CASE DETECTIVE Series

24-Year-Old Woman With Menorrhagia, Mucosal Bleeding, and Easy Bruising

Case-3

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PMH

- A **24-year-old woman** with a complex medical history including
  - **Ehlers-Danlos syndrome with hypermobility subtype**
  - **Mast cell activation syndrome**
  - **Eosinophilic esophagitis**
  - **Postural orthostatic tachycardia syndrome (POTS)**
- presented to the emergency department (ED) for evaluation of **menorrhagia, muscle cramps, and fatigue** of 3 weeks' duration.
- Her home medications included
  - **albuterol** (90 µg/inhaler to be used every 6 hours as needed),
  - **cyanocobalamin** (1000 µg daily)
  - **diphenhydramine** (50 mg twice a day)
  - **epinephrine** (0.3 mg/0.3 mL by auto-injector as needed)
  - **fexofenadine** (180 mg twice a day)
  - **ketotifen** (2 mg twice a day)
  - **montelukast** (10 mg daily at bedtime)

PMH

- Diagnostic evaluation at that time was notable for
  - **normocytic anemia** with a **hemoglobin level of 6.8 g/dL**
  - **mean corpuscular volume of 93.2 fL**
  - hematocrit level of 22% (reference range, 35.5% to 44.9%)
- **platelet count of 217 × 109/L** (reference range, 157 to 371 × 109/L), and the patient **received a transfusion of 1 U of packed red blood cells**
- Prior to presentation, the patient's **baseline hemoglobin level** ranged from **13 to 14 g/dL** within the previous 12 months.
- **Pelvic ultrasonography** was performed and revealed **no abnormalities**.
- A regimen of **5-mg oral medroxyprogesterone** once daily was prescribed, and the patient was discharged from the ED with outpatient follow-up scheduled.
- At her **gynecology follow-up appointment**, her menorrhagia was reported to have stopped.

PMH and presentation

- The following month, she experienced **recurrent menorrhagia** that was characterized as menses requiring her to change her menses pad every 2 to 3 hours with use of up to **7 pads per day**.
- Additionally, the patient also noted **increased fatigue**, **new-onset bruising of her lower extremities**, and **mucosal bleeding** **provoked while brushing her teeth**.
- She return to the ED for further evaluation. **In the ED,**
  - her **temperature** was 36.6 °C,
  - **heart rate** was 126 beats/min,
  - **blood pressure** was 93/65 mm Hg, and
  - **oxygen saturation** was 96% while breathing room air.
- Her body mass index was 20.4 kg/m^2.

Presentation & PE

- Physical examination revealed a young woman **in no acute distress**. Examination of the head and neck revealed **no lymphadenopathy**, but there was **gingivitis and ecchymoses of the soft palate**.
- Auscultation of her chest was notable for a **tachycardic heart rate** without murmurs, and her **lungs were clear** bilaterally.
- Examination of her abdomen revealed **mild diffuse tenderness** **without distention.**
- Her skin examination was notable for **petechiae of the lower extremities**, **mild nonpitting edema of the feet**, **prominent ecchymoses of the plantar surfaces of the feet**, and **pale appearance of the skin**.
- Her neurologic assessment documented **5/5 strength of biceps and hip flexion**; however, the patient was **unable to ambulate due to weakness and pain** while bearing weight. **Tenderness to palpation was present on the plantar surfaces of both feet.**

Initial Labs

- Initial laboratory studies revealed the following:
- **Hemoglobin 9.8 g/dL** (11.6 to 15.0 g/dL); mean corpuscular volume 85.7 fL (78.2 to 97.9 fL); platelet count, 168 × 109/L
- **Elevated international normalized ratio of 1.6** (0.9 to 1.1); **prolonged prothrombin time (PT) of 19.1 s** (9.4 to 12.5 s); and partial thromboplastin time (PTT) of 24 s (25 to 37 s).
- A **peripheral blood smear** revealed 3 to 5 **spherocytes**/HPF, 3 to 5 **target cells**/HPF, and the presence of **Döhle bodies**.
- **Iron studies** revealed iron level of 48 µg/dL (35 to 145 µg/dL), **suppressed total iron binding capacity of 234 µg/dL** (250 to 400 µg/dL), and percent saturation of 21% (14% to 50%).
- **Testing for hemolysis** revealed the following:
  - LDH, 190 U/L (122 to 222 U/L)
  - **Total bilirubin, 2.6 mg/dL** (≤1.2 mg/dL); **direct bilirubin, 0.4 mg/dL** (0.0 to 0.3 mg/dL);
  - Direct antiglobulin test (DAT), **negative.**
- The patient's ferritin level was 113 µg/L (11 to 307 µg/L), **reticulocyte count was 3.53%**, and vitamin B12 level was 475 ng/L (180 to 914 ng/L).

PMH

- Regarding the patient's **surgical history**, she had previously undergone **multiple spinal procedures** as well as **wisdom teeth extraction with no complications or excessive bleeding** reported with any of the procedures.
- Prior to the patient's hospitalization, she was being evaluated for **numerous food intolerances** previously attributed to mast cell activation syndrome. Despite negative results on skin prick testing for common allergies, **the severity of her intolerances resulted in a progressively limited diet.** For several months, the patient reported eating only **oatmeal**.

Given this patient's history and clinical presentation, which one of the following is the most likely explanation for her anemia and easy bruising?

A. Hemolysis

B. Inherited coagulopathy

C. Accidental rat poison ingestion

D. Nutrient deficiency

E. Acquired inhibitor coagulopathy

Which one of the following is the most appropriate laboratory study that should be obtained for the assessment of the patient's bleeding and anemia at this point?

a. DAT

b. Dilute Russell viper venom time test

c. Prothrombin mixing study

d. Erythrocyte sedimentation rate

e. von Willebrand profile

Progress Note

- To assess for the **possibility of a coagulation factor deficiency** as a cause of the patient's coagulopathy, she underwent **a prothrombin mixing study**, which revealed **normalization of the PT**.
- **Vitamin K deficiency** is the main cause of coagulation factor VII deficiency–associated prolonged PT that corrects on a mixing study.
- Concern for **additional vitamin deficiencies** prompted further testing, which revealed **multiple nutrient deficiencies**.
  - **vitamin C** level was less than 0.1 mg/dL (0.4 to 2.0 mg/dL)
  - **vitamin K** level was 0.04 ng/mL (0.10 to 2.20 ng/mL)
  - **vitamin A** level was 5.7 µg/dL (32.5 to 78.0 µg/dL)
  - **folate level** was 3 µg/L (≥4.0 µg/L)
  - **vitamin E** level was 4.6 mg/L (5.5 to 17.0 mg/L)

Which one of the following comorbidities could be contributing to the patient's bleeding?

a. Eosinophilic esophagitis–associated gastrointestinal hemorrhage

b. POTS-associated cytopenias

c. Mast cell activation syndrome and malnutrition from food aversion

d. Ectopic pregnancy–associated blood loss

e. Ehlers-Danlos syndrome and platelet dysfunction

Based on this patient's presentation, which one of the following is an additional important therapeutic intervention to consider for treatment and prevention of her underlying disease?

a. Psychiatric assessment for anxiety-associated oral intake

b. Intravenous iron infusion

c. Packed red blood cell transfusion

d. Aminocaproic acid

e. Hydroxychloroquine

If the patient's primary medical problem remains untreated, which one of the following additional symptoms may develop?

A. Thrombosis

B. Diarrhea

C. Esophageal strictures

D. Pneumothorax

E. Follicular hyperkeratosis and perifollicular hemorrhage

Progress note

- The patient was considered to be **symptomatic from vitamin C and vitamin K deficiency** given her menorrhagia, gum bleeding, and petechiae and required treatment at this time.
- **She was treated with**
  - vitamin C (1000 mg/d orally)
  - vitamin D3 (5000 U daily)
  - vitamin B12 (2000 µg daily)
  - folic acid (1 mg)
  - thiamine (500 mg in 5% dextrose with sodium chloride)
  - **3 days of intravenous vitamin K** (1 mg in 0.9% normal saline) **with transition to oral vitamin K (5 mg/d).** Within 3 days of vitamin supplementation, her gum bleeding and menorrhagia resolved.
- The patient **met with the psychiatry team** and was discharged with a regimen of vitamin C (1000-mg tablet daily), vitamin D3 (5000 U/d), cyanocobalamin (1000-µg tablet daily), folic acid (1-mg tablet daily), thiamine (100-mg tablet daily), and vitamin K1 (5 mg/d).
- At follow-up in the hematology clinic 4 months later, **her hemoglobin level had normalized and her bleeding had not recurred.**

Vitamin C

- Vitamin C is **absorbed in the distal small intestine** via transport that can absorb up to 180 mg/d.2
- Levels usually **start to deplete 4 to 12 weeks after decreased oral intake**.
- Vitamin C has **multiple roles**, including assisting in
  - fatty acid transport
  - **collagen synthesis**
  - neurotransmitter synthesis
  - prostaglandin metabolism
  - nitric oxide synthesis
- Its role in collagen synthesis is what predisposes an individual with vitamin C deficiency to experience increased bleeding.
- Ascorbic acid is an **oxide donor** necessary **in the production of hydroxyproline**, which is an essential component of collagen.
- Vitamin C deficiency is defined as serum concentration below 11.4 mg/dL.

Vitamin K

- Vitamin K is **a key element in the coagulation pathway**, and this fact has been harnessed to produce predictable anticoagulant effects through vitamin K antagonism pharmacotherapy.
- It indirectly affects clotting by **serving as a cofactor for γ-glutamyl carboxylase**, which leads to the **formation of clotting factors including factors II, VII, IX, and X**.
- Additionally, **vitamin K is involved in the pathway to create proteins C, S, and Z, osteocalcin, and matrix Gla protein**.
- It is estimated that in healthy adults, about 8% to 31% have vitamin K deficiency.
- There is **usually a dietary component causing vitamin K–associated coagulopathy**. For example, one case report described a female presenting with severe menorrhagia secondary to vitamin K deficiency in the context of poor diet consisting of energy drinks over a span of 6 months

Ehlers-Danlos syndrome

- Ehlers-Danlos syndrome is caused by a **mutation in collagen leading to fragility of capillaries and perivascular connective tissue that can contribute to bleeding**.
- **Type IV, vascular type**, **has the highest bleeding risk and arterial rupture can occur**. A study reported that only 8% reported no history of bruising or bleeding.
- **76% of women** with a known diagnosis of hypermobile Ehlers-Danlos syndrome had **menorrhagia.**
- **Up to 40%** of patients with Ehlers-Danlos syndrome reported **an abnormal bleeding severity score**
- **7% having prolonged PT and PTT**
- **90% of patients having platelet function abnormalities.**