Ehlers–Danlos Syndrome Type IV (Vascular): Gastrointestinal Features

29

Liam Zakko

Ehlers–Danlos syndrome is a group of inherited connective tissue disorders caused by a defect in the synthesis of collagen. Severity of the disease depends on the mutation inherited. The disorder occurs in approximately one in 5,000 births [1].

Gastrointestinal (GI) signs and findings include [2, 3]:

- Epigastric discomfort, hematemesis, melena, abdominal pain, constipation, peritoneal signs
- In general, Ehlers–Danlos Syndrome is characterized by skin hyperextensibility, joint hypermobility, and wound-healing abnormalities
- Type IV (vascular) Ehlers–Danlos is most often associated with GI pathology
- Type IV has less skin hyperextensibility; major skin finding is very translucent skin with easily visible veins (particularly on the chest); thin faces, pinched nose, and large eyes
- Common GI pathology includes:
  - Esophagus: hiatal hernia, esophageal diverticula, macroesophagus, esophageal rupture with forceful vomiting
  - Gastric: volvulus from adhesions, severe peptic ulcer disease due to mucosal fragility
  - Small intestine: perforation due to studded diverticula on the mesentery border, megaduodenum leading to bacterial overgrowth, intramural hematoma, and bleeding
  - Colon (see Fig. 29.1) [4]: perforation (particularly type IV disease); rectal prolapse

The pathogenesis lies in the specific collagen formation defect [3, 5]:

- Type IV: autosomal dominant disease with mutation in *COL3A1* gene, which codes for type III procollagen; patients have quantitative and/or qualitative defects in type III collagen (*see* Fig. 29.2) [4].
- Type I, II: abnormalities of type V and type I collagen inherited in an autosomal dominant pattern; worse clinical disease with type I
- Type III; mutation in *COL3A1* and/or *TNXB* genes leading to small joint hyperextensibility (usually mild clinical disease) in an autosomal dominant or autosomal recessive pattern

The pathology may show typical features [3, 5]:

- Decreased dermal thickness with increased lamellae around dermal blood vessels
- Increased elastic fibers; finer (decreased diameter) and more loosely organized collagen
- Fibroblasts have dilated endoplasmic reticulum

The diagnosis is made by considering [1–3, 5, 6]:

- Family history of Type IV Ehlers–Danlos
- Four main clinical findings: rupture of blood vessels or internal organs (arterial rupture, intestinal rupture, uterine rupture during pregnancy); striking facial appearance (thin lips/philtrum, small chin, thin nose, large eyes); easy bruising; translucent skin
- Also see: acrogeria, hypermobility of small joints, early onset varicose veins, tendon/muscle rupture, arteriovenous carotid/cavernous sinus fistula, pneumothorax, chronic joint dislocations, congenital dislocation of the hips, talipes equinovarum, gingival recession
- Cultures of fibroblasts show abnormal type III collagen production
- Genetic testing can reveal *COL3A1* mutation
- Type I–III Ehlers–Danlos based on clinical findings of skin hyperextensibility, joint hypermobility, and wound healing abnormalities

Differential diagnosis of Ehlers–Danlos should include [1–3]:

- Neoplasm
- Diverticulitis
- Inflammatory bowel disease
- Colitis
- Steroid use

L. Zakko (✉)
Yale Department of Internal Medicine, Yale New Haven Hospital, 20 Yale Street New Haven, CT 06510, USA
e-mail: liam.zakko@yale.edu

G.Y. Wu et al. (eds.), *Atlas of Dermatological Manifestations of Gastrointestinal Disease*,
DOI 10.1007/978-1-4614-6191-3_29, © Springer Science+Business Media New York 2013

There is no cure for this disease but treatment includes [1–3]:

- Symptomatic treatment for GI conditions: H2-antagonists/proton pump inhibitors and antibiotics for those with *Helicobacter pylori* to prevent gastric ulcers; laxatives to prevent constipation that often leads to perforations requiring surgical treatments; anastomosis can lead to recurrent perforation and breakdown due to weak fibrous tissue (therefore, perforation may require colectomy); surgery is also often complicated by wound dehiscence and infection.

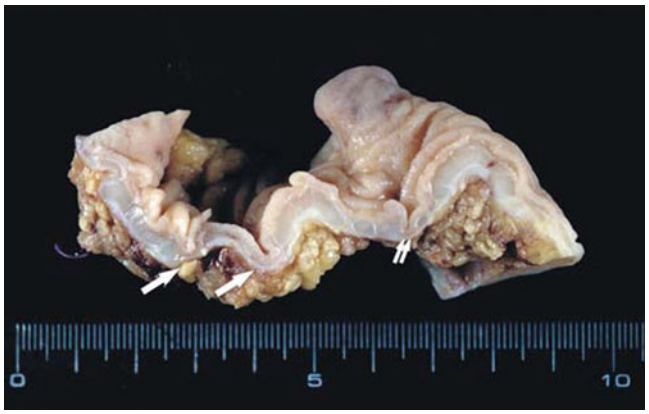

Fig. 29.1 Gross appearance of the resected colon from a patient with Ehlers–Danlos syndrome. The muscularis propria has abrupt changes in thickness, and in some areas, it is practically absent (*large arrows*). In some areas, diverticula penetrating through the muscularis propria can be seen (*small arrows*) (Reprinted from Bläker et al. [4]; with permission)

References

1. Malfait F, Wenstrup RJ, Paepe AD. Clinical and genetic aspects of Ehlers–Danlos syndrome, classic type. Genet Med. 2010;12:597–605.
2. Solomon JA, Abrams L, Lichtenstein GR. GI manifestations of Ehlers–Danlos syndrome. Am J Gastroenterol. 1996;91:2282–8.
3. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers–Danlos syndrome type IV, the vascular type. N Eng J Med. 2000;342:673–80.
4. Bläker H, Funke B, Hausser I, et al. Pathology of the large intestine in patients with vascular type Ehlers-Danlos syndrome. Virchows Arch. 2007;450:713–7.
5. Smith LT, Schwarze U, Goldstein J, Byers PH. Mutations in the COL3A1 gene results in Ehlers–Danlos syndrome type IV and alterations in the size and distribution of the major collage fibrils of the dermis. J Invest Dermatol. 1997;108:241–7.
6. Ward SK, Roenigk HH, Gordon KB. Dermatological manifestations of gastroenterological disorders. Gastroenterol Clin North Am. 1998;27:624–5.
7. Watanabe A, Shimada T. The vascular type of Ehlers–Danlos syndrome. J Nippon Med Sch. 2008;75:254–61.

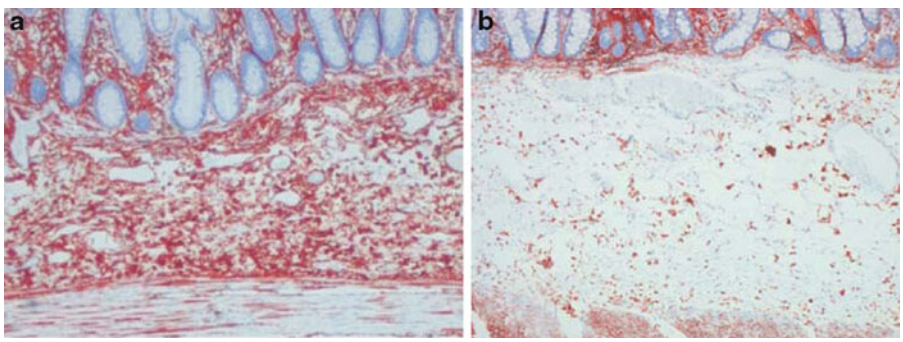

Fig. 29.2 A photomicrograph of colon sections from a patient with Ehlers–Danlos syndrome Type IV (**a**). Immunohistochemical staining for collagen type III is markedly decreased compared to a normal control specimen (**b**) (Reprinted from Bläker et al. [4]; with permission)