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Intestinal Perforation in Children as an Important Differential Diagnosis of Vascular Ehlers-Danlos Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 6
Final Diagnosis: Colonic perforation secondary to vascular Ehlers Danlos Syndrome
Symptoms: Abdominal pain • constipation
Medication: —
Clinical Procedure: Loop colostomy followed by total colectomy and ileostomy
Specialty: Surgery

Objective: Unusual clinical course

Background: Ehlers-Danlos Syndrome (EDS) is a group of connective tissue disorders with heterogeneous clinical features associated with varying genetic mutations. EDS type IV, also known as vascular EDS (vEDS), is the rarest type but has fatal complications, including rupture of major vasculature and intestinal and uterine perforation. Intestinal perforation can be spontaneous or a consequence of long-standing constipation, a common symptom among patients with EDS.

Case Report: We present a case of a 6-year-old boy with the previous diagnosis of vEDS who presented with colonic perforation from a stercoral ulcer. He underwent diagnostic laparoscopy and loop colostomy, with an uneventful postoperative course. Unfortunately, he developed a second colonic perforation 14 months after the initial episode and underwent total abdominal colectomy with end ileostomy.

Conclusions: Intestinal perforation is a well-documented and devastating complication of vEDS. However, spontaneous intestinal perforation is extremely rare in a young child. Therefore, the diagnosis of vEDS should be included in the differential diagnosis if a child presents with intestinal perforation. There is no clear guideline available for surgical management of colonic perforation in patients with vEDS, but total abdominal colectomy appears to provide the best chance of preventing recurrent perforation.

MeSH Keywords: Constipation • Ehlers-Danlos Syndrome • Intestinal Perforation

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Background

Ehlers-Danlos Syndrome (EDS) is a group of connective tissue disorders associated with several identified genetic mutations and presenting with heterogeneous clinical features. Hypermobile joints, easy bruising, and fragile skin are the well-known features of EDS. Depending on the subtype, signs and symptoms can vary, including characteristic facial features of thin lips, small chin, thin nose, and large eyes, short stature, clubfoot, delayed walking, mitral valve prolapse and other solid organ prolapse, spontaneous pneumothorax, and inguinal hernia. Classical EDS results most commonly from the mutation of COL5A1 gene on chromosome 9q34.3 or COL5A2 gene on 2q32.2 and is associated with mutation of type IV collagen [1]. Vascular Ehlers-Danlos Syndrome (vEDS) is the rarest subtype, occurring in about 1 in 100 000 live births [2], but is the most morbid form of EDS. Vascular EDS is associated with a genetic defect in type III collagen formation localized to the COL3A1 gene on chromosome 2q32.2, which affects the synthesis, processing, and interaction of collagen with other proteins [3]. The inheritance pattern is predominantly autosomal dominant, although biallelic variants and *de novo* variants have been reported [4,5]. Median survival with vEDS has been reported to be 48 years, with death often occurring from rupture of major vessels or complications from intestinal perforation or uterine rupture during delivery [6,7]. Most intestinal perforations are spontaneous, with colonic perforation being the most common. However, given the rarity of the disorder, there is no clear guideline regarding the optimal management of colonic perforation in these patients.

The average age of patients with reported intestinal perforation is 22 years old. Here, we present a case of a 6-year-old white boy who suffered potentially preventable initial colonic perforation from heavy stool burden followed by a second colonic perforation. We also review the literature for optimal surgical management of colonic perforation in patients with vEDS.

Case Report

The patient was a 6-year-old white boy with a history of vEDS who presented to a local emergency room with severe generalized abdominal pain. He and his parents described generalized abdominal pain that had started 4 days previously and acutely worsened, especially with movement, on the morning of his presentation. The patient did not have nausea, vomiting, fever, melena, or hematochezia. According to his parents, he had reported to them that he had daily bowel movements including a "normal" bowel movement the previous day.

His initial presentation for vEDS occurred at age 1, when he was found to have excessive bruising and frequent epistaxis compared to his siblings, as well as delayed wound healing (Table 1). Later, he was also noted to have mild hindfoot valgus, joint weakness and hyperflexibility, and mild telecanthus, as well as bilateral lower lid ptosis. Initially, he was evaluated for inherited coagulation disorders, including von Willebrand's disease and hemophilia, but the results were normal. Given these results and his features, he then underwent genetic work up for EDS when he was 3 years old. He was found to have a COL3A1 mutation with an exon 28 skip, resulting in the lack of 18 amino acids in the pro-α1(III) chains, and was diagnosed with vEDS. He had no family members affected with EDS or any other connective tissue disorder. His previous surgical history included bilateral inguinal hernia repair and orchidopexy at 4 weeks of age, before his diagnosis, and no difficulty with bleeding or healing was noted at that time. He had taken aminocaproic acid (Amicar®) for bruising and bloody bowel movements in the past, but at presentation he was only taking daily vitamin C.

His physical exam at the referring hospital noted tachycardia, mild to moderate distress, and multiple bruises throughout his body. On the abdominal exam, he had a soft, non-distended abdomen with mild tenderness throughout, hypoactive bowel sounds, and no rebound or guarding. An abdominal plain film was unremarkable. A computed tomography (CT) scan showed small to moderate intraperitoneal free fluid with peripheral edema just below the kidneys and scattered foci of extraluminal gas along the left paracolic gutter, suggesting diffuse peritonitis (Figure 1). The appendix appeared normal in caliber, but an appendicolith was present. He was transferred to our facility for surgical management.

Upon our evaluation, he was tachycardic but normotensive and afebrile. He was awake and alert but had tenderness to percussion, pain with movement, and voluntary guarding. Although he had multiple bruises, especially along his shins, he did not have the characteristic facial features of patients with EDS, was normal in height (82th percentile) and weight (75th percentile), and had normal-appearing skin. His laboratory studies were unremarkable, without leukocytosis. However, given his radiographic finding of free air, he was taken to the operating room for urgent exploratory laparoscopy.

Initial inspection revealed a copious amount of purulent fluid with some feculent particulates throughout his abdomen, especially along the left lateral abdomen. The appendix was visualized in the right lower quadrant and appeared normal. The small bowel and ascending and transverse colons were likewise inspected laparoscopically and appeared normal. There was very hard stool in the colon from the splenic flexure to the sigmoid colon. An area of granulation tissue and inflammatory change was noted just distal to the splenic flexure. The splenic flexure and descending colon were mobilized and

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Table 1. A timeline of the patient's signs and symptoms related to the diagnosis of vEDS and associated specialties and diagnostic tests.

Age	Presentation	Specialty	Diagnostic tests	Differential diagnosis	Interventions
2 weeks	Bilateral inguinal hernia with right undescended testis	Pediatric surgery	NA	NA	Bilateral inguinal hernia repair and right orchidopexy
12 months	Right ankle pronation Excessive bruising	Pediatrics	NA	NA	observation
17 months	Excessive bruising delayed wound healing	Pediatrics	Normal CBC, ESR, INR, AST, ALT VWD screening test – marginally decreased VWF activity	VWD Hemophilia	Hematology referral
21 months	Excessive bruising	Hematology	Platelet function assay Factor IX activity, INR, PTT, fibrinogen level	Platelet function defect dysfibrinogenemia	Orthopedic referral
23 months	Hypermobile joints mild bilateral genu valgus hindfoot valgus	Orthopedic surgery, Hematology, Genetic medicine	NA	Connective tissue disorders including EDS type I or II	Physical therapy Orthotics Referral for genetic testing
3 years	Bloody stools	Hematology	None	EDS	Aminocaproic acid
	Cardiac murmur	Cardiology	TTE: tri-leaflet, functional bicuspid aortic valve	NA	Observation
	Bloody stool	Gastroenterology	NA	Constipation Juvenile polyps Vascular malformation	MiraLAX
3 years 9 months			**Genetic testing confirms COL3A1 mutation consistent with vascular EDS**		
6 years	Colonic perforation	Pediatric surgery	Abdominal x-ray, Abdominal CT		Loop colostomy
7 years 9 months	Reperforation of colon	Pediatric surgery	Abdominal CT		Total colectomy and end ileostomy

NA – not applicable; CBC – complete blood count; ESR – erythrocyte sediment rate; LFT – liver function test; INR – international normalized ratio; AST – aspartate aminotransferase; ALT – alanine aminotransferase; VWD – Von Willebrand disease; PTT – partial thromboplastin time; TTE – transthoracic echocardiogram; EDS – Ehlers-Danlos syndrome; CT – computed tomography.

exteriorized through the midline umbilical incision. His tissues were very friable and elastic. A 1-cm perforation of the colon was identified on the lateral mesenteric border of the descending colon. No other perforations were found. The compromised segment of the bowel was brought out through the abdominal wall to form a loop colostomy. Because of significant capillary bleeding, aminocaproic acid was administered intraoperatively and for 24 h postoperatively. Postoperatively, the patient's INR rose to 1.7 but normalized in 2 days after vitamin K was administered. Since mutation of COL3A1 gene has been known to alter structure and production of collagen, as well as other proteins interacting with collagen [3], and there is some evidence suggesting malabsorption in patients with EDS, we assessed albumin, pre-albumin, total protein, and c-reactive protein (CRP) levels. His albumin was 2.0 g/dL, total protein of 4.5 g/dL, and pre-albumin of 8.2 mg/dL, with normal CRP. Due to the slow return of bowel function with ongoing nausea and emesis, he was started on parenteral nutrition on postoperative day 3. He was able to tolerate oral diet slowly starting on postoperative day 6, and was able to wean off of parenteral nutrition on postoperative day 11. Before discharge, he was having stool output from the colostomy and was discharged

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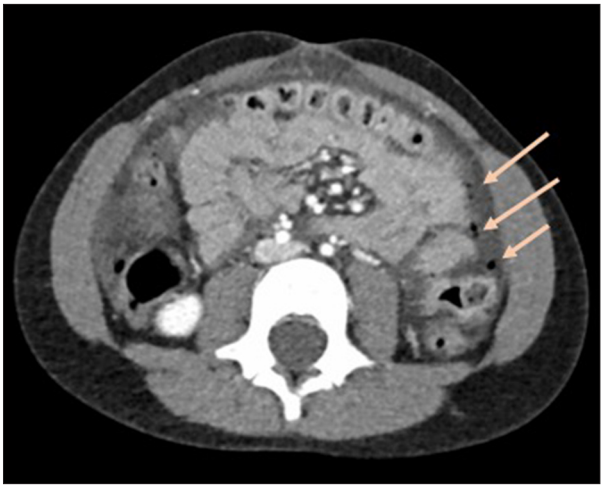

Figure 1. Axial contrast-enhanced CT of the abdomen just below the kidneys demonstrates edema in the periphery of the abdominal cavity, consistent with peritonitis. Scattered foci of extraluminal gas along the left paracolic gutter (arrows). Rounded foci of gas along ascending colon were confirmed to be within haustral folds on reformatted images.

home on postoperative day 11. His wound continued to heal without complications and he was having regular ostomy output with a daily regimen of polyethylene glycol.

After extensive discussions and second opinions, the patient and his parents were satisfied with the loop colostomy and decided not to pursue the restoration of bowel continuity given the risks of a second operation.

Fourteen months after the initial presentation, the patient presented to a local emergency room with sudden onset abdominal pain along with non-bloody, non-bilious emesis. He was afebrile but appeared to be ill, and he was tachycardic, with a leukocytosis of 18 000 cells/μL. An abdominal CT scan showed pneumoperitoneum and foci of extraluminal air most prominently near the splenic flexure where the previous perforation was. The patient was transferred to our facility for further care, and he was taken to the operating room emergently. There was no frank fecal contamination, but the diffuse cloudy purulent-appearing fluid was noted throughout the abdomen. Upon closer inspection of the colon, there was an obvious but very small perforation at the splenic flexure proximal to his loop colostomy. The entire small bowel was examined, and no other abnormality or perforation was found. Based on the discussion with the parents before the operation, the patient underwent total abdominal colectomy with end ileostomy. During the operation, he again was noted to have significant capillary bleeding, and was given tranexamic acid. The following day, he was given 1 unit of packed red blood cells for tachycardia and decrease in hemoglobin from 8.4 g/dL to 6 g/dL postoperatively. He had an unremarkable postoperative course, with the return of bowel function on postoperative day 4, and was discharged home on postoperative day 7. The patient recovered without any postoperative complications. Eleven months after the second operation, the patient and his parents elected to restore bowel continuity to improve his quality of life. Therefore, after extensive discussions and preoperative workup including consultation with a pediatric hematologist, the patient underwent laparoscopic ileostomy takedown, ileorectal anastomosis, and diverting ileostomy. Once the patient has fully recovered from this operation, the ileostomy will be taken down.

Discussion

Intestinal perforation is a well-documented and potentially life-threatening complication of vEDS. There are 203 reported cases in the English literature of spontaneous intestinal perforation in EDS. However, it is very unusual for this to happen in a young child, with the average age at the time of initial perforation being 21.8±13.5 years old. Among 149 patients whose demographics were reported, 79 patients were female and 70 patients were male. The most common site is the sigmoid colon, with 74 patients [6,8–40], but perforations of the colon other than sigmoid, small intestine, rectum, stomach, and esophagus have been reported [6,36,41,42]. Out of 154 patients with a reported survival outcome, 35 deaths were reported. Eleven patients died after the initial perforation, 4 patients died from vascular complications, 4 patients died from multiorgan failure or subsequent infection, 4 patients died from the anastomotic leak, 2 died from recurrent perforation, 1 patient died from evisceration, 1 patient died from splenic rupture, and 8 patients died from unspecified causes. Among the reported cases of "spontaneous" colonic perforation, 12 patients were documented as presenting with constipation [11,13,14,21,26,38,43,44].

Given the relative rarity of vEDS, there is no clear guideline regarding prevention and management of intestinal perforation in patients with vEDS. However, given our patient's heavy stool burden and hard stool in the left colon, the initial perforation in his case could have been compounded by stercoral ulceration. Constipation is a commonly associated gastrointestinal manifestation of EDS [45]. Reviewing our patient's medical history, he was treated for constipation starting at age 3, but treatment was discontinued. He self-reported his bowel movements to his parents and told them they were "normal" but they said they had not seen his stool for several years. Constipation is a common problem in children, and most of them do not suffer life-threatening consequences. However, in patients with a diagnosis of vEDS, given the potentially life-threatening and morbid consequences of intestinal perforation,

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it is especially important for parents and pediatricians to be aware of the potential dangers of constipation and to remain vigilant about bowel management and monitoring.

Although our patient had a relatively uncomplicated recovery after both surgeries, there are multiple reports of patients with vEDS after surgical repair of bowel perforation suffering catastrophic consequences from poor wound healing and wound dehiscence [8,10,13,21,37,46,47]. Several case reports note tissue fragility found during operations in patients with vEDS, as seen in our patient. At the time of the initial operation, he was found to have poor nutritional status and elevated INR, although he was reported to have a good appetite and to have eaten normal meals. It has been suggested that intestinal dysmotility seen in patients with EDS may lead to dilatation of the GI tract, bacterial overgrowth, and malabsorption [22]. Given the close reciprocal relationship between intestinal motility and gut microbiota and its effect on nutritional and immune regulation [48], it is possible that malnutrition is not uncommon in patients with EDS. However, the effect of low levels of albumin, pre-albumin, and protein on wound healing in this patient population has not been described. Although there is no strong evidence supporting the benefit of a high-protein diet in patients with EDS, there is some evidence suggesting daily high-dose vitamin C therapy aids wound healing when recovering from injuries [49].

In addition to poor wound healing and tissue fragility, we and others have noted easy intraoperative bleeding [21,23,40]. Although our patient did not require any transfusion, he received aminocaproic acid intraoperatively. While there are few guidelines regarding perioperative use of anti-fibrinolytic agents in patients with vEDS, some reports noted successful use of these agents, as well as desmopressin and factors VII and VIII, to control bleeding [50–53]. Moreover, studies showing platelet dysfunction and coagulation factor deficiency in patients with vEDS may further support their use when unusual bleeding is noted [54].

Unfortunately, our patient suffered a second colonic perforation 14 months after his initial perforation. Recurrent bowel perforation has been reported in 49 out of 187 patients (26.2%). The most common operation performed at the initial injury is resection or primary repair of the perforation with colostomy creation (57 out of 112 colonic perforations), with eventual colostomy reversal (44 out of 52 reported subsequent operation) or total abdominal colectomy with ileorectal anastomosis (11 out of 52). Eight patients did not undergo a reversal procedure, 7 patients had bowel continuity restored at the time of the first operation, and 3 patients had total abdominal colectomy and end ileostomy at the time of the initial operation. Out of 35 patients with reported recurrent perforation, 27 patients (77.1%) had a remaining colon. Out of 14 patients who underwent TAC either as an initial operation or subsequent operation, 2 patients (14.2%) suffered recurrent small bowel perforation. One patient who underwent TAC and ileorectal anastomosis developed anastomotic stricture and 1 patient developed anastomotic leak and fistula. Based on these reports, total abdominal colectomy appears to have the highest chance of reducing recurrent perforation, as non-colonic perforation is extremely rare. However, given some risks of anastomotic leak, bleeding, and tissue fragility, the benefits and risks of restoring intestinal continuity in pediatric patients should be considered on an individual basis.

Conclusions

Intestinal perforation is a well-documented and serious complication of vEDS. Spontaneous intestinal perforation is extremely rare in young patients; therefore, vEDS should be considered in the differential diagnosis if pediatric patients present with symptoms of intestinal perforation. If a patient with a known diagnosis of vEDS presents with signs and symptoms of intestinal obstruction, the provider should have heightened awareness of potential perforation, given the fragility of the tissues. Although there is no clear guideline regarding the optimal surgical management of intestinal perforation in patients with vEDS, based on our literature review, total abdominal colectomy may reduce potential reperforation. Decisions regarding the restoration of intestinal continuity should be made after careful discussions between the surgeon and the patient, given the potentially devastating complications reported in this population.

Conflict of interest

None.

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