

## Conservative management of small bowel perforation in Ehlers-Danlos syndrome type IV

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### Abstract

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders caused by collagen synthesis defects. EDS type IV, or vascular EDS, is caused by loss-of-function mutations in the type III pro-collagen gene (*COL3A1*). Common complications of EDS type IV include gastrointestinal bleeding and bowel perforations, posing diagnostic and therapeutic dilemmas for both surgeons and gastroenterologists. Here, we describe a complicated case of EDS type IV in a 35-year-old caucasian female who presented with overt gastrointestinal bleeding. The patient had a prior history of spontaneous colonic perforation, and an uncomplicated upper endoscopy was performed. A careful ileoscopy was terminated early due to tachycardia and severe abdominal pain, and a subsequent computed tomography scan confirmed the diagnosis of ileal perforation. The patient was managed conservatively, and demonstrated daily improvement. At the time of hospital discharge, no further episodes of gastrointestinal blood loss had occurred. This case highlights the benefit of conservative management for EDS patients with gastrointestinal hemorrhage. It is recommended that surgical treatment

should be reserved for patients who fail conservative treatment or in cases of hemodynamic instability. Finally, this case demonstrates the necessity for a higher threshold of operative or endoscopic interventions in EDS type IV patients.

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**Key words:** Type-IV Ehlers-Danlos syndrome; Gastrointestinal hemorrhage; Bowel perforation; Conservative management; Non-operative; *COL3A1*; Connective tissue disorder

**Core tip:** Gastrointestinal bleeding and bowel perforations are known complications of Ehlers-Danlos syndrome (EDS) type IV. Tissue fragility and hemorrhage tendency pose diagnostic as well as therapeutic dilemmas for both surgeons and gastroenterologists. We performed an upper gastrointestinal endoscopy and ileoscopy in a bleeding patient with history of EDS type IV. The upper endoscopy procedure was uneventful with minimal air used for luminal distension. A small bowel perforation was found. This case highlights the tissue fragility and serosal tears that can occur upon slight handling. Conservative management proved the best course of action.

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### INTRODUCTION

Ehlers-Danlos syndrome (EDS) comprises of a heterogeneous family of inherited connective tissue disorders

known for its features of fragile, hyperextensible skin, hypermobile joints, and tissue fragility. EDS type IV, also known as vascular EDS, is an inherited connective tissue disorder caused by loss-of-function mutations of the pro- $\alpha$ -1 chains of type III pro-collagen (*COL3A1*). Vascular EDS causes severe fragility of connective tissues with increased risk of arterial and gastrointestinal (GI) rupture and complications during surgical and radiological interventions. Spontaneous vascular dissection, GI perforation, or organ rupture are the presenting signs in the majority of adults identified to have EDS type IV<sup>[1-3]</sup>. Diagnostic criteria for EDS type IV includes reduced levels of type III collagen protein or identification of the *COL3A1* gene along with two of the following diagnostic criteria: (1) easy bruising; (2) thin skin with visible veins; (3) characteristic facial features (in some individuals); and (4) rupture of arteries, uterus, or intestines<sup>[3]</sup>. These aberrations in collagen processing correlate with reduced strength of the vascular and hollow organ soft tissue, abnormalities of the large and small bowel architecture including abrupt changes in the caliber of the lamina muscularis, secondary diverticula formation, and strongly reduced expression of collagen 3<sup>[4]</sup>.

We report a complicated clinical course of a 35-year-old female with EDS type IV and multiple complications (including spontaneous colonic perforation with ileostomy, spontaneous pneumothorax, carotid artery dissection, and multiple orthopedic joint surgeries), who presented with overt GI bleeding.

## CASE REPORT

A 35-year-old Caucasian female with history of EDS type-IV was transferred to our institution for evaluation of overt GI bleeding. She was diagnosed with classical vascular EDS type-IV at age 16 with easy bruising, thin skin with visible veins, characteristic facial features, and positive family history of EDS in her mother and grandmother. She had a stroke secondary to carotid artery dissection at age 17, ruptured ovarian cyst at 19, postpartum spontaneous sigmoid perforation at 23, spontaneous pneumothorax at 26, and multiple orthopedic surgeries for joint dislocations. The spontaneous colonic perforation at age 23 occurred during labor and required colon resection with resultant ileostomy. She presented to an outside institution with sharp abdominal pain, vomiting, and bright red blood present in the ileostomy pouch. The patient was unable to keep food down and had had several episodes of vomiting over the course of the previous 24 h. She was hemodynamically stable and in no acute distress, but laboratory results revealed hemoglobin of 12 g/dL, which subsequently dropped to 6.1 g/dL, blood urea nitrogen of 60 mg/dL and creatinine of 3.1 mg/dL. An initial abdominal computed tomography (CT) scan was positive for some abdominal distension but no signs of intestinal obstruction or perforation. The subsequent upper endoscopy was normal, and no bleeding site was identified. The patient was then transferred to

our institution's medical intensive care unit due to the unknown source of the GI bleeding and to manage the particular complexity of her case.

The gastroenterology team determined that the patient was actively bleeding into her ileostomy pouch. Considering the worsening renal parameters, all further imaging studies were suspended. After weighing the risks and benefits with the patient, in view of her history of EDS and spontaneous bowel perforations, an upper GI endoscopy and possible ileoscopy was planned. The upper endoscopy was performed safely with minimal luminal distension, and no evidence of active bleeding was found. At the time of the upper endoscopy, however, fresh blood emerged from the ileostomy; this issue was addressed by performing an additional ileoscopy using the utmost care and following the same principles as above. However, after the scope was advanced less than 10 cm, the patient developed tachycardia and severe abdominal pain, which prompted early termination of the procedure. Abdominal CT scan revealed free air and extravasation of oral contrast into the peritoneum, confirming the diagnosis of ileal perforation. CT angiography was negative for extravasation of parenteral contrast. Following surgical consultation about the patient's prior abdominal surgical interventions and complexity of the case, and discussion with the patient, a conservative management procedure was designed to address the ileal perforation. The patient was treated with nasogastric suction, antibiotics, and blood transfusions as needed, and total parental nutrition and bowel rest. The patient demonstrated daily improvement and spontaneous resolution of the bleeding. After four days, the patient was able to tolerate oral intake. On day 7 of hospitalization, the patient was discharged in stable condition. Ultimately, no etiology for GI hemorrhage was found.

## DISCUSSION

Ehlers-Danlos syndrome is a heterogeneous group of hereditary disorders of connective tissue, whose prevalence is estimated between 1/10000 and 1/25000, with no ethnic predisposition<sup>[5]</sup>. According to the Villefranche classification, there are 6 clinical types<sup>[6]</sup>, with type IV, or vascular EDS, accounting for about 5%-10% of cases<sup>[7]</sup>. The symptoms of each EDS type differs based on the causative gene and inheritance pattern. As a result, the genetic heterogeneity of EDS is very strong. Moreover, each clinical entity of EDS needs to be considered as a different disease that results from different causative gene based on clinical symptoms and family history (Table 1).

Based on Villefranche diagnostic criteria (Table 2)<sup>[6]</sup>, the combination of any two of the major diagnostic criteria should have a high specificity for vascular EDS and further testing is strongly recommended to confirm the diagnosis. The presence of one or more minor criteria supports the diagnosis of vascular EDS but is not sufficient to establish the diagnosis<sup>[5]</sup>. Vascular EDS is

**Table 1** Classification of Ehlers-Danlos syndrome

New classification, Villefranche (1997)	Former classification Berlin (1988)	MIM number <sup>1</sup>	Inheritance	Biochemical defects
Classic	Type I	130000	AD	COL5A1
	Type II	130010		COL5A2
Hypermobility	Type III	130020	AD	Unknown
Vascular	Type IV	130050	AD	COL3A1
Kyphoscoliosis	Type VI	225400	AR	Lysyl hydroxylase
Arthrochalasia	VIIA, VII B	130060	AD	COL1A1, COL1A2
Dermatosporaxis	VII C	225410	AR	Type I collagen N-peptidase
Others	V	305200	XR	
	VIII	130800	AD	
	X	225310	AR	
	XI	147900	AD	

It's adapted from Beighton *et al*<sup>[6]</sup>, Wenstrup *et al*<sup>[17]</sup> and Steinmann *et al*<sup>[18]</sup>. <sup>1</sup>The MIM number is a numerical assignment for inherited diseases, genes and functional segments of DNA. AD: Autosomal dominant; AR: Autosomal recessive; XR: X-linked recessive.

**Table 2** Vascular Ehlers-Danlos syndrome: Villefranche diagnostic criteria

Major diagnostic criteria	Minor diagnostic criteria
Arterial, digestive or uterine fragility or rupture	Positive family history
Thin, translucent skin	Sudden death in a close relative
Extensive bruising	Acrogeria
Characteristic facial appearance	Hypermobility of small joints
	Tendon and muscle rupture
	Talipes equinovarus (clubfoot)
	Early onset varicose veins
	Spontaneous pneumo or hemothorax

It's adapted from Germain *et al*<sup>[9]</sup> and Beighton *et al*<sup>[6]</sup>.

an autosomal dominant inherited disease caused by one allele mutation of the *COL3A1* gene, which encodes type III procollagen. This mutation results in qualitative and quantitative abnormalities of mature type III collagen. Systemic arteries that are rich in type III collagen may undergo dissection, aneurysm, or rupture. In addition to vascular complications, ruptures of hollow organs that are rich in type III collagen, *i.e.*, intestines and uterus, are also characteristic<sup>[8]</sup>. Pneumothorax is also a frequent complication, as the pleura also contains a high degree of type III collagen. While rare in childhood, EDS type IV complications occur in approximately 25% of 20-year-old diagnosed with vascular EDS<sup>[3]</sup>. Further, by age 40, 80% of diagnosed individuals have no less than one complication<sup>[9]</sup>. The median age of death is estimated to be 50 years, with the most common cause of death being arterial rupture. Pepin *et al*<sup>[11]</sup> reported that the likelihood of death was greatest after organ rupture (45%) and least after bowel rupture (2%). In view of the multitude of clinical presentations, symptoms, natural history and prognosis, EDS type IV should be assessed separately within the group of EDS.

Understanding the GI manifestations of EDS type IV is necessary for both surgeons and gastroenterologists. The two main complications are perforation and bleeding. *In vitro* electromyographic studies of the colonic tissue suggest a possible link between abnormal myogenic

activity and colonic perforations<sup>[10]</sup>. Of the perforations, most occur within the colon, more specifically the recto-sigmoid junction. Leake *et al*<sup>[11]</sup> reported that bleeding into the wall of the gut might precede local necrosis and subsequent perforation. This hypothesis was supported by microscopy findings of submucosal edema in small bowel sections, vascular dilatation with focal hemorrhage, perforation, and organized inflammation in the serosal surface<sup>[11]</sup>.

Our case posed an endoscopic and surgical dilemma due to the complicated history of the patient. There is very limited data available concerning the safety of GI procedures in patients with EDS. Although some reports suggest avoiding elective procedures such as endoscopy, colonoscopy, angiography, nasogastric tube placement, and enema administration due to perforation or dissection<sup>[12,13]</sup>, there are also case reports of performing upper endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) safely<sup>[14,15]</sup>. In our patient, who had overt bleeding with significant hemodynamic instability, we believed that potential risk of ileoscopy was justified. Given the fact that our index case was a classical EDS type IV with complicated surgeries in the past, safety and caution were our paramount concerns. While the rarity of this syndrome precludes an evidence-based approach to management, previous cases served as a guide in the clinical care of this patient. We performed upper GI endoscopy uneventfully and in spite of using minimal air for luminal distension; the patient developed tachycardia and severe abdominal pain during ileoscopy, prompting early termination of the procedure. Abdominal CT scan revealed free air and extravasation of oral contrast into the peritoneum, confirming the diagnosis of ileal perforation. These events and findings served to emphasize the tissue fragility in EDS patients due to the collagen deficiency and the high risk of serosal tears that can occur upon minimal handling, as noted by many operating surgeons. For our patient, conservative care proved to be the best course of action. The overt bleeding was self-limited and the perforation was managed with bowel rest induced by antibiotics and total parental nutrition (Table 3).

In conclusion, our case highlights the clinical dilem-

**Table 3** Endoscopic procedures reported in Ehlers-Danlos syndrome patients

Ref.	Age/sex	Procedure	Outcome/treatment
Hawk <i>et al</i> <sup>[15]</sup>	41/F	ERCP Sphincterotomy	No complication Non-pulsatile bleeding (conservative management)
Kahn <i>et al</i> <sup>[19]</sup>	45/F	ERCP	Bile duct rupture (conservative management)
Rana <i>et al</i> <sup>[20]</sup>	33/M	Colonoscopy	Perforation (Surgical intervention)
Baichi <i>et al</i> <sup>[14]</sup>	51/F	Upper endoscopy	No complication
Present case	35/F	Upper endoscopy Ileoscopy	No complication Perforation (conservative management)

F: Female; M: Male; ERCP: Endoscopic retrograde cholangiopancreatography.

mas in the management of GI complications of EDS type IV and stresses the importance of conservative management. Surgical interventions should be reserved for hemodynamically/clinically unstable patients who fail to respond to supportive measures. Colonoscopy or small bowel enteroscopy carry a higher risk when compared to upper GI endoscopy, which can be safely performed. Angiography can be associated with arterial dissection<sup>[16]</sup>. Endoscopists should be prepared for bleeding and perforations in these high-risk patients with appropriate pre-endoscopic surgical back up.

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