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Gynecologic and Surgical Complications in Type IV Ehlers-Danlos Syndrome

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Abstract

BACKGROUND—Although type IV Ehlers-Danlos syndrome is a rare condition, it is critical that physicians be aware of this disease because it presents unique management challenges.

CASE—We present a young woman who was admitted with a pelvic abscess after having a miscarriage and an appendiceal perforation. She had an exploratory laparotomy secondary to a persistent pelvic abscess and endured multiple postoperative complications. Based on her family history and physical characteristics, type IV Ehlers-Danlos syndrome was diagnosed.

CONCLUSION—The decision to proceed with surgery should be weighed against tissue fragility in patients with type IV Ehlers-Danlos syndrome. A conservative, multidisciplinary team approach addresses whether to proceed with surgery and minimize postoperative complications if surgery is performed.

Type IV Ehlers-Danlos syndrome (OMIM # 130050) is a rare subtype (prevalence 1/100,000–250,000 live births) that can lead to arterial, bowel, and uterine rupture.[1] It is critical for obstetrician–gynecologists to consider this diagnosis in the appropriate clinical setting and tailor their surgical treatment for patients with this diagnosis. We present a young woman with pelvic pain secondary to a persistent pelvic abscess. Before her admission, she had a loss of a twin pregnancy as a complication of a ruptured appendicitis. Based on her history and examination, type IV Ehlers-Danlos syndrome was diagnosed and confirmed with molecular testing. This case highlights the complications of surgical management in a patient with Type IV Ehlers-Danlos syndrome. We also review the clinical characteristics for diagnosis and summarize the literature regarding surgical management of type IV Ehlers-Danlos syndrome.

CASE

Our patient is a 30-year-old woman who conceived twins through in vitro fertilization at an outside institution. At 17 weeks of gestation, she had a laparoscopic appendectomy for a ruptured appendix. Her postoperative course was complicated by chorioamnionitis and

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miscarriage. Three weeks later, she was seen in the emergency department at an outside institution with worsening pain, and a repeat laparoscopy was performed for evacuation of an abscess.

The patient presented to our institution for the first time 9 days after her second laparoscopy with increasing left lower quadrant pain, fever, and leukocytosis. Computed tomography (CT) showed a 2.8×3.3×3.7-cm left pelvic fluid collection, and, in this clinical setting, a diagnosis of pelvic abscess was made. She was admitted and treated with 3 days of intravenous Ertapenem followed by oral Augmentin. After resolution of her fever and leukocytosis, she was discharged with oral Augmentin for 14 days and oxycodone for pain.

The patient formally transferred her care to our institution and was monitored by both the general gynecology and reproductive endocrinology and infertility teams as an outpatient. She continued to have significant pelvic pain. Repeat CT examination showed persistence of a complex left pelvic fluid collection. The clinical team discussed either continued conservative management with observation or surgical treatment of presumed tuboovarian abscess and adhesive disease. The patient elected to proceed with surgery and was taken to the operating room 2 months after her discharge from our institution. An open surgical approach was planned as a result of concern for significant adhesive disease.

Exploratory laparotomy showed an edematous left tube with numerous adhesions. No abscess or fluid collection was seen. Left salpingectomy was performed and no intraoperative complications were observed. The surgeons noted fragility of the skin and fascia during the procedure.

On postoperative day 2, the patient developed a high fever with a leukocytosis, and intravenous Piperacillin, Tazobactam, and Vancomycin were administered for presumed surgical site infection. The medications were changed to Doxycycline and Metronidazole as a result of acute renal insufficiency. A CT scan showed a new 15-cm pelvic fluid collection. Interventional radiology placed a drain and culture of the purulent fluid grew vancomycin-resistant *Enterococcus* species and *Candida glabrata.* Blood and urine cultures were negative. The antibiotics were switched to intravenous Linezolid, Metronidazole, and Micafungin. The patient was stable until postoperative day 15, when she developed subcutaneous crepitus and induration over the middle portion of the lower abdomen. Exploratory laparotomy for debridement of presumed necrotizing fasciitis revealed instead a large right-sided suprafascial abscess beginning 8 cm below the costal margin extending down to the mons pubis and from the right flank to the umbilicus.

Based on the patient's extensive postsurgical complications and protracted course from her pelvic abscess, an underlying connective tissue disorder was suspected and a genetics consultation was obtained to assist with identification of the diagnosis. The genetics team noted the patient's features of soft, translucent skin, small joint hypermobility, large, prominent eyes, a narrow nose, malar hypoplasia, thin lips, and narrow, tapered fingers. A review of the patient's family history revealed that the patient's mother had died during childbirth from a ruptured cerebral aneurysm. This history triggered a suspicion that the patient's mother may have had a connective tissue disorder. A clinical diagnosis of type IV

Ehlers-Danlos syndrome was made based on the patient's physical characteristics, clinical course, and family history. The diagnosis was confirmed with molecular testing; sequencing of the *COL3A1* gene showed a missense mutation in exon 12 causing a substitution of a glutamine for a glycine, one of the most common mutations of *COL3A1* diagnostic of type IV Ehlers-Danlos syndrome.[1] With the diagnosis of type IV Ehlers-Danlos syndrome, the patient had an evaluation of aortic root with an echocardiogram and a magnetic resonance angiography with intravenous contrast to evaluate the vascular tree for potential aneurysms or dissections. The aortic root was normal in size and she had no aneurysms but had tortuosity of her carotid arteries. Given the autosomal-dominant inheritance pattern of type IV Ehlers-Danlos syndrome, her immediate family was offered genetic counseling.

The patient was discharged from the hospital on postoperative day 22. Before discharge, the maternal morbidity and mortality risks of a future pregnancy, including a 12% risk of uterine or vascular rupture in pregnancy, were discussed with the patient. She has opted to adopt in the future should she desire a family. Future care will include vascular surveillance using CT and magnetic resonance imaging for aneurysm or dissection and prompt evaluation for arterial or bowel rupture should she develop severe pain. She was advised to avoid trauma contact sports, heavy lifting, weightlifting, and medical interventions such as arteriograms, elective surgery, and colonoscopy secondary to fragility of her vasculature and tissues.

Less than 3 weeks after her discharge from the hospital, the patient experienced a spontaneous ileal perforation, which required resection of 40-cm distal ileum and an end-to-end bowel anastomosis. Postoperatively, she developed a distal enterocolonic fistula. She has had a protracted postoperative course with percutaneous drainage of the fistula, total parenteral nutrition, chronic abdominal pain, and nausea requiring multidisciplinary care.

COMMENT

Type IV Ehlers-Danlos syndrome is unique from the other seven types of Ehlers-Danlos syndrome because it is caused by a defect in type III collagen formation. Type III collagen is mainly found in blood vessels and hollow organ walls. This mutation can result in catastrophic events such as vascular rupture, vascular aneurysm, uterine rupture, or bowel perforation.[1] Pepin et al[2] observed 220 individuals with type IV Ehlers-Danlos syndrome and showed that 25% had arterial, bowel, or other hollow organ complications by age 20 years and 80% had at least one complication by age 40 years. The most common cause of death was arterial dissection or arterial rupture. In contrast, individuals with classical Ehlers-Danlos syndrome (types I and II) have defects in formation of type V collagen leading only to hyperextensible joints and elastic skin; however, they are not at increased risk of hollow organ or vascular rupture.[1,3]

Individuals with type IV Ehlers-Danlos syndrome often have characteristic signs and symptoms; however, these findings can be subtle. Type IV Ehlers-Danlos syndrome can be diagnosed clinically if two of the four major criteria are met. These criteria are: 1) arterial rupture; 2) intestinal rupture; 3) uterine rupture in pregnancy; and 4) a family history of type IV Ehlers-Danlos syndrome. The presence of two or more minor criteria should also lead to consideration of the diagnosis but is not sufficient to establish diagnosis. The minor criteria

are: thin translucent skin, hypermobile small joints, and easy bruising. The diagnosis can be confirmed with molecular testing to identify a mutation in the *COL3A1* gene on chromosome 2q31. Direct sequencing will identify mutations in *COL3A1* in 95% of patients.[1]

As illustrated in our patient, type IV Ehlers-Danlos syndrome poses a unique challenge to gynecologists because surgery can result in a complicated postoperative course secondary to tissue friability. When surgical treatment is necessary, it is recommended to target the approach and minimize surgical exploration to avoid inadvertent damage to other tissues.[4] It is also important to avoid surgery if at all possible.[5] In general, surgical approach is more likely to be successful when the surgeon is aware of the diagnosis of type IV Ehlers-Danlos syndrome and understands the associated tissue fragility.

Although the clinical features of type IV Ehlers-Danlos syndrome can be subtle, as a result of the clinical significance, one must have a high index of suspicion in the appropriate setting. If our patient had been diagnosed earlier in her clinical course and there was knowledge of her tissue fragility, this may have influenced pivotal management decisions. If her diagnosis was known, the decision to proceed with the first exploratory laparotomy may have been postponed and drainage with interventional radiology may have been considered as another option. In patients with type IV Ehlers-Danlos syndrome, if surgery is necessary, targeted gentle surgical technique by experienced surgeons is important. Nevertheless, even with these management changes, the patient may have still had a persistent tuboovarian abscess with a complicated hospital and postoperative course secondary to her underlying disease and tissue fragility.

In conclusion, although vascular Ehlers-Danlos syndrome is a rare collagen disorder, it is important to be aware of this disorder because it is often difficult to diagnose unless one is mindful of the characteristic history and examination findings noted in this case. Knowledge of this diagnosis can be critical to patient care in gynecology. The principles to use are: 1) conservative management if possible; 2) avoidance of or minimal surgery to avoid excessive damage to delicate tissues; and 3) use of a multidisciplinary approach to care.

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