Iliac artery dissection and rupture in a patient with classic Ehlers-Danlos syndrome due to *COL5A1* null variant

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ABSTRACT

This is a case of a 46-year-old woman who presented with right common iliac artery dissection preceded by a left common iliac artery dissection and rupture 6 years earlier. Both iliac arteries required repair. Based on her presentation, she met the clinical diagnostic criteria for vascular Ehlers-Danlos syndrome; however, the genetic workup demonstrated that she had classic Ehlers-Danlos syndrome due to a null variant in *COL5A1*, which is rarely associated with arteriopathy. (J Vasc Surg Cases Innov Tech 2024;10:101443.)

Keywords: Classic Ehlers-Danlos syndrome; COL5A1; Connective tissue disorder; Genetic arteriopathy; Iliac artery aneurysm; Iliac artery dissection

Classic Ehlers-Danlos syndrome (cEDS) due to autosomal dominant inheritance of pathogenic variants in *COL5A1* and *COL5A2* is rare, affecting 1 in 20,000 individuals.[1-3] This condition is characterized by skin hyperextensibility, atrophic scarring, and generalized joint hypermobility due to a reduction in type V collagen production. There have been rare cases of arteriopathy described in association with cEDS.[4-9] We present a case of a 46-year-old woman with cEDS who presented with a spontaneous right common iliac artery (CIA) dissection at age 46 and underwent open surgical repair. This was preceded by a spontaneous left CIA dissection and rupture 6 years prior. The patient provided written informed consent for the report of her case details and imaging studies.

CASE REPORT

A 46-year-old woman who never smoked was referred with a 2-month-old diagnosis of a spontaneous right CIA dissection extending into the common femoral artery (CFA) discovered during workup for dull right "groin" pain. Computed tomography angiography (CTA) revealed the patient had aneurysmal dilation with a right iliac artery dissection to 1.8 cm (Fig 1).

Her history was remarkable for a ruptured left CIA with hemorrhagic shock 6 years prior when she was 40 years old for which she underwent repair. A review of her medical records demonstrated that she presented to the emergency department 1 day earlier with a complaint of left pelvic pain. The workup included a non–contrast-enhanced computed tomography scan, which showed a 1.7-cm left CIA (Fig 2). The operative report described the repair as an aorta-to-internal iliac artery (IIA) bovine–carotid bypass via a retroperitoneal transplant incision and jump graft to the left CFA via longitudinal femoral exposure. Her postoperative course was complicated by an incisional hernia requiring subsequent repair. Additionally, the jump graft to the left CFA thrombosed; however, she had adequate collateral circulation and had no intermittent claudication in the left lower extremity. She was diagnosed with essential hypertension after the left CIA dissection. At the time of the current presentation, she was being treated with losartan, diltiazem, and hydralazine because she was allergic to beta-blockers.

Also relevant in her history was a clinical diagnosis of cEDS at age 34 years. This was in the setting of a history of easy bruising since childhood and characteristic physical examination features that included soft, doughy, hyperextensible skin in which the upper portion of the dermis could be separated from the lower portion (characteristic of cEDS). She also had bluish sclera, small and large joint hypermobility, and a severe pectus excavatum deformity (Fig 2). Additional history included a secundum atrial septal defect for which she had undergone an uncomplicated transvenous Amplatzer atrial septal defect occluder (Abbott Cardiovascular) closure. Her family history was notable for a paternal aunt and cousin who had undergone an "aortic repair" and were noted to have "blue" aortic tissue, and a paternal grandfather who died of a left ventricular rupture.

The presentation and family history raised the question of a vascular Ehlers-Danlos syndrome (VEDS) diagnosis, in addition to cEDS. Genetic testing, including deletion/duplication analysis, demonstrated no pathogenic variants in *COL3A1*, thus, excluding the diagnosis of VEDS. Genetic testing was also negative for any of the other heritable aortopathy genes. The only pathogenic variant was the deletion of exon 1 in *COL5A1*, which confirmed the diagnosis of cEDS. This deletion is predicted to result in loss of transcription and translation of the affected allele,

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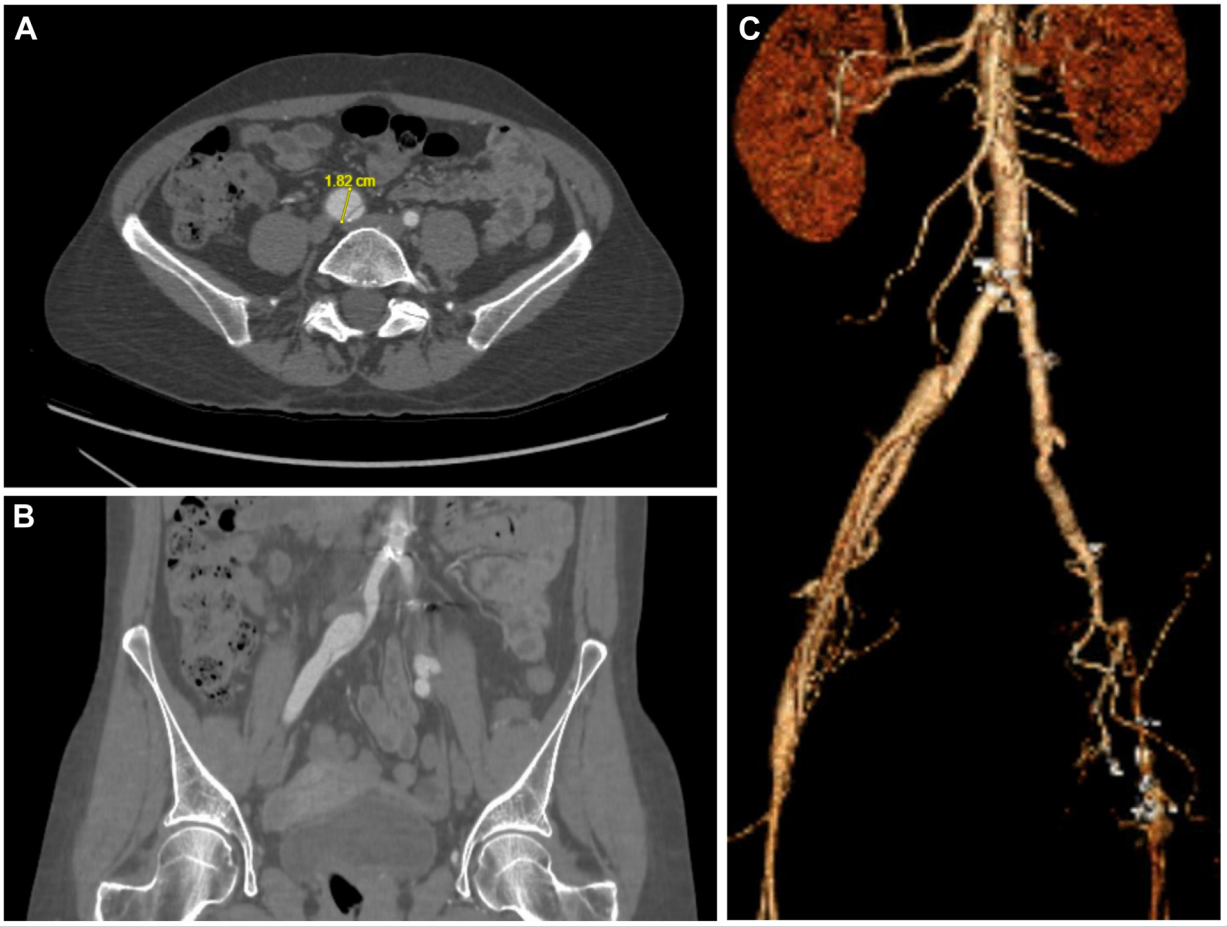

Fig 1. Computed tomography angiography (CTA) of the patient. Axial (**A**) and coronal (**B**) projections demonstrating the dissected right common iliac artery (CIA) aneurysm measuring 1.8 cm in maximum diameter. **C,** Three-dimensional reconstruction of patient's vascular anatomy, including previously repaired left iliac artery with an aorta to right internal iliac artery (IIA) bypass and dissected distal right CIA.

causing *COL5A1* haploinsufficiency, which is the most common disease mechanism in cEDS.[2] Additional workup included evaluation for *AEBP1* and aortic carboxypeptidase-like protein, which was also negative.

Given her history of iliac artery rupture at a diameter of <2 cm, she was scheduled for elective repair of her right iliac artery (Fig 2). However, she developed new right lower quadrant discomfort and tenderness over the right iliac artery; thus, she was reevaluated with repeat CTA. Although CTA showed no rupture or further aneurysmal degeneration, the aneurysm was symptomatic and, therefore, repaired urgently. The interval between the initial diagnosis of the right CIA dissection to repair was 4 months.

The right CIA retroperitoneal exposure was via a paramedian incision extending from a few centimeters superior to the umbilicus. The rectus muscle was mobilized laterally, preserving its innervation and perfusion from the lateral vessels. She had dense retroperitoneal adhesions to the aortic bifurcation, proximal CIAs, and ureter. The large distal aortic lumbar arteries were preserved. The distal aorta and distal portion of the left CIA to IIA bypass were circumferentially dissected for clamp placement. Once heparinized, an end-to-end, 8-mm Dacron interposition bypass was placed from the proximal right CIA to the distal external iliac artery using running 5-0 Prolene sutures with posterior wall pledgets for the proximal anastomosis and circumferential felt for the distal anastomosis (the choice of pledgets vs circumferential felt wrapping was determined by the ease of placement). This was followed by an end-to-side, 8-mm Dacron bypass from the right IIA to the bypass (Fig 3). The estimated blood loss was 1500 mL. On postoperative day 2, she developed sudden right lower quadrant abdominal pain associated with a decrease in hematocrit from 44% to 29%. CTA demonstrated a large retroperitoneal hematoma with compression of the inferior vena cava and ureter causing hydronephrosis (Fig 3). This prompted operative exploration and evacuation of 1 L of hematoma; however, no discrete source of bleeding was identified. The incision was closed primarily. Her course was complicated by ileus, requiring placement of a nasogastric tube on postoperative day 5. Repeat CTA on postoperative day 7 demonstrated re-accumulation of the retroperitoneal hematoma; however, because this was asymptomatic, it was managed nonoperatively. Given the delay in

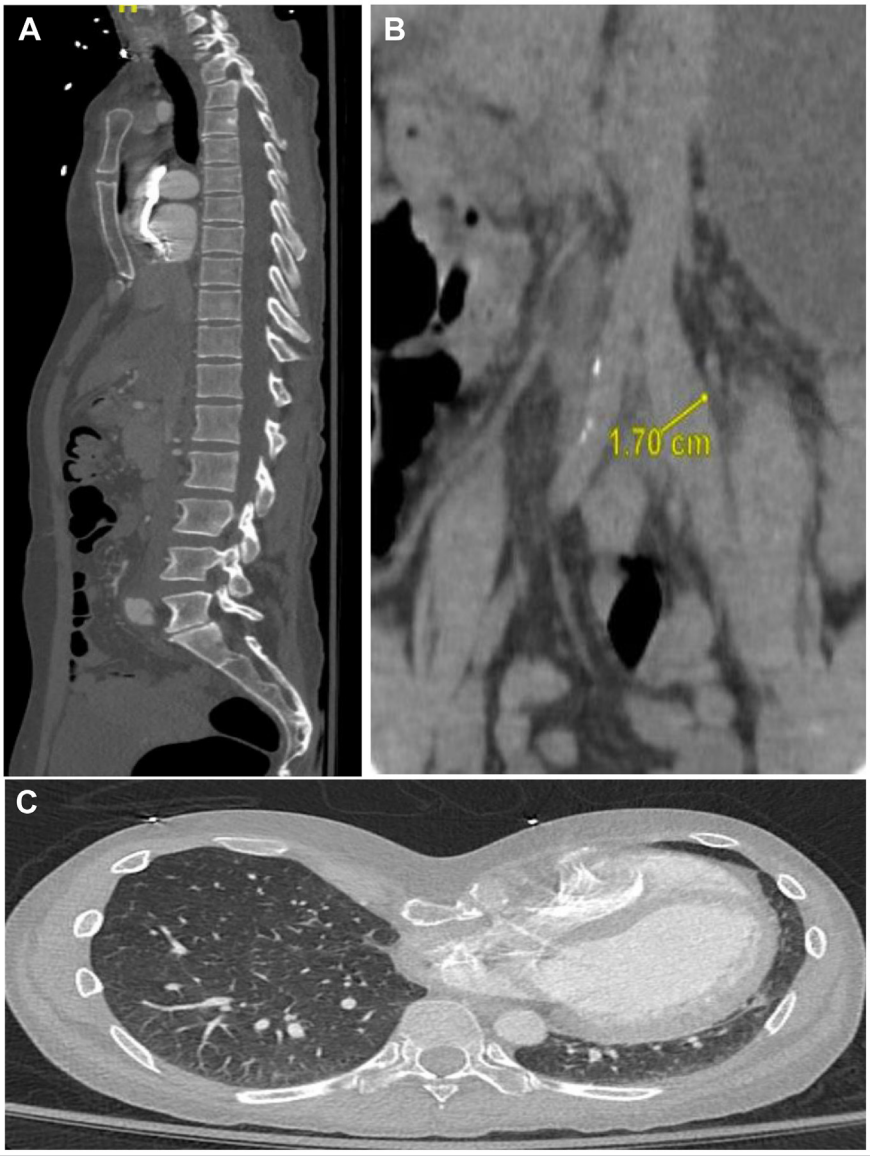

Fig 2. Computed tomography angiography (CTA) of the patient 1 day before the left common iliac artery (CIA) rupture. **A,** Sagittal projection with absence of thoracolumbar spinal lordosis or kyphosis. **B,** Left CIA aneurysm measuring 1.7 cm. **C,** Visible pectus excavatum deformity with unusually narrow anteroposterior dimension.

the return of bowel function, total parenteral nutrition was started. Her bowel function returned on postoperative day 11, and the patient was discharged home on postoperative day 12. Her incision healed without a hernia, and she has been followed up for 2 years with annual CTA (Fig 4). Subsequent planned surveillance imaging is duplex ultrasound of the abdominal aorta and iliac arteries.

DISCUSSION

Ehlers-Danlos syndrome (EDS) is a heterogenous group of 13 connective tissues disorders that share in the triad of joint hypermobility, skin hyperextensibility, and tissue fragility.[3] VEDS is the subtype commonly associated with aortic and arterial aneurysms and dissections and accounts for 5% of all EDS cases.[3] In the present case, our patient's presentation and clinical course were suggestive of VEDS, and she met the clinical diagnostic criteria for VEDS.[3] However, genetic testing was important, because the results demonstrated that she did not have VEDS and that she had a VEDS-like condition, in this case, cEDS. To date, six other similar cases have been reported in patients with cEDS (Table).[4-6,10] With the increasing usage of genetic testing, we anticipate that patients who might have in the past been clinically diagnosed with VEDS would be reclassified based on the results of genetic testing.

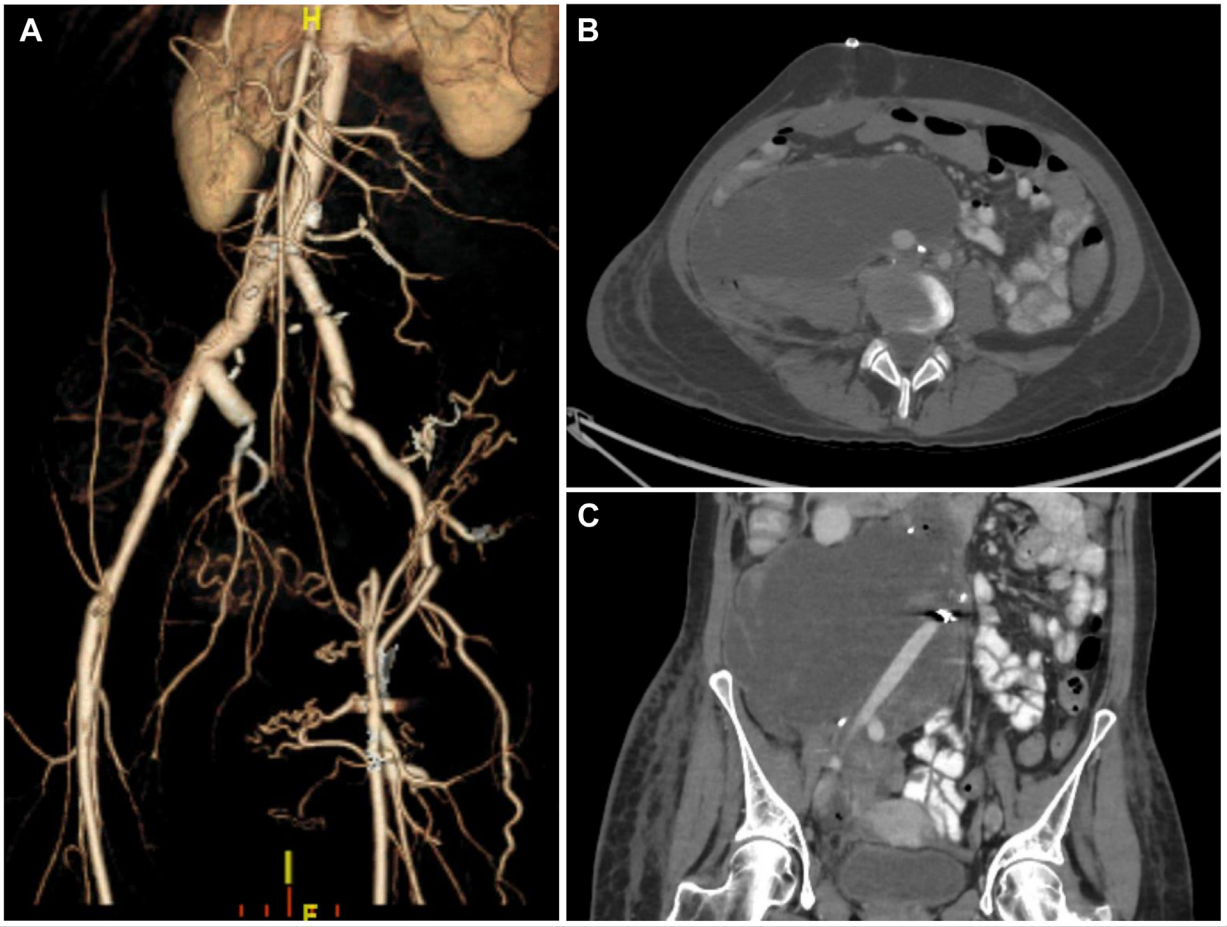

Fig 3. Computed tomography angiography (CTA) of the patient after elective repair of right iliac artery. **A,** Three-dimensional reconstruction showing interposition right common iliac artery (CIA) to external iliac artery bypass using an 8-mm Dacron graft and end-to-side reconstruction of the right internal iliac artery (IIA) using an 8-mm Dacron graft. Axial (**B**) and coronal (**C**) images showing large postoperative retroperitoneal hematoma.

Our previous work with the Low Frequency Disease Consortium describing a multi-institutional experience in VEDS diagnosis, demonstrated that nearly 10% of the submitted cases had nonpathogenic variants in *COL3A1* and, thus, did not have VEDS.[10] We did not have additional genetic workup in that cohort; thus, it is difficult to estimate how many patients had cEDS or other VEDS-like conditions. Our case and the previous study are is relevant to vascular surgeons who encounter aneurysms and dissection in young individuals and who should be aware that cEDS can have associated arteriopathy similar to VEDS, and, thus, genetic testing is indicated to establish the diagnosis. Additionally, *COL5A1* has been described in cases that have the appearance of fibromuscular dysplasia.[10]

Vascular manifestations of cEDS include aortic root dilation,[11] which our patient did not have. Easy bruising and hernias are minor diagnostic criteria in cEDS, and both were seen in our patient. The number of identified pathogenic variants resulting in different forms of EDS continues to grow with the increasing availability of genetic testing. In our patient's case, her arteriopathy might be due to a second, as yet to be identified, pathogenic variant causing a second hit phenomenon. An additional consideration is the possibility of mosaicism.[12] We did not perform genetic testing on the tissue and, thus, cannot confirm nor exclude this possibility.

Patients with cEDS requiring repair of arterial aneurysms or dissections should be counseled regarding a known increased risk of bleeding.[13] Heparin reversal and the use of topical hemostatic agents could mitigate this risk; however, large data to validate the optimal approach are lacking. Given the lack of large natural history studies for this particular population, precautions similar to those undertaken in the care of patients with VEDS undergoing operative aortic or arterial repairs can be practiced, with a low threshold to obtain imaging studies if the postoperative course is unexpected.[14-18]

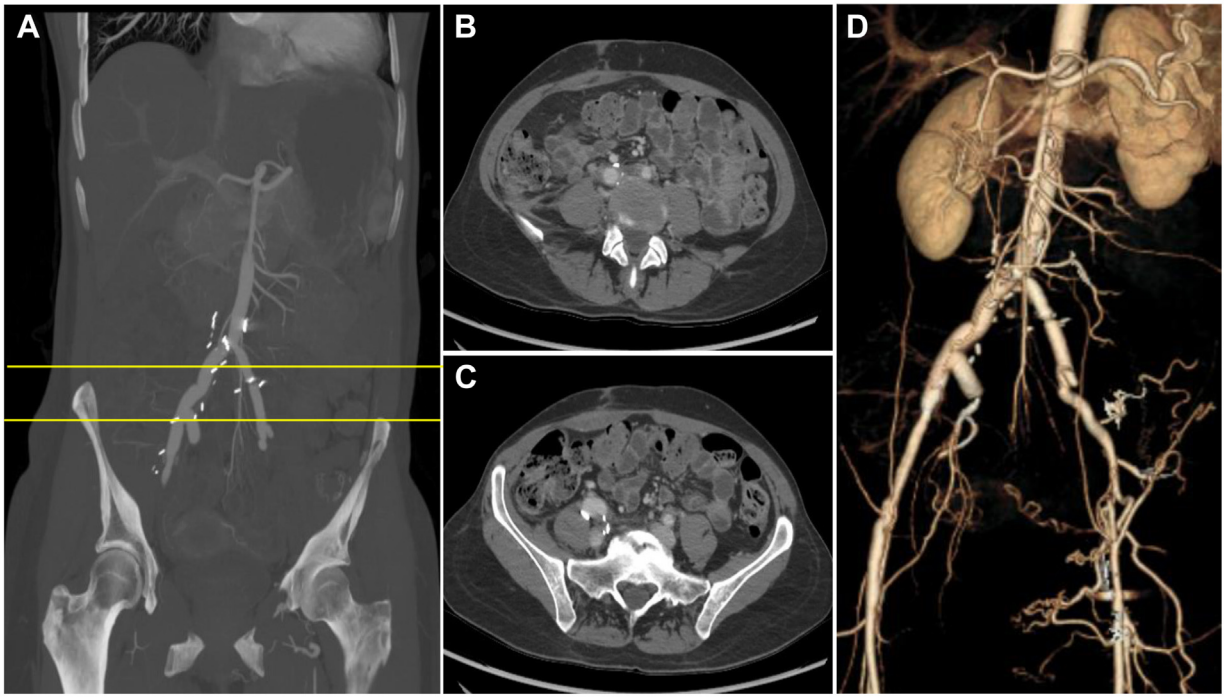

Fig 4. Computed tomography angiography (CTA) including three-dimensional reconstruction of the patient 11 months postoperatively. **A,** Coronal images showing stability of bilateral repairs and resolution of large retroperitoneal hematoma. *Yellow lines* indicate level of axial image slices in superior (**B**) and inferior (**C**) views. **D,** Three-dimensional reconstruction of final postoperative imaging.

Table. Summary of case reports describing patients with genetically confirmed classic Ehlers-Danlos syndrome (cEDS) and iliac arteriopathy

Investigator	Age, years; sex	*Col5A1* variant	Presenting symptoms	Family history
Borck et al, 2010[4]	42; Male	*COL5A1* c.3184 C>T, p. Arg1062[a]	Left CIA rupture after arterial ligation and iliac femoral bypass grafting; recurrent inguinal hernias; easy bruising since childhood; varicose veins	None
Mehta et al, 2012[5]	43; Male	*COL5A1* c.2185 C>T, p.Gln729[a] a heterozygous (single) frameshift mutation in exon 23	Isolated CIA dissection with aneurysm occurring during exercise; uncovered stent in right CIA; iatrogenic left CIA dissection, treated with stenting; recurrent skin tears, joint laxity, tendon rupture; prior knee and elbow surgical repair	Two children with joint laxity, atrophic scars, and skin hyperextensibility

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Table. Continued.

Investigator	Age, years; sex	*Col5A1* variant	Presenting symptoms	Family history
Monroe et al, 2015[6]	34; Male	*COL5A1* c.4610 G>T, p.Gly1537Val	Right iliac artery rupture causing death due to uncontrollable hemorrhage in operating room; on autopsy, tissues were compared to "rice paper"; translucent skin; hypermobility	Mother died of renal artery rupture; brother died at 43 years old of subarachnoid hemorrhage and had a previous ruptured left subclavian artery at age 15 and celiac artery aneurysm repaired at age 18 with significant bleeding
Richer et al, 2020[10]	54; Male	*COL5A1* c.1540 G>A, p.(Gly514Ser)	CIA and external iliac artery dissection with rupture; atrophic scars; velvety and doughy skin; recurrent joint subluxation	Daughter and nephew with same mutation with subluxation; no dissections
Richer et al, 2020[10]	44; Female	*COL5A1* c.1540 G>A, p.(Gly514Ser)	CIA dissection; abdominal striae; wound dehiscence	Unknown
Richer et al, 2020[10]	52; Female	*COL5A1* c.1540 G>A, p.(Gly514Ser)	External iliac artery dissection; atrophic scars; wound dehiscence	Unknown

CIA, Common iliac artery.
[a]Indicates a mutation resulting in a stop codon.

CONCLUSIONS

Arteriopathy, including aneurysms, dissections, and rupture, is a rare complication of cEDS. Pathogenic variants in *COL5A1* should be considered in the differential diagnosis of patients presenting with a clinical phenotype similar to VEDS, and genetic testing should be performed to confirm the diagnosis.

DISCLOSURES

None.

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