Woman with a Bleeding Diathesis

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61 year-old Indian female with history of hypercholesterolemia presents to an outside hospital (OSH) with worsening vaginal bleeding, hematochezia, nausea, and vomiting starting three days prior to admission. Patient also had a global persistent headache for approximately 24 hours at the time of admission. Otherwise, the patient denied any fever, chills, abdominal pain, or trauma. The patient noted no previous episodes of bleeding or easy bruising in her past. She notes that her menstrual periods were always regular and not subjectively heavy. Last menstrual period was 10 years ago. Patient has had two pregnancies in her obstetric history for which she delivered vaginally without bleeding complications. The patient denied recent antibiotic use. She had no change in diet and no prior transfusions. At the OSH, the patient was noted to be orthostatic at presentation with mild tachycardia but was stabilized with intravenous fluids and transfusions of packed red cells. Patient's nausea and vomiting resolved with antiemetics at the OSH. Nasogastric lavage was negative for blood. Laboratory results revealed patient to have markedly elevated prothrombin time (PT) and activated partial thromboplastin time (aPTT) with an INR greater than 20. The patient was initially treated with fresh frozen plasma (FFP) and high doses of vitamin K. The patient denied any warfarin use and she did not know anyone currently on the medication. CT scan of the head showed left subdural hematoma without midline shift or hydrocephalus. The patient was immediately transferred to the Jefferson Neurosurgical service. The patient was subsequently deemed a poor surgical candidate and was continued on supportive treatment with blood products and vitamin K. At time of transfer to the medicine service, the patient developed respiratory distress with severe hypoxia requiring intubation. The patient was admitted to the intensive care unit (ICU) for ventilator-dependent respiratory failure secondary to Transfusion Related Acute Lung Injury (TRALI). After five days, the patient was extubated and transferred to the medicine floor team in stable condition for further management of her bleeding diathesis.

The patient's past medical history was significant only for hypercholesterolemia but the patient was on no medications. The patient had a cholecystectomy 12 years ago and a laminectomy 7 years ago. Psychiatric history was notable for depression with prior suicide attempt five years prior to admission. Family history was negative for any bleeding disorder or malignancy. Social history revealed no alcohol use, substance use, or smoking. The patient was a homemaker.

On physical exam after transfer from the ICU, the patient was afebrile with a pulse of 85 beats per minute, a respiratory rate of 16 breaths per minute, and a blood pressure of 132/72mmHg. In general, the patient was in no acute distress. She was well nourished, well developed, and appeared her stated age. The patient's head was normocephalic and atraumatic. Her eyes showed equally round and reactive to light pupils and anicteric sclera. Her extra-ocular muscles were intact. Her mucous membranes were moist, her oropharynx was clear, and there were no petechiae or stomatitis in the oral cavity. Her neck was supple with no lymphadenopathy, no thyromegaly, no JVD or carotid bruits. Her heart was regular with no murmurs, gallops, or rubs. Her lungs had minimal scattered bilateral rales and mild bibasilar crackles. Her abdomen was soft, non-distended, non-tender. There were no appreciable masses or organomegaly. Her rectal exam revealed moderate external hemorrhoids. There was normal rectal tone, stool was dark brown and heme positive. There was no frank blood. There was no clubbing, cyanosis, or edema in the extremities. Her neurologic exam revealed no focal deficits with cranial nerves II-XII grossly intact. There was also no nystagmus, no dysmetria on finger to nose, and deep tendon reflexes were equal and symmetric. Her skin revealed small ecchymoses on upper extremities. See Table 1 for the baseline laboratories at time of transfer to the medicine floor service.

The remainder of the hospital course was notable for the continued elevations in her PT. Multiple transfusions of FFP and multiple injections of high-dose vitamin K initially normalized the PT and aPTT at the time of transfer from the neurosurgical service. Subsequent coagulation labs revealed a continually rising PT requiring the titration of the vitamin K dose from 10mg daily to 50mg twice daily. For two weeks, the patient had high doses of vitamin K and any dose

Table 1.

Laboratory Test	Laboratory Value
White blood cells	6.7
Hemoglobin	9.3
Hematocrit	28.3
Platelet count	212
Sodium	147
Potassium	3.7
Chloride	111
Bicarbonate	29
BUN	8.0
Creatinine	0.9
Glucose	104
Protein	7.0
Albumin	4.0
Total biliribuin	0.9
AST	26
ALT	21
Alkaline phosphatase	80
PT	24.6
INR	2.08
aPTT	38.0

taper led to a rapid rise in PT (See Table 2). The platelet count remained stable and hemolysis labs were negative. Her DIC panel revealed a mildly elevated D-dimer and a markedly elevated fibrinogen. Mixing studies performed on the second day of admission revealed normalization of elevated coagulation factors with mixing indicating a deficiency of factors rather than a presence of an inhibitor. Despite the elevated PT, there was no further evidence of active bleeding during the remainder of the hospitalization. Repeat head CT revealed a slowly resolving subdural hematoma and the hemoglobin remained stable. The patient was seen by gynecology and gastroenterology but no active interventions were planned as an inpatient.

Of concern was the patient's psychiatric history with a prior suicide attempt. The patient was initially placed on one to one nursing especially given the continuing elevations in her hemostatic labs. The patient repeatedly denied depression or suicidal ideations. She was evaluated by the psychiatry department at Jefferson and was deemed safe for discharge home. Approximately one month after discharge, the patient's PT was stable on oral vitamin K.

Table 2.

	Day 1	Day 2	Day 3	Day 4	Day 6	Day 7	Day 31	Day 32
PT	12.6	29.1	18.2	25.2	24.6	31.7	14.6	14.6
INR	1.0	3.47	2.45	5.17	2.08	2.88	1.07	1.07
aPTT	41.3	40.9	43.6	46.1	38	45		
PT mix		13.1						
aPTT mix		32.7						
Daily Vit K dose	10mg	20mg	40mg	50mg	100mg	100mg	20mg**	20mg**

* Transfer to the medicine floor **Oral dose

Discussion

The history and presentation of the patient suggest a diagnosis of an acquired hemostatic disorder rather than an inherited or congenital disease. The patient did not have any memorable episodes of bleeding in her past and no one in her family had a problem with bleeding that she could report. Acquired bleeding diathesis can be categorized into two major categories, platelet defect versus coagulation disorder.

A quantitative platelet disorder can induce bleeding usually with platelet counts below 50,000. Diseases such as idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), or heparin induced thrombocytopenia (HIT) can precipitously drop the platelet count. The patient did not have a significant decline in her platelet count, nor did she show any clinical signs of TTP (mental status changes, fever, renal failure, hemolytic anemia). The patient had also never been on heparin. A qualitative platelet dysfunction can be medication-induced (ASA, NSAIDs, clopidogrel, ticlopidine), or associated with a medical condition such as uremia, myelodysplastic syndrome (MDS), or von Willebrand disease (VWD). The patient was not on any medications and had good renal function. The diagnosis of MDS can be one of exclusion especially when an elderly patient presents with anemia (typically macrocytic) or pancytopenia with no clear etiology. Diagnosis was not pursued because of low clinical suspicion and a bone marrow biopsy was clearly not indicated in this case. VWD is the most common inherited bleeding disorder with a prevalence of approximately 1%. A negative family history does not rule out VWD since the clinical presentation can be variable and subclinical. Most women with milder VWD

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will usually report heavy menstrual periods and post-partum bleeding. The patient presented with heavy bleeding for three days of sudden onset. Inherited VWD would be very unlikely in this case since more severe forms of VWD would manifest at a much earlier age. Acquired VWD is a possibility but the disorder is associated with comorbidities such as malignancies and autoimmune disorders that were not evident in the patient. Furthermore, VWD can cause an elevation of the aPTT because it is the carrier of factor VIII, but it will not cause critical elevations of PT and aPTT. Ristocetin cofactor assay to test qualitative function of von Willebrand factor was not performed.

Acquired coagulation disorders with elevated PT and aPTT can be caused by liver disease, deficiency or inhibitors to factor V or X, deficiency of fibrinogen or prothrombin, disseminated intravascular coagulation (DIC), or high doses of warfarin with or without heparin. Vitamin K deficiency alone would not cause elevations in aPTT. The patient had normal liver function and had mixing studies that normalized during the hospitalization. A mixing study mixes the plasma of the patient with elevations in PT or aPTT with plasma that has normal coagulation function. A normalization of the coagulation labs would indicate a deficiency of factors that were replaced by the normal plasma whereas a continued elevation in PT or aPTT would indicate the presence of an inhibitor (antibody or medication). Acute DIC is most commonly associated with trauma, sepsis, or malignancy and treatment is aimed at the underlying cause. Supportively, the patient can be treated with FFP or cryoprecipitate if the fibrinogen is low. The patient only had a mild elevation in the D-dimer (fibrin degradation product) and elevation in fibrinogen (acute phase reactant). There was no evidence of hemolysis and the platelet count was stable.

The marked elevations in the PT and aPTT that responded to vitamin K are most consistent with warfarin toxicity. The patient denied any use of the medication and she could not have ingested the drug accidentally. Also concerning was the difficulty of normalizing her coagulation defect even weeks after the inciting event. Rodenticides are warfarin derivatives with extremely high potencies. They are designed to be antagonists of vitamin K but they are much more fat soluble and their half lives are many weeks compared to the 2-3 days of coumadin. The patient had a urine test performed during the hospitalization to detect levels of the commonly used “super-warfarins” of rodenticides like bromodiolone and difenacoum but the test result was negative. Three weeks into the hospitalization, a serum assay for a specific warfarin derivative called brodifacoum was sent to an outside laboratory. The result was positive for 0.1µg/mL. This chemical is a second-generation anticoagulant with a half-life of 157 days. It is retained in tissues at high rates and can remain in organ systems for years. The chemical is rapidly absorbed by the gut and quickly causes gastrointestinal hemorrhage. The mystery of how the patient ingested rodenticide was confounded by her psychiatric history of depression and prior suicide attempt. She repeatedly denied suicidal ideations and the psychiatry department did not feel she was a threat to herself at this time. Criminal investigation was discussed but quickly dismissed when the patient clearly expressed her desire not to pursue inquiries. The patient was discharged on day 32 with instructions for close follow-up.

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