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Spontaneous Colon Perforations Associated with a Vascular Type of Ehlers-Danlos Syndrome

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Key Words
Spontaneous colonic perforations · Ehlers-Danlos syndrome · Connective tissue

Abstract
Ehlers-Danlos syndrome, vascular type (vEDS) (MIM #130050) is an autosomal dominant disorder caused by mutation in the type III collagen gene, *COL3A1*, leading to fragility of blood vessels, bowel and uterus that leads to spontaneous rupture. We report a previously undiagnosed vEDS patient with bowel complications. A 20-year-old female patient was referred to our hospital with abdominal pain. Computed tomography showed notable dilatation of the sigmoid colon with intraperitoneal fluid. Laparotomy revealed dilatation of the sigmoid colon, breakdown of serosa and muscularis propria of the sigmoid colon with impending perforation, and intra-abdominal hemorrhage caused by breakdown of the mesenterium. Resection of the sigmoid colon with Hartmann's pouch and an end colostomy were performed. Physical examination showed joint hypermobility, translucent skin with venous prominence and facial structure abnormalities. Genetic analysis using cDNA extracted from the patient's fibroblasts by reverse transcriptase polymerase chain reaction direct sequencing showed a missense mutation within the triple helix region of *COL3A1* (c.2150 G>A; Gly717Asp).

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Introduction

Ehlers-Danlos syndrome (EDS) is a clinically, genetically and biochemically heterogeneous group of inherited connective tissue disorders. The major manifestations of EDS are skin fragility, skin hyperextensibility and joint hypermobility [1, 2]. The disorder was first reported in 1668 [3], but it was not until the early 1900s that the characteristics of the syndrome were described by Ehlers [4] and Danlos [5]. Six types of EDS have been described on the basis of clinical, genetic and/or biochemical differences [6]. EDS is now considered a heterogeneous group of disorders, the most lethal of which is the vascular type (vEDS), formerly called type IV EDS (MIM #130050) [7]. It is caused mainly by glycine substitution mutation in the triple helix region of the type III collagen gene (*COL3A1:* MIM #120180), leading to extreme fragility of blood vessels, bowel and uterus and thus leading to spontaneous rupture [8]. The following is an account of a previously undiagnosed vEDS patient with bowel complications who was managed at our institution.

Case Report

A 20-year-old female patient was referred to our hospital with abdominal pain, nausea and vomiting. Physical examination revealed mild hypotension and a distended, tender abdomen. Her vital signs were a temperature of 37.9°C, a heart rate of 98 beats per minute and a blood pressure of 97/49 mm Hg. Laboratory studies found a white blood cell count of 12,250/mm^3. A computed tomography scan showed notable dilatation of the sigmoid colon with intraperitoneal fluid (fig. 1). An emergent laparotomy revealed dilatation of the sigmoid colon, breakdown of the serosa and muscularis propria of the sigmoid colon with impending perforation, and intra-abdominal hemorrhage caused by breakdown of the mesenterium of the sigmoid colon (fig. 2). As the rest of the intestine was normal, resection of the sigmoid colon with Hartmann's pouch and an end colostomy were performed. The macroscopic appearance of the resected colon showed strong alteration of the bowel wall, with some areas showing a complete lack of the lamina muscularis propria (fig. 3a). Histological findings of the resected specimen showed mucosal necrosis with leukocytic infiltration (fig. 3b). The postoperative course was uneventful, and the patient was discharged from the hospital 1 month after entry. Careful physical examination showed joint hypermobility, translucent skin with venous prominence and facial structure abnormalities (crooked nose and large eyes). Because of the uncommon intraoperative and clinical findings, there was a high suspicion of connective tissue disorder. Genetic analysis using cDNA extracted from the patient's fibroblasts by a reverse transcriptase polymerase chain reaction direct sequencing method showed a nucleotide change at c.2150 G>A on exon 32 (GenBank ID: NM_000090.3) as the reference. This nucleotide change resulted in the amino acid change of glycine at position 717 to aspartate within the triple helix region of *COL3A1* (Gly717Asp), which confirmed a diagnosis of vEDS (fig. 4). No specific therapy has been shown to delay or prevent further complications. Lifelong close follow-up should be continued in this patient.

Discussion

EDS comprises a group of hereditary connective tissue disorders with different genetic backgrounds and heterogeneous clinical features. The overall incidence is 1 in 150,000 [6]. Common to all of these types is an underlying defect in either collagen production or

processing. Though uncommon, vEDS is the most severe type. It accounts for 3–6% of all EDS cases [9]. The disease is caused by heterozygous germline mutations in the type III procollagen gene *(COL3A1)* [10–13]. The diagnosis of vEDS depends on the combination of clinical manifestations, family history and the demonstration of collagen type III qualitative and/or quantitative defects. As type III collagen is most abundant in vessels and hollow organ soft tissue, defects in type III collagen production result in vascular and hollow organ complications [14]. The clinical features of vEDS include prematurity, low birth weight, congenital dislocation of the hips, club feet, easy bruising, thin and translucent skin displaying prominent venous patterns, hypermobility of small joints, constipation, arterial aneurysms and ruptures, spontaneous pneumothorax and colonic perforations [15].

Since skin and joint manifestations are less prominent than in the other types of EDS, the diagnosis of vEDS often is missed until the patient presents with a major complication such as spontaneous arterial or bowel rupture [16]. The first complication occurs by age 20 in 25% of cases, and in 80% of cases by age 40 [16]. As the most common complications of the disease are in the gastrointestinal tract and vascular systems, surgical approaches are troublesome for surgical teams [17]. Early diagnosis of peritonitis is critical so that an appropriate therapy can be instituted expeditiously, including correction of fluid and electrolyte abnormalities, institution of antibiotic therapy and surgical repair of the underlying lesion [18]. As the tissues are extremely fragile, it is essential to avoid invasive techniques. Sutures tend to tear them out, bowel walls are extremely friable and anastomosis is arduous. Small vessels are equally fragile, occasioning difficult hemostasis, oozing and hematoma formation [19–21].

Although spontaneous bowel perforation has been reported in the literature with more than 50 cases documented, the surgical management and outcomes of this manifestation of vEDS have varied considerably. In a retrospective review of the literature, 41 colonic perforations were reported, 80% of which were in the sigmoid colon. Of these patients, 66% were treated with resection and diversion, with 18 eventually undergoing restoration of intestinal continuity. A total of 55.6% of these patients suffered a re-perforation, some with three or four perforations. Eleven patients underwent total abdominal colectomy, 7 with ileoproctostomy [22]. The treatment of bowel perforation in these patients is controversial. Different surgical procedures have been advocated, but there is no large serial study currently available to demonstrate the superiority of any one option.

Women with vEDS have an increased risk of complications of pregnancy as well as a 50% risk of having an affected child [14]. Major complications of pregnancy can occur in the antenatal period, during labor and delivery, and postpartum. A maternal mortality of up to 25% has been reported due to rupture of the artery, bowel or uterus [1]. The complications of pregnancy include rupture of the bowel, aorta, vena cava or uterus, vaginal laceration, postpartum uterine hemorrhage, varicose veins, uterine and/or bladder prolapse, joint laxity, abdominal herniation and wound dehiscence [23]. These patients who become pregnant should be considered at high risk and should receive regular follow-up at specialized centers.

No specific therapy has been shown to delay or prevent further complications [24], and the long-term natural history of this anatomy in vEDS is confrontational. However, knowledge of the disease can influence surgical procedures and genetic counseling. Lifelong close follow-up should be continued in these patients.

Disclosure Statement

Akira Yoneda has no conflict of interest.

Author Contributions

Kazuya Okada, Hitoshi Okubo, Mitsutoshi Matsuo and Hiroki Kishikawa contributed equally to this work; Banyar Than Naing, Atsushi Watanabe and Takashi Shimada contributed new analytic tools; Akira Yoneda wrote the paper.

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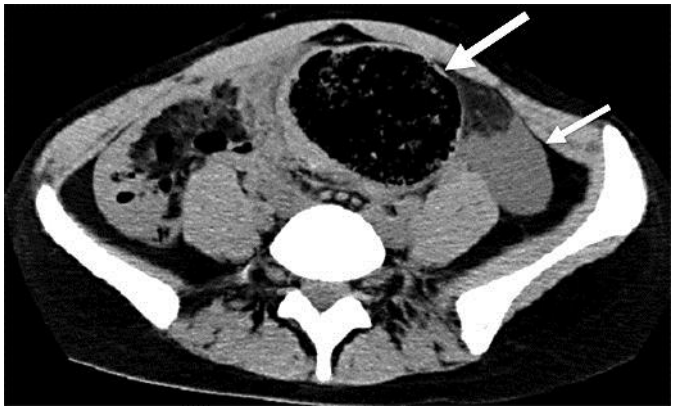

Fig. 1. Computed tomography scan of the abdomen displayed notable dilatation of the sigmoid colon (large arrow) with intraperitoneal fluid (small arrow).

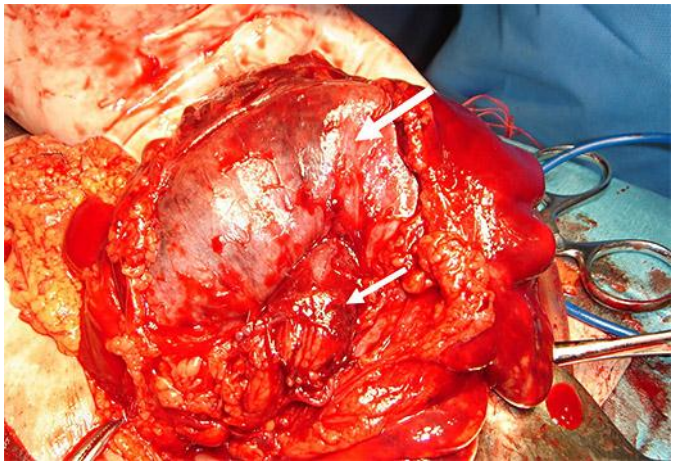

Fig. 2. Operative findings showed dilatation of the sigmoid colon, breakdown of serosa and muscularis propria of the sigmoid colon with impending perforation (large arrow), and intra-abdominal hemorrhage caused by breakdown of the mesenterium of the sigmoid colon (small arrow).

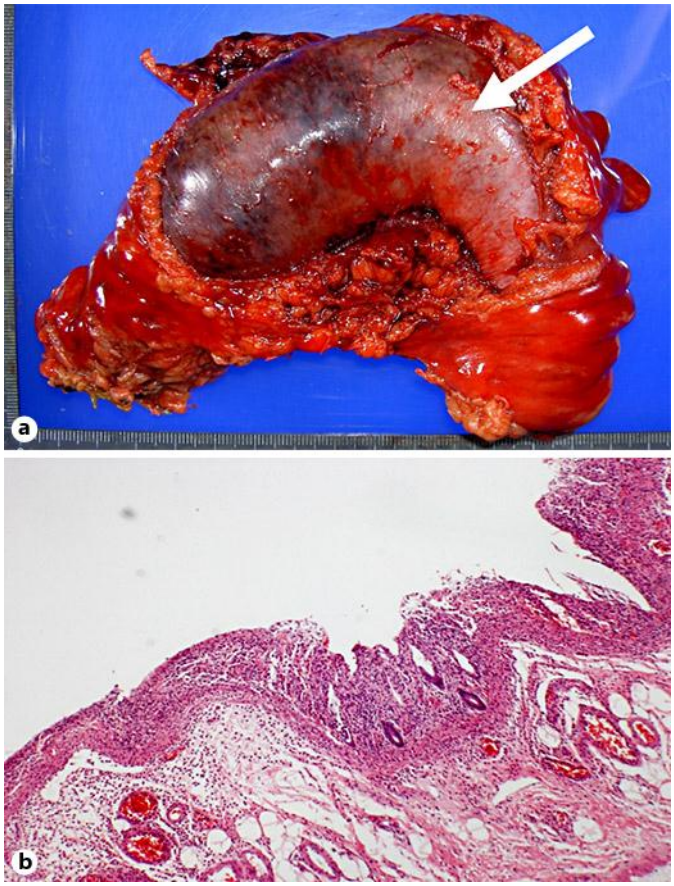

Fig. 3. **a** Macroscopic appearance of the resected colon. The architecture of the bowel wall is strongly altered, with some areas showing a complete lack of the lamina muscularis propria (arrow). **b** Histological findings of the resected specimen showed mucosal necrosis with leukocytic infiltration (HE, ×100).

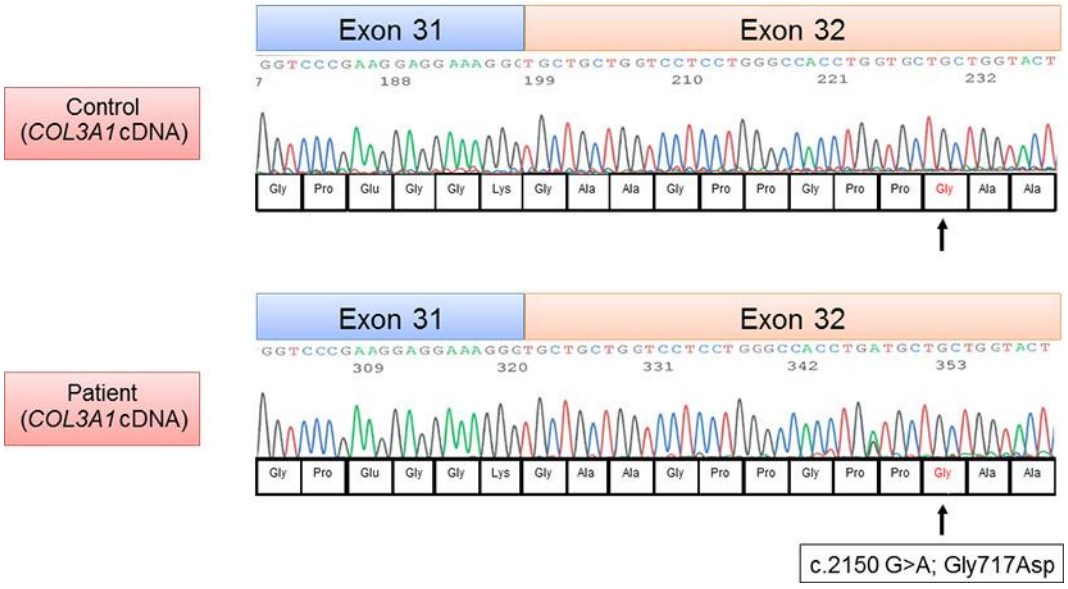

Fig. 4. *COL3A1* gene mutation detected using cDNA extracted from the patient's fibroblasts. A heterozygous mutation was found within exon 32 of the *COL3A1* gene at c.2150 G>A, leading to Gly717Asp (arrow) (GenBank ID: NM_000090.3 as the reference).