Multidisciplinary hybrid approach to management of a thoracoabdominal aneurysm in a patient with both Loeys-Dietz and vascular Ehlers-Danlos syndrome

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ABSTRACT

Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome are genetic aortopathies that result from abnormal collagen matrix formation associated with vascular complications and early death. Identification of simultaneous COL3A1 and SMAD3 mutations as well as subsequent open and endovascular repair have not been reported. We present a case of a staged complete aortic replacement in a patient with a 7-cm aneurysm of his aortic arch and confirmed genetic mutations for Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome. This case highlights that, despite increased operative risk, successful staged repair of the entire aorta can be achieved in a patient with multiple severe genetic aortopathies. (J Vasc Surg Cases Innov Tech 2024;10:101519.)

Keywords: Aortopathy; Thoracoabdominal aneurysm; Loeys-Dietz; Ehlers-Danlos

Loeys-Dietz syndrome (LDS) and vascular Ehlers-Danlos syndrome (vEDS) are genetic aortopathies associated with vascular complications including aortic aneurysm and dissections.[1,2] LDS is an autosomal dominant disorder linked to a mutation involved in TGFBR1, TGFBR2, and SMAD3.[2,3] Patients with LDS classically exhibit hypertelorism, cleft palate, and arterial tortuosity, as well as aortic aneurysms and dissections.[4] vEDS is an autosomal dominant mutation in COL3A1 that results in defective or decreased type III collagen. It is characterized by joint hypermobility, skin elasticity, easy bruising, spontaneous bleeding, and a variety of vascular complications.[5,6]

Endovascular and open repairs have been described previously[7-9]; however, the optimal approach is unclear, and some surgeons consider specific mutations a contraindication to repair owing to significant morbidity and mortality resulting from bleeding, poor arterial wall strength, and tissue fragility.

We present a staged hybrid aortic repair in a patient with confirmed genetic mutations for both LDS and vEDS.

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CASE REPORT

A 34-year-old man presented with an aneurysm of the aortic arch. Four years prior, he underwent an ascending aortic repair for a type A dissection at an outside institution and was then lost to follow-up. His past medical history was notable for easy bruising and his family history included an aortic aneurysm in his grandmother and a son with bilateral clubfeet and a bicuspid aortic valve. Computed tomography angiography demonstrated residual dissection through the visceral segment with degeneration of his aortic arch to 7.0 cm (3.9 cm 4 years prior), a 4-cm infrarenal aneurysm, and a 2.7-cm left common iliac aneurysm (Fig 1).

This case was discussed at our institutional multidisciplinary thoracic aortic program, which includes vascular surgery, cardiac surgery, cardiology, and medical genetics and aims to comprehensively determine the optimal treatment. Given his age and family history, genetic testing was ordered, and a staged repair was planned to begin with a left carotid to subclavian transposition and zone 2 aortic arch replacement. Subsequently, a thoracic endovascular aortic repair (TEVAR) extension to the celiac artery and finally open thoracoabdominal aortic aneurysm repair was performed. Informed consent has been obtained from the patient for publication of the case report and accompanying images.

Operative technique

Left carotid to subclavian transposition. In preparation for a zone 2 arch replacement with a frozen elephant trunk, a left carotid to left subclavian artery transposition with circumferential felt wrapping of the subclavian artery was performed. This procedure was completed without complication, despite extremely friable tissues.

Zone 2 aortic arch replacement with frozen elephant trunk

The patient returned to the operating room on postoperative day 2 and underwent zone 2 aortic arch replacement and a

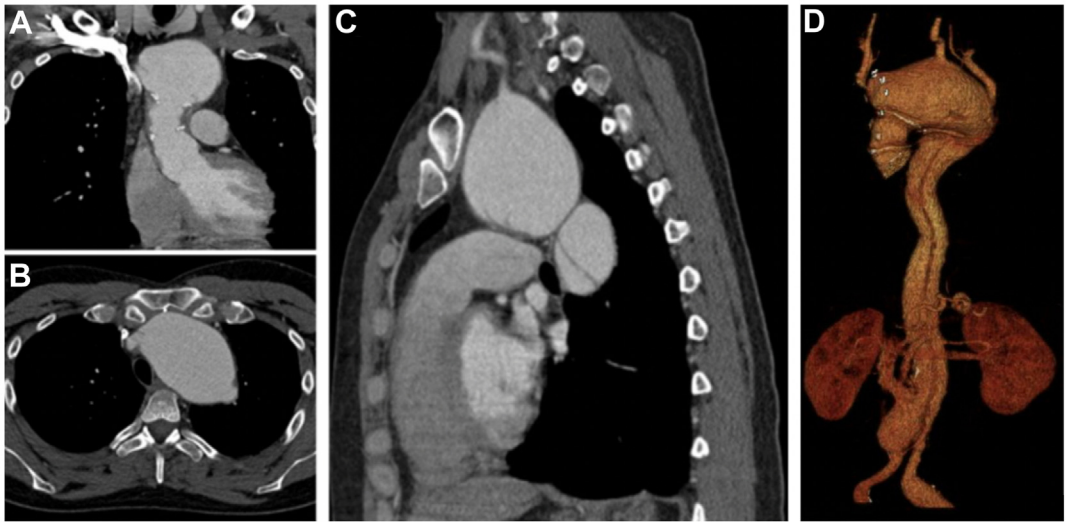

Fig 1. Preoperative computed tomography angiography (*CTA*) demonstrated degeneration of the aortic arch to 7 cm. **(A)** Coronal view, **(B)** axial view, **(C)** sagittal view, and **(D)** three-dimensional postprocessing images of a CTA examination demonstrating the degeneration of the aortic arch to 7 cm, a 4 cm infrarenal aortic aneurysm, a left common iliac aneurysm that reached 2.7 cm, and a residual aortic dissection extending into the infrarenal aorta.

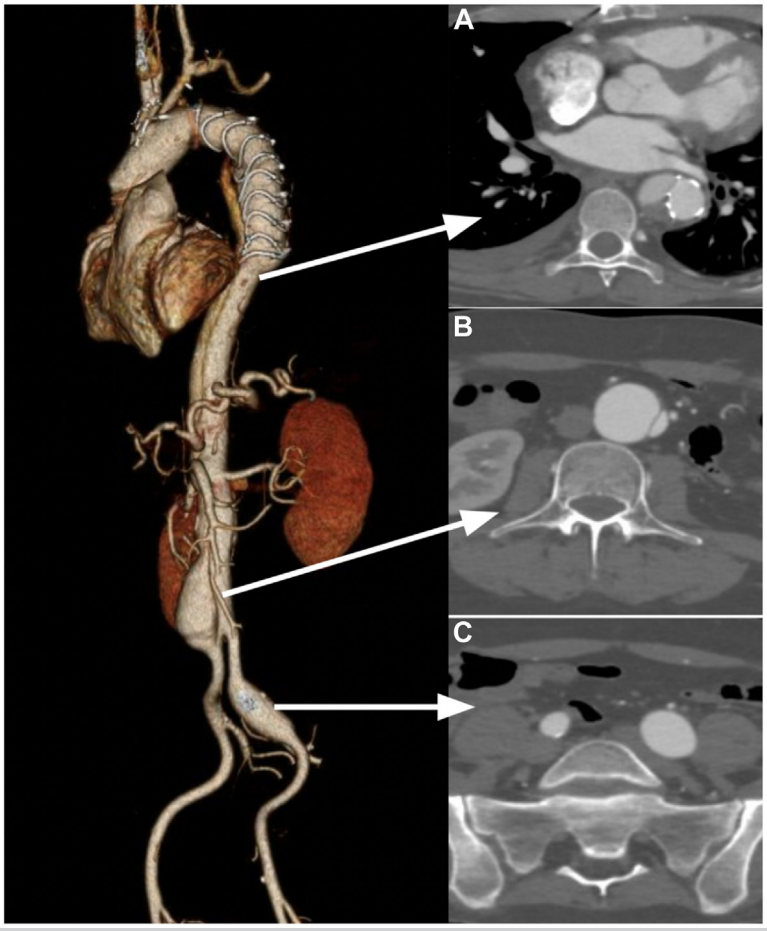

Fig 2. Computed tomography angiography (*CTA*) after zone 2 arch replacement with a frozen elephant trunk axial view demonstrated **(A)** residual dissection of the distal thoracic aorta with lack of distal seal **(A)**, an infrarenal abdominal aortic aneurysm **(B)**, as well as a left common iliac artery aneurysm **(C)**.

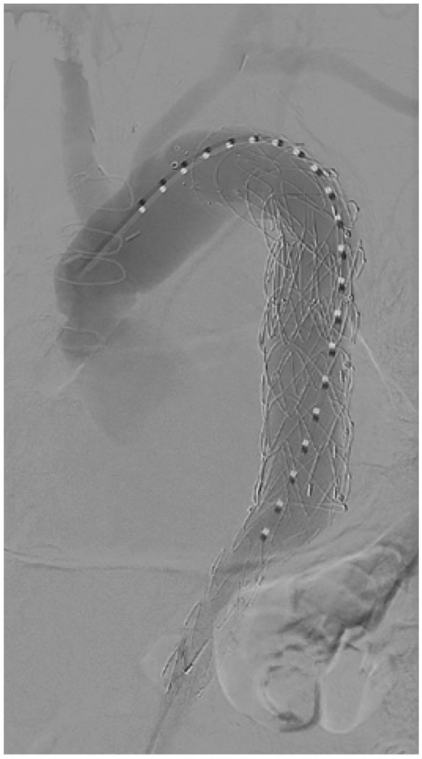

Fig 3. Completion angiogram demonstrated widely patent arch vessels.

frozen elephant trunk using the Thoraflex hybrid graft (Terumo Medical, Somerset, NJ). The frozen elephant trunk is a hybrid technique that allows to treat the aortic arch as well as the descending thoracic aorta simultaneously, combining a distal endovascular stent graft and a proximal open surgical repair.

This stage began with a redo sternotomy, right axillary artery cannulation and careful percutaneous left common femoral artery access under ultrasound guidance. Intravascular ultrasound examination confirmed the wire position in the aortic true lumen. The patient underwent cardioplegia followed by circulatory arrest, the graft was deployed over the previously placed wire, and anastomoses performed using reinforced using felt strips.

The patient experienced a prolonged postoperative course owing to a nondisabling ischemic stroke, deep venous thrombosis and a spontaneous retroperitoneal hematoma, but was discharged home independently on postoperative day 52 (Fig 2).

TEVAR extension

During recovery, genetic testing confirmed both vEDS and LDS. Specifically, he was noted to be heterozygous for a pathogenic variant in COL3A1 [NM_000,090.3:c.855_872del, p.(Leu289_Gly294del)], a gene that encodes the proα1(III) chains of type III procollagen, and heterozygous for a pathogenic variant in SMAD3 (NM_005,902.4:c.401-6G>A), a gene that encodes the protein SMAD3, a participant in the transforming growth factor-β signaling pathway.

Three months after aortic arch repair and owing to his residual aortic aneurysm with the lack of a distal seal, he underwent TEVAR extension via percutaneous single common femoral artery access. Care was taken with ultrasound guidance and a decision was made to utilize a single 22F Dry Seal (W. L. Gore & Associates, Flagstaff, AZ) to minimize manipulation of the access site.

After intravascular ultrasound examination and an arteriogram, TEVAR extensions using a 38- to 34-mm × 150-mm followed by 32- to 28-mm × 150-mm Terumo Relay tapered endografts were deployed relining the Thoraflex to level of the celiac artery (zones 3-5) (Fig 3). Devices were landed into the surgical graft proximally and without oversizing of the distal native aorta. Because the patient had chronic dissection and would need completion aortic repair, no distal seal was expected, and oversizing was not performed to avoid the risk of further entry tears. The TEVAR device was extended to the level of the celiac to improve his opportunity for aortic remodeling, decrease retrograde perfusion to his arch aneurysm, and stage him for an open thoracoabdominal aneurysm repair. The access site was closed successfully. The patient was discharged home on the postoperative day 2 without complication.

Open thoracoabdominal aortic aneurysm repair

At the 6-month follow-up, imaging showed excellent aortic remodeling without residual aneurysmal degeneration; however, by 12 months the patient developed severe degeneration of his distal thoracic aorta to 5 cm from 2.6 cm 4 months earlier (Fig 4). After multidisciplinary discussion with the patient, including a high concern for morbidity and mortality, the patient elected to proceed with completion aortic repair.

A left thoracoabdominal incision starting in the sixth intercostal space was performed. Via this retroperitoneal exposure the diaphragm was transected using an ENDO-GIA stapler and then vascular control was obtained around his TEVAR, each visceral vessel, and the iliac arteries distally. The infrarenal aorta and iliac vessels were clamped and a bottom-up approach was undertaken to maximize inline visceral perfusion. Of note, a graft was fabricated on the back table from two bifurcated Dacron grafts to ensure sufficient limbs for all four visceral vessels, as well the perfusion catheter.

Using this approach, the infrarenal aorta was clamped and bilateral common iliac artery anastomoses performed with felt wrapping, the patient was then placed into venous-arterial extracorporeal membrane oxygenation (ECMO) via a right common femoral vein sheath and an arterial cannula connected into the anterior limb to maintain distal perfusion. The visceral vessels then were bypassed in a sequential fashion until all visceral vessels were perfused via the ECMO circuit. Finally, the prior TEVAR was clamped and the proximal anastomoses was performed incorporating all layers of the aorta, as well as the TEVAR device and reinforced with external Teflon felt.

The patient's hospital course was uncomplicated, and he was discharged home on postoperative day 14. At the 2-month follow-up, the patient returned to baseline, with normal cardiovascular function, blood pressure control with a beta-blocker, angiotensin 2 receptor antagonist, aspirin, and a statin (Fig 5).

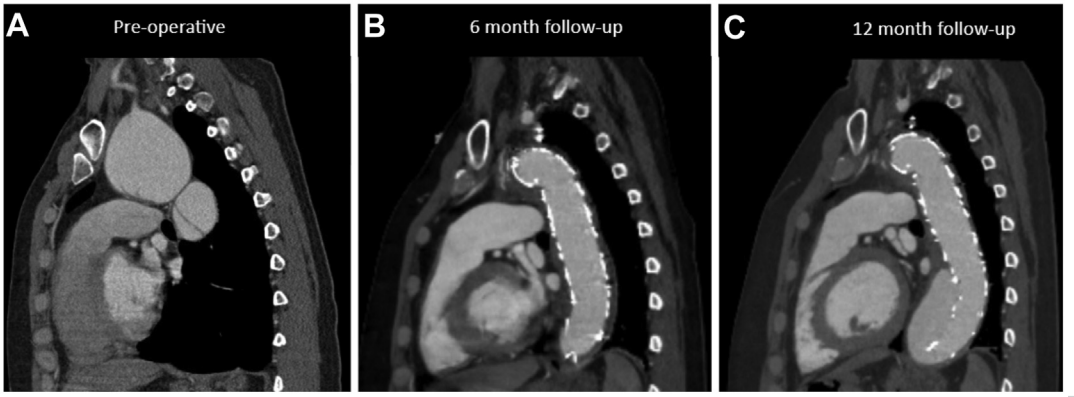

Fig 4. (A) Preoperative computed tomography angiography (*CTA*) sagittal view demonstrated degeneration of the aortic arch up to 7 cm. **(B)** Postoperative 6-month follow-up sagittal view demonstrated excellent aortic remodeling after staged repair. **(C)** Postoperative 12-month follow-up sagittal view demonstrated new degeneration of the distal thoracic aorta.

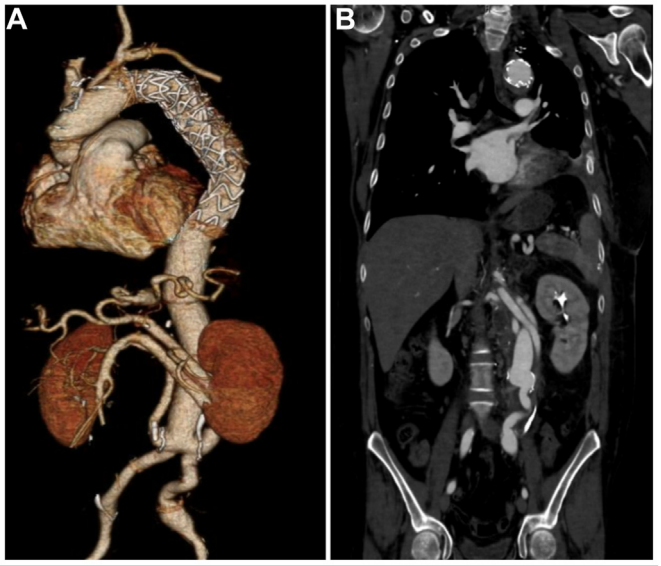

Fig 5. One-month postoperative computed tomography angiography (*CTA*). **(A)** Three-dimensional postprocessing images of a CTA demonstrating the complete aortic repair **(B)** Coronal CTA image demonstrating patent visceral vessels.

He is scheduled for routine ongoing multidisciplinary follow-up with genetic cardiology and vascular surgery.

DISCUSSION

The presented case describes the first reported case of a patient with severe aortopathy owing to both LDS and vEDS. There are important considerations to be highlighted. First, although open aortic surgery remains the gold standard in patients with genetic aortopathies,[10-12] endovascular repair has been successful in selected cases for patients with LDS as well as vEDS.[13-15] Nonetheless, the use of endovascular techniques has historically presented challenges owing to increased risks of access site complications, including retrograde dissections, vessel perforation, and pseudoaneurysm formation.[16,17]

The hybrid approach provided the optimal repair with careful endovascular technique and allowed the patient to be staged adequately, as has been described previously in patients without simultaneous genetic aortopathies.[18,19] In his case, complete repair would have increased the already high risk of morbidity, including bleeding, prolonged operative time, and spinal cord ischemia, all of which were avoided successfully. Intraoperative considerations for his open procedures included gentle tissue handling and felt wrapping of all anastomoses, standard practice for all patients with genetic aortopathies. Additionally, a bottom-up approach using ECMO and direct retransfusion allowed for the time needed for delicate tissue work without prolonged visceral ischemia or massive blood loss.

Endovascular techniques also contributed to successful completion, despite the delicate tissues. All endovascular devices were landed in prior surgical grafts, avoiding risk for retrograde dissection and postdeployment ballooning was avoided to decrease the risk of new entry tears. Despite prior percutaneous access and no tactile differences between subcutaneous tissue and vessel walls (similar to passing a needle through a single stick of soft butter), closure devices were placed successfully in the correct location based on pulsatile bleeding arising from the flush marker lumen and confirmed with ultrasound guidance. No additional devices were deployed in either stage of repair. Percutaneous access is routine for all our patients (including those with genetic aortophathy) at our institution. Finally, the decision was made to use only single site access and place a larger Dry Seal sheath through which to deploy the TEVAR to avoid access site manipulation.

CONCLUSIONS

The case is the first to be reported of a patient with a confirmed genetic mutation for both LDS and vEDS. This case demonstrates that, with multidisciplinary preoperative planning and careful technique, successful treatment can be achieved even for patient with multiple aggressive genetic mutations using a hybrid approach and percutaneous access.

DISCLOSURES

None.

REFERENCES

1. Shalhub S, Byers PH, Hicks KL, et al. A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed vascular Ehlers-Danlos syndrome. *J Vasc Surg*. 2019;70:1543–1554.
2. MacCarrick G, Black JH 3rd, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.
3. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet*. 2005;37:275–281.
4. Goyal A, Keramati AR, Czarny MJ, Resar JR, Mani A. The genetics of aortopathies in clinical cardiology. *Clin Med Insights Cardiol*. 2017;11:1179546817709787.
5. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med*. 2000;342:673–680.
6. Black 3rd JH. Chapter 140: aneurysms caused by connective tissue abnormalities. In: Cronenwett J, Johnston W, eds. *Rutherford's vascular surgery*. 7th ed. Philadelphia: Elsevier; 2023.
7. Bellamkonda KS, Dardik A, Nassiri N. Endovascular repair of a dissecting pararenal abdominal aortic aneurysm in a patient with type III Loeys-Dietz syndrome. *J Vasc Surg Cases Innov Tech*. 2020;7:10–15.
8. Tenorio ER, Tallarita T, Mirza AK, Macedo TA, Oderich GS. Endovascular repair of large intercostal artery patch aneurysm using branch stent-graft in a patient with Loeys-Dietz syndrome. *J Thorac Cardiovasc Surg*. 2020 Feb;159:e95–e99.
9. Eleshra A, Panuccio G, Spanos K, et al. Endovascular repair of post-dissection thoracoabdominal aortic aneurysm in patients with vascular Ehlers-Danlos syndrome. *J Endovasc Ther*. 2021;28:804–811.
10. Czerny M, Schmidli J, Adler S, et al. EACTS/ESVS scientific document group. Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch: an expert consensus document of the European Association for Cardio-Thoracic surgery (EACTS) and the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2019;57:165–198.
11. Svensson LG, Kouchoukos NT, Miller DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg*. 2008;85:S1–S41.
12. Khalique Z, Lyons OT, Clough RE, et al. Successful endovascular repair of acute type B aortic dissection in undiagnosed Ehlers-Danlos syndrome type IV. *Eur J Vasc Endovasc Surg*. 2009;38:608–609.
13. Pellenc Q, Girault A, Roussel A, et al. Optimising aortic endovascular repair in patients with Marfan syndrome. *Eur J Vasc Endovasc Surg*. 2020;59:577–585.
14. Shalhub S, Eagle KA, Asch FM, LeMaire SA, Milewicz DM. GenTAC investigators for the genetically Triggered thoracic aortic aneurysms and cardiovascular conditions (GenTAC) consortium. Endovascular thoracic aortic repair in confirmed or suspected genetically triggered thoracic aortic dissection. *J Vasc Surg*. 2018;68:364–371.
15. Bade MA, Queral LA, Mukherjee D, Kong LS. Endovascular abdominal aortic aneurysm repair in a patient with Ehlers-Danlos syndrome. *J Vasc Surg*. 2007;46:360–362.
16. Cikrit DF, Miles JH, Silver D. Spontaneous arterial perforation: the Ehlers-Danlos specter. *J Vasc Surg*. 1987;5:248–255.
17. Tinelli G, Ferraresi M, Watkins AC, et al. Aortic treatment in connective tissue disease. *J Cardiovasc Surg*. 2019;60:518–525.
18. Naiem AA, Doonan RJ, Steinmetz OK. Hybrid repair of a Thoracoabdominal aortic aneurysm associated with Loeys-Dietz syndrome. *EJVES Vasc Forum*. 2021;51:23–26.
19. Solomon JR, Braverman AC, Ohman JW. Endovascular and hybrid repair in patients with heritable thoracic aortic disease. *Ann Vasc Surg*. 2022;87:124–139.

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