Severe FVII deficiency presenting with Heterotopic gastric mucosa: Hoofbeats may be a zebra

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Abstract

Gastrointestinal (GI) tract bleeding can present as symptomatic anemia in children. This presentation warrants evaluation for GI tract pathology and consideration of coagulation assays to rule out an underlying bleeding diathesis. A male child was diagnosed with a rare bleeding disorder, severe (<1%) factor VII (FVII) deficiency during evaluation of severe iron deficiency anemia (IDA) secondary to recurrent GI bleeding. Despite adequate prophylaxis for the underlying bleeding disorder, continued GI bleeding and anemia led to further evaluation and identification of a rare small intestinal tract lesion, heterotopic gastric mucosa (HGM). Surgical treatment of the lesion resulted in complete symptom resolution and abated the need for prophylactic factor replacement therapy.

INTRODUCTION

A child presenting with iron deficiency anemia without dietary causes or frank blood loss, should prompt an evaluation for gastrointestinal (GI) bleeding. The presence of other bleeding symptoms and/or a positive family history of bleeding warrants investigating for an underlying bleeding diathesis. Severe Factor (F)VII deficiency is an autosomal recessive rare bleeding disorder which can present with GI bleeding,[1,2] and is treated with prophylactic FVII replacement therapy.[3] If bleeding continues despite prophylaxis, an in-depth evaluation should be performed to assure no other GI tract pathology is present. HGM is a rare lesion with unknown prevalence which is in the differential diagnosis of lower GI tract bleeding.[4-9]

Here we present the pathway to diagnosis and the management of a young male with severe FVII deficiency followed for a decade for anemia and GI bleeding who was ultimately found to have a rare small intestinal lesion, HGM, as an explanation for his symptoms. This case represents the first documented report of a severe FVII deficient individual presenting with a rare small bowel lesion, masquerading as non-responsive GI bleeding.

CASE DESCRIPTION

A 7-year-old Caucasian male presented to his pediatrician with microcytic hypochromic anemia with a hemoglobin of 7 g/dl and was treated for two years with oral iron supplementation. Family denied dietary causes, competitive sports participation, hematochezia, or melena. Family reported excessive bruising and intermittent prolonged seasonal epistaxis. Mother reported persistent oozing for 4 days post a dental procedure as a toddler but denied bleeding post tonsillectomy and adenoidectomy at 3 years. There was no family history of bleeding or consanguinity reported.

At 9 and 11 years of age, the patient required red blood cell transfusions for severe symptomatic (hemoglobin ranging 4-6 g/dl; reticulocytes ~10-20%) IDA. Prior to the admissions for severe anemia, the family denied preceding episodes of epistaxis. Extensive testing included otolaryngology evaluation, stool hemoccult test,

conventional and capsule endoscopy and a technetium-99m-tagged red blood cell scan; all procedures failed to locate a source of bleeding except for demonstrating findings of chronic gastritis. Per hematology consultation, he was evaluated for a bleeding disorder and was found to have a prolonged prothrombin time (PT) and INR of 86 secs and 8, respectively. Further evaluation revealed severe FVII deficiency with an activity level <1%. He was treated with Vitamin K replacement with 10 mg intravenously along with an oral antifibrinolytic agent, Aminocaproic acid, and was restarted on oral iron therapy prior to discharge.

The patient presented at age 11 to the Indiana Hemophilia & Thrombosis Center (IHTC) for ongoing management of severe FVII deficiency following the above admission. On our initial evaluation, his hemoglobin was 10 g/dl and ferritin of 6. Family evaluation revealed that his mother had a borderline FVII activity of 69% (normal adult range 67-143%), while father was not available for testing. He underwent genotyping for the FVII mutations and was found to be compound heterozygous (Supplemental Table S1).

Due to the persistent GI bleeding, the patient was initiated on FVII prophylaxis with recombinant FVIIa at ˜50 mcg/kg once weekly with close gastroenterology follow up, treatment of gastritis with a proton pump inhibitor, and continued oral iron supplements; the patient was followed with laboratory monitoring for anemia with weekly hemoglobin and reticulocyte counts, and stool hemoccult testing was ensured. The once weekly prophylaxis regimen was chosen via a shared decision-making process as the patient was averse to central venous line placement and had severe anxiety with peripheral venous access. As the stool hemoccult remained intermittently positive over the next 5years, his prophylaxis regimen was escalated to three times weekly at ˜30 mcg/kg/dose. Of note, FVII inhibitor testing was negative throughout follow up. Ongoing GI evaluation with upper gastrointestinal series, endoscopy and colonoscopy twice over a span of five years, did not diagnose a source of GI bleeding. The frequency of procedural evaluations was limited due to the family's distance from the center. IDA continued and required another red blood cell transfusion at 16 years, and intravenous iron therapy at age 17 years; the persistence of GI bleeding prompted a repeat capsule endoscopy which revealed a bleeding lesion in the small bowel, beyond the ampulla of vater. A follow up endoscopy revealed a polypoid mass in the proximal jejunum and biopsy was performed. Pathologic evaluation revealed jejunal mucosa with gastric heterotopia and reactive foevolar hyperplasia, with gastric foveolar metaplasia confirmed on Alcian Blue/Periodic acid-Schiff (PAS) stain, and negative for dysplasia or malignancy (Figure 1). The patient underwent robotic assisted jejunal resection with re-anastomosis under hemostatic management of rFVIIa and intravenous tranexamic acid. Pathology revealed a 1.5 x 1 x 1 cm polyp in proximal jejunum diagnosed as polypoid gastric heterotopia, negative for dysplasia or carcinoma (Figure 2). The patient was treated with tapering doses of rFVIIa and tranexamic acid coverage through postoperative day 14 until he returned to prophylaxis with rFVIIa three times weekly. Over the following two months, rFVIIa prophylaxis was weaned and ultimately able to be discontinued without symptom recurrence over three subsequent years of follow-up. Current treatment regimen is rFVIIa and adjunctive tranexamic acid on-demand for injury related bleeds and procedures.

DISCUSSION

FVII deficiency is an autosomal recessive rare bleeding disorder with an estimated prevalence of 1 in 500,000. Diagnosis is challenging due to absence of a family history of bleeding, variable range of symptoms in affected individuals, reagent sensitivity to detect a prolonged PT, and lack of correlation of bleeding symptoms with FVII levels.[1,2] Based on data from the European Network of Rare Bleeding Disorders (EN-RBD), the International Society of Thrombosis and Hemostasis (ISTH) reclassified severe FVII deficiency as levels <10% in which major spontaneous bleeding can be noted including intracranial hemorrhage (ICH), hemarthrosis and GI bleeding.[10] ICH has been reported in 10-15% and GI bleeding in 10.4% of cases.[11] Per the Seven Treatment Evaluation Registry (STER), life-threatening bleeding warrants short term (<12 months) or long-term prophylaxis (1 to >10 years) to prevent recurrent bleeding. Prophylaxis regimens vary from frequent (three times weekly) to infrequent ([?]2 times weekly) infusions; frequent dosing is usually administered as divided doses with a total dose of 90 μg/kg/weekly and has been efficacious in preventing recurrent bleeding.[3]

Our patient presented with a prolonged clinical course with a 10 year period of episodes of acute on chronic anemia, with recurrent gastrointestinal bleeding, which is an uncommon presentation of severe FVII defi-

ciency. GI bleeding was noted in only two patients in the STER registry who presented at age 4 and 12.5 years.[3]Despite treatment with prophylaxis, persistent gastrointestinal bleeding ultimately led to identification of the bleeding source and the diagnosis of the rare condition of gastric heterotopia.

Common causes of lower GI bleeding in pediatrics include rectal fissure, hemorrhoids, rectal prolapse, juvenile polyp or vascular malformation. Gastric heterotopic tissue in the small intestine is a rare etiology for lower gastrointestinal (GI) bleeding in children. The most common and well-known example of gastric heterotopic tissue in the small bowel is a Meckel's diverticulum. The origin of HGM's is usually considered to be a lesion which originates from the primitive gut epithelium as a congenital anomaly which dissociates from the primordial stomach at the fourth week of gestation and undergoes hyperplasia over time.[12] HGM can present as mild dyspepsia, GI bleeding or intestinal obstruction,[4-9,13,14] and is best diagnosed by capsule endoscopy if in the small bowel, as upper and lower endoscopy is limited to duodenum and colon; imaging including ultrasound, CT or MRI is not sensitive for polypoid masses, and tagged scans accurately localize GI bleeding sites is only˜52% of cases.[15] Observation is recommended unless there is bleeding or other complications such as intestinal obstruction. Our patient was diagnosed by the second capsule endoscopy as documentation of small bowel pathology with capsule endoscopy is ˜45-76%.[13] There have been a handful of published case reports of pediatric patients with lower gastrointestinal bleeding due to gastric heterotopia of the small intestine[4-9,13,14] but as yet, none of these cases have included a pediatric patient with an underlying bleeding disorder, thus making this case of particular interest.

This clinical scenario emphasizes the need for a collaborative and diligent evaluation by the multispecialty team to identify the root cause for persistent GI bleeding which could be obscured by other explanations.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

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FIGURES AND LEGENDS Figures Figure 1: Histological appearance of HGM Figure 2: Polypoid Heterotopic gastric mucosa in proximal jejunum