Surgical Pitfalls in a Patient with Type IV Ehlers-Danlos Syndrome and Spontaneous Colonic Rupture

Report of a Case

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PURPOSE: This paper intends to stress the importance of early diagnosis and discuss surgical treatment of Type IV Ehlers-Danlos syndrome (EDS-4), an autosomal dominant connective tissue disease characterized by typical features of the face and extremities, inappropriate and easy bruising, and extreme tissue fragility, which may lead to dramatic and often fatal complications, mostly spontaneous arterial or intestinal rupture. METHODS: We report the case of a 41-year-old female who presented with spontaneous perforation of the sigmoid colon. RESULTS: The patient was seen over a nine-year period, during which time she required six operations and presented with a great number of surgical complications including stenosis of an end-colostomy, repeated subocclusive episodes caused by intraperitoneal adhesions, and enterocutaneous fistulas, finally ending with an ileostomy and short bowel syndrome. It is only after a difficult laparotomy for ovarian cyst excision, marked by numerous adhesions and friable bowel, that the diagnosis of EDS-4 was considered and established. CONCLUSIONS: In case of "idiopathic" spontaneous perforation of the colon in a young adult, features of EDS-4 should be thoroughly looked into and, if found, skin fibroblast culture with collagen Type III analysis performed. The surgical treatment of choice consists of subtotal colectomy and permanent end-ileostomy. In case of patient refusal, a second-stage ileorectal anastomosis can be performed but carries the high risk of anastomotic leakage. [Key words: Ehlers-Danlos syndrome, Type IV; Collagen, Type III; Colonic perforation; Complications]

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Ehlers-Danlos syndrome (EDS) is a heterogeneous family of genetically determined connective tissue disorders, characterized by joint laxity and fragile, hyperelastic, and easily bruisable skin; ten subtypes have already been described. Ehlers-Danlos syndrome Type IV (EDS-4), an abnormality of Type III collagen, is a life-threatening disease because of its typical complications of spontaneous arterial or colonic rupture; however, it lacks the characteristics of hyperelastic skin and joint laxity.[1,2] Colonic rupture typically happens in young adults and is usually situated in the sigmoid colon.[3,4] A case of EDS-4 with spontaneous perforation of the sigmoid colon, followed over a nine-year period, is reported, which illustrates almost the whole clinical spectrum of the disease and multiplicity of surgical problems and complications arising from this condition.

REPORT OF A CASE

A 41-year-old female with constipation presented with rapid onset of abdominal pain in the left lower quadrant and fever. On physical examination, there were signs of pelvic peritonitis. At laparotomy, a covered perforation of the sigmoid colon was found. Sigmoid resection was performed with an end colostomy and Hartmann's pouch. Macroscopic appearance of the rest of the colon was normal. A diagnosis of spontaneous colonic perforation because of fecal impaction was retained. Because of necrotic stenosis of the stoma, repeat laparotomy was performed two months later. Numerous small bowel adhesions demanded extensive lysis, and a new colostomy was set. Because of severe local inflammation, the left tube and ovary and the rectal stump were resected. The patient was discharged from the hospital one month later.

She was hospitalized again four months after the second operation for bowel continuity restoration. Because of poor vascularization and unsound aspect

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of the remaining colon, colectomy was completed with an ileorectal anastomosis; a protective lateral ileostomy was installed and continuity restored three weeks later. During both of these laparotomies, extensive intraperitoneal adhesions were again noted, as well as abnormal tissue fragility, with iatrogenic intestinal perforations, necessitating small bowel resection. The postoperative course was satisfactory, and the patient was discharged from the hospital three weeks after the second laparotomy.

Two years after presentation, she was repeatedly seen over a six-month period for recurrent intestinal subocclusion because of ileorectal anastomotic stenosis and multiple adhesions that were treated conservatively.

The patient was not heard from again until seven years after initial admission, when she presented with two months of symptoms of relapsing subocclusion because of extrinsic compression of the rectum by a right ovarian cystic mass, revealed by endoscopy and computed tomography (CT) scan. Surgery was avoided, and a yellowish liquid was aspirated under CT scan guidance. Intestinal passage resumed almost immediately, and the patient was discharged symptom-free the following day.

She was readmitted two months later with identical symptoms. A new CT scan showed relapse and enlargement of the ovarian cyst. Aspiration evacuated hemorrhagic liquid. Despite the major surgical risk and because of rapid recurrence and bleeding of this ovarian cyst, laparotomy was performed. Tremendous intraperitoneal adhesions, with intestinal tissue described by the surgeon as "fragile as wet cigarette paper," resulted in an extremely long and difficult operation, with numerous perforations. This necessitated resections of several segments of the small intestine, involving a total length of 60 to 80 cm, before partial resection of the cyst could be achieved.

EDS-4 was finally suspected. Thorough personal history revealed that the patient had been born prematurely (at seven months). She had always experienced excessively easy bruising, had had bilateral stripping of varicose veins, had been treated for spontaneous pneumothorax, and had had upper front teeth removed because of periodontal disease. Both of her parents had died of cancer in their mid-sixties, and none of her five brothers and sisters had histories evocative of EDS-4.

On physical examination, the patient was of short stature (150 cm, 43 kg); she exhibited facial features typical of EDS-4 (Fig. 1), a pinched, crooked nose and large excavated eyes. Her skin was very thin, without hyperextensibility; there was no joint laxity. Her hands were acrogeric, with deformity of three fingers on her right hand (Fig. 2).

To establish the diagnosis, a skin biopsy was obtained. Cultured skin fibroblasts were shown to produce a structurally abnormal Type III collagen, retained within the cells. Regular Type III collagen was normally secreted, but in greatly decreased amounts.

The postoperative course was marked by a persistent septic state caused by recurrent intra-abdominal abscesses and enterocutaneous fistulas, which were treated conservatively in repeated hospital stays. Because of intractable persistence of multiple fistulas that were impossible to fit with appliances and severe handicapping and despite surgical risk, she was eventually addressed to a specialized center where she underwent total abdominal dissection, resection of fistulized or severely damaged small bowel segments, terminal ileostomy, and closure of the rectum. She was left with only 130 cm of small intestine, which provoked a malabsorption syndrome and required she consume hypercaloric nutrition.

The patient is now 50 years of age, recovering from the last operation, and gaining weight; all of her fistulas are closed. She eats normally but needs parenteral nutritional support, which she manages herself at home.

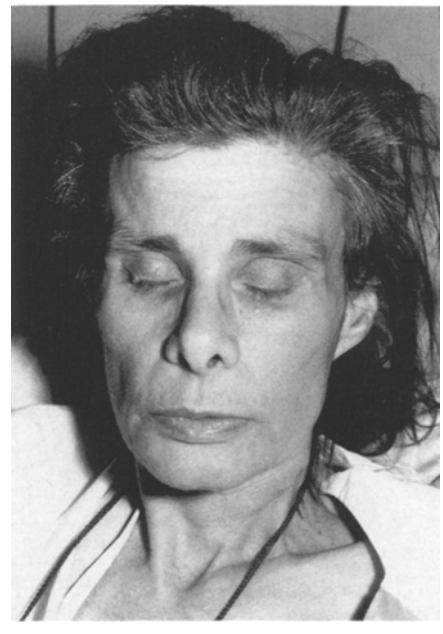

Figure 1. Facial features of EDS-4. Note pinched, crooked nose and large eyes, set widely apart, with excavated orbitae.

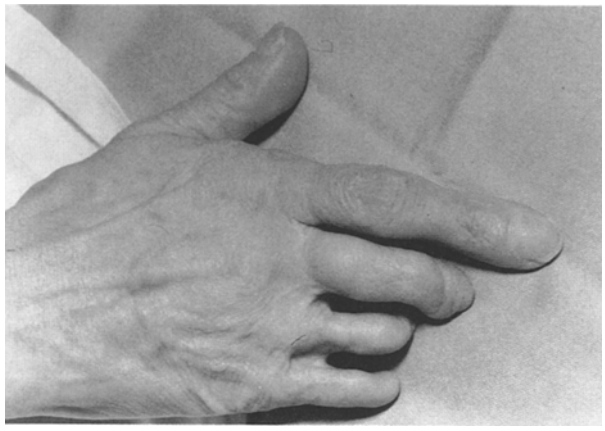

Figure 2. Acrogeria. Note thin, wrinkled skin of the hand, giving it a prematurely aged appearance. Also note deformity of the last two fingers caused by an amniotic band.

DISCUSSION

The clinical spectrum of EDS-4 is wide; all of the signs and symptoms summed up in Table 1 are never met in a single patient. They include typical facial features (*i.e.*, a thin, pinched nose and large eyes, with a staring and prominent appearance because of paucity of adipose tissue) and acrogeria (defining hands with fine fingers and covered by thin and wrinkled skin, which looks prematurely aged). The hallmarks of the disease, however, are severe surgical complications, some of which are frequently fatal, and account for the reduced life expectancy of these patients, resulting in a mean age at death of 35 to 40 years.[1, 2] These are spontaneous ruptures of the colon (mainly sigmoid)[3–9] or the gravid uterus,[10] aneurysms, arteriovenous fistulas or spontaneous rupture of large arteries,[6] and pneumothorax; splenic rupture has also been reported.[11]

Table 1.
Clinical Spectrum of EDS-4

Prematurity and low birth weight*	Keratoconus	
Short stature*	Periodontal	disease*
Acrogeria*	Varicose	veins*
Typical facial features (nose and eyes)*	Thrombophlebitis	
Translucent skin with visible venous pattern*	Aneurysm arteriovenous	or fistula
Inappropriate bruising*	Spontaneous rupture	arterial
Clubfoot	Spontaneous rupture*	colonic
Shoulder or hip dislocation	Spontaneous rupture of the	graviduterus
Cheloid scars	Spontaneous pneumothorax*	

* Clinical signs exhibited by reported case.

In view of the medical history of our patient who exhibited an unusually large number of clinical signs for EDS-4 (Table 1), it may seem surprising that the diagnosis had not been established earlier. Obviously, the rarity of this disease is to blame; there are no figures available regarding its incidence, but, to our knowledge, only 21 cases of EDS-4-related intestinal rupture have been reported so far. Nevertheless, earlier diagnosis would certainly have refrained us from performing the ovarian cyst excision attempt and prevented the last cycle of complications, which kept our patient hospitalized for the better part of the last two years. At any rate, she has benefited with a remarkably long survival in view of the life expectancy of EDS-4 patients and the number of complications she incurred.

Surgery in these patients has a high morbidity because of extreme fragility of tissues, which are often described as tearing like "wet blotting paper." Sutures tend to tear them out; bowel walls are extremely friable and anastomosis arduous; small vessels are equally fragile occasioning difficult hemostasis, oozing, and hematoma formation.[6, 12–14] This has been largely described in the case report. Blood vessel fragility might have accounted for the episode of heavy bleeding in the ovarian cyst after drainage.

Other surgical complications or difficulties displayed by our patient have been described incidentally in other case reports, notably enterocutaneous fistulas,[3] stenosis of anastomosis or stoma,[4] and tremendous intraperitoneal adhesions, which, when associated with intestinal fragility, cause surgery to be laborious and frustrating.[3, 4, 12–14]

Some authors consider rectoscopy to be absolutely contraindicated in patients with EDS-4, especially after spontaneous perforation.[6, 9, 14] It is remarkable that our patient underwent a number of rectoileoscopies without any adverse consequences.

EDS-4 results from Type III collagen defects, genetically determined in an autosomal-dominant manner. However, a significant proportion of the cases (50 percent) represents new mutations[1]; this is certainly the case for our patient, as neither of her parents suffered from the disease, both of whom died in their mid-sixties from cancer. Cells from individuals with EDS-4 synthesize large quantities of structurally abnormal Type III collagen, which are stored inside the cell, and smaller amounts (12.5 percent) of normal Type III collagen normally secreted.[1, 15, 16] Diagnosis

of EDS-4 is based on quantitative and biochemical analysis of Type III collagen secreted by cultured skin fibroblasts, a study that definitely confirmed the diagnosis for our patient.

Treatment of colonic perforation in EDS-4 patients is controversial; different surgical procedures have been advocated, but there is no large series available to demonstrate the superiority of one option. The simplest approach is to perform a classical Hartmann's procedure with a distal mucous fistula; in this case, it is widely accepted that there should be no reanastomosis, as a permanent end-colostomy greatly reduces the risk of recurrence.[3, 10] Yet, this does not totally prevent perforation proximally to the stoma.[4] Another option is to perform immediate subtotal colectomy to prevent relapse of colonic perforation, an almost unavoidable event[3, 4, 11]; since ruptures of the rectum or small intestine are extremely rare,[3, 9] this procedure almost totally prevents intestinal reperforation. Primary ileorectal anastomosis or two-stage ileorectal anastomosis can then be done.[8, 9, 14] However, because of tissue friability, intestinal anastomosis carries an important risk of leakage, associated with a high mortality.[3, 4] Thus the safest option would be a one-stage, subtotal colectomy, with Hartmann's pouch and permanent ileostomy,[4] but this is unacceptable to many of these young EDS-4 patients. Unfortunately, it seems that the choice of surgical treatment will result from a balance between safety and handicap. In this regard, it has to be noted that our patient ended up with a permanent end-ileostomy after six laparotomies, an operation that might have been performed nine years earlier had the diagnosis been established.

The case reported here is interesting because of the large number of typical EDS-4 features exhibited but mostly because it clearly illustrates the chain of complications into which the surgeon can be dragged, especially related to intestinal fragility and intraperitoneal adhesions, when the diagnosis is unrecognized. Unless a life-saving procedure is needed, we believe that laparotomy should be avoided at all costs in these patients. In case of spontaneous colonic rupture in a young adult without any obvious cause at laparotomy, such as diverticulitis, neoplasia, Crohn's disease, infectious or ischemic colitis, and in the absence of corticosteroid therapy, the possibility of EDS-4 should be considered, as the differential diagnosis is very limited; it comprises stercoraceous ulcers of the colon, alkaline medication and hypothyroidism.[17] Thorough personal and family medical history and clinical examination should be obtained, searching for typical signs and symptoms of the disease and, if found, skin fibroblasts culture should be performed to definitely establish the diagnosis. In case of colonic rupture, a complication carrying a high mortality, total colectomy with permanent ileostomy should be performed as soon as the diagnosis is established. For those patients who absolutely refuse a permanent stoma, an ileoproctostomy can be done in one or two stages.

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