Article published online: 2024-11-26

THIEME OPEN ACCESS

Case Report

Rapid Aneurysmal Degeneration and Repair of Thoracic Aortic Aneurysm in a Patient with Concomitant Vascular Ehlers–Danlos and Loeys–Dietz Syndromes

Arjune S. Dhanekula, MD[1] Sara Zettervall, MD[1] Ioannis Dimarakis, MD, PhD[1] Scott Deroo, MD[1]

[1] Division of Cardiothoracic Surgery, Department of Surgery, University of Washington Medical Center, Seattle, Washington

Aorta (Stamford)

Address for correspondence Ioannis Dimarakis, MD, PhD, Division of Cardiothoracic Surgery, Department of SurgeryUniversity of Washington Medical Center, 1959 NE Pacific Street Box #356410, Seattle, WA 98195-6410 (e-mail: ijd22@uw.edu).

Abstract

Vascular Ehlers–Danlos (vEDS) and Loeys–Dietz syndrome 3 (LDS3) are connective tissue disorders with diverse systemic manifestations. Most notable in these disorders, though, are their aggressive aortopathies, often presenting early in life with aneurysmal disease or dissection. Herein we present the case of a 33-year-old patient, previously lost to follow-up, who underwent complex reoperative arch replacement after ascending and hemiarch replacement for Type A aortic dissection 6 years prior. Postoperative genetic testing revealed both vEDS and LDS, a unique genotype that has not been described before in the literature.

Keywords

- Loeys–Dietz syndrome
- Ehlers–Danlos syndrome
- cardiac surgery
- outcomes

Introduction

Vascular Ehlers–Danlos (vEDS) and Loeys–Dietz syndromes (LDS) are connective tissue disorders with diverse systemic manifestations. Most notable in these disorders are their aggressive aortopathies, often presenting early in life with aneurysmal disease or dissection. vEDS has a median life expectancy of 50 years, largely driven by vascular rupture/dissection and gastrointestinal perforation. A total of 66% of arterial emergencies in this population occur in the thoracic aorta.[1] In LDS, most patients will either suffer dissection or have elective surgery on their thoracic aorta before the age of 40.[2] Current guidelines recommend early aortic surgery on both these populations to prevent aortic dissection and rupture.[3]

Case Presentation

We present the case of a 33-year-old man treated with emergency isolated ascending aortic replacement for a Stanford Type A dissection at another institution 6 years prior. His postoperative course was complicated by a transient ischemic attack and lower extremity malperfusion requiring iliac artery balloon angioplasty. Following recovery and discharge, he was subsequently lost to follow-up.

After the patient's son was diagnosed with a bicuspid aortic valve, he sought to reestablish care. Computed tomography angiography (CTA) revealed degeneration of his arch and descending thoracic aorta (DTA). His entire aorta grew, but most so in the arch; it now measured 7 cm, a 3-cm increase from his last available scan 4 years prior (►**Fig. 1**). Patient was otherwise asymptomatic and continued to work in a manual labor job. He did note a history of easy bruising and thin skin.

Urgent repair was thus planned. He first underwent carotid–subclavian transposition due to significant displacement of his head vessels from his aneurysm. The transposition was technically difficult due to this displacement, along with friable, thin tissues and inadvertent lung parenchymal injury.

received
August 8, 2023
accepted after revision
September 4, 2024

DOI https://doi.org/10.1055/s-0044-1795131.
ISSN 2325-4637.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

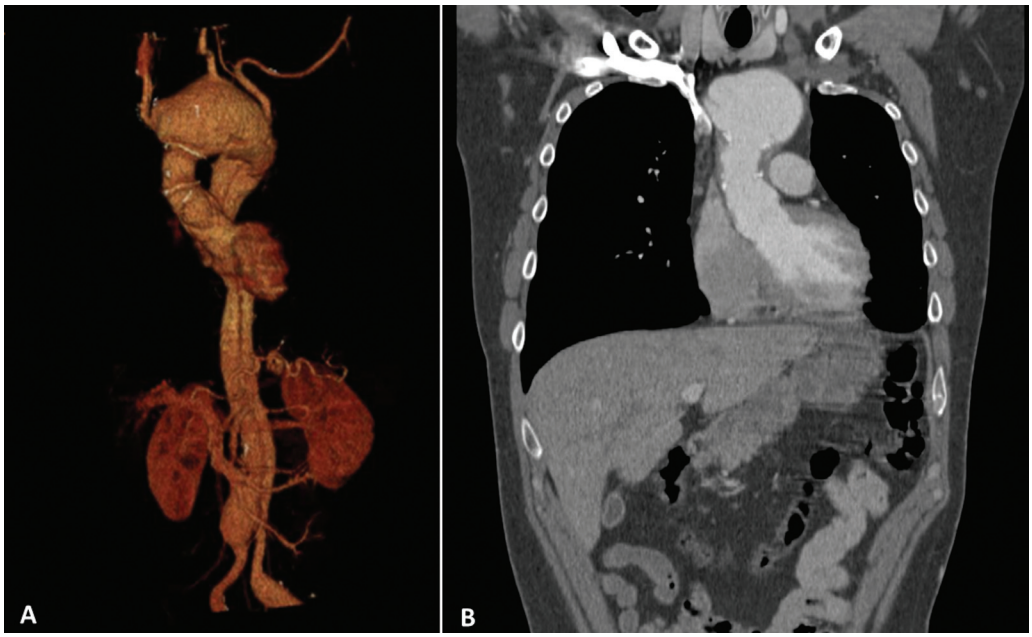

Fig. 1 (**A**) Three-dimensional reconstruction of preoperative CTA demonstrating intact, short-segment, proximal aortic repair with the remainder of the distal aorta chronically dissected. The aortic arch is profoundly aneurysmal with a maximum dimension of 7 cm. There are additional aneurysms present at the level of the iliac arteries. (**B**) Representative coronal section demonstrating profound aneurysmal arch degeneration distal to the site of previous ascending aortic replacement. CTA, computed tomography angiography.

The following day, patient underwent arch replacement under deep hypothermic circulatory arrest at 18°C with antegrade cerebral protection via the right axillary artery. The prior graft was opened, and the aortic valve was normal on inspection. The aorta was resected in zone 2, the true lumen was confirmed with a wire placed under intravascular ultrasound. He underwent total aortic arch replacement using the frozen elephant trunk technique, deploying a ThoraFlex device (32 mm graft, 30 mm × 150 mm thoracic endovascular aortic repair [TEVAR] stent, Terumo Aortic, Sunrise, FL). Similar to the carotid–subclavian transposition procedure, all aortic tissue was thin and extremely friable intraoperatively. This also manifested with significant bleeding from the distal arch suture line after cross-clamp removal that necessitated further reparative attention. We were ultimately able to wean from bypass, administer protamine, and achieve hemostasis after a prolonged period.

The patient had a protracted postoperative course, with reintubation on postoperative day (POD) 3 after being extubated the day prior. He remained intubated over the next 10 days secondary to lower respiratory tract infection. He also suffered a spontaneous retroperitoneal bleed on POD 25 that was managed conservatively. He ended up discharging to home after over a month in the hospital.

Genetic testing performed while in the hospital revealed that the patient has both vEDS (COL3A1 mutation [c.855_872del]) and LDS (SMAD3 mutation [c.401-6G > A]). Both mutations are known pathogenic variants for each syndrome. To our knowledge, this is the first known report of any person with both vEDS and LDS.

Following rehabilitation, he underwent extension TEVAR to the celiac artery 3 months later. At his most recent clinic visit 8 months post-operatively he has returned to his baseline functional status. Follow-up CTA demonstrated an intact aortic repair with sac regression in his covered DTA with proximal false lumen thrombosis (►**Fig. 2**).

Discussion

The most recent 2017 international classification of the Ehlers–Danlos syndrome (EDS) recognizes 13 subtypes with definite diagnosis relying on molecular confirmation with identification of causative variant(s) in the respective gene.[4] vEDS (previously referred to as EDS Type IV) is an autosomal dominant genetic disorder with clearly defined major, minor, as well as minimal criteria suggestive of this disorder. The molecular basis of diagnosis lies in the identification of a heterozygous mutation in the *COL3A1* gene that encodes Type 3 collagen in vast majority of cases.

LDS is inherited in an autosomal dominant manner with approximately 75% of probands presenting with a de novo pathogenic variant.[2] Five subtypes of LDS have been described with specific genotype–phenotype correlations. LDS3 has a strong predisposition for osteoarthritis with severity of aortic disease in individuals with a heterozygous pathogenic variant in SMAD3 being similar to the respective severity seen in LDS1 and 2.[5] SMAD3 (location 15q22.33, exon count 15) belongs to the receptor-activated SMADs protein family of the transforming growth factor better canonical signaling pathway.[6] SMADs are located within the cytoplasm being able to transmit signals from the cell membrane directly to the nucleus. The phenotype of LDS3 patients may overlap with that of aneurysm syndromes such as Marfan syndrome and LDS syndrome. From the cardiovascular standpoint, features are similar to LDS including

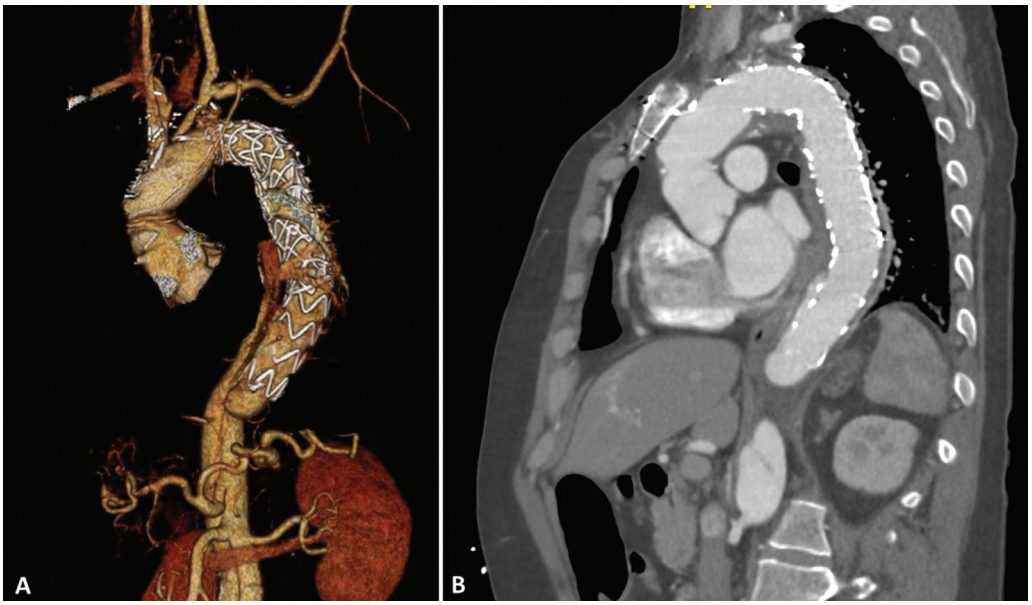

Fig. 2 (A) Three-dimensional reconstruction of 8-month postoperative CTA demonstrating an intact aortic repair. The previously present aneurysmal aortic arch has been completely resected and is replaced with an aortic graft. There is an intact left subclavian-left carotid transposition. There is a TEVAR device present in the descending thoracic aorta with complete false lumen thrombosis of the proximal descending thoracic aorta. There is residual dissection of the aorta encompassing the distal portion of the descending thoracic aorta extending distally. (**B**) Representative sagittal section demonstrating intact aortic arch repair with FET and TEVAR extension. CTA, computed tomography angiography; FET, frozen elephant trunk; TEVAR, thoracic endovascular aortic repair.

thoracic aortic aneurysms at the level of the sinus of Valsalva with aneurysms and tortuosity throughout the arterial tree.[7] Interestingly, a SMAD3 mutation has been described in which affected adult patients did not reveal any radiological evidence of osteoarthritis.[8]

Large-scale analysis of standardized genome sequencing and associated phenotypic data of rare disease patient cohorts may allow for the identification of novel genetic associations.[9] Survival in vEDS is affected by underlying mutation type and molecular mechanism with emergency surgery for arterial events approximating 70%.[10] In addition to lifestyle and emergency care advice, timely diagnosis and initiation of contemporary medical treatment may have a beneficial impact on subsequent vascular events.[11]

Traditionally, there has been hesitancy to offer open vascular repair to patients with vEDS due to concern for excessive tissue fragility and increased operative complexity.[12] As such, many patients with this condition may be left unrepaired or incompletely repaired resulting in excess mortality. In this case, our patient had well-known mutations in both COL3A1 and SMAD3 resulting in profound tissue fragility. To illustrate this, a simple purse-string suture placed in the right atrium cut completely through the tissue upon snaring of the venous cannula such that a large hole was present in the atrium and the cannula rendered free-floating. Given the lack of tissue integrity, it was necessary to reinforce all anastomoses with external Teflon felt strips. Despite this, and the use of the large collar on the Thoraflex device to remove anastomotic tension, our zone 2 arch anastomosis demonstrated several areas of significant tearing and bleeding while rewarming on cardiopulmonary bypass. Ultimately it became clear after placement of several large, pledgeted repair sutures, any attempt at further repair was likely to result in additional tearing and catastrophic failure. Protamine administration, clotting factors including prothrombin complex concentrate, and judicious use of packing and digital pressure ultimately resulted in proximal false-lumen thrombosis and hemostasis.

Although both vEDS and Loeys–Dietz disease are rare diseases, the concomitant presence of both causative mutations in one person has heretofore been unreported. Importantly, reoperative open repair of a large arch aneurysm was possible and resulted in an overall excellent outcome at 8 months. Careful tissue handling, reinforcement of all anastomoses, and an attempt to avoid repair sutures placed after the aorta is pressurized are critical to technical success.

Here we demonstrate that although traditionally aortopathy patients are thought to have one causative mutation with variable expressivity and/or penetrance, it is possible to have two distinct mutations in different pathways affecting vascular integrity.[13] With more widespread genetic testing, it may be possible to identify additional individuals harboring multiple genetic mutations in pathways common to aortopathies. Further research will look to identify possible links between known aortopathies as well as seek to understand the impact of multiple genetic mutations with implications for the vascular system.

Conflict of Interest
None declared.

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