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Plummer-Vinson Syndrome With Concomitant Factor VII Deficiency

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Background: Plummer-Vinson syndrome (PVS), a rare disorder characterized by dysphagia, iron deficiency anemia, and esophageal webs, has principally been described in middle-aged women. This disorder is uncommon in the 21st century because of the abundance of iron-fortified foods. Clotting factor deficiencies are also rare. Factor VII deficiency is a bleeding disorder characterized by the absence of a critical protein in the coagulation cascade.

Case Report: We present a case of PVS associated with factor VII deficiency in a 26-year-old African American female. The patient had a history of anemia that was repeatedly attributed to menstrual bleeding and dysphagia for 10 years. She presented with symptomatic anemia requiring transfusion. She reported a history of food getting stuck in her chest, and workup revealed esophageal webs with no evidence of overt luminal gastrointestinal bleeding. Coagulation laboratory tests revealed the incidental finding of a borderline increased prothrombin time. Hematologic studies confirmed the presence of factor VII deficiency.

Conclusion: To our knowledge, no case has been published about a patient diagnosed with PVS and concomitant factor VII deficiency. Our case illustrates several learning points: (1) PVS is an uncommon disorder that may still be diagnosed in a developed country in the 21st century; (2) PVS requires close follow-up and esophageal surveillance because of the increased risk of esophageal cancer; (3) factor VII exhibits a high degree of phenotypic variability; (4) phenotype in factor VII deficiency does not always correlate with factor VII activity, although life-threatening spontaneous bleeding is not expected with levels >2%.

Keywords: *Anemia, dysphagia, factor VII deficiency, Plummer-Vinson syndrome*

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INTRODUCTION

Iron deficiency anemia is the most common anemia worldwide.[1,2] Its prevalence is higher in females of reproductive age compared to males, and it is often attributed to menstrual losses.[3,4] Other etiologies include occult bleed, limited dietary iron intake, or malabsorption. Anemia in this patient population requires careful evaluation of multiple organ systems. Chronic iron deficiency anemia may manifest as Plummer-Vinson syndrome (PVS), also called Paterson-Brown-Kelly syndrome or sideropenic dysphagia, which is the classical triad of dysphagia, iron-deficiency anemia, and esophageal webs. Exact data about epidemiology of the syndrome are not available. PVS is extremely rare but has most frequently been described in women aged 40-70 years rather than in women of younger reproductive age.[5,6]

Hemostasis is a delicate multiphase process that involves interactions among the endothelial cells, platelets, and coagulation factors.[7] Aberrancy in any of the components of hemostasis can manifest as a life-threatening bleed or can be asymptomatic and incidentally detected on routine laboratory tests. Clotting factor deficiencies are very rare and may initially be identified through prolonged activated partial thromboplastin time (aPTT) or prothrombin time (PT). Factor VII deficiency, also known as Alexander disease, is the most common of the rare coagulation disorders with an estimated incidence of 1:500,000.[8] Bleeding symptoms of factor VII deficiency are commonly mild and often manifest as bleeding from the skin and mucous membranes. Life-threatening central nervous system and gastrointestinal (GI) bleeds manifest in the first 6 months of life.[9]

Although celiac disease, thyroid disease, and rheumatoid arthritis have been associated with PVS, to our knowledge, no cases of PVS and concomitant blood factor deficiency have been reported.[5,10,11] We present a case of iron deficiency anemia and factor VII deficiency manifesting as PVS.

CASE REPORT

A 26-year-old African American female with history of anemia presented to our emergency department with dizziness and headache. The headache started on the morning of presentation when the patient awakened from sleep; was bilateral and throbbing; and was not associated with phonophobia, photophobia, or neck pain. The patient reported experiencing episodic dizziness and shortness of breath with exertion for 2-3 months and had noticed blood-tinged stools during her last 4 bowel movements. Upon further

questioning, she revealed a history of dysphagia without odynophagia to solid foods for more than 10 years, manifesting in having to take small bites of food and chew for a prolonged time compared to friends and family. She denied progression of dysphagia over time and denied associated weight loss. The dysphagia had been evaluated by esophagogastroduodenoscopy (EGD) 3 years prior; however, the scope could not be advanced because of luminal narrowing, and the patient was lost to follow-up. In her teens, she was diagnosed with iron deficiency anemia attributed to menorrhagia and monitored with monthly hemoglobin evaluation by her primary care physician. Her last transfusion was 4 years prior to presentation.

She had also been on oral and intravenous iron supplements but stopped taking them 2 years prior. Menorrhagia management included combined estrogen- and progesterone-containing oral contraceptives for the previous 2 years, followed by an intrauterine device that had fallen out 1 year prior to presentation. Menstrual flow consisted of 3-4 pads per day for 5 days with occasional large clots but no breakthrough bleeding between cycles. She denied nasal or gum bleeding and had had 1 wisdom tooth extraction without incident. Family history was significant for menorrhagia and a postpartum hemorrhage requiring blood transfusion in her mother. The patient had never used tobacco or drugs, and she drank 1-2 glasses of wine occasionally, approximately 5 times per year.

On examination, the patient was normotensive (blood pressure 129/84 mmHg) and tachycardic (heart rate 109 bpm). She was afebrile with a temperature of 36.8°C. Oxygen saturation was 100% on room air. Physical examination was remarkable for a slim, African American female with conjunctival pallor and sinus tachycardia on cardiac auscultation. She had no cheilitis, petechiae, ecchymoses, or sites of active bleeding; however, rectal and pelvic examination were deferred. The rest of the physical examination was within normal limits.

Initial laboratory results revealed a microcytic anemia with anisocytosis, hemoglobin of 4.2 g/dL (reference range, 11.5-15.1 g/dL), mean corpuscular volume of 62.5 fL/red cell (reference range, 82-97 fL/red cell), and red blood cell distribution width of 26.8% (reference range, 11.7%-14.9%). Ferritin level was 2 ng/mL (reference range, 11-306 ng/mL). The tests also revealed a PT of 13.4 seconds (reference range, 9.4-11.7 seconds), correlating with an international normalized ratio (INR) of 1.25 (reference range, 0.86-1.09), in the setting of normal aPTT and liver function tests. Thyroid-stimulating hormone, prolactin level, and urine pregnancy were unremarkable. Ultrasound of the pelvis revealed a hemorrhagic cyst in the ovary; no structural abnormalities were detected in the uterus.

Complete blood count results and symptoms were consistent with symptomatic iron deficiency anemia, and the patient received 3 units of packed red blood cells. Repeat hemoglobin after blood transfusion was 7.3 g/dL.

Given her history of chronic dysphagia and new onset hematochezia, an underlying GI pathology was a concern. The patient was evaluated with EGD and colonoscopy. EGD revealed 2 nonobstructive upper esophageal webs seen at 15 and 17 cm from the incisors (Figure) with no evidence of bleeding. The colonoscopy was unremarkable with no evidence of bleeding. The association of dysphagia, iron deficiency anemia, and esophageal webs established the diagnosis of PVS.

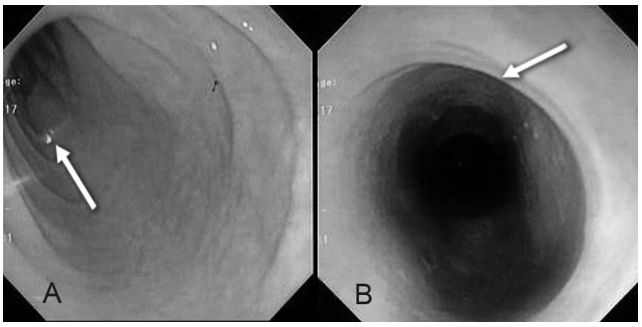

Figure. Esophageal webs (A) 15 cm and (B) 17 cm from the incisors (arrows). The combination of dysphagia, iron deficiency anemia, and esophageal webs helped establish the diagnosis of Plummer-Vinson syndrome.

Recall that the patient presented with an elevated PT/INR, normal aPTT, and normal liver function tests. Given the patient's chronic dysphagia, the concern was that she might be malnourished and in turn be vitamin K deficient. The patient was administered two 10 mg oral phytonadione (vitamin K1) tablets. At 24 and 48 hours after administration, her PT measures remained persistently elevated at 13.8 seconds and 13.8 seconds (INR=1.29), respectively. To further evaluate the coagulation system, a mixing study was performed on day 3 of the patient's hospital stay. The mixing study revealed that the patient's PT was borderline increased at 13.0 seconds but subsequently corrected to 12.1 seconds with a 1:1 mixing study. Her aPTT was normal at 26.2 seconds. The prolonged PT/INR in the setting of normal aPTT suggests a defect in the extrinsic pathway of the coagulation cascade. Factor VII assay revealed severely decreased activity at 36% (reference range, 70%-140%).[12] The prolonged PT/INR, normal aPTT, and decreased factor VII activity established the diagnosis of factor VII deficiency.

The patient's remaining hospital course was uneventful. For her iron deficiency anemia and esophageal webs, she was initiated on liquid oral iron supplementation consisting of 325 mg ferrous sulfate (65 mg of elemental iron) 3 times daily. The patient was discharged home on day 4 of hospitalization with liquid oral iron supplementation as outlined above, along with docusate 100 mg every evening to prevent iron-induced constipation. She was provided with follow-up appointments at our benign hematology and gastroenterology clinic. She did not require treatment for her factor VII deficiency. However, the patient was counseled that if she needed surgery in the future, treatment with plasma infusion was advised if she were undergoing a blind procedure. Precautions would not be needed, however, if adequate visualization could permit control of the bleeding.

The patient continued to be assessed at outpatient appointments with gastroenterology and benign hematology and remained on the same dose of oral iron supplementation. After 6 months of oral iron supplementation, repeat EGD showed no improvement in the upper esophageal rings. Because of the patient's continued dysphagia, a wire-guided Savary-Gilliard dilation was performed. Dilation was performed with a size 6 mm dilator, followed by a 7 mm

dilator. Postdilation assessment with a pediatric gastroscope revealed adequate mucosal tear with blood show at both rings as expected. No biopsies were taken. No immediate postdilation complications were encountered. At subsequent visits with gastroenterology and benign hematology, improvement in the patient's dysphagia symptoms was noted.

DISCUSSION

To our knowledge, this case illustrates the first reported instance of factor VII deficiency and iron deficiency anemia manifesting as PVS. The prevalence of iron deficiency has decreased dramatically since the 1970s, and iron deficiency anemia is uncommon in the western world today because of the fortification of foods with absorbable forms of iron.[13,14] The patient's extremely low ferritin level demonstrated that she was profoundly iron deficient. However, the description of her menstrual bleeding amount did not account for such a profound decrease in hemoglobin. The evaluation of the anemia was performed in a systematic fashion, examining endocrine, genitourinary, and GI causes and eventually eliciting the history of dysphagia and visualizing esophageal webs to establish the diagnosis of PVS.

GI mucosal surfaces are especially vulnerable to iron deficiency because of high cell turnover. Numerous articles on the pathophysiology theorize that a deficiency of iron-dependent oxidative enzymes causes gradual degradation of the pharyngeal muscles that leads to mucosal atrophy and formation of webs.[5,6,15,16] Despite these theories, the exact pathogenesis of how iron deficiency leads to formation of esophageal webs is unknown.

Treatment for PVS includes iron replacement therapy for the anemia, as well as invasive treatment such as argon plasma coagulation therapy and esophageal dilation for the esophageal webs.[6,12] Argon plasma coagulation is a non-contact thermal method of hemostasis that has been used to control bleeding from certain lesions in the GI tract and to debulk tumors for which surgery is not recommended.[17-19] Crespo Pérez et al published a report of using this technology to treat esophageal webs in a patient with PVS.[20] Of note, our patient had concomitant factor VII deficiency that hampered the use of argon plasma coagulation dilation. Mercury-/tungsten-filled bougies (Maloney/Hurst), bougienage dilators (bougie passed over a guidewire; Savary-Gilliard or American), and through-the-scope (balloon) dilators are the esophageal dilators commonly available.[6,21] Esophageal webs may worsen over time, and PVS is associated with an increased risk of esophageal cancers; therefore, endoscopic surveillance and close follow-up are necessary.[5,15,16]

The patient's factor VII deficiency was undiagnosed. Congenital factor VII deficiency exhibits a high degree of phenotypic variability, ranging from mild mucocutaneous bleeding to life-threatening brain and GI hemorrhage.[9,12,22-25] The correlation between factor VII activity and the tendency to bleed has been difficult to establish because of the variability in phenotype. Our patient's factor VII activity of 36% was likely high enough to prevent spontaneous lethal bleeding, as spontaneous life-threatening bleeds tend to occur in homozygous or compound heterozygous individuals with factor VII activity levels $<2\%$.[9,22-25] Given the patient's possibility of future childbirth or invasive surgery in the setting of factor VII deficiency and her increased risk for upper GI tract cancers, close follow-up is required.

CONCLUSION

A number of learning points can be drawn from this case. Iron deficiency anemia is still prevalent in a developed country where iron fortification of food is common. If a patient presents with iron deficiency anemia and dysphagia, a high suspicion for PVS is warranted. Anemia is a complex diagnosis that requires a thorough evaluation of the patient in terms of history, physical examination, and laboratory workup. Any abnormality in these elements requires further investigation. Also, PVS is associated with an increased risk of esophageal cancer and requires close follow-up and surveillance. Factor VII exhibits a high degree of phenotypic variability, and a deficiency in factor VII does not always correlate with factor VII enzyme activity.

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