Coronary artery aneurysm in Loeys-Dietz syndrome: a case report

Zachary T. Jost 1*, Charlie J. SangIII 2, Pongtawat Lertwilaiwittaya 3, and Gregory D. Chapman 4

1Department of Internal Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; 2Department of Internal Medicine and Pediatrics, University of Alabama at Birmingham, Birmingham, AL, USA; 3Department of Medical Genetics, University of Alabama at Birmingham, Birmingham, AL, USA; and 4Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

Received 12 January 2022; first decision 2 February 2022; accepted 11 May 2022; online publish-ahead-of-print 13 May 2022

Background
Loeys-Dietz syndrome (LDS) is a connective tissue disorder that commonly presents with vascular abnormalities. Owing to the rarity and severity of the condition, consensus guidelines for aortic surgery thresholds vary. In addition, evaluation of coronary arteries in patients with LDS (either routinely or before aortic root surgery) remain undefined. In this case report, we discuss a patient with LDS who found to have an ectatic aortic root and a coronary artery aneurysm and discuss guidelines for evaluation and management in this patient population.

Case summary
A 48-year-old woman was incidentally found to have a 45 mm ectatic aortic root during evaluation for a neck mass. As part of pre-operative evaluation for aortic root replacement, left heart catheterization revealed a left main coronary artery aneurysm. Family history revealed aortic aneurysms, sudden cardiac death, and tall height. Physical examination was notable for pectus excavatum and elongated limbs. Workup for inflammatory aetiologies of aortic root dilation was negative. Genetic testing revealed a heterozygous pathogenic TGBF3 variant, consistent with LDS Type 5. She subsequently underwent two-vessel coronary artery bypass, excision of her left main coronary artery aneurysm, and ascending aortic replacement.

Discussion
In this case, we describe a patient with LDS who was noted to have a coronary artery aneurysm, a rare finding in the initial presentation of disease. In addition, we examine guidelines regarding evaluation of management of aortic root disease and coronary aneurysms.

Keywords
Case report • Coronary aneurysm • Thoracic aortic aneurysm • Loeys-Dietz Syndrome • Connective tissue disorder

ESC Curriculum
2.4 Cardiac computed tomography • 3.4 Coronary angiography • 7.5 Cardiac surgery • 9.1 Aortic disease

Learning points
- Overviewing the pathophysiology and vascular manifestations of Loeys-Dietz Syndrome.
- Overviewing the diagnosis and management of thoracic aortic disease.
- Routine coronary computed tomographic angiography for pre-operative evaluation in patients with LDS may be considered before aortic root repair.
Introduction

Loeys-Dietz Syndrome (LDS), characterized by multisystem involvement including hypertelorism, bifid uvula, cleft palate, and aortic aneurysms, is an autosomal dominant connective tissue disorder. While arterial aneurysms have been described in almost all side branches of the aorta, coronary artery aneurysms are limited to case reports. In this report, we describe a patient with an incidentally diagnosed coronary artery aneurysm in the setting of LDS and review important diagnostic and therapeutic considerations.

Timeline

Case presentation

A 48-year-old woman with history of juvenile myoclonic epilepsy presented to her primary care physician with complaints of a neck mass. Family history revealed a paternal abdominal aortic aneurysm, a son who is 2 m tall with a 2.13 m wingspan and pulmonary blebs, a daughter with hypoplastic right heart syndrome, a paternal grandmother with ruptured aortic aneurysm, and easy bruising noted in various family members. Given her family history and chief complaint, a computed tomographic angiography (CTA) was obtained, incidentally revealing a 45 mm ectatic aortic root. She was referred to a local cardiothoracic surgeon, and as part of pre-operative evaluation for aortic root replacement, underwent left heart catheterization, which revealed an ostial left main lesion with a post-stenotic aneurysm (Figure 1A).

Several months later, she presented to our institution with 1 week of dyspnoea. Physical examination was notable for heart rate 53 bpm, blood pressure 99/64 mmHg, respiratory rate 12, and saturating 100% on room air. She was in mild distress. The oropharynx revealed a high palate. Cardiac examination revealed a normal rate and regular rhythm, without murmurs. Lungs were clear to auscultation with symmetric chest rise. Musculoskeletal examination revealed pectus excavatum, positive thumb and pinky signs bilaterally, positive knee sign bilaterally, and ability to touch floor without bending knees, resulting in a Beighton score of 7.

Given her history of an ostial left main lesion with post-stenotic dilation, there was concern her dyspnoea represented an anginal equivalent or progression of aortic dilation with potential valvular involvement, leading to left ventricular dysfunction. An echocardiogram was obtained and was concerning for a dissection flap within the aortic root, consistent with Type A aortic dissection (see Supplementary material online, Video S1). Emergent CTA was obtained without dissection but...
The patient was recovering well without any ongoing complaints.

At her 1-month follow-up, the differential for multiple vascular aneurysms included inflammatory aetiologies such as vasculitis or infection, as well as mixed connective tissue disorders. Owing to the craniofacial, skeletal abnormalities, and family history in the setting of vascular anomalies, a syndromic connective tissue disease, such as Marfan syndrome, Ehlers-Danlos syndrome, or LDS, was favoured. Laboratories obtained were notable for C-reactive protein 3.15 mg/L (ref.: 0.0–10.9), erythrocyte sedimentation rate 8 mm/hr (ref.: 0–20), homocysteine 13.7 µMol/L (ref.: 5.0–15.0), non-reactive treponema, hepatitis C, and human-immunodeficiency virus antibodies. Given the negative workup for inflammatory aetiologies and her family history, an Invitae Aortopathy Comprehensive Panel was obtained and revealed a heterozygous pathogenic variant in TGFBR3 variant, consistent with autosomal dominant LDS Type 5 (OMIM #615582).

She elected to return to her local hospital for definitive management and underwent two-vessel coronary artery bypass with saphenous vein graft to obtuse marginal branch and left internal mammary artery to the left anterior descending artery; in addition to having excision of her left main coronary artery aneurysm and ascending aortic replacement with a 30 mm Hemashield graft. At her 1-month follow-up, the patient was recovering well without any ongoing complaints.

**Discussion**

The estimated prevalence of LDS is less than 1 in 100,000 persons. The diagnosis of LDS in a proband is made in a patient with a heterozygous pathogenic variant in SMAD2, SMAD3, TGFBR2, TGFBR3, or TGFBR1, and either aortic root enlargement or type A dissection or compatible systemic craniofacial, skeletal, vascular, or cutaneous features. The subtypes of LDS are based on genotypes and are named LDS1-LDS5 according to their genotype. The TGFBR3 variant noted in our patient, consistent with LDS5, occurs in 1–5% of LDS variants. TGF-beta signalling plays a significant role in vascular remodelling, and a mutation may lead to dysregulation in the pathway responsible for maintaining vascular integrity. This potentiates extra-cellular membrane degradation and increases susceptibility to aortic dilatation and dissection, as well as other clinical features found in LDS.

Vascular disease is common in LDS, with aortic root dilatation occurring in more than 95% of probands. Thoracic aortic aneurysms in patients with LDS may grow faster than 10 mm/yr, resulting in death at a mean age of 26 years. Arterial aneurysms have been described in almost all side branches of the aorta including (but not limited to) the subclavian, renal, superior mesenteric, hepatic, and coronary arteries. Although there are multiple reports of coronary artery dissection associated with LDS, the contribution of LDS to coronary artery aneurysm formation is undefined. Coronary aneurysms have been reported after valve-sparing aortic root replacement, but this is believed to be largely surgery-related and not an LDS-specific complication. We believe this represents the first reported case of a spontaneous coronary artery aneurysm in association with LDS.

Owing to the presence of vascular disease in the patient population, it is recommended imaging be performed of the complete arterial tree from the head through the pelvis by MRA or CTA at the time of diagnosis, followed by repeat aortic imaging at 6 months, and yearly magnetic resonance imaging from the cerebrovascular circulation to the pelvis, thereafter. For all patients with thoracic aortic aneurysms, stringent control of hypertension, lipid profile optimization, smoking cessation, and other atherosclerosis risk-reduction measures should be instituted. Medical therapy includes beta blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and statins. Although an earlier intervention has been proposed for aortic diameters ≥42 mm in LDS patients, ESC recommends intervention for aortic diameters ≥50 mm, equal to that of Marfan patients; although a lower threshold of 45 mm can be considered in patients with family history of dissection, size increase >3 mm/year, severe aortic or mitral regurgitation, or desire for pregnancy. A lower threshold for surgery has been suggested given the young age of the patient population, the general tolerance of surgery, and the rarity of complications related to tissue fragility.
The most common cause of coronary artery aneurysms in adults is atherosclerotic disease, accounting for up to 50% of cases. The second most common cause in adults (and most common in children) is Kawasaki Disease, with aneurysm formation in 10–15% of patients during the initial disease state. The remaining aetiologies of coronary artery aneurysms can be attributed to additional vasculitic diseases (such as Takayasu), connective tissue disorders (most commonly Marfan and Ehlers-Danlos), infection, or congenital causes. Currently, routine imaging of coronary arteries is not recommended in patients with LDS. This may reflect the severity of the condition, with complications often arising at an early age – as previous guidelines surrounding routine coronary evaluation often focused on atherosclerotic coronary artery disease. Given the uniqueness of this finding, routine imaging with other aforementioned studies would likely create increased healthcare costs with little benefit on a population level. We believe it would be reasonable, however, to obtain coronary CTA for evaluation specifically in patients with LDS before aortic root repair.

The importance of a multidisciplinary specialized care team (heart team) can be emphasized in this case. While our patient's initial evaluation and surgical care were not performed at our centre, we would advocate for coronary CTA for coronary pre-operative evaluation (rather than traditional angiography) given her low clinical likelihood of having atherosclerotic coronary disease. We would also advocate for arterial revascularization (rather than venous grafting) during operative repair in this case; however, due to the degree of this patient's left main lesion, we believe that the patency of the vein graft should be maintained.

**Conclusion**

In this case, we present a patient who was incidentally noted to have a coronary artery aneurysm during pre-operative workup for aortic root repair. Although there is some debate on the contribution of the primary disease process on coronary artery aneurysms versus secondary outcomes of aortic root surgery on coronary artery aneurysms, this case report suggests that the primary pathophysiology of LDS may contribute to coronary artery aneurysms. Current guidelines for LDS surveillance do not suggest routine coronary artery imaging. This case presents the idea that routine coronary CTA for pre-operative evaluation in patient with LDS may be warranted.

**Lead author biography**

Dr. Zachary Jost, MD was born in Henderson, KY, USA, and grew up in Perry, GA, USA. He received his undergraduate degree in Biological Science from the University of Georgia and studied medicine at the University of Kentucky College of Medicine. He is currently a resident at the University of Alabama-Birmingham Medical Centre where he plans to pursue a career in Cardiovascular Medicine.

**Supplementary material**

**Supplementary material** is available at [European Heart Journal – Case Reports](https://doi.org/10.1093/europace/euz171) online.

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

**Consent:** The authors confirm that written consent for the creation, submission, and publication of this report (and all associated contents) has been obtained from the patient in line with COPE guidelines.

**Conflict of interest:** There are no conflicts of interest to report.

**Funding:** There are no sources of funding to declare.

**References**

1. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Mirzaa GM, Amemiya A. eds. GeneReviews®. Seattle (WA): University of Washington. 1993.
2. Loughborough WW, Minhaj KS, Rodrigues JCL, Lyen SM, Burt HE, Manghat NE, Brooks MJ, Stuart G, Hamilton MCK. Cardiovascular manifestations and complications of Loeys-Dietz syndrome: CT and MRI imaging findings. Radiographics 2018; 38:275–286.
3. Izgal R, Alom S, Brünseid J, Harky A. Loeys-Dietz syndrome pathology and aspects of cardiovascular management: a systematic review. Vascular 2021:29:3–14.
4. Erbel R, Aboyans V, Boileau C, Bossé E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Jung B, Manolis JA, Meiboom F, Nienaber CA, Roffi M, Rousseau H, Szechten U, Siméon PA, von Almen RS, Vrints CJM, ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European society of cardiology (ESC). Eur Heart J 2014;35:2873–2926.
5. Agraval A, Bajaj S, Schwartz J, Lopez J. Spontaneous coronary artery dissection in Loeys-Dietz syndrome: role of optical coherence tomography in diagnosis and management. J Invasive Cardiol 2015;27:E196–E198.
6. Fattori R, Sangiorgio P, Marucci E, Rettile M, Witschmeier A, Greco C, Colombo M. Spontaneous coronary artery dissection in a young woman with Loeys-Dietz syndrome. Am J Med Genet A 2012;158A:1216–1218.
7. Blinc A, Mayer A, Rudolf G, Tasić J, Pretrnar Oblak J, Berden P, Peterlin B. Clinical exome sequencing as a novel tool for diagnosing Loeys-Dietz syndrome type 3. Eur J Vasc Endovasc Surg 2015;50:161–1621.
8. Kaadan MI, MacDonald C, Ponzi M, Duran J, Niewel K, Piller L, Lin A, Weinberg I, Wood MJ. Lindsay ME Prospective Cardiovascular genetics evaluation in spontaneous coronary artery dissection. Circ Genom Precis Med 2018;11:e001933.
9. Jawaid Y, Aqath O, Mansoor K, Ajmeri AN, Fofie F, Amro A, Dial L. Loeys-Dietz syndrome complicated by right coronary artery pseudoaneurysm. Case Rep Cardiol 2018;2018:8014820.
10. Cereda A, Garascia A, Sorinami P, Klugmann S, Artioli D, Soriano F, Oreglia JA. Embolic myocardial infarction due to coronary artery aneurysm in a patient with Loeys-Dietz syndrome. EuroIntervention 2016;12:61.
11. Carrel T, Schoenhoff F, Cameron D. A Loeys-Dietz patient with a transatlantic odyssey: repeated aortic root surgery ending with a huge left main coronary aneurysm. Interact Cardiovasc Thorac Surg 2017;24:143–144.
12. MacCarrick G, Black JH III, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, Sponsorlel PD, Loeys B, Dietz HC. Loeys-Dietz syndrome: a primer for diagnosis and management. Genet Med 2014;16:576–587.
13. Hiratzka LF, Bakris GL, Beckman JA, Black HR, Calkins H, Craiff-V, Casey DE Jr, Eagle KA, Hermann LK, Isbellacher EM, Kazerouni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 2010 ACCF/AHA/ACC/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. Anesth Analg 2010;111:279–315.
14. Riembau V, Böckler D, Brunkwall J, Cao P, Chiesa R, Coppi G, Czerny M, Fraedrich G, Haulon S, Jacobs M, Lachat ML, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 2010 ACCF/AHA/ATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. Anesth Analg 2010;111:279–315.
15. Sherif S A, Tok OO, Taşkınyüz Ö, Göktekin O, Kılıç İD. Coronary artery aneurysms: a review of the epidemiology, pathophysiology, diagnosis, and treatment. Front Cardiovasc Med 2017;4:24.

16. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey Robert F, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh B J, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Neumann F J, Sechtern U, Banning AP, Boraños N, Bueno H, Bugiardini R, Chieffo A, Crea F, Czerny M, Delgado V, Dendale P, Flachskampf FA, Gohlke H, Grove EL, James S, Katritsis D, Landmesser U, Lettino M, Matter CM, Nathoe H, Niessner A, Patrono C, Petronio AS, Pettersen SE, Piccolo R, Piepoli MF, Popescu BA, Räber L, Richter DJ, Rolfi M, Roithinger FX, Shlyakhto E, Silber S, Simpson IA, Sousa-Uva M, Vardas P, Wiktorowski A, Zamorano JL, Achenbach S, Agewall S, Barbato E, Bax JJ, Capodanno D, Cuisset T, Deaton C, Dickstein K, Edvardsen T, Escaned J, Funck-Brentano C, Gersh BJ, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Prescott E, Saraste A, Storey RF, Svitil P, Valgimigli M, Windecker S, Aboyans V, Baigent C, Collet J-P, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbée D, Halvorsen S, Hindricks G, Jung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen S, Petronio AS, Richter DJ, Rolfi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Benkhedda S, Metzler B, Sujayeva V, Casyn B, Kuslugucuz Z, Velchev V, Panayi G, Kals P, Haahr-Pedersen SA, Kabil H, Aina T, Kaukonen T, Czajla G, Pagapo Z, Woehrer J, Kanakakis J, Tóth K, Guðrúnsson T, Peace A, Aronson D, Ricco C, Elezi S, Mirrakhimov E, Hansson S, Sarkis A, Babarskenie R, Beissel J, Maempel AJC, Reveno V, de Grooth GJ, Pejko H, Juileba V, Lipiec P, Santos J, Chioceel O, Duplyakov D, Bertelli L, Dikic AD, Studenčan M, Bunc M, Alfonso F, Bäck M, Zellweger M, Aammad F, Yıldırı̇m A, Sirenko Y, Clapp B. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–477.