidosis
Scurvy
Ehlers–Danlos syndrome
Cryoglobulinemia

Qualitative Platelet Disorders

A 50-year-old obese woman who recently underwent bilateral knee replacement surgery was referred for evaluation due to prolonged postoperative bleeding. Her past medical history is significant for hypothyroidism and dyslipidemia. She underwent tonsillectomy as a teen and believes that she had bleeding issues postoperatively. She does report what might have been heavier menstrual cycles in the past. Her physical exam was unremarkable, and laboratory testing demonstrated a mild anemia, but with a normal platelet count and normal PT and aPTT.

Acquired Platelet Disorders

Normal platelet function is contingent on both the quantity and quality of platelets. While quantitative platelet disorders are often easily discerned based on the low platelet counts and evaluation of the peripheral smear, qualitative platelet disorders can often be missed. A detailed history can often provide clues to an underlying disorder. Patients with qualitative platelet disorders tend to bleed immediately after insults and hemostatic challenges and rarely present with serious bleeding unless the underlying defect is severe. While congenital disorders of platelet function are an important cause of bleeding, acquired platelet function disorders are more relevant due to a relatively higher prevalence. Secondary or acquired platelet function disorders can be diagnosed based on their history, duration of symptoms, and associated medical illnesses. Common causes include cirrhosis, uremia, drugs, and hematological malignancies such as myeloma or other paraproteinemias.

While an increased PT, PTT, and thrombocytopenia can be observed in patients with severe hepatic dysfunction, bleeding can be observed even when these tests are normal. This may be due to an acquired platelet dysfunction in patients with cirrhosis. Defects in platelet adhesion along with impaired thromboxane A2 synthesis have been proposed as possible mechanisms (Escolar et al. 1999). Platelet aggregation may be abnormal, and the bleeding time is prolonged in these patients. Uremia also leads to qualitative platelet dysfunction similar to patients with cirrhosis. Usually anemia and thrombocytopenia are also observed in patients with severe renal dysfunction. While the cause for the hemostatic defects is likely multifactorial, defective arachidonic acid pathway and cytoskeletal assembly along with storage pool disorders have been thought to contribute to platelet dysfunction in patients with renal failure (Weigert and Schafer 1998). Ecchymoses, epistaxis, and gastrointestinal and genitourinary bleeding are commonly observed. Symptoms ameliorate with treatment of the underlying disorder, but desmopressin (DDAVP) has been used to help stop or prevent bleeding in

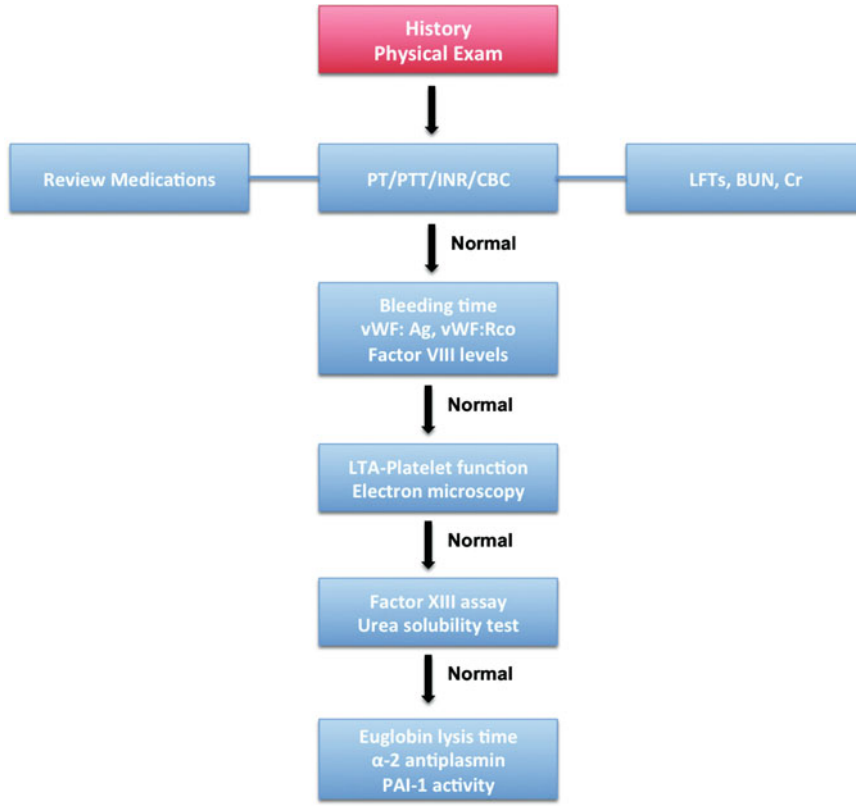

Fig. 6.1 Algorithm to evaluate patients suspected of having an underlying coagulation disorder but with a normal platelet count, PT, and aPTT. *LTA* light transmission platelet aggregometry, *vWF:Ag* von Willebrand antigen, *vWF:Rco* ristocetin cofactor activity

patients with uremia. Cardiopulmonary bypass can also cause significant platelet dysfunction due to hypothermia, complement activation, and a decrease in glycoproteins Ib and IIb/IIIa leading to decreased platelet adhesion to the endothelium and aggregation.

Although the incidence of venous thromboembolism with the use of immune modulators such as lenalidomide has received greater attention, acquired coagulopathies in patients with plasma cell dyscrasias can predispose patients to an increased bleeding risk. The abnormal paraproteins found in patients with multiple myeloma and Waldenström macroglobulinemia can affect all stages of platelet function including adherence, activation, and aggregation. Coating of platelets by antibody, particularly IgM, leads to binding to platelet glycoproteins that can result in platelet dysfunction. In addition to thrombocytopenia, pseudo-thrombocytopenia due to M-protein-induced ex vivo platelet agglutination can be observed (Eby 2009). Acquired vWD, due to absorption of von Willebrand factor (vWF) onto the surface of malignant lymphoid cells aberrantly expressing receptors for vWF and formation of vWF–autoantibody immune complexes, has also been noted (Eby 2009).

Inherited Disorders of Platelet Function

A 53-year-old female was referred for evaluation regarding a possible coagulation disorder to explain her previous procedure-related bleeding complications. Throughout her lifetime she had experi-

(continued)

enced heavy nosebleeds at times, easy bruising, and heavy menstrual cycles. Several years ago she underwent open reduction with internal fixation of a femur fracture and experienced significant bleeding postoperatively that required the administration of packed red blood cells. She subsequently required emergent surgery to relieve a bowel obstruction and was empirically treated with DDAVP preoperatively given anesthesia's concern for a coagulation disorder. She had no postoperative bleeding complications after the bowel surgery in contrast to her previous surgery. Her records indicate that previous coagulation studies including the PT, PTT, ristocetin cofactor activity, and vWF antigen have all been normal.

Bernard–Soulier Syndrome

Inherited qualitative platelet disorders, while not common, are an important cause of bleeding in the face of normal coagulation tests. Bernard–Soulier syndrome (BSS) is a rare autosomal recessive bleeding disorder due to a defect in glycoprotein GP1b-V-IX complex (Lanza 2006). The GPIb–V–IX complex binds vWF allowing platelet adhesion and platelet plug formation following vascular injury. Therefore, a defect in the aforementioned complex can lead to bleeding diathesis with normal coagulation profile and a low to normal platelet count. Typical clinical manifestations include epistaxis, menorrhagia, and gingival and gastrointestinal bleeding. Severe bleeding can occur with trauma and invasive procedures; however, prognosis is usually good with supportive care. The diagnosis of BSS is established based on prolonged bleeding time (PFA) and defective ristocetin-induced platelet agglutination (RIPA) along with a low or absent expression of the GPIb–V–IX complex (Lanza 2006). However, it is often difficult to differentiate BSS from other non-muscle myosin heavy chain (MYH9)-related platelet disorders such as May–Hegglin, Fechtner, Epstein, and Sebastian syndromes that are also associated with macro-thrombocytopenia. The diagnosis of BSS can be corroborated by quantitative analysis of GPIb–V–IX complex (CD42a–d) expression on the platelets or genetic testing (Althaus and Greinacher 2009). Treatment of bleeding associated with trauma or surgery usually involves platelet transfusions. Antiplatelet agents such as aspirin should be avoided. DDAVP and recombination factor VIIa can be used in some patients to ameliorate bleeding. Hematopoietic stem cell transplant is an option in patients with severe life-threatening bleeding (Locatelli et al. 2003). Gene therapy may also be a promising approach for treatment of BSS in future (Kanaji et al. 2012).

Glanzmann Thrombasthenia

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder characterized by a defect in platelet integrin αIIbβ3 (GPIIb/IIIA) resulting in impaired platelet aggregation though it can also be acquired (see below). GT is caused by mutations across the ITGA2B and ITGB3 genes (Nurden et al. 2012). Patients usually present with mucocutaneous bleeding and a normal platelet count without any evidence of platelet clumping. Platelet aggregometry is typically abnormal. GT can occur in combination with defects in leukocyte adhesion. Therefore, newborns with leukocytosis and severe bacterial infections should be evaluated for GT. Patients can present with severe mucocutaneous bleeding and tend to become refractory to platelet transfusions due to development of alloantibodies to GPIIb/IIIA. Recombinant factor VIIa and hematopoietic stem cell transplant have been used in such cases with success (Connor et al. 2008). Acquired GT is rarely observed but may be seen in conditions such as pregnancy, systemic lupus erythematosus, and GPIIb/IIIA antagonist (e.g., abciximab) therapy due to the development of antibodies to the GP IIb/IIIa complex.

Platelet Storage Pool Disease

Storage pool disease is characterized by defects in platelet granules that can involve the α-granules or the dense (δ) granules. α-granules contain fibrinogen, factor V, thrombospondin, platelet-derived growth factor (PDGF), and vWF. The δ granules contain ADP, ATP, calcium, and serotonin, giving them an intrinsic electron density and dark appearance under electron microscopy (EM).

Defects in α-granules lead to the gray platelet syndrome (GPS) and the Quebec platelet disorder (QPD). GPS is an autosomal recessive disorder characterized by gray-appearing platelets, devoid of the red-staining α-granules on a peripheral smear. Electron microscopy corroborates the absence of α-granules (Nurden and Nurden 2011). Patients usually have normal to somewhat decreased platelet counts with mild bleeding and often present with splenomegaly and early-onset myelofibrosis. A variant of GPS, Medich giant platelet disorder, has also been described, where in addition to a decrease in α-granules the platelets contain membranous inclusions resembling cigars or scrolls White el al (2004).

QPD, on the other hand, has autosomal dominant inheritance with high penetrance. This disorder is characterized by large amounts of urokinase plasminogen activator (uPA) leading to increased conversion of stored platelet plasminogen to plasmin resulting in abnormal proteolysis of proteins stored in α-granules (Nurden and Nurden 2011). Genetic analysis has identified tandem duplication of PLAU, the uPA gene, as the underlying defect in QPD (Paterson et al. 2010). Patients present with normal to slightly low platelet count and delayed bleeding following invasive surgical procedures; anti-fibrinolytics such as ε-aminocaproic acid or tranexamic acid can be used to ameliorate their symptoms (Hayward and Rivard 2011).

Deficiency in dense granules leads to inherited syndromes such as Hermansky–Pudlak and Chediak–Higashi. Hermansky–Pudlak, an autosomal recessive syndrome due to mutations in HPS genes, is associated with oculocutaneous albinism, colitis, and pulmonary fibrosis in addition to a dense granule storage pool disease. Chediak–Higashi disease, a rare autosomal recessive disease due to mutation in the lysosomal trafficking regulator (LYST), is characterized by mild bleeding due to storage pool deficiency, recurrent infections, oculocutaneous albinism, neurological defects, and recurrent infections.

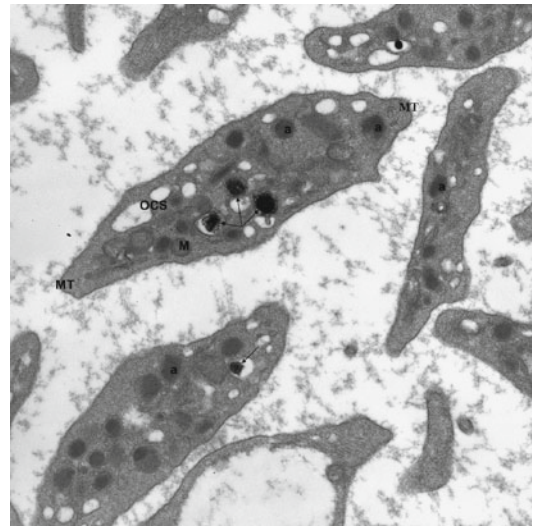

Fig. 6.2 Transmission electron microscopy of thin section of platelets: Several delta granules (*arrows*) are seen. Alpha granules (a) are observed. Microtubules (MT) are seen in cross section at either end of the top platelet. Mitochondria (M) and the open canalicular system (OCS) are present. Uranyl acetate lead citrate, ×30,000. *Photo courtesy of Dr. Tibor Nadasdy and Edward Calomeni*

These aforesaid dense granule diseases usually have normal coagulation tests. Platelet function testing should involve light transmission aggregometry (LTA) and EM. An EM picture of dense granule disease is shown below (Fig. 6.2).

Scott Syndrome

Scott syndrome, a very rare bleeding disorder, occurs due to a defect in the translocation of phosphatidyl serine from the inner to the outer platelet membrane. This hinders the binding of factors Va and Xa to the platelet membrane resulting in

impaired thrombin formation from prothrombin. Bleeding episodes are usually mild to moderate. Recently mutations in the splice-acceptor site of the TMEM16F gene have been reported to be associated with this entity (Suzuki et al. 2010).

Going back to the previous case, given her history of mucosal type bleeding, and bleeding after the surgical procedure that she did not receive DDAVP, there was a high level of clinical suspicion for an underlying coagulation disorder. The PT, PTT, and repeat vWD disease studies were normal in this patient. Additionally, a PFA was normal, but formal platelet aggregation studies were abnormal, demonstrating an absent secondary wave of platelet aggregation. Platelet electron microscopy studies were also consistent and showed a decreased number of dense granules (3.5 dense granules per platelet, range 4.0–6.0). These laboratory data were consistent with a diagnosis of a platelet storage pool disorder.

Drug-Associated Platelet Dysfunction

A 62-year-old female was referred for evaluation after having what was thought to be excessive bleeding after a minor dermatologic procedure. Previous pregnancies and surgical procedures in the past have been uneventful and without excessive bleeding. Her past medical history is notable for coronary artery disease for which she takes a baby aspirin daily and a recent diagnosis of depression for which she was started on a selective serotonin reuptake inhibitor. Her physical exam was remarkable only for multiple ecchymoses on her arm. Her CBC was normal, and both the PT and PTT were found to be normal.

Medications are a common cause of bleeding diatheses and are often overlooked due to an apparent lack of effect on coagulation testing. Warfarin affects vitamin K-dependent coagulation factors, so changes in PT and INR are expected. However, other agents can cause functional defects in the components of coagulation, without affecting the screening tests used for clinical evaluation. Commonly used agents that affect clotting include antiplatelet agents such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and herbal supplements.

Aspirin along with NSAIDs is one of the most commonly used drugs, and its use is facilitated by its ease of availability. Aspirin, the most commonly used antiplatelet agent, acetylates cyclooxygenases [greater cyclooxygenase-1 (COX-1) inhibition] irreversibly, thus preventing thromboxane A2 synthesis. By inhibiting prostanoid synthesis they inhibit platelet aggregation, leading to an increased bleeding risk. While the bleeding risk may be small particularly at low doses, the effect is often accentuated by the combined use of other antiplatelet agents such as clopidogrel or vitamin K antagonists such as warfarin. NSAIDs reversibly inhibit COX-1, generally to a lesser degree than aspirin. These agents are associated with increased bleeding due to inhibition of platelet aggregation. COX-2-selective NSAIDs do not appear to modify platelet activity and have a decreased bleeding risk, particularly gastrointestinal.

Clopidogrel and prasugrel are thienopyridines that work as ADP antagonists by inhibiting P2Y12 receptors, thus inhibiting platelet aggregation. While effective in reducing the risk of cardiovascular thrombosis, these agents augment bleeding risk due to inhibition of platelet function. However, these agents do not cause complete platelet antagonism. On the other hand, GPIIb/IIIa receptor antagonists such as abciximab and eptifibatide can cause severe bleeding due to irreversible inhibition of platelet aggregation.

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed agents for the treatment of depression. In addition to blocking the reuptake of serotonin in neurons, they also block reuptake in platelets

(Serebruany et al. 2003). The latter effect depletes intracellular stores of serotonin resulting in inhibition of aggregation of platelets and an increased risk of bleeding. While bleeding associated with SSRIs alone is often mild, the bleeding risk may be augmented when used in combination with antiplatelet and nonsteroidal anti-inflammatory agents (Labos et al. 2011; de Abajo and Garcia-Rodriguez 2008). Valproic acid, a commonly used antiepileptic agent commonly known to cause thrombocytopenia, can also cause increased bleeding with normal platelet counts. This is often due to abnormal platelet function and acquired vWD (Acharya and Bussel 2000). These effects are often reversed with dose reduction or cessation of the drug.

Many patients rely on herbal and vitamin supplements to help promote their general well-being. Since these agents are not FDA regulated or extensively studied, their mechanisms of action and adverse effects are often poorly characterized. Without a detailed and accurate history, the use of herbal supplements is often missed. Some of the commonly used herbal supplements such as garlic and ginkgo biloba among others can increase bleeding risk without any associated abnormalities in the coagulation function tests (Stanger et al. 2012). These agents may promote bleeding by inhibiting platelet aggregation or affecting coagulation factor levels. Moreover, these agents can potentiate the activity of other antiplatelet agents such as aspirin or indomethacin leading to increased bleeding. Also, commonly used supplements such as fish oil or vitamin E have been shown to cause bleeding tendencies in higher doses.

After a complete history and examination of the patient, it became increasingly clear that her post-procedure bleeding and increased ecchymoses may be related to the use of both aspirin and the SSRI. While SSRIs alone may not impair platelet function to the point that patients experience clinically relevant bleeding complications, their use in concert with other medications that impair platelet function such as aspirin can lead to clinically significant impairment of platelet function. The absence of bleeding complication after previous hemostatic challenges argues against a congenital platelet function abnormality.

Clotting Factor Abnormalities

A 25-year-old woman is evaluated at a hematology clinic. She recently underwent a routine tooth extraction and reported what she felt was increased bleeding 5 h later after the procedure. Her past medical history was unremarkable with no other surgical procedures, but she did report occasional nosebleeds and heavy menstrual cycles for as long as she can remember. Physical examination was unremarkable.

While deficiency of coagulation factors is expected to manifest an abnormality in the PT or the aPTT, many times factor levels may not be sufficiently low to produce alterations in these coagulation tests. Patients with such factor deficiencies usually have mild, if any, bleeding and are often discovered at the time of surgery. Typically, alterations in PT or aPTT are observed when the factors are less than 50 % of normal. There are three major clotting factor deficiencies or defects that are associated with bleeding diathesis but with normal coagulation tests. These include factor XIII deficiency, milder forms of vWD, and fibrinolytic pathway defects.

Factor XIII Deficiency

Factor XIII (fibrin-stabilizing factor) is a transglutaminase that circulates in the plasma as a tetramer of two catalytic A subunits and two carrier B subunits (Nourbakhsh et al. 2011). Activated factor XIII is formed in the presence of calcium

and fibrin catalyzed by thrombin. Factor XIIIa cross-links fibrin monomers to form a meshwork that leads to stabilization of the clot. Congenital factor XIII deficiency is inherited as an autosomal recessive disease and can involve either the A or the B subunits. Mutations in subunit A (type 2 defect) cause severe bleeding and usually manifest as umbilical cord bleeding in neonates, whereas mutations in subunit B (type 1 defect) cause mild bleeding and are often subclinical (Hsieh and Nugent 2008). Homozygous patients are characterized by intracranial hemorrhage, ecchymosis, and prolonged bleeding after injury or surgery. Poor wound healing and excessive scar formation are also seen in some patients. However, spontaneous bleeding does not usually occur in patients with factor XIII levels greater than 3–5 %.

Acquired factor XIII deficiency can also occur in liver disease, leukemia, myelodysplastic syndrome, sepsis, and disseminated intravascular coagulation. Additionally, autoantibodies against factor XIII can bind to plasma factor XIII interfering with its normal function. Standard laboratory tests to assess clotting such as platelet count, bleeding time, PT, and aPTT are typically within normal limits in patients with factor XIII deficiency. Therefore, patients with persistent bleeding symptoms and normal coagulation tests should be evaluated for factor XIII deficiency. The diagnosis is established based on increased solubility of the clot in 1 % monochloroacetic acid or 5 M urea, indicating clot instability and factor XIII deficiency (Hsieh and Nugent 2008). An abnormal solubility test indicates that the activity of factor XIII is less than 10 %. It is important to know that patients with alpha-2 antiplasmin deficiency can also demonstrate clot instability (see below). Factor XIII antigen levels and activity are measured using ELISA and photometric assays, respectively.

Treatment involves administration of cryoprecipitate and fresh frozen plasma, and prophylactic administration of these agents is used in patients with a prior history of intracerebral hemorrhage. Recombinant factor XIII-A2 has been shown to be a potentially effective alternative for factor XIII replacement in patients with congenital factor XIII deficiency (Lovejoy et al. 2006). On the other hand, patients with acquired factor XIII deficiency due to autoantibodies are treated with steroids, immunoglobulins, or rituximab (off-label use).

von Willebrand Disease

vWD is the most common and best-characterized primary hemostatic disorder with an estimated prevalence of about 1 % (Bowman et al. 2010). It can be categorized into three major forms: inherited, acquired, and platelet type. Inherited forms of vWD can be due to a qualitative or a quantitative deficiency of vWF, a multimeric protein that is required for platelet adhesion. While abnormalities in intrinsic pathway and thus alteration in aPTT are expected with vWD, milder forms can have a normal PT and aPTT, with an increased bleeding time. Type 1 vWD, which is due to a heterozygous quantitative deficiency of vWF, is the mildest and most common form of vWD and accounts for approximately 75 % of patients with vWD. Type 2 vWD is due to qualitative defects in vWF, and type 3 vWD is due to a homozygous, quantitative deficiency in vWF. Patients usually present with bleeding involving the skin and mucous membranes, with menorrhagia as a common initial presentation in women. Also, while a deficiency of factor VIII could lead to an abnormal aPTT, patients with mild hemophilia with greater than 30–40 % of the mean normal concentration of factor VIII would have normal or near-normal aPTT.

Testing for vWD should include vWF-Ag plasma levels, factor VIII assay as vWF acts as a carrier protein for factor VIII in plasma, and the ristocetin cofactor assay. It is important to note that since vWF is an acute-phase reactant, it can increase in response to stress and pregnancy. Additionally, estrogen can increase the synthesis of vWF and can similarly normalize vWD testing. Therefore, normal levels do not necessarily exclude a diagnosis in patients with history of bleeding diathesis, and at least two sets of labs should be performed. Treatments include DDAVP and factor concentrates that may con-

tain both vWF and factor VIII. DDAVP promotes the secretion of stored vWF from the endothelial cells and can be used to achieve hemostasis prior to surgery. Hyponatremia and seizures are severe side effects associated with DDAVP use; therefore, close monitoring of electrolytes and fluid restriction in the postoperative period is warranted. Plasma-derived concentrates such as cryoprecipitate, which contains more concentrated vWF/factor VIII, can also be used.

Fibrinolytic Pathway Defects

Alpha-2 Antiplasmin

While defects in coagulation cascade find a prominent role in the evaluation of bleeding diathesis, fibrinolytic pathways are often overlooked, as they are extremely rare. Fibrinolysis ensures the resolution of clots that are formed in response to tissue injury. To prevent excess bleeding and tissue damage, this process is strictly regulated.

Alpha-2 antiplasmin is the primary inhibitor of plasminogen, and congenital deficiency of alpha-2 antiplasmin has been associated with increased bleeding due to increased fibrinolysis (Carpenter and Mathew 2008). Although very rare, it is important to keep this diagnosis in mind during evaluation of bleeding diathesis, as typical screening tests for coagulation are usually normal. Inherited as autosomal recessive, bleeding associated with alpha-2 antiplasmin deficiency is often delayed after trauma or surgical procedures. While homozygous individuals present with severe bleeding during childhood, heterozygous patients tend to have milder bleeding or asymptomatic and bleeding occurs with trauma, surgery, or dental extraction. An acquired deficiency can be seen in patients with severe renal or liver disease. The euglobulin lysis time (ELT) can be used for assessment of patients and is shorter in patients with alpha-2 antiplasmin deficiency.

Plasminogen Activator Inhibitor-1 Deficiency

Plasminogen activator inhibitor-1 (PAI-1) is an important component of the coagulation cascade. It regulates fibrinolysis by controlling degradation of thrombin, with a deficiency leading to an increased bleeding risk (Mehta and Shapiro 2008). Affected patients usually have mild to moderate bleeding symptoms such as epistaxis, menorrhagia, and delayed bleeding after trauma or surgical procedures. Spontaneous bleeding is usually rare. Making the diagnosis can be very challenging due to the lack of sensitive and standardized assays (Mehta and Shapiro 2008). While it is important to assay both antigen and activity levels for diagnosis, vWD and platelet function disorders should be ruled out prior to evaluation of PAI-1 deficiency. Anti-fibrinolytic agents (e.g., ε-aminocaproic acid or tranexamic acid) are the mainstay of therapy.

Routine coagulation studies were performed to evaluate her for a coagulation disorder. Given her history of epistaxis, heavy menstrual cycles, and excess bleeding after a tooth extraction, there was concern for an underlying coagulation disorder. Her CBC and PT were both found to be normal, but the PTT was slightly prolonged at 36 s (range, 24–34 s). Ristocetin cofactor activity was found to be mildly decreased at 35 % (40–200 %), vWF antigen was low at 40 % (50–180 %), and factor VIII levels were 40 % (75–220 %), consistent with a diagnosis of type I vWD.

Abnormal Vascular Fragility

Easy bruising is observed not only in cases of defects in clotting factors or platelet function but also in disorders that affect the integrity of blood vessels. Abnormalities in vascular fragility associated with conditions such as vasculitis, cryoglobulinemia, scurvy, and amyloidosis can present with increased bleeding but without any observed alterations in PT, PTT, or platelet counts. Spontaneous, recurrent, and easy bruising is usually the hallmark of these disorders. A wide range of symptoms, ranging from mucosal bleeding and subcutaneous hematomas to excess

menstrual bleeding can occur. Postsurgical bleeding is immediate and can be severe. Skin discoloration due to recurrent bleeding and subsequent hemosiderin deposition is present. Typically, symptoms associated with connective tissue disorders such as delayed wound healing, joint hypermobility, and hyperextensibility of skin can be observed.

Ehlers–Danlos syndrome is an inherited connective tissue disorder due to defects in synthesis of collagen. In addition to hyperextensibility and joint hypermobility, the disorder is characterized by increased vascular fragility leading to easy bruising. Laboratory studies such as PT, PTT, and bleeding time are usually normal. The Hess (or tourniquet test or Rumpel–Leede test) test can be used to diagnose abnormal vascular fragility. While no specific treatment is available, supportive interventions such as ascorbic acid, which helps to cross-link collagen fibrils, and DDAVP may improve bleeding symptoms (Rydz and James 2012).

Amyloidosis can cause an acquired factor X deficiency due to absorption of this factor by amyloid fibrils in the liver and spleen, leading to increased bleeding. Additionally, the increased vascular fragility in these patients can accentuate the bleeding diathesis. Treatment of the underlying amyloidosis may help ameliorate the bleeding symptoms. Interestingly, in these cases, factor Xa levels can be used as a surrogate for monitoring the response of amyloidosis to treatment.

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