Persistent postpartum bleeding

MARC TRIBBLE, MD, AND MICHAEL T. JOHNSTON, MD

CASE PRESENTATION

MARC TRIBBLE, MD: A 35-year-old white woman delivered her first child, a healthy daughter, 4 weeks prior to admission. The pregnancy was uncomplicated until 1 hour after delivery, when vaginal bleeding, which responded to administration of oxytocin and methylergonovine, occurred. After discharge, she continued to have intermittent vaginal bleeding, with passage of a large clot. Dilatation and curettage was performed for presumed retained products of conception. A few days later, the patient continued to have heavy spotting and passage of clots, along with intermittent low-grade fevers. She received methylergonovine again as an outpatient and began a course of oral antibiotics for possible endometritis.

The patient continued to have vaginal bleeding at home. At 3 weeks postpartum, she went to the emergency department. A magnetic resonance imaging scan of the pelvis revealed an abnormal appearance of the uterus, suspicious for placenta accreta. In addition, a 10-cm mass was noted posterior/superior to the bladder, with partial compression of the left ureter; the appearance of this mass was most consistent with a hematoma. Further workup revealed a partial thromboplastin time (PTT) of 67 seconds. Other laboratory tests, including prothrombin time (PT), platelet count, and D-dimers, were within normal limits.

The patient required multiple transfusions for persistent blood loss. To control the bleeding, an abdominal hysterectomy was performed. Pathologic examination confirmed the diagnosis of placenta accreta. A left salpingo-oophorectomy also was performed due to severe endometriosis noted at surgery. Postoperatively, the patient continued to have vaginal spotting with passage of clots. She was then transferred to Baylor University Medical Center (BUMC).

The patient's history included infertility due to endometriosis. This was her first pregnancy, which resulted in a vaginal delivery of a full-term female, a product of in vitro fertilization. Prior surgeries included breast implants, a diagnostic laparoscopy, and the recent hysterectomy. She had no history of anemia or easy bruising or bleeding and had received no transfusions prior to delivery. Her family had no history of bleeding disorders. The patient was born in South America, and both she and her husband were dentists in West Texas. She denied smoking, recent alcohol use, and illicit drug use.

Table 1. Admission laboratory values

Sodium	137 mEq/L	White blood cell count	$9.9 \times 10^3/\mu\text{L}$
Potassium	3.4 mEq/L	Differential	90% neutrophils (6 bands)
Chloride	106 mEq/L		6% lymphocytes
Bicarbonate	26 mEq/L		4% monocytes
Blood urea nitrogen	4 mg/dL	Hemoglobin	12.3 g/dL
Creatinine	0.7 mg/dL	Hematocrit	35%
Glucose	188 mg/dL	Platelets	$158 \times 10^3/\mu\text{L}$
Albumin	2.6 g/dL	Partial thromboplastin time	43.5 seconds
Total bilirubin	0.8 mg/dL	Prothrombin time	10.4 seconds
Alkaline phosphatase	86 U/L	Fibrinogen	499 mg/dL
Aspartate aminotransferase	34 U/L	D-Dimers	0.2–0.4 $\mu\text{g/mL}$
Alanine aminotransferase	20 U/L	Fibrin split products	<5 mg/L
Urine: 1+ protein, trace glucose, 3+ blood, 0 white blood cells, 100+ red blood cells			
Cultures: No growth in urine or blood			

She denied nosebleeds, bleeding gums, sore throat, headache, cough, hemoptysis, pleurisy, nausea, vomiting, hematemesis, hematochezia, melena, dysuria, and urinary frequency. She experienced some incisional pain and frequent loose stools after the hysterectomy. She was still passing vaginal clots when she was transferred to BUMC.

Medications upon transfer included ceftazidime, meperidine, compazine, aminocaproic acid, diphenhydramine, promethazine, and lorazepam. She had no known drug allergies.

Upon initial evaluation at BUMC, the patient was lying on her side in moderate distress due to abdominal discomfort. Her blood pressure was 132/82 mm Hg; heart rate, 92 beats per minute; respiratory rate, 18 breaths per minute; and temperature, 38.5°C (101.2°F). The patient was 62 kg (138 lbs) and 160 cm (63 inches) tall. She had a clear oropharynx and no gingival bleeding or petechiae. Lungs were clear and heartbeat was regular. Staples were still in place for the midline lower abdominal incision, with no signs of infection. The patient had a moderate amount of postoperative tenderness. Neither the liver nor spleen

From the Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Marc Tribble, MD, Department of Internal Medicine, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246.

was palpable. Bowel sounds and mild gaseous distention were present. Rectal examination revealed brown stool, guaiac negative. Pelvic examination revealed normal external genitalia and a normal vagina. A slow ooze was present at the vaginal cuff. A bimanual examination confirmed the presence of a large vaginal cuff hematoma, without marked tenderness. There was no cyanosis, clubbing, or edema in her extremities. Laboratory data are summarized in Table 1.

DIFFERENTIAL DIAGNOSIS

MICHAEL T. JOHNSTON, MD: This 35-year-old patient had an uncomplicated first pregnancy, the product of in vitro fertilization. One hour after delivery, she began having vaginal bleeding, which was initially controlled. After she was discharged, the vaginal bleeding resumed and persisted for several weeks. She went to the emergency department, where a magnetic resonance imaging scan revealed evidence of placenta accreta as well as a large retroperitoneal hematoma. She received multiple blood transfusions and ultimately had an abdominal hysterectomy to control the bleeding. Nevertheless, the bleeding persisted, and she was transferred to BUMC. Past medical history, family medical history, and physical examination were not particularly revealing. The PTT was abnormal, and the PT, D-dimers, and platelet count were normal.

The first question is whether this case represents a congenital bleeding disorder or an acquired bleeding disorder. The fact that the patient had no personal or family history of bleeding problems tends to suggest the latter. In addition, the patient had previous surgical procedures without bleeding complications. We can therefore reasonably assume that this is an acquired bleeding disorder.

The second question is whether this patient's presentation is consistent with a defect in primary hemostasis or secondary hemostasis. Table 2 summarizes the differences between the two. Because her bleeding was delayed by an hour, a retroperitoneal hematoma was present, and no facts in the case suggest a defect

Figure. The coagulation pathway, showing the *intrinsic pathway*, which begins with factor XII and ultimately terminates with the activation of factor X; the *extrinsic pathway*, which begins with factor VII and terminates with the activation of factor X; and the *common pathway*, which involves the activation of factor X and ultimately leads to the formation of the fibrin clot. From Handlin RI. Bleeding and thrombosis. In Facci A, ed. *Harrison's Principles of Internal Medicine*, 14th edition. New York: McGraw Hill, 1998. Reprinted with permission of The McGraw Hill Companies.

in primary hemostasis, we can determine that this probably represents a defect in secondary hemostasis.

To pinpoint the defect, we review the coagulation pathway (Figure). Since the patient had a consistent isolated elevation of the PTT, we can immediately eliminate the extrinsic and common pathways from consideration. Defects involving the extrinsic pathway are typically associated with an elevated PT but normal PTT. The common pathway usually manifests defects with both an elevated PT and PTT. That leaves the intrinsic pathway, with its various factors, which will be discussed individually.

Factor XII, high-molecular-weight kininogen, and prekallikrein are known as contact factors. Congenital deficiencies of any of these 3 factors will result in an isolated elevation of the PTT. However, such defects do not generally result in bleeding, as these factors have been shown to be necessary for in vitro coagulation but not in vivo coagulation. Given these facts, we can eliminate those 3 from consideration.

Most patients with congenital factor XI deficiency do not have any significant bleeding problems, although there are cases where such patients had significant hemorrhage after surgery or trauma. Some patients with factor XI deficiency even have variability in their bleeding patterns, bleeding after one surgery but not another. While a defect in this factor cannot be completely ruled out, it would be extremely unlikely for it to reveal itself with postpartum bleeding.

Factor IX and factor VIII are both involved in activating factor X. Congenital deficiencies of these factors lead to hemophilia. This patient does not have hemophilia: there is no personal or family history of bleeding disorders; the patient has been stressed in the past with

Table 2. Differences in the clinical manifestations of disorders of primary and secondary hemostasis

Manifestation	Defects of primary hemostasis (platelet defects)	Defects of secondary hemostasis (plasma protein defects)
Onset of bleeding after trauma	Immediate	Delayed—hours or days
Sites of bleeding	Superficial—skin, mucous membranes, nose, gastrointestinal and genitourinary tracts	Deep—joints, muscle, retroperitoneum
Physical findings	Petechiae, ecchymoses	Hematomas, hemarthroses
Family history	Autosomal dominant	Autosomal dominant or X-linked recessive
Response to therapy	Immediate, local measures effective	Requires sustained systemic therapy

From Handlin RI. Bleeding and thrombosis. In Facci A, ed. *Harrison's Principles of Internal Medicine*, 14th edition. New York: McGraw Hill, 1998. Reprinted with permission of The McGraw Hill Companies.

surgical procedures without bleeding complications; and hemophilia is inherited in a sex-linked recessive fashion, making it extremely unusual in a woman.

After reviewing the deficiencies of the factors of the intrinsic pathway, we still do not have a reasonable explanation for our patient's bleeding. I now discuss some miscellaneous conditions.

Since the patient had postpartum bleeding and fever, one could ask if there was an underlying process triggering disseminated intravascular coagulation. However, disseminated intravascular coagulation leads to an elevated PT, an elevated PTT, a diminished platelet count, a diminished fibrinogen, elevated fibrin split products, and elevated D-dimers. The patient did not meet many of these criteria.

Von Willebrand's disease, which may be associated with an elevated PTT because it is intimately associated with factor VIII, is another possibility. We are not given a bleeding time for this case; typically, patients with von Willebrand's disease will have an elevated bleeding time. However, the patient does not have von Willebrand's disease: there is no personal or family history of bleeding disorders. Also, it would be extremely unusual for our patient to manifest the disease postpartum. Pregnant women with von Willebrand's disease will synthesize an excessive amount of von Willebrand's factor due to the hormonal changes occurring during pregnancy.

A laboratory test known as the mixing test was probably done in this case but not mentioned in the clinical scenario. It can help with the diagnosis of an abnormal PTT. The mixing test takes patient plasma and mixes it—usually 1:1—with control plasma, and then the PTT of the mixture is determined. A correction of the PTT in the mixture identifies a deficiency of one or more factors of the intrinsic pathway. We've already discussed that congenital deficiencies with many of these factors are extremely unlikely in this case. So I propose that in the mixing test, the PTT did not correct. What does that tell us?

That introduces inhibitors. Inhibitors are autoantibodies. They can be nonspecific or specific. Inhibitors are seen in only a few subsets of patients: 1) patients with underlying hemophilia who receive exogenous factor replacement and then develop antibodies against such replacement; 2) patients with an underlying immunological source, such as solid tumors, lymphoproliferative disorders, lupus, and rheumatoid arthritis; 3) otherwise healthy patients who may have an underlying disorder that has not yet been discovered; and 4) postpartum women. This fits nicely with our patient.

Nonspecific inhibitors include antibodies against phospholipid protein complexes. These antibodies tend to manifest themselves with thrombotic events and not bleeding events. In a very small subset of patients with lupus anticoagulant, bleeding problems may occur when immune complexes significantly decrease the amount of prothrombin in the body. This rare situation does not describe this patient because prothrombin is a component of the common pathway, which should lead not only to an elevated PTT but an elevated PT as well.

Specific inhibitors of the intrinsic pathway most commonly involve factors XI, IX, and VIII. Which specific inhibitor is involved in this case? We can rule out a spontaneously acquired inhibitor to factor XI because it is extremely rare and it is not

known to be associated with postpartum bleeding. Inhibitors to factor IX and factor VIII have been reported to develop in patients postpartum. Factor IX, though, is extremely rare, with only 2 or 3 reported cases in the literature. Factor VIII, on the other hand, has been well documented among postpartum women in the literature.

An acquired factor VIII inhibitor fits the facts of this case. It explains the acquired nature of this disorder, our premise that this was a defect in secondary hemostasis, the way the bleeding occurred, and the isolated elevation of the PTT.

DISCUSSION

MARC TRIBBLE, MD: Our patient did indeed have *acquired hemophilia A*, which is a result of a *factor VIII inhibitor*. The patient's condition was diagnosed after a coagulation profile revealed an isolated elevation of the PTT. Other coagulation parameters were normal. The next test done was a check of individual factor levels, which revealed low factor VIII activity, at 7% of normal. A factor inhibitor screen was performed, and the result was positive, with a titer of 2 Bethesda units initially and then 4 units upon retesting after transfer to BUMC. This test is performed by incubating serial dilutions of the patient's plasma with normal plasma for 2 hours. The factor VIII level in the mixture is then checked and compared with a control. A Bethesda unit is the plasma dilution that causes a 50% reduction in factor VIII activity. Values can range from 1 to 500 Bethesda units (1). Using the Bethesda scale allows for a more quantitative means of gauging a patient's response to therapy.

Acquired hemophilia A is rare, with the incidence ranging from 1 case per 1 million to 1 case per 5 million individuals per year. Inhibitors to essentially all of the clotting factors have been reported, but the factor VIII inhibitor is the most common and the most clinically significant. Most patients diagnosed with this disorder are >50 years of age; one recent study identified an average age of 61 years (2). The disorder is equally distributed among men and women (1).

About half of the cases are idiopathic, arising in healthy, usually elderly, individuals. In the remaining half of cases, an underlying disorder can be identified: 14% were in the postpartum period, 15% had rheumatoid arthritis, 12% had malignancies, 10% had lupus, 10% had drug reactions, 8% had dermatologic diseases, 8% had other autoimmune diseases, 7% had chronic respiratory disorders, 5% had received multiple transfusions, and 11% had other chronic systemic illnesses (3).

The inhibitor of factor VIII is an autoantibody of the IgG class. It is not clear how this antibody interrupts the coagulation cascade, but it may prevent binding of factor VIII to phospholipid, which is important in the activation of factor X (1).

Generally, patients with acquired hemophilia A present with hematomas or large bruises after relatively minor trauma. They may have large retroperitoneal blood collections, as our patient did, which was pressing on her left ureter, or they may have gastrointestinal or intracranial bleeding. In some instances, bleeding into the confined space of an extremity may produce a compartment syndrome, which is one of the severe complications of this disorder (1).

In contrast with patients who have hereditary hemophilia A, patients with the acquired form rarely have hemarthroses (1).

Patients who develop hemophilia A during the postpartum period usually present within 1 to 4 weeks after delivery. Development of the inhibitor is much more common in association with a woman's first pregnancy. In general, if a postpartum patient is diagnosed and receives appropriate treatment for this disorder, it does not recur during later pregnancies.

Treatment consists of blood products to replace blood loss, as well as clotting factors and immunosuppressants. While human factor VIII concentrate may seem like a logical choice for treatment, it can be dangerous with patients who are "high responders"—whose immune system responds to the infusion of factor VIII by increasing antibody levels and thus making the situation worse. For that reason an animal-derived product, porcine factor VIII, has been used to help maintain patients' clotting ability while other treatments are used to stop antibody production. Before administering porcine factor VIII, it has to be determined that the patient's antibody does not cross-react with the animal-derived factor VIII. This treatment usually works best with patients who have antibody titers that are <50 Bethesda units.

Also available now are prothrombin complex concentrates (e.g., Konyne, Autoplex T), a combination of clotting factors that contains activated forms of factors X and VII and thus bypasses the inhibited intrinsic arm of the cascade (4). Because the patient receives activated clotting factors, there is a risk of converting patients to a thrombotic state, so they must be monitored for signs of disseminated intravascular coagulation or deep venous thrombosis.

Another treatment that's available is a recombinant form of factor VIIa (NovoSeven). This is thought to react with tissue factor and thus activate factor X, stimulating the common coagulation cascade and bypassing the intrinsic arm, which is inhibited (5).

Regarding immunosuppressants, steroids and, in most cases, cytotoxic chemotherapy are given, similar to the treatment of other autoimmune-mediated disorders. In addition, intravenous immune globulin has been used with some success. As in many cases where intravenous immune globulin is used, the exact mechanism of action is unclear. However, it is thought that anti-idiotypic antibodies are present in pooled human immunoglobulin that neutralize the acquired inhibitor (1).

Plasmapheresis and plasma exchange are not useful in the treatment of this disorder. The factor VIII inhibitor is in the IgG class of autoantibodies, and plasmapheresis is not effective in treating IgG-mediated processes because most of the IgG is present in the extravascular space and therefore not cleared effectively by plasma exchange.

Most patients receive a combination of these treatments. In one recent study, the median duration of patient inhibitor was

18 to 27 months, although some patients have cleared their inhibitor in 6 to 12 months (6).

The patient discussed above received blood and factor VIII transfusions prior to her surgery in an attempt to normalize her PTT. This helped initially but became less effective with continued transfusions, and she was taken to surgery. She was then transferred to BUMC for further management. She was started on high-dose steroids and received intravenous cyclophosphamide. In addition, she received NovoSeven through intravenous infusion every 2 hours until her condition stabilized. Her antibody did not react with porcine factor VIII, so this was a possible treatment option, but it was not necessary in this case.

The retroperitoneal hematoma did not produce any significant clinical effects, and subsequent computed tomography scans showed a decrease in its size.

The patient continued to have some vaginal clots, and work-up revealed active extravasation from 2 branches of the left internal iliac artery. Interventional radiologists were consulted, and they were able to embolize the vessels and stop the bleeding.

The patient's laboratory values improved: PTT returned almost to the normal range, hematocrit remained stable, serial inhibitor titers showed decline of the inhibitor from 4 Bethesda units to none, and factor VIII level rose from 7% to 17%. She received a second dose of cyclophosphamide and was discharged 3 weeks after her transfer to BUMC, which was a total of 7 weeks after delivery. She was maintained on prednisone as an outpatient. In an office visit a few weeks later, it was noted that the inhibitor had returned, and the patient was briefly readmitted to receive intravenous immune globulin and further chemotherapy (vincristine). It has now been 4 months since her delivery date, and the patient and baby are doing well.

1. Beutler E, Lichtman MA, Coller BS, eds. *Williams Hematology*, 5th ed. New York: McGraw Hill, 1994:1486–1489, L95–96.
2. Bossi P, Cabane J, Ninet J, Dhote R, Hanslik T, Chosidow O, Jouan-Flahault C, Horellou MH, Leynadier F, Liozon E, Pouchot J, Robin JP, Sanderson F, Schaeffer A, Sicard D, Staikowsky F, Wechsler B, Zittoun R. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *Am J Med* 1998; 105:400–408.
3. Green D. Cytotoxic suppression of acquired factor VIII:C inhibitors. *Am J Med* 1991;91(5A):14S–19S.
4. Solymoss S. Postpartum acquired factor VIII inhibitors: results of a survey. *Am J Hematol* 1998;59:1–4.
5. Pruthi RK, Nichols WL. Autoimmune factor VIII inhibitors. *Curr Opin Hematol* 1999;6:314–322.
6. Michiels JJ, Hamulyak K, Nieuwenhuis HK, Novakova I, van Vliet HH. Acquired haemophilia A in women postpartum: management of bleeding episodes and natural history of the factor VIII inhibitor. *Eur J Haematol* 1997;59:105–109.