GI Manifestations of Ehlers-Danlos Syndrome.

Jeffrey A. Solomon, M.D., Lisa Abrams, M.D., and Gary R. Lichtenstein, M.D.

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Ehlers-Danlos syndrome (EDS) is an inherited disorder of connective tissue that is distinguished not only by the triad of skin hyperextensibility, articular hypermobility, and tissue fragility but also by its heterogeneity on clinical, genetic, and biochemical grounds. The phenotypical variance that characterizes this syndrome often makes its recognition difficult, and failure to recognize the disease despite a classic course is not uncommon. Diagnosis is paramount, however, so life-threatening associations can be searched for and unique principles of management can be instituted. Patients are prone to GI catastrophes such as perforation and massive bleeding which can be compounded by grave surgical and vascular complications. A thorough knowledge of the GI manifestations of EDS and their management is mandatory to prevent unnecessary morbidity and mortality.

INTRODUCTION

In 1899, Edvard Ehlers reported a patient who demonstrated a constellation of symptoms including recurrent hematomas, lax digits, and extensible skin. Nine years later; Henri-Alexandre Danlos associated posttraumatic tumors with the manifestations presented by Ehlers. The term Ehlers-Danlos syndrome (EDS) currently describes a group of connective tissue disorders distinguished not only by the triad of skin hyperextensibility, articular hypermobility, and tissue fragility but also by its heterogeneity on clinical, genetic, and biochemical grounds. The Berlin nosology currently designates nine subtypes of the Ehlers-Danlos syndrome (1, 2). Clinical differences have defined six types, and biochemical analysis has added three more. The heterogeneity and phenotypical variability of Ehlers-Danlos syndrome sometimes makes its recognition challenging. Failure to recognize the hallmark signs of the syndrome despite a classic course is not uncommon. Identification of the syndrome is paramount, however, because of its potentially life-threatening associations and unique principles of management. Ehlers-Danlos syndrome is often thought of as a rare entity and its true incidence is unknown, but it has become a more common finding because of recognition of milder cases (4). Patients with this hereditary genetic disorder are prone to GI catastrophes that can be compounded by grave surgical and vascular complications. A thorough knowledge of

the GI manifestations of Ehlers-Danlos and their management is mandatory to prevent unnecessary morbidity and mortality.

COLLAGEN PHYSIOLOGY

There are five different types of collagen in humans that are distinguished by the combination and composition of their three subunits. Type I collagen comprises approximately 90% of total body collagen and is found in fibrous connective tissues such as tendons, ligaments, and bone. Type II collagen is a constituent of hyaline cartilage, and Type III can be found in highly cellular structures such as liver and blood vessels. The remaining types, IV and V, are located in the basement membrane and in connective tissue, respectively. Collagen molecules consist of three helical chains of hydrogen bonded to each other to form a superhelical cable. Procollagen is the intracellular precursor of collagen and differs from collagen in that the individual monomers contain propeptides at their amino and carboxy terminal ends. Before procollagen molecules are secreted from cells, some proline and lysine residues are hydroxylated by propyl hydroxylase, and lysyl hydroxylase and amino groups may be oxidized by lysyl oxidase. Ultimately, the stability of collagen fibers depends on inter? and intra? chain interactions that are stabilized by these reactions. Once procollagen is secreted, it is acted on by procollagen peptidase, which removes propeptides and permits the orderly formation of collagen fibers. The synthesis of competent collagen fibers therefore requires both the correct primary structure and critical posttranslational modifications (5-7).

The molecular biology of EDS highlights its heterogeneity. Historical abnormalities and patterns of inheritance can be defined for EDS types I, II, and III, but no specific genetic or enzymatic abnormalities have been identified. In other types of EDS, defects have been show to exist at several steps of posttranslational modification needed to form competent collagen fibers. Type IV EDS is thought to result from structural defects in the pro-I III collagen chain, which results in reduced or abnormal secretion of type III collagen. Type V EDS is due to a defect in lysyl oxidase, and Type VI EDS has been traced to a deficiency of lysyl hydroxylase, both of which result in ineffective intra? and interchain bond formation (3). Type VII is due to a defect in procollagen peptidase, which causes collagen fiber formation to become disorganized and weakened. (8).

DIAGNOSIS

The diagnosis of Ehlers-Danlos syndrome is based on clinical presentation, family pedigree analysis, and, when known, demonstration of specific biochemical or genetic

defects. Correct diagnosis and classification is important because of different natural histories and modes of inheritance. Despite recent advances, considerable overlap exists, and it is not always possible to classify particular individuals. Although mush phenotypical variation exists, each type of EDS displays the three cardinal features of hyperextensible skin, hypermobile joints, and tissue fragility to some degree (1). Recognition of the disease on clinical grounds can be difficult because skin elasticity and joint mobility are graded, subjective traits. Physical examination, however, remains the initial step in diagnosis of EDS. Findings include skin that is hyperextensible and velvety in texture, which has been likened to the feeling of a wet chamois. Tissue fragility results in "fish mouth" wounds after minor trauma. "Cigarette paper" scars may result because of poor wound healing. Subcutaneous spheroids, which may be calcified, and pseudotumors can sometimes be found. Typical facial features and body habitus have also been documented (Table 1). Attempts to quantify joint mobility have been made on the basis of five maneuvers that involve passive dorsiflexion of the fifth finger beyond 90?, passive apposition of the thumb to the flexor aspect of the forearm, hyperextension of the elbows and knees beyond 10?, and flexion of the trunk so that the palms rest on the floor. Pedigree analysis may be helpful to classify patients who are thought to have EDS because inheritance patterns differ between types (1). Ultimately, the diagnosis may rest on demonstrating the presence of known molecular defects in the individual. In cases in which the biomolecular defect is not known, quantification of collegen and ultrastructure analysis may be helpful (10).

GI MANIFESTATIONS AND MANAGEMENT

Oral and dental manifestations can occur to some extent in all variants but are most common and severe in EDS VIII (periodontal type). Patients suffer from breakdown of gums and alveolar bone and premature loss of teeth. Teeth are often maldeveloped, being abnormally small with incisors lacking crenation. Odontogentic keratocysts can be seen, and teeth are prone to fracture after minor stress. The buccal mucosa is easily stretched, and the tongue may be hypermobile with the ability to illicit Gorlin's sign (the ability to touch the tip of the tongue to the tip of one's nose). Gingival fragility with oozing of blood is common after minor trauma such as brushing and cleaning. Hemostasis after tooth extraction can also be problematic. Articular laxity may manifest as recurrent subluxation of the temporo-mandibular joint (1). Management should focus not only on effective hemostasis and patient education, but more so on the recognition of these manifestations as symptoms of a systemic disease with the need to correctly classify the individual and monitor for more serious complications.

Esophagus

Structural defects are commonly seen. Giant epiphrenic diverticula and megaesophagus have been reported but are far less frequent than hiatal hernias, which are a common abnormality (1). Patients present with mild symptoms of epigastric discomfort and can be successfully managed with conservative treatment (11). The hyperextensibility of certain types of EDS is thought to decrease somewhat with age, therefore surgery is usually deferred when possible to help minimize the rate of surgical complications (13). If a life-threatening situation such as hemorrhage, incarceration, or strangulation develops, however, urgent surgery is appropriate (12). One of the most severe complications is that of esophageal rupture requiring urgent surgery, which has been reported after forceful vomiting (15).

Stomach

Peptic ulceration is frequent, but given its incidence in the general population, it is unlikely that EDS predisposes to ulceration (11). Complications of peptic ulcer disease, however, are more likely to occur and can be quite severe in EDS, especially in the vascular type. It has been postulated that the lack of supporting tissue around blood vessels potentiates bleeding (16). Presenting symptoms range from mild epigastric discomfort to severe hematemesis and melena. Most case reports predate the advent of histamine-2 receptor antagonists, proton pump inhibitors, and the fiber optic endoscope; however the principles of management used in the past can still be applied to EDS patients today. Conservative, noninvasive techniques should be the mainstay of therapy. Although there are no reports concerning the incidence of complications from endoscopy in EDS, the catastrophic potential, especially in patients with severe forms, argues against its use as the primary diagnostic modality. Radiographic contrast studies have been used successfully in the past and may now be supplemented by noninvasive testing for Helicobacter pylori. Past experience favors medical treatment when possible; satisfactory results have been obtained, and surgical repair is often tedious and complicated because of tissue friability (11). Patients who manifest severe visceral and vascular complications of EDS may be prone to lethal sequelae of peptic ulcer disease, such as posterior erosion of duodenal ulcers in the aorta, and should therefore be treated aggressively and monitored closely. Gastric diverticula are common and have no reported sequelae, but diverticula on other parts of the GI tracts, such as the gallbladder and small intestine are thought to act as a nidus for perforation (11, 18, 19). The presence of gastric diverticula should alert the physician to the potential for this

consequence. Tissue laxity as well as structural anomalies associated with EDS, such as diaphragmatic eventration, hiatal hernia, kyphoscoliosis, and intraabdominal adhesions, are thought to predispose to gastric volvulus (14). This has been managed with conservative therapy unless complications requiring surgery develop (20). Gastric infarction without evidence of hiatal hernia or volvulous that required partial gastrectomy has been reported as well as gastric malrotation presenting as failure to thrive in a newborn (21, 22). Symptomatic gastropareisis has also been seen. The approach to EDS patients needs to be individualized; differentials should be broad, and consideration must be given to the type of EDS and the potential for complications if invasive procedures are performed.

Small intestine.

Distal to the pylorus, the lack of tissue integrity begins to manifest as one of the most ominous presentation of EDS: perforation. Although perforation is more common in the large intestine, its occurrence in the small intestine is also well documented. Presentation can vary from emesis and hematemesis to crampy abdominal pain with spontaneous peritonitis. The findings at laparotomy in these patients are often remarkably similar. The small intestine is usually studded with diverticula located on the mesentric border of the duodenum and jejunum, measuring 1-3 cm (23, 24). Perforations can occur through diverticula as well as macroscopically normal bowel. Perforations have been managed with resection and performing end-to-end anastomoses (25). It is interesting to note that end-to-end anastomoses have been achieved without complication in the small bowel whereas similar surgery in the colon frequently leads to breakdown, suggesting that small bowel may be less prone to complication. The loss of strength of connective tissue may interfere with the ability to wall off infectious processes and therefore increases the risk of abcess formation leading to increased morbidity and mortality when perforations occur (23). Diverticula, however, are not the only abnormality that are though to lead to perforation. Intramural jejunal hematomas have been demonstrated in patients presenting with both upper GI bleeding and abdominal pain. Bleeding and hematoma extension may occur because of a lack of surrounding normal tissue support. Intramural hematomas may then cause focal areas of necrosis in bowel wall, leading to perforation (16). Therefore, hematemesis, especially in the absence of known peptic ulcer disease, may also be a harbinger of impending perforation. Megaduodenum has been reported in several patients (1, 25). Although this abnormality has not been associated with per-

foration, it has been linked to bacterial overgrowth and malabsorptive states. It is thought that the megaduodenum creates situation similar to blind loop leading to bacterial overgrowth. Clinical response is often achieved with antibiotic therapy (23). Dilation of the entire small bowel from the ligament of Trietz to the terminal ileum has been observed without evidence of malabsorption or bacterial overgrowth (25). Therefore, factors other than dilation, such as altered motility, may also play a role in malabsorptive states in these patients.

Large intestine

Spontaneous perforation of the colon is one of the most commonly reported GI complications of EDS. Although surgery can be problematic, a thorough familiarity with management of colonic perforation can help provide early warning of impending perforation, prevent recurrence, and decrease operative morbidity and mortality. Perforations can occur at any age, but unlike many manifestations of EDS that decrease with age, perforations tend to be rare in childhood and occur predominantly in late teens to the 5th decade (26). Perforations are most commonly located in the sigmoid colon but can occur anywhere. They may be multifocal and are slightly more frequent in women for unknown reasons. Spontaneous perforations are common in the sigmoid colon, but traumatic perforations are more likely to occur in the rectum. Patients can present with abdominal pain, vomiting, peritoneal signs, or hematochezia. A long history of constipation and chronic intermittent abdominal pain may be elicited (27, 28). Type III collagen is the major supportive constituent of the bowel, so it is not surprising that patients with type IV EDS, who have a deficiency in this type of collagen, are more prone to perforation than other types of EDS. How this deficiency in type III collagen may ultimately lead to perforation has important consequences in the management of patients with perforation. As mentioned previously, a history of constipation often precedes perforation. This common history as well as surgical and pathological findings indicates that constipation has an important role in the pathogenesis of colonic perforation in EDS patients (17, 29). Often, the colon is filled with hard, impacted feces. Sometimes impacted stool is found in the peritoneal cavity or in walled off cavities in close proximity to the area of perforation (17, 19). Fecal impaction has been implicated in the formation of dissecting intramural hematomas and tears in the seromuscular coat, which may predispose to perforation (13). EDS patients with a defect in type III collagen may be uniquely predisposed to perforation after straining fecal impaction due to a lack of tissue strength that leads to disruption of the bowel wall (30). Furthermore, chronic constipation and straining with increased intraluminal pressures, disrupted or thin muscular layers, decreased

tensile strength of connective tissue, and uncoordinated muscular activity may place EDS patients at risk for diverticula formation (31). These intrinsic defects in the bowel wall may then act as a nidus for perforation (32). Although sometimes gross examination of the bowel is normal and without evidence of diverticula, microscopic examination of bowel can reveal microdiverticula that may perforate (27). Fecal impaction may play an important role in perforation, so EDS patients should be on a strict bowel regimen including laxatives and high fiber diets. Enemas should not be used because colonic distention may result in perforation. Patients should also be instructed of the potential dangers of manual disempaction. To help prevent traumatic perforations, extreme care should be taken when performing physical examinations or passing nasogastric tubes. Although it has been performed without complications in a limited number of patients, endoscopy should be avoided.

When bowel perforations are diagnosed, surgical intervention is mandatory. Invasive procedures in EDS can run from uneventful to catastrophic. Surgery is complicated by fragile tissue that can possess as little as 20% of the tensile strength of normal tissue. Problems arise from bleeding due to vascular instability and from difficulty closing wounds because sutures pull out of integument and bowel that has been likened to "cold porridge" in consistency (27). Surgery in EDS requires special considerations, so management appropriately begins with correctly diagnosing both the presence of a perforation and EDS. The clinical presentation of EDS varies greatly, and therefore some patients may present initially with colonic perforation without a previous diagnosis of EDS, and others will have previous manifestations suggesting a lack of tissue integrity such as rectal prolapse, uterine prolapse, or a history of previous colonic perforation (27). The presence of a perforation in a young patient, without a predisposing factor such as neoplasm, diverticulitis, colitis, steroid use, or inflammatory bowel disease, mandates the consideration on EDS (33). Findings at laporotomy suggest that some patients may have had unrecognized perforations before presentation and perforations tend to recur and be multifocal, so a high index of suspicion for perforation should be maintained in patients known to have EDS (17). Surgical treatment of bowel perforation in EDS differs from that in most other patients because perforations tend to recur and anastmoses tend to breakdown. Because of these common occurrences, original recommendations called for resection of the involved colon and end colostomy and either creation of a Hartman's pouch with the rectal stump or placement of a distal mucous fistula (27). Restoration of bowel continuity is not recommended because of the high incidence of recurrent perforations (33). Permanent colostomy, despite the young age

of some patients, has been recommended. Despite the magnitude of this surgery, it cannot be considered curative, and perforations may recur, especially if there is evidence of colostomy stenosis. Therefore, even after a colostomy is placed, stool softeners remain an important therapy as well as careful surveillance for evidence of colostomy stenosis. The safest procedure is considered to be a total colectomy with Hartman's pouch and permanent Brook's ileostomy (26). For patients who object to permanent ostomy, total colectomy with ileoproctostomy has been proposed (33). Although perforation of the remaining rectum is rare, complications can arise from breakdown or stenosis of the anastomosis, and death as a result of this breakdown has been reported (26). Prophylactic colectomy has been advised in cases in which colonic ectasia develops and perforation is thought to be inevitable; however, the early recognition of constipation and its treatment may prevent the risk of development of ectasia (28). In the postoperative period, EDS patients are prone to certain complications. Because of low tissue strength and poor wound healing, wound dehisence and incisional hernias may occur. In these situations, the use of wound packs and abdominal binders has been recommended (27). The use of stay sutures at a distance from the wound as well as the use of measures to decrease intraabdominal pressure by preventing cough, ileus, and bladder outlet obstruction has been advised for prophylaxis against dehisence (26). A high rate of wound infection has also been reported, and it is advised that structures should be removed as soon as possible; however, this must be balanced against the propensity for poor healing and dehisence (34). Colonic fistulas, colostomy breakdown, hematoma formation, vascular accidents, prolonged bleeding, and multiple intraperitoneal adhesions are not infrequent and underscore not only the need to handle abdominal contents carefully intraoperatively but also the problematic nature of surgical procedures in EDS patients (33, 35).

Rectum.

The presence of tissue hyperextensibility in EDS may manifest in the rectum as rectal prolapse, which usually presents during infancy, The symptoms of tissue laxity reportedly decrease with age, so it is not surprising that spontaneous resolution of infantile rectal prolapse has been reported in several cases by age 5 yr (11). There are, however, case reports of rectal prolapse persisting up to the 6th decade. Surgical repair is not without significant risk and death has been reported due to intraoperative rupture of the iliac artery and vein (37). The role that chronic constipation plays in furthering prolapse in not known, but strict bowel regimens may be of some use. The differential diagnosis of hematochezia should also include rectal and anal causes. There are several

case reports of rectal bleeding after the passage of hard stool that were most likely due to splitting of the anal mucosa due to inherent tissue fragility. Brisk herorrhoidal bleeds have also been reported. Once again, the use of stool softeners cannot be overstated (38).

Appendix

EDS patients who present with abdominal pain are often young, and therefore appendicitis is a diagnosis that is often entertained. There have been six case reports of appendicitis in EDS patients; however, a pathological diagnosis was obtained in only one patient. It has been proposed that the properties of the intestinal tract in individuals with EDS should decrease the incidence of appendicitis. The pathophysiology of appendicitis is thought to involve high intraluminal pressures that act to cause insipissated material to block the appendix. The tissues of EDS patients is hyperextensible, so blockage should theoretically occur less frequently. Colonic motility studies, however, have suggested the presence of abnormal bowel motility patterns in the large intestine of EDS patients. Altered motility may interfere with the ability of the appendix to clear and predispose to inflammation despite increased distensibility. There are a multitude of abdominal processes associated with EDS that may be associated with abdominal pain that mimics appendicitis. Whether appendicitis is a common or rare occurrence in EDS patients is not known; however, the diagnosis of appendicitis should always be suspected in patients presenting with typical abdominal pain, but other diagnoses must also be entertained (31, 36).

Vasculature

When considering the differential diagnosis of acute abdominal pain in EDS patients, the vascular system must always be considered (35). Vascular accidents are probably the most feared sequelae of EDS because of the extreme difficulty of repair and subsequent mortality. Vascular complications that have been reported include aneurysm, rupture, dissection, varcosities, and arteriovenous fistula formation. They are most common in type IV EDS but have also been described in types I and II. Patients are often young, and the diagnosis is commonly missed. Although patients with vascular catastrophes may present with pain that has been attributed to other intraabdominal processes such as appendicitis or cholecystitis, finding clues to the proper diagnosis begins with the patient's history. Prior histological confirmation of the eccymotic types of EDS or other symptoms that may suggest this phenotype, such as a history of subclavian, popliteal, or other arterial rupture, postpartum hepatic rupture, or a history of spontane-

ous bowel perforation, should raise suspicion for a vascular etiology of the pain. Once this possibility has been raised, the patient should be imaged with the diagnosis of arterial rupture or aneurysm in mind. Invasive studies such as an angiography are contraindicated in these patients because of a high rate of complications such as arterial laceration, false aneurysm, arterial venous fistula formation, and even death (39). Newer, noninvasive diagnostic modalities such as magnetic resonance angiography and CT are preferable, but their roles has yet to be explored in detail in these patients. Often, the proper diagnosis is instead reached at the time of laporotomy, or unfortunately, during postmortem analysis.

Collagen accounts for the integrity of vessel walls and their supporting matrix, so all major arteries and vascular organs should be considered at risk. Splenic involvement is not uncommon and carries a grave prognosis (11, 25). Retroperitoneal hemorrhages due to splenic artery ruptures have also been reported (37). Aortic involvement is also quite common. Single and multiple aneurysms have been documented. When these aneurysms rupture, mortality is high. In cases in which surgery is deemed too risky, dissections have been managed successfully with antihypertensive therapy (40). Finally, microvascular disease causing capillary hemorrhage has been postulated to be responsible for cases of pancreatis associated with EDS (18). Unfortunately, despite the devastating course of the vascular complications, few preventative measures can be taken short of avoiding trauma and respecting vascular structures during surgery. Screening imaging studies are problematic because many arterial rupture occur independent of prior aneurysm formation (40). Antihypertensive therapy has been mentioned for the treatment of aortic dissection that is inoperable. Such therapy has also been proposed for prophylactic purposes in patients who suffer from Marfan's syndrome (41). Routine use of antihypertensive therapy for EDS patients thought to be at significant risk for vascular complications has never been investigated but may prove effective. A thorough work-up for EDS should be undertaken in any young patient who presents with an arterial aneurysm. Furthermore, the lack of clinical suspicion even with negative family history should not discourage postmortem analysis in cases of unexplained multifocal hemorrhage so that genetic analysis and family counseling can take place.

CONCLUSION

Although once though to be extremely rare, more and more cases of EDS are being reported, and it is conceivable that patients may present in nonacademic settings without

a known diagnosis. EDS can have manifestations from mouth to anus, some of which are benign, and others can be lethal. A thorough knowledge of the GI manifestations of Ehlers-Danlos and their management is mandatory to prevent unnecessary morbidity and mortality. The appropriate management of such patients begins with the realization that there is a systemic illness, EDS, present that may involve multiple organ systems. This needs to be followed by the proper classification of the type of EDS. EDS syndrome should always be suspected in young patients who present with bowel perforations or vascular accidents. Differential diagnoses should always be broad, and treatment must take into consideration not only the known complications of EDS but also the propensity of the particular patient to manifest them. Even when assymptomatic, patients should be followed carefully, and prophylactic measures such as stool softeners should be used. Finally, genetic analysis and family counseling are mandatory.

In vitro studies have shown that dexamethasone can modify defects in the extracellular matrix found in several types of EDS (9). The clinical implications of this are not clear, however, and although EDS is a rare entity, some day it may prove to be a successful target of gene therapy.