Case studies in heritable vascular disease: Proceedings of the UTHealth Houston Multidisciplinary Aortic Conference

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ABSTRACT

Heritable thoracic aortic disease is caused by dominantly inherited mutations in more than a dozen genes, including *TGFB2* mutations that cause Loeys-Dietz syndrome. McGovern Medical School at UTHealth Houston convenes a regular conference that includes cardiothoracic and vascular surgeons, cardiologists, geneticists, radiologists, and pathologists to formulate multidisciplinary approaches for the management of complex heritable thoracic aortic disease cases. In this report, we highlight the unique management of individuals with distinct presentations of Loeys-Dietz syndrome owing to *TGFB2* mutations. (J Vasc Surg Cases Innov Tech 2025;11:101684.)

Keywords: Heritable thoracic aortic diseases; HTAD; *TGFB2*; Loeys-Dietz syndrome; LDS; Genetic testing; Aortic dissection

Aortic disease is a multifactorial condition that predisposes to sudden cardiovascular deaths. Thoracic aortic dissection (TAD), a rare type of aortic disease, occur in 5 to 10 per 100,000 individuals per year.[1] Genetic factors strongly influence the development of TAD, thoracic aortic aneurysms (TAAs), and other types of thoracic aortic disease. Approximately 20% of individuals with TAD have a first-degree relative with aortic disease, termed heritable thoracic aortic disease (HTAD).[2] Knowledge of the mutated gene can predict clinical presentations and inform management of HTAD cases with direct benefits to patient care.

Many single gene mutations cause HTAD and are usually inherited as an autosomal dominant trait in families.[3] One example is the *TGFB2* gene, which is associated with Loeys-Dietz syndrome (LDS).[3,4] *TGFB2* mutations cause a distinctive syndromic presentation of TAA, with a high probability of arterial dissection, as well as musculoskeletal and pulmonary malformations.[4]

A multidisciplinary approach to diagnosis and management that draws on the unique perspectives of specialist clinicians and researchers can significantly improve patient outcomes. For more than a decade, the UTHealth Multidisciplinary Aortic and Vascular Conference has convened to highlight clinical and genetic features of HTAD cases, review state-of-the-art medical and interventional treatments, and formulate a collaborative care plan with our experienced panel of specialists. Participants include cardiothoracic and vascular surgeons, clinical geneticists, genetic counselors, cardiologists, and cardiovascular pathologists. As appropriate, we may invite colleagues and expert consultants from other institutions to contribute to these discussions. This conference is scheduled as a monthly conference, and the patients presented are usually patients who underwent a recent intervention, had an admission owing to aortic disease, or are seen in the clinic by one of the participating faculty. We usually present patients with known genetic disease or those who are ≤65 years and present with an aortic pathology.

We obtained written informed consent to disclose individual clinical information from the subjects of these case vignettes.

CASE REPORT 1

A 33-year-old female physician was evaluated in clinic. Three weeks before, she had presented to the emergency room with crushing substernal chest pain, visual changes, and lower extremity weakness. She was diagnosed with an acute type A_9 aortic dissection and a 5.4-cm TAA involving the root and proximal ascending aorta, presenting with cardiogenic shock, owing to acute severe aortic regurgitation (Fig 1).

After emergent valve-sparing root and ascending replacement (David procedure), her postoperative course was complicated by acute renal injury, pericarditis (treated with colchicine), chest pain controlled with a multimodal pain regimen, and

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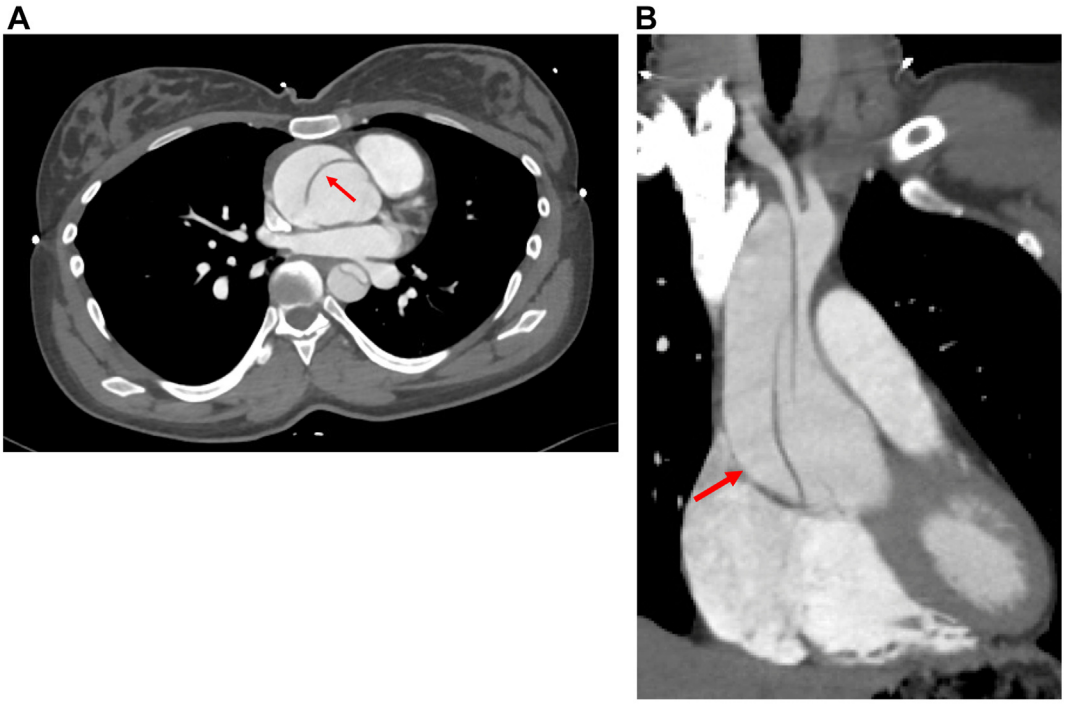

Fig 1. Computed tomography angiography (*CTA*) images of the chest demonstrating type A9 aortic dissection. **(A)** Axial images demonstrating the dissection flap in the proximal ascending aorta (*red arrow*) with ascending thoracic aortic aneurysm (*TAA*) measuring 5.4 cm. **(B)** Coronal view of CTA of the chest demonstrating type A dissection and ascending aortic aneurysm (*red arrow*).

coagulopathy. She was discharged home with prescriptions for aspirin, atorvastatin, colchicine, and metoprolol succinate.

Five weeks after surgery, the patient had recovered and experienced no residual symptoms. She had no history of hypertension or any other medical diagnoses. She never smoked, drank alcohol, or used recreational drugs. Physical examination was remarkable for mild retrognathia, long palpebral fissures, mild lumbar scoliosis, hyperextensible knees, hyperflexible elbows and wrists, and pes planus. Family history is significant; her father had been diagnosed with TAA; mother with lupus; brother with TAA, scoliosis, spinal stenosis, and degenerative joint disease; one maternal aunt with lupus; and her paternal grandfather died suddenly from a cardiac event in his 50s. All other family members are without medical conditions and no one is known to have had a TAD. The patient's genealogical tree is summarized in Fig 2. A transthoracic echocardiogram demonstrated normal biventricular function. The resuspended aortic valve was thin and pliable without residual regurgitation.

Computed tomography angiography (CTA) of the chest, abdomen, and pelvis performed 1 month after her initial aortic dissection identified a residual type B aortic dissection with stable mild residual dilation of the proximal descending thoracic aorta (3.8 cm) and left common iliac artery (2.1 cm). At 18 weeks after surgery, a repeat CTA demonstrated progressive dilation of the proximal descending thoracic aorta to 4.2 cm. Genetic tests identified a pathogenic variant in *TGFB2* (p.Y126Sfs*19) that is consistent with LDS. Aortic pathology demonstrated marked elastin fiber damage, mild accumulation of extracellular matrix material, and increased fibrosis in the intimal, subintimal, and medial layer (Fig 3). Owing to the progressive dilation in her follow-up CTA, she underwent intensive surveillance imaging at 3-month intervals. In the following studies, there was a continued slow growth of 2 to 3 mm in each scan. Therefore, the patient underwent an open thoracoabdominal aortic aneurysm (TAAA) extent II repair. She recovered well and was discharged home at POD 6. She was readmitted on postoperative 20 owing to occlusion of the left renal artery bypass graft. She underwent catheter-guided thrombectomy and angioplasty. Owing to significant graft tortuosity, placement of a stent was not feasible. At the 3-month follow-up, CTA demonstrated patent bypasses and good perfusion to both kidneys. The patient is currently following up in the clinic with routine annual follow-ups.

CASE REPORT 2

A 33-year-old man presented to the emergency room with chest tightness, neck pain, and moderate exertional dyspnea. CTA disclosed an acute type A aortic dissection and a TAA involving the root and proximal ascending aorta. He underwent emergent aortic mechanical valve replacement with a composite graft (modified Bentall procedure) and replacement of the ascending aorta and hemiarch. Postoperative CTA revealed normal arch and descending thoracic aortic diameters but dilation of the left common iliac artery (1.6 cm). He recovered uneventfully with no significant postoperative complications

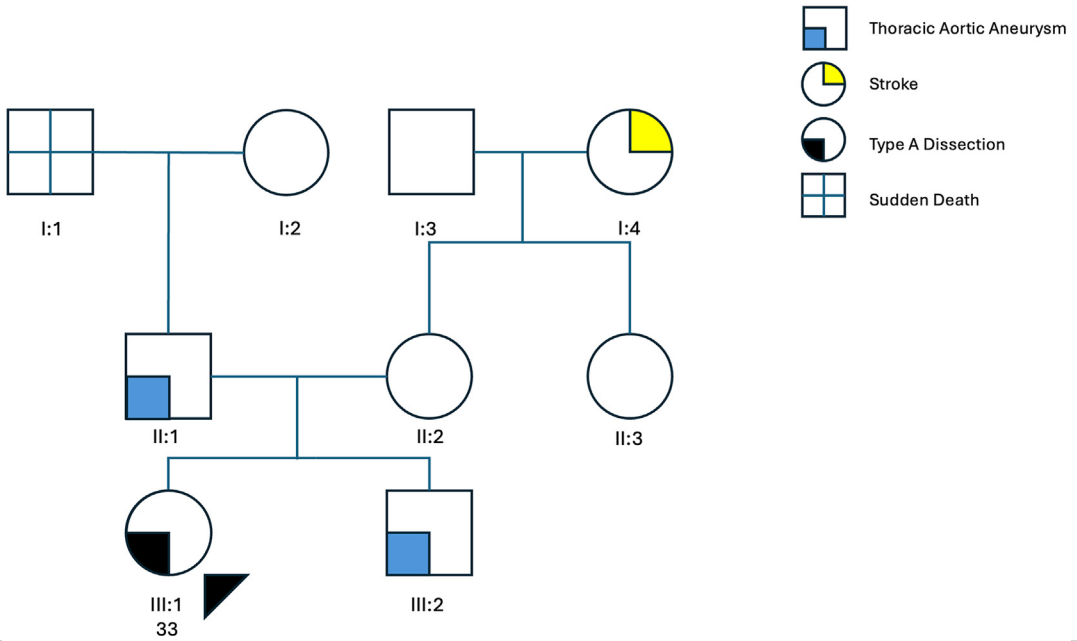

Fig 2. Pedigree chart representing the family history of the proband (III:1) with a *TGFB2*-related thoracic aortic disease (case 1). The proband, a 33-year-old woman, presented with an acute type A dissection and thoracic aortic aneurysm (*TAA*). Her father (II:1) and brother (II:2) were diagnosed with TAAs, and her paternal grandfather (I:1) died suddenly, likely from an unrecognized aortic event. The chart also notes other relevant cardiovascular features, such as the proband's mother (I:4), who suffered a stroke. Genetic testing confirmed the presence of a *TGFB2* mutation in the proband.

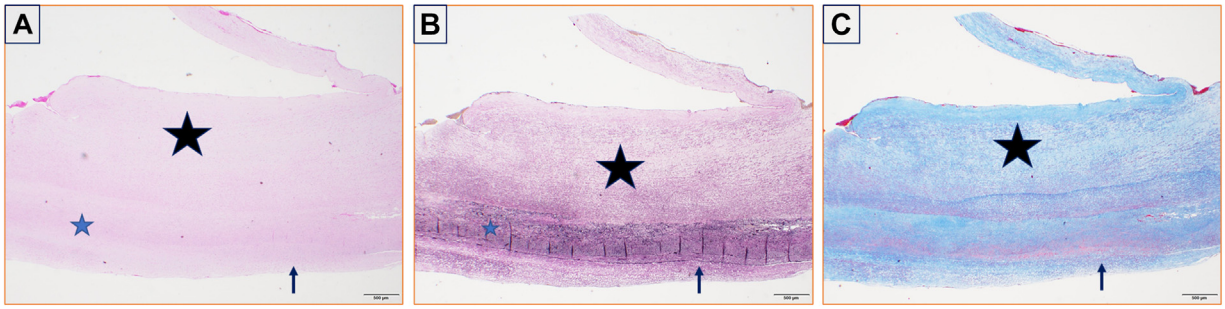

Fig 3. (A) Hematoxylin and eosin stain. **(B)** Special stain elastin. **(C)** Special stain trichrome. The black arrow indicates the intima. The red star indicates the medial elastin damage and loss. A black star indicates the healed, fibrotic false lumen. This aortic specimen demonstrates a chronically dissected aortic wall, with a healed false lumen, fibrothickening of the intima, and significant medial elastin fiber damage and loss.

and was discharged on hospital day 8 with prescriptions for amlodipine, enoxaparin, losartan, metoprolol, and warfarin.

After 1 month, the patient had recovered completely and denied any residual symptoms. His physical examination was significant for a high arched palate with retrognathia, striae, pes planus, joint hypermobility, and lower extremity varicosities. He never smoked or used recreational drugs and drank alcohol socially. He had no family history of TAA or aortic dissection (Fig 4). On physical examination, he was normotensive with appropriate mechanical valve sounds and a brisk systolic ejection murmur.

At 14 months after dissection, surveillance images showed a new focal dissection in the proximal segment of the brachiocephalic artery (2.3 cm) and dilation of the right iliac artery (1.6 cm). Within 3 years, the diameter of the brachiocephalic artery (2.9 cm), aortic arch (4.2 cm), and proximal descending thoracic aorta (5.4 cm) had significantly increased (Fig 5).

He underwent extent II TAAA repair with bypasses to the celiac, mesenteric, and renal arteries, as well as bypass to intercostal arteries T9 to T12. His recovery was complicated by coagulopathy from warfarin for his mechanical valve with chest wall hematoma that required drainage. Genetic tests identified a de novo pathogenic variant in *TGFB2* (p.R330 C) that is consistent with LDS. Aortic pathology demonstrated thickening of the true intima by atherosclerotic plaque and a pseudointima lining the false lumen. Medial degeneration with focal necrosis and disruption of elastic fibers is also present (Fig 6).

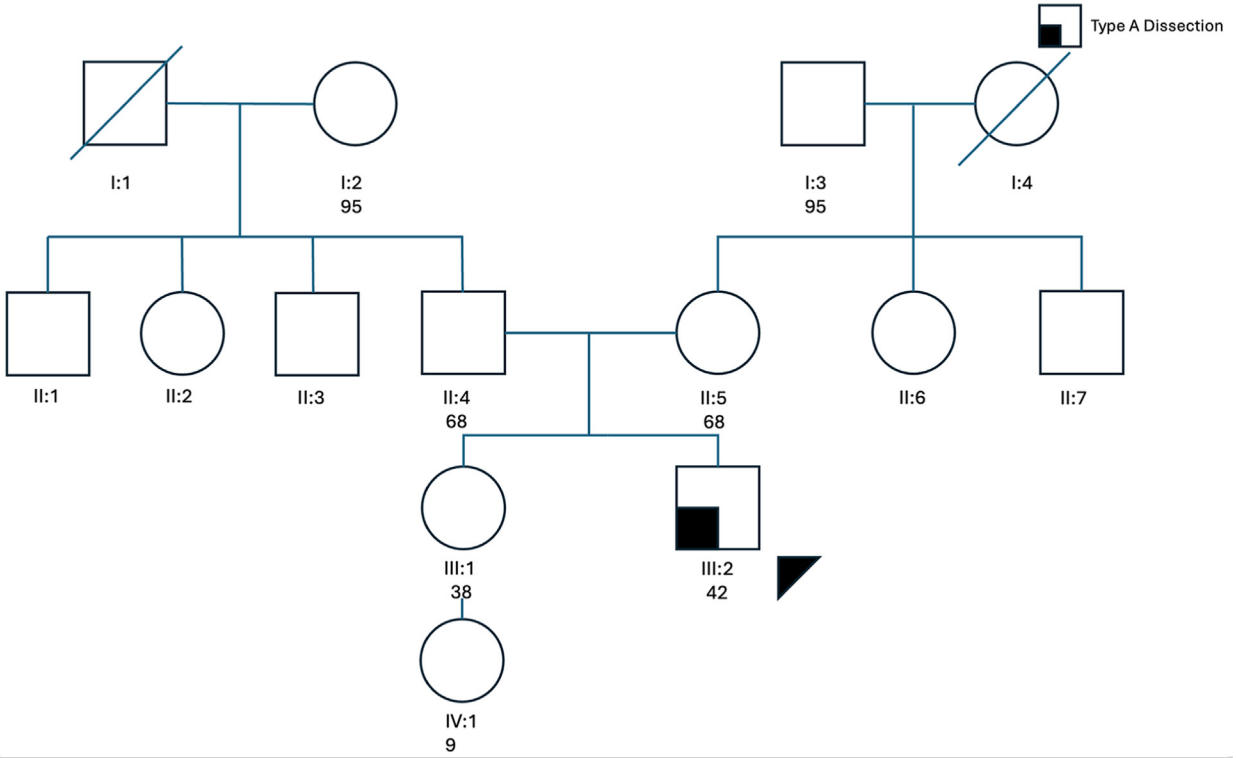

Fig 4. Pedigree chart representing the family history of a 33-year-old man (III:2) (case 2) who presented with an acute type A aortic dissection. The proband's father (II:5) and mother (II:4) are unaffected and alive at age 68. Genetic testing identified a de novo *TGFB2* mutation in the proband (III:2).

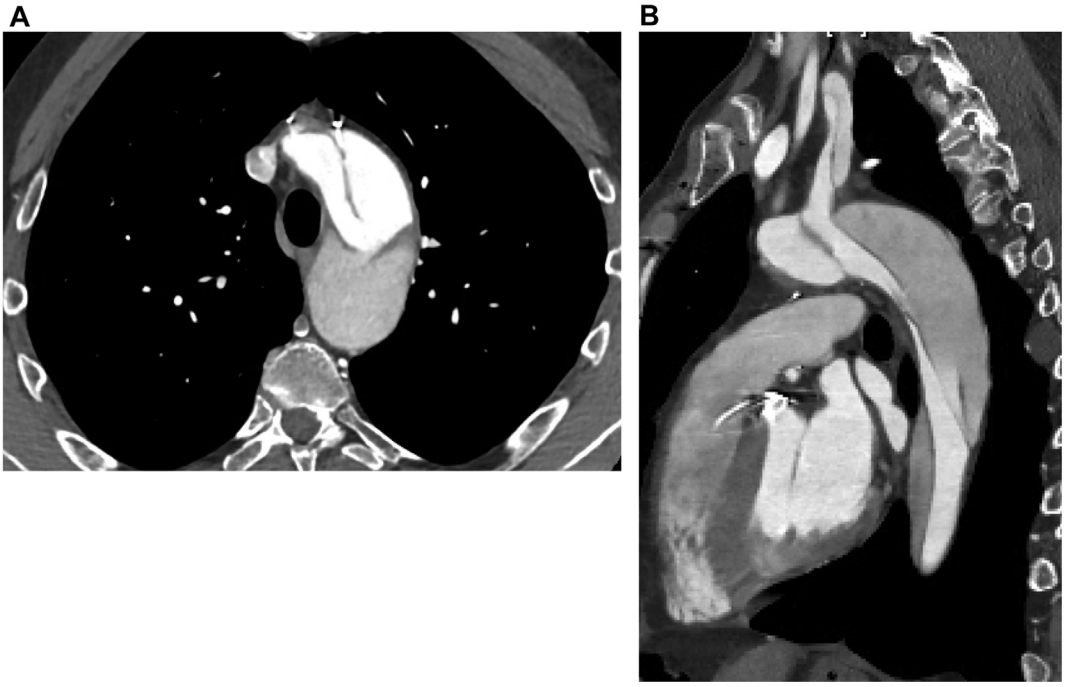

Fig 5. Computed tomography angiography (*CTA*) images of the chest demonstrating chronic type B aortic dissection. **(A)** Axial image. **(B)** Sagittal view.

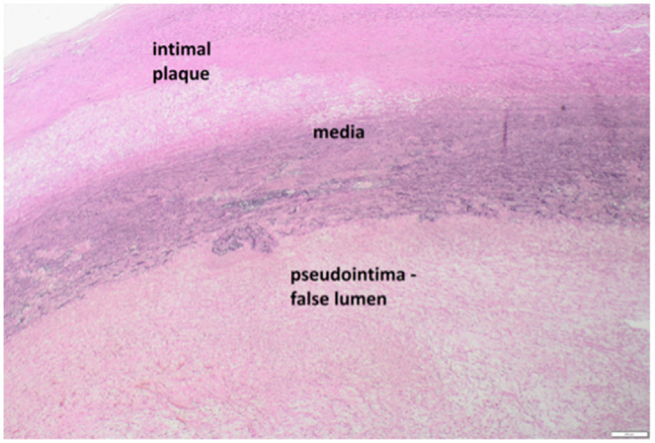

Fig 6. Section from a chronic dissection shows the layer between the true and false lumens. The true intima is thickened by an atheromatous plaque and the false lumen is lined by a pseudointima, resulting from organized thrombus. The media shows loss of elastic fibers. Elastic tissue stain. Scale bar, 200 μm.

He continues to undergo frequent surveillance imaging, which has disclosed progressive dilation of his proximal brachiocephalic artery. He is also being followed for severe venous insufficiency in the left lower extremity with pronounced varicose veins.

CASE REPORT 3

A 38-year-old woman presented to the clinic for follow-up after an acute type A aortic dissection at age 30 that involved her aortic root and right coronary artery. At the time of the dissection, her aortic root was 5.0 cm. She underwent aortic valve, root, and ascending replacement with a porcine bioprosthetic valve. Magnetic resonance angiography (MRA) showed a chronic thoracoabdominal aortic dissection that extended to the bilateral iliac arteries without residual aortic dilation. She was obese (32.8 kg/m^2) and hypertensive (153/95 mm Hg). Her examination was remarkable for micrognathia, kyphosis, flat feet, joint hypermobility, and varicose veins. She was prescribed losartan for hypertension, but did not return immediately to clinic for follow-up.

She reported that her mother was diagnosed with a thoracoabdominal aneurysm at age 68. Her son was diagnosed with a TAA at age 10, that increased to 4.3 cm by age 18. Her sister was diagnosed with an aortic root aneurysm and moderate aortic regurgitation at age 43. Both of her sister's children were diagnosed with aortic aneurysm, at ages 10 and 15, and both have undergone repair for pectus excavatum, one of whom survived a type A dissection at age 23, when his aortic root was measured at 5.4 cm. The patient's genealogical tree is summarized in Fig 7.

Over the next 5 years, surveillance images showed the ascending aorta diameter at 4.0 cm and ascending root diameter at 3.4 cm. She also developed an anastomotic right coronary artery aneurysm. She lost weight (BMI 30.1 kg/m^2) and did not develop new cardiovascular symptoms but remained hypertensive. Genetic testing revealed a pathogenic variant in *TGFB2* (p.C380 F), consistent with the diagnosis of LDS. She is currently under close surveillance with annual head to pelvis imaging and periodic high-resolution imaging of her coronary arteries.

CASE REPORT 4

A 53-year-old woman presented to our genetic and cardiothoracic clinics for evaluation of her chronic type B aortic dissection and TAAA. She is a former smoker with hyperlipidemia, hypertension, and thyroid disease. At age 43, at another hospital, she underwent an urgent modified Bentall repair with a mechanical aortic prosthesis owing to an aortic root aneurysm (4.6 cm) with severe aortic regurgitation. She recovered uneventfully and returned to an active life without cardiovascular symptoms. Eight years after the procedure, at age 51, she developed a de novo type B dissection with extension to the innominate artery, right carotid artery, descending aorta, and infrarenal descending aorta. She underwent a redo sternotomy with the completion of ascending and aortic arch repair with elephant trunk with ostial reattachments of the branch arteries. Her postoperative course was complicated by acute kidney injury and respiratory insufficiency. One year later, she presented to the hospital owing to a hypertensive urgency. CTA revealed a new distal thoracoabdominal dissection, which was stabilized after intensive medical therapy. By 3 years, images showed a progressive increase in the maximum thoracoabdominal aortic diameter to 4.1 cm.

This patient is the sister of the patient described in case 3 (Fig 7) and carries the same pathogenic variant of *TGFB2* (p.C380 F). She is currently under close surveillance with annual MRA neck-to-pelvis imaging.

DISCUSSION

These case vignettes depict different presentations of LDS caused by mutations of the *TGFB2* gene. LDS is an autosomal dominant arteriopathy characterized by predisposition to arterial aneurysms and dissections that can occur anywhere in the vasculature.[5] LDS can be caused by a variety of gene mutations that affect transforming growth factor-beta signaling, including *TGFBR1*, *TGFBR2*, and *SMAD3*.[6-8] A distinctive feature of LDS is the recurrence of disease in distal aortic segments and in branch vessels. LDS also displays musculoskeletal features that are similar to Marfan syndrome, including scoliosis, pectus deformities, and pes planus.[9] Arterial tortuosity, hypertelorism, asthma, eczema, venous disease, and facial dysmorphism tend to be more pronounced in LDS than in Marfan syndrome.[9]

Current clinical guidelines for medical management of thoracic aortic disease do not vary based on the underlying cause: hypertension control to <130/80 mm Hg, typically with a beta-blocker, such as metoprolol and/or an angiotensin receptor blocker, such as losartan, statin therapy to achieve a ≥50% reduction in low-density lipoprotein, and smoking cessation. Follow-up imaging with transthoracic echocardiography, computed tomography,

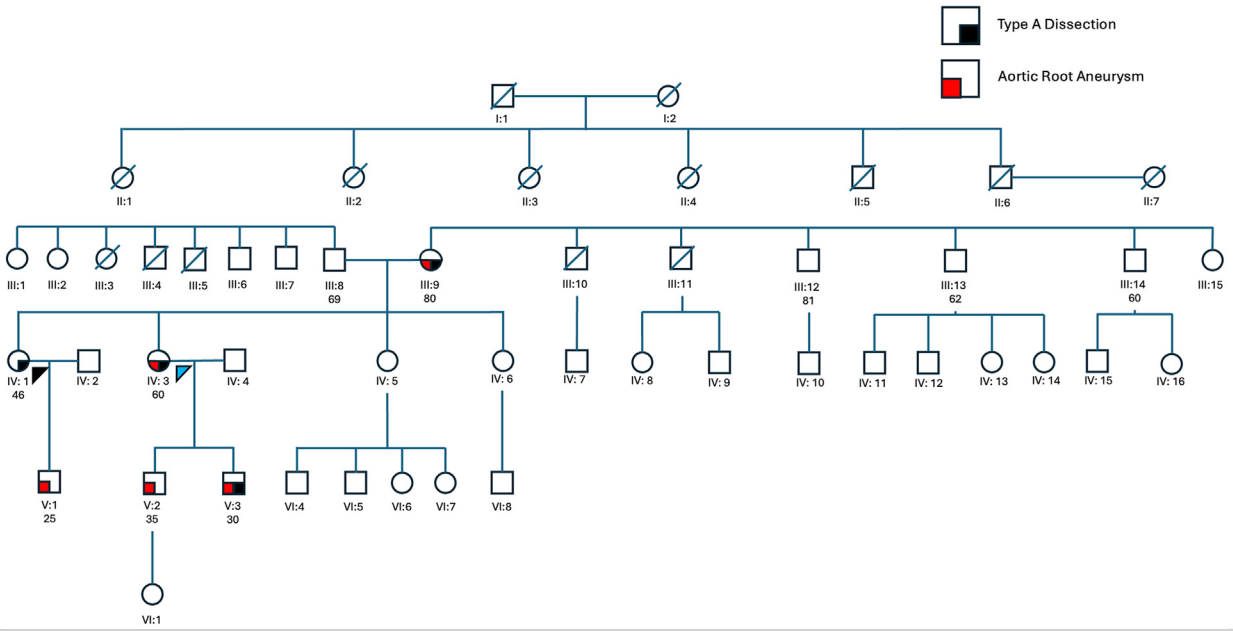

Fig 7. This pedigree depicts the family history of two related individuals with *TGFB2*-related aortic disease: Proband IV:1 (*black triangle*) from case vignette 3 and proband IV:3 (*blue triangle*) from case vignette 4. Proband IV:1 presented with an acute type A dissection at age 30. Proband IV:3 had type A and B dissection and aortic root aneurysm, also requiring surgical repair. Other family members (III:9, V:2, and V:3) exhibited aortic aneurysms and dissections. Ages of diagnosis or death are indicated below the respective family members.

or magnetic resonance imaging every 6 to 12 months is also recommended. In contrast with nonsyndromic presentations of TAA, when the threshold for intervention is usually set at 5.5 cm, surgical intervention for TAAs in LDS patients is indicated when the aneurysm diameter is >4.0 or 4.5 cm, reflecting the predisposition for rapidly progressive aortic disease with dissections at relatively small diameters in LDS. For *TGFB2* patients, the current guideline-recommended threshold for intervention is 4.5 cm.[10]

All four cases follow a similar clinical pattern—an initial presentation with proximal thoracic aortic disease (aneurysm or type A dissection) and subsequent progressive thoracoabdominal disease. Cases 1, 3, and 4 had a positive family history, and case 2 had a de novo mutation. Case 2 displayed dental crowding, striae, pes planus, joint hypermobility, and varicose veins, which are typical manifestations of LDS, but may be subtle and can be missed on cursory examination. Several relatives developed aortic aneurysms in childhood, illustrating how familial screening is vital in preventing sudden deaths owing to dissection in these families. Current guidelines recommend genetic testing of all first-degree relatives and cascade testing of the children of affected relatives when LDS is diagnosed.

In other cases, LDS features were less prominent. In patients without syndromic features or a family history, a high index of suspicion may be required to prompt a genetic evaluation. One such marker of severity in LDS may be the propagation of arterial disease to cervical arteries and the distal aorta after type A dissections. It is also worth noting that these individuals recovered completely after their initial aortic events, providing a window of opportunity to intervene and alter the natural history of LDS-related arterial disease.

Our imaging follow-up plan depends on the aortic pathology. If the patient has only an ascending aneurysm when repaired and no complications—or complaints are noted during postoperative follow-up—then imaging is scheduled on an annual basis. If the patient develops aortic dissection or has aneurysms in different sections of the aorta, then imaging is scheduled within 1 to 3 months of surgery and, if stable, again in 6 months and annually thereafter. If there is concern for progressive aortic enlargement, then we more frequent follow-up imaging is scheduled (sometimes every 3 months) until findings are stable or surgery is recommended. For the first year, we usually follow-up with CTA (especially for patients with acute dissection) to accurately compare with the initial perioperative images. Once findings are stable, we transition the patient, when possible, to MRA or magnetic resonance imaging, to avoid radiation exposure.

Another important aspect to highlight—because two of the vignette patients are women of childbearing age—is the benefit of a multidisciplinary approach to family planning and preconception counseling. At our institution, we participate in a multidisciplinary center for cardiac and vascular disease in women, with a special focus on high-risk pregnancies owing to cardiovascular

disease. In our conversations with women of childbearing age who have aortopathies, we discuss pregnancy and family planning, and we refer them for to an obstetrician and/or maternal-fetal medicine specialist if they do not already have an established provider.

Two of the four patients required open TAAA repair, which remains our standard of care for patients with HTAD. However, if the patient is not a good surgical candidate, then endovascular repair is considered. It is important to note that not all proximal repairs give us a good proximal landing zone for endovascular repair and, in cases where it is suitable, there remains a concern for the distal landing zone. In these cases, we plan surgical interventions carefully at a multidisciplinary discussion, considering the patient's individual surgical risk and anatomy.

These four cases illustrate the various clinical manifestations of LDS and the high risk of developing subsequent arterial disease after the index event. Although several of these patients were being observed carefully—and were on appropriate medical therapies—they nonetheless developed progressively enlarging aneurysms or new dissections. LDS patients require lifelong management and follow-up to prevent death owing to recurrent aortic events.

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DISCLOSURES

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REFERENCES

1. Mathur A, Mohan V, Ameta D, Gaurav B, Haranahalli P. Aortic aneurysm. *J Transl Int Med*. 2016;4:35–41.
2. Isselbacher EM, Cardenas CLL, Lindsay ME. Hereditary influence in thoracic aortic aneurysm and dissection. *Circulation*. 2016;133:2516–2528.
3. Regalado ES, Morris SA, Braverman AC, et al. Comparative risks of initial aortic events associated with genetic thoracic aortic disease. *J Am Coll Cardiol*. 2022;80:857–869.
4. Boileau C, Guo DC, Hanna N, et al. *TGFB2* mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. *Nat Genet*. 2012;44:916–921.
5. Lindsay ME, Schepers D, Bolar NA, et al. Loss-of-function mutations in *TGFB2* cause a syndromic presentation of thoracic aortic aneurysm. *Nat Genet*. 2012;44:922–927.
6. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-β receptor. *N Engl J Med*. 2006;355:788–798.
7. 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.
8. van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. *Nat Genet*. 2011;43:121–126.
9. MacCarrick G, Black JH, Bowdin S, et al. Loeys–Dietz Syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.
10. Isselbacher EM, Preventza O, Black JH, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American heart association/American college of cardiology joint committee on clinical practice guidelines. *Circulation*. 2022;146:e334–e482.

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