Residents' Clinic

54-Year-Old Man With Dyspnea and Abdominal Wall Bruising

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A 54-year-old obese man presented with progressive shortness of breath of 2 weeks' duration. He also described pleuritic pain in his left lower rib area but denied having cough, orthopnea, fever, or hemoptysis. During the preceding 5 days, he had noticed the onset of bruising around his umbilicus and down his left flank. The patient denied having abdominal pain and had noticed no change in the mild abdominal bloating that had troubled him for more than 10 years.

The patient was taking warfarin as treatment for deep venous thrombosis (DVT) of his left leg, which had occurred spontaneously 3 months previously and had been diagnosed by ultrasonography. He stated that his international normalized ratio (INR) had been in the therapeutic range of 2 to 3. The last recorded INR was 2.7, determined 3½ weeks earlier. The patient also had obstructive sleep apnea, gout, hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic renal insufficiency (baseline creatinine level, 2.0 mg/dL), and gastroesophageal reflux disease. In addition to warfarin therapy, he was taking ramipril (5 mg/day), gemfibrozil (600 mg twice daily), furosemide (20 mg twice daily), potassium supplements, and ranitidine (150 mg twice daily).

The patient's blood pressure was 130/70 mm Hg, pulse rate was 106/min, and respirations were 26/min. He was afebrile and alert; his body mass index was 32 kg/m². His chest was dull to percussion two thirds of the way up on his left side, with diminished breath sounds. There was no rub. Apart from tachycardia, findings on a cardiovascular examination were unremarkable. Substantial bruising was noted around his umbilicus (Figure 1) and down his left flank. His abdomen was not tender, there were no palpable masses or organomegaly, and bowel sounds were normal. Initial laboratory findings were as follows (reference ranges shown parenthetically): leukocyte count, 10.4 × 10⁹/L (3.5-10.5 × 10⁹/L); hemoglobin concentration, 10.0 g/dL (13.5-17.5 g/dL); platelet count, 317 × 10⁹/L (150-450 × 10⁹/L); mean corpuscular volume, 86.0 fL (81.2-95.1 fL); serum sodium, 138 mEq/L (135-145 mEq/L); serum potassium, 4.4 mEq/L (3.6-4.8 mEq/L); blood urea nitrogen, 56 mg/dL (6-21 mg/dL); and serum creatinine, 2.4 mg/dL (0.8-1.2 mg/dL). His INR was 1.63 (he had not taken warfarin for 4 days because of the bruising). Electrocardiography revealed sinus tachycardia, and chest radiology showed a large left pleural effusion (Figure 2).

1. Which one of the following would most likely explain this patient's abdominal wall bruising?
   a. Acute hemorrhagic pancreatitis
   b. Rupture of the spleen
   c. Perforated duodenal ulcer
   d. Retroperitoneal bleeding
   e. Inferior vena caval (IVC) obstruction

Cullen sign (periumbilical ecchymosis) and Turner sign (flank bruising), clinical signs that are often harbingers of a grave intra-abdominal process, are often taught in medical school but are rarely encountered in medical practice. These signs are classically associated with severe acute hemorrhagic pancreatitis; however, in the current case, the absence of abdominal pain and vomiting, as well as normal findings on physical examination, makes this diagnosis unlikely. Similarly, both rupture of the spleen and perforation of duodenal ulcers have been reported in patients with such signs, but these diagnoses are unlikely based on our patient's clinical presentation. The patient's anemia, in the setting of anticoagulation, most likely suggests retroperitoneal bleeding, which can certainly present relatively silently without severe abdominal pain or tenderness. A vena caval obstruction is unlikely, particularly in the setting of chronic anticoagulation, and could not explain the pattern of bruising.

Findings on abdominal computed tomography (CT) showed no intra-abdominal bleeding source. Thoracentesis of the left pleural effusion showed frankly bloody fluid and fulfilled the criteria for a hemothorax—a bloody pleural effusion in which the pleural fluid hematocrit is greater than 50% of the whole blood hematocrit. This likely represented the source of bruising.
2. Which one of the following conditions is the least likely cause of the hemothorax in this patient?
   a. Aortic dissection
   b. Coagulopathy
   c. Pulmonary infarction
   d. Pulmonary vascular malformation
   e. Tuberculosis

   Unlike hemorrhagic pleural effusions, spontaneous (nontraumatic) hemothorax is rare. Aortic dissection is the major reported cause of systemic bleeding into the pleural space. Surprisingly, it is not always associated with immediate death. Numerous cases have reported hemothorax due to dissection that precedes death by days to weeks. A hemothorax is frequently associated with anticoagulant therapy, occurring most commonly when the patient’s anticoagulation is supratherapeutic or within the first week of initiation of anticoagulant therapy for acute pulmonary embolus with pulmonary infarction. Although pulmonary arteriovenous fistulas more commonly rupture into bronchi, intrapleural rupture does occur and is a well-recognized cause of spontaneous hemothorax. Tuberculosis rarely causes spontaneous hemothorax; when spontaneous hemothorax does occur, it is generally associated with active pulmonary tuberculosis. Based on the patient’s history and findings, this seems unlikely.

   To rule out a large pulmonary embolus and infarction, contrast-enhanced chest CT including the pulmonary arteries was performed. No pulmonary embolism was evident. There was no indication on CT or in the subsequent clinical course to suggest either an aortic dissection or an arteriovenous malformation. The hemothorax was partially drained via a chest tube; however, the patient subsequently required an open decortication procedure for complete drainage. No pleural lesion was identified. It was concluded that the hemothorax had occurred spontaneously in the setting of anticoagulation. Details about the patient’s anticoagulation history were obtained from his local physician. There was no clear evidence that the patient’s INR had been supratherapeutic. His INR had been under good control, with all his values between 2.0 and 3.15 in the preceding 2 months. The patient was scheduled for a routine reassessment the week after his presentation to our institution. He had neither altered his diet nor started taking any new medications in the weeks before the bleeding. Repeated Doppler ultrasonography of his lower extremities showed no DVT.

3. Which one of the following therapeutic options is most appropriate for further treatment of our patient’s spontaneous DVT, which occurred 3 months earlier?
   a. Reinitiate warfarin to a goal INR of 2 to 3
   b. Administer subcutaneous low-molecular-weight heparin (LMWH) for 3 months
   c. Observe
   d. Administer low-dose warfarin
   e. Use an IVC filter

   Traditionally, the treatment of unexplained DVT has been with warfarin, to a goal INR of 2 to 3, for a total of 3 to 6 months. At the time of his presentation, the patient had received therapy for approximately 3 months. Recently, investigators recognized that continuation of systemic anticoagulation for more than 3 months decreases the likelihood of recurrence of thromboembolic disease. However, that study excluded all patients with severe bleeding complications. Based on the ultrasonographic documenta-
tion of resolution of the patient's DVT, we thought that the risk of reinitiating anticoagulation postoperatively, with either warfarin or LMWH, outweighed potential benefits of future clot prevention. Since the patient had already received anticoagulant therapy for a little more than 3 months with no residual clot, our strategy was observation. There is no current evidence for the use of low-dose warfarin for the prevention of recurrent venous thromboembolic disease, although evaluation of this is currently under way in the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial. In the only randomized trial of placement of IVC filters early in the course of DVT, the small decrease in the rate of pulmonary embolism was offset by an increase in the long-term rate of recurrent DVT.

Close observation was recommended. However, 4 weeks later, the patient presented with DVT in his right leg. To assess the cause of recurrent DVT, he was evaluated for an underlying thrombophilia.

4. Which one of the following factors would most likely predispose this patient to his recurrent condition?
   a. Deficiency of antithrombin III
   b. Deficiency of protein C
   c. Deficiency of protein S
   d. Activated protein C resistance
   e. G20210A prothrombin mutation

A deficiency of the natural coagulation inhibitor antithrombin III is an inherited autosomal dominant trait that predisposes to thrombosis and occurs in 1 in 2000 individuals. Activated protein C, in conjunction with protein S, proteolizes factors Va and VIIIa, which prohibits prothrombin activation to thrombin. Deficiencies of either protein C or S, usually autosomal dominant disorders, predispose patients to venous thrombosis. However, such deficiencies are uncommon. Taken together, deficiencies of antithrombin III, protein C, or protein S account for only about 5% of cases of idiopathic venous thrombosis. A single point mutation in the factor V gene (factor V Leiden), which converts arginine 506 to glutamine and makes the molecule resistant to degradation by activated protein C, accounts for almost all the cases of true activated protein C resistance. With approximately 3% of the worldwide population heterozygous for this mutation, it is the most common inherited prothrombotic state, accounting for perhaps 20% of such states. The substitution of A for G at position 20210 of the prothrombin gene is another recognized thrombophilic mutation, present in 2% of the general population and in 6% of patients with thrombosis.

On testing, the patient was found to be homozygous for the factor V R506Q (Leiden) mutation, a condition that increases the risk of venous thromboembolic disease 20- to 80-fold.

Because our patient had had a successful recovery from the hemothorax and subsequent thoracotomy, we elected to reinitiate warfarin therapy to a goal INR of 2 to 3 for life. If a major bleeding event recurs, reevaluation will be necessary, and the issue of an IVC filter will be readdressed. Understanding that his condition was inherited, the patient asked about the implications of his diagnosis in regard to his daughter and her risk of thromboembolic disease.

5. Which one of the following recommendations is correct for this patient's daughter (assuming that her mother does not carry the factor V mutation)?
   a. She should begin prophylactic LMWH if she becomes pregnant
   b. She should be counseled against having children because of the risk of transmission of the mutation
   c. She should never take the oral contraceptive pill
   d. She should take warfarin for life because of her high risk of venous thromboembolic disease
   e. She has an increased risk of fetal loss and stillbirth

Assuming that her mother is not a carrier of the mutation, the daughter is heterozygous for the Leiden mutation. Such a person has a 5- to 10-fold increased risk (2%) of pregnancy-related venous thrombosis. Prescribing LMWH during the high-risk period of late pregnancy (third trimester and the puerperium) could be considered, but because of the associated inconveniences, cost, risks of bleeding, and thrombocytopenia, LMWH cannot be recommended in a woman with no history of thrombosis. In fact, among women with factor V Leiden mutation, estimates suggest that the risks of complications associated with anticoagulant prophylaxis are as high as the risk of death due to puerperal thrombosis. Certainly anticoagulation would not be indicated throughout pregnancy. The daughter should be informed about the potential risk of transmission of the abnormal gene and thrombophilic tendency to a child. However, such a risk is not a contraindication to conception. Investigators have estimated that the use of oral contraceptives in women who are carriers of the factor V mutation leads to a death rate due to pulmonary emboli of 5.7 per 100,000 patient-years, approximately a 9-fold increase over women who are not carriers. To prevent 3 episodes of venous thromboembolism, 1000 young women heterozygous for the factor V mutation would need to refrain from taking oral contraceptives. Therefore, the decision for or against recommending oral contraception should be made on a case-by-case basis. The absolute annual incidence of a first episode of venous thrombosis is 0.25%; it increases to 1.1% in those older than age 60. The risk of major bleeding with warfarin has been re-
ported as 2% per year, with a fatal bleeding rate of 0.4% per year. Thus, in asymptomatic carriers, warfarin is not indicated for prophylaxis. Carriers of the factor V Leiden mutation have a greater risk of fetal loss (particularly miscarriage) than noncarriers. This is likely related to placental thrombosis.

**DISCUSSION**

Cullen first reported periumbilical bruising in association with ruptured ectopic pregnancy in 1918. Since then, it has been reported in many conditions hallmarked by intra-abdominal hemorrhage including hemorrhagic pancreatitis, perforated duodenal ulcers, splenic rupture, adenocarcinoma of the liver, intra-abdominal lymphomas, and metastatic carcinomas. The most likely explanation is that blood tracks along fascial planes to the periumbilical area where muscular support is weak. To our knowledge, ours is the first reported case of a hemothorax presenting with Cullen and Turner signs. Possibly, our patient has a small left-sided diaphragmatic defect through which the blood tracked.

The so-called factor V Leiden mutation refers to the substitution of glutamine for arginine 506 in factor V. This substitution impairs protein C inactivation of factor V and allows further activation of prothrombin to thrombin, thereby promoting a thrombophilic state. The prevalence of this mutation has been well studied; approximately 5% to 6% of Europeans are heterozygous, making this the most common inherited thrombophilic tendency in Caucasians. This mutation is essentially absent in people of African, Far Eastern, or native American origin. The presence of this mutation may account for 25% of patients with recurrent DVT or pulmonary embolism.

**REFERENCES**


Correct answers: 1. d, 2. e, 3. c, 4. d, 5. e