

# Case report of Loeys-Dietz syndrome presenting with coronary artery aneurysm

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## Background

Loeys-Dietz syndrome (LDS) is a heritable disorder that presents with thoracic aortic aneurysm and/or dissection caused by a mutation in one of the transforming growth factor-B receptor or ligand genes. It is associated with widespread familial arterial aneurysm and rupture.

## Case summary

We present a case of a 70-year-old male with a family history of heritable thoracic aortic aneurysm disease who presented to the emergency department with chest pain. His presenting electrocardiogram was significant for ST elevation in the inferior leads with complete heart block. Computed tomography-angiography was done to rule out aortic dissection, which was negative for aortic dissection but did reveal 3.9 cm infrarenal abdominal aortic aneurysm and 2.7 cm bilateral iliac artery aneurysms. He was then taken for invasive angiography and was found to have aneurysmal dilation of the entire right coronary artery measuring up to 6 mm with 100% occlusion secondary to thrombus in the distal segment. He was found to have obstructive disease in the left anterior descending artery and first and second obtuse marginals (OMs). Genetic testing performed confirmed a pathogenic mutation in the *TGFBR1* gene (*TGFBR1* c.934G > A p.Gly312Ser) consistent with the diagnosis of LDS.

## Discussion

Although LDS is known to cause arterial aneurysms throughout the arterial tree, there have been no other cases of primary coronary aneurysms reported in this patient population. This case represents the first description of a patient with genetically confirmed LDS presenting with coronary artery aneurysm.

## Keywords

Genetics • Coronary anomaly • Acute myocardial infarction • Case report

## ESC Curriculum

3.1 Coronary artery disease • 3.2 Acute coronary syndrome • 9.7 Adult congenital heart disease

## Learning points

- Although uncommon, coronary artery aneurysm can be present in patients with patients with Loeys-Dietz syndrome with *TGFBR1* mutations.
- Close monitoring of patients with LDS is necessary with special attention on routine imaging to coronary anatomy to screen for presence of coronary aneurysm and risk for dissection.
- Aggressive modification of atherosclerotic risk factors is necessary in LDS patients as these risks can lead to development of aneurysms in unusual locations such as coronary arteries.

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## Introduction

Coronary artery aneurysms (CAA) are most commonly seen as a result of atherosclerosis. Rarely, connective tissue disorders have been implicated in the causation of CAA. Coronary artery aneurysms have been seen in Marfan and Ehlers-Danlos syndromes<sup>1</sup> but are not well described in association with Loeys-Dietz syndrome (LDS). Loeys-Dietz syndrome is an autosomal dominant disorder caused by a mutation in one of the transforming growth factor-B (TGFR-B) receptor or ligand genes. It is associated with widespread familial arterial aneurysms but reports of CAA are rare.<sup>2,3</sup>

## Timeline

Day 1, 0 h	Patient presents to the emergency room with chest pain and found to have ST elevation myocardial infarction (STEMI) and complete atrioventricular block on electrocardiogram (ECG)
Day 1, 0.5 h	Computed tomography-angiogram (CTA) performed and acute aortic dissection ruled out
Day 1, 1 h	325 mg aspirin and 180 mg ticagrelor load and taken to catheterization lab, temporary transvenous pacemaker placed via right internal jugular vein
Day 1, 1 h 20 mins	Balloon angioplasty of aneurysmal right coronary artery (RCA), decision for coronary artery bypass graft (CABG) referral
Day 3	Confirmation of LDS with <i>TGFBRI</i> c.934G > A p.Gly312Ser via records received. Decision for concomitant aortic root replacement during CABG
Day 7	Coronary artery bypass grafting with saphenous vein grafts to the left anterior descending, the first obtuse marginal (OM), and the posterior descending artery. Right coronary artery ligation distal to aneurysm. Aortic root replacement with 25 mm Konect biologic aortic valve

## Case presentation

A 70-year-old male with a long-standing smoking history but without known cardiac disease presented to the emergency department with the chief complaint of chest pain that had been ongoing for 45 min and radiating to the left arm. On exam he was noted to be in significant distress due to pain. The patient's blood pressure was 133/103 mmHg and his heart rate was 39 beats per minute. His facial features were not overtly dysmorphic, uvula was normal in appearance, and scoliosis was noted. There were no murmurs, rubs, or gallops, and pulses were of normal amplitude.

His past medical history was significant for a recent diagnosis of LDS, renal cell carcinoma, poorly controlled non-insulin dependent diabetes mellitus, chronic kidney disease, well-controlled hypertension, chronic obstructive pulmonary disease, oncocytic salivary tumour, infrarenal abdominal aortic aneurysm, significant tobacco abuse, and an asymptomatic-acquired posterior diaphragmatic hernia.

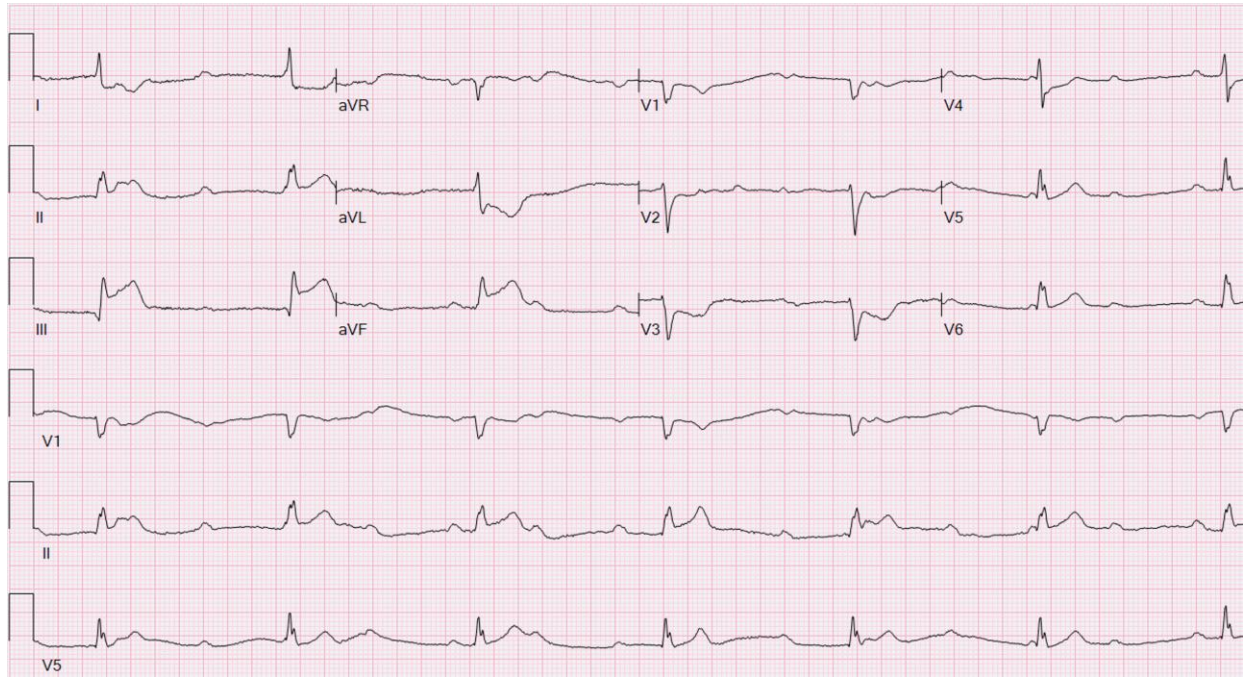
Family history was notable for heritable thoracic aortic aneurysm disease (h-TAAD) with Type A dissection in his mother, prophylactic

ascending aortic replacement in one sister, sudden death at age 40 in another sister, and late onset abdominal aortic aneurysm disease in his father. The living sister had presented to orthopaedics at age 22 years for scoliosis and a clinical diagnosis of 'Marfan syndrome' was made at that time. Subsequently, echocardiograms were performed on first degree family members and based on aortic dilation and some physical features, a diagnosis of 'Marfan syndrome' was made in mother, sister, and the patient. Relatives were followed regularly by general cardiology with aortic diameters <5 cm. One year prior to the patient's presentation, the sister was referred to the Marfan and Related Aortopathies clinic at which time genetic testing was performed that revealed a pathogenic mutation in the *TGFBRI* gene (*TGFBRI* c.934G > A p.Gly312Ser) consistent with the diagnosis of LDS. The patient then underwent a targeted sequencing study and was found to have this same mutation.

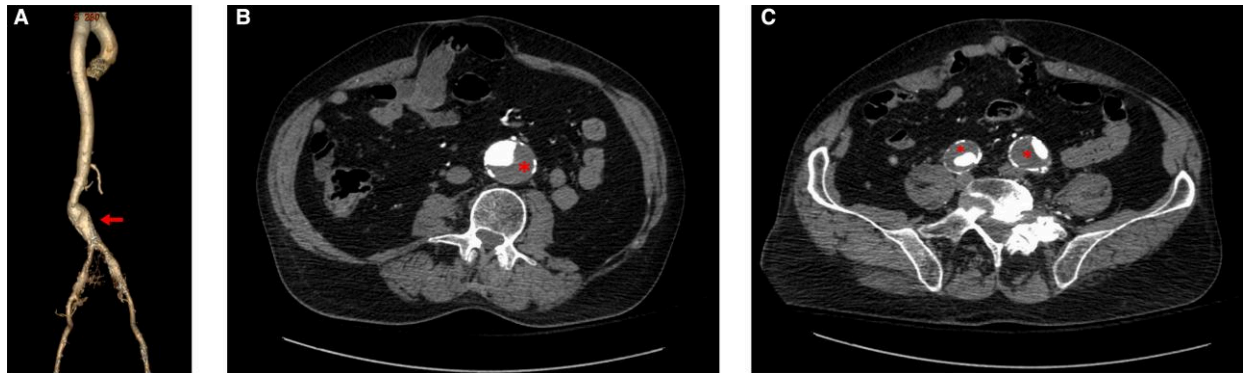
On the ECG, the patient was found to have ST segment elevation in the inferior leads with complete atrioventricular block (Figure 1). Computed tomography-angiography was done to rule out aortic dissection given the history. This was negative for aortic dissection but did reveal a stable 3.9 cm infrarenal abdominal aortic aneurysm and 2.7 cm bilateral iliac artery aneurysms, all with non-obstructive thrombus present (Figure 2). The aortic root was dilated at 4.2 cm. After confirmation of absence of aortic dissection, the patient was loaded with aspirin and ticagrelor and taken emergently for invasive coronary angiography. He was found to have aneurysmal dilation of the entire RCA measuring up to 6 mm in the mid-RCA. The distal RCA had 100% occlusion secondary to thrombus. The left anterior descending artery (LAD) had 70% stenosis at the proximal segment, 80% at the mid segment, and 70% stenosis distally. The OM 1 branch of the left circumflex artery had 90% stenosis and OM2 branch had 80% stenosis (Figure 3). Intravascular ultrasound was performed on the RCA, which revealed no evidence of atherosclerotic plaque or plaque rupture in the aneurysmal vessel (Figure 4). Spontaneous echo contrast suggestive of thrombus was present.

The patient underwent balloon angioplasty of the 100% occluded RCA with a 3.0 × 5 mm semicompliant angioplasty balloon, resulting in thrombolysis in myocardial infarction (TIMI) 2 flow (Figure 5). The severe aneurysmal nature of the RCA proved prohibitive for coronary stenting. Due to complete atrioventricular block at presentation with an inferior STEMI a temporary transvenous pacemaker was placed. The patient was stabilized with these measures. Given the presence of multivessel coronary artery disease, he was referred for CABG. To allow for antiplatelet therapy washout, surgery was performed 5 days later. Given his underlying connective tissue disorder with family history of dissection, concomitant aortic root replacement was recommended. Although the left internal mammary artery did not appear affected, saphenous vein grafts were used to bypass to the LAD, the first OM, and the posterior descending artery given the patient's underlying arteriopathy, the potential for subsequent involvement of the muscular arteries, and the age of the patient. The RCA was ligated proximally and distally to the aneurysm. Intraoperative findings of RCA dissection and thrombosis were noted. The aortic root and valve were replaced with 25 mm Konect biologic aortic valve.

The patient's post-operative course was complicated by right ventricular failure, post-operative haemorrhage, and refractory ventricular tachycardia and ventricular fibrillation. Right ventricular failure was likely a result of ischaemia, although no repeat coronary angiography was performed to assess patency of the grafts. This required right ventricular assist device placement and veno-arterial extracorporeal membrane oxygenation. He subsequently developed multiorgan dysfunction, sepsis, and intraparenchymal frontoparietal haemorrhage. He was transitioned to comfort care measures at the request of the family and died 3 weeks post-operatively.



**Figure 1** Presenting electrocardiogram with ST segment elevation in the inferior leads and 3rd degree atrioventricular block.



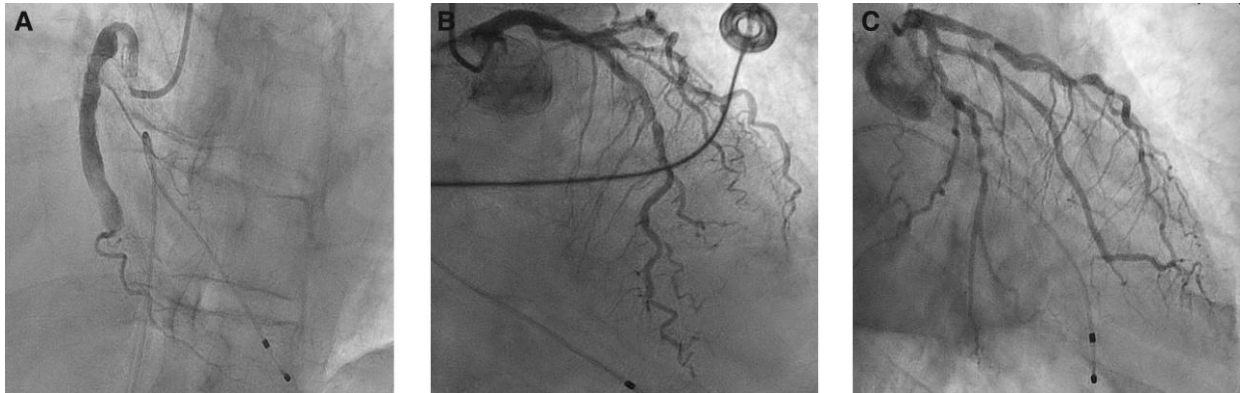
**Figure 2** (A) Three-dimensional reconstruction of aorta demonstrating 3.9 cm aneurysm. (B) Computed tomography-angiography of aneurysmal abdominal aorta with intramural thrombus and (C) Iliac arteries with non-obstructive thrombus.

## Discussion

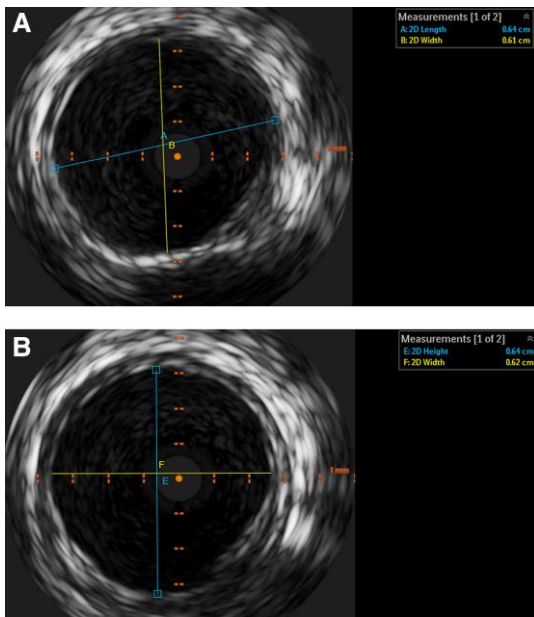
Loeys-Dietz syndrome is an autosomal dominant disorder associated with thoracic aortic aneurysmal disease. The syndrome occurs secondary to abnormalities in the TGF $\beta$ -B signalling pathway. Mutations can occur in several genes within this pathway, but the eponym is used to refer to disease caused by mutations in the first two genes originally described (*TGFBR1* and *TGFBR2*).<sup>2</sup> Distinct facial features (hypertelorism, bifid uvula, cleft palate) may or may not be present. Vascular features include arterial tortuosity, and aneurysms throughout the arterial tree, including cerebral aneurysms. Aneurysms in this disorder have a higher propensity for rupture or

dissection than what has been described with Marfan syndrome.<sup>2,3</sup> In light of the more malignant natural history, early surgical intervention and close monitoring of the entire arterial tree are recommended.<sup>2</sup>

Coronary artery aneurysm is, in itself, uncommon in the general population with an incidence anywhere from 0.3%.<sup>4</sup> The pathogenesis is thought to be due to underlying atherosclerosis and is highly linked to smoking. Genetic causes such as Marfan syndrome, Ehlers-Danlos syndrome, and fibromuscular dysplasia have been implicated.<sup>1</sup> Treatment of CAA depends on the clinical presentation but ranges from medical management (statins, angiotensin converting enzyme inhibitors, beta blockers, anti-thrombotics) to surgical management with exclusion of the aneurysm.<sup>1,4</sup>



**Figure 3** Coronary angiography (A) aneurysmal dilation of the entire right coronary artery (~6 mm) with total occlusion of the distal right coronary artery. (B) Anteroposterior cranial view showing 70% proximal left anterior descending artery, 80% mid-LAD, and 70% distal left anterior descending artery stenosis. (C) Showing 90% stenosis of the obtuse marginal 1 and 80% stenosis of the obtuse marginal 2.



**Figure 4** Intravascular ultrasound still frame images of the mid right coronary artery showing significant aneurysmal dilation. Measuring 6.1 × 6.4 mm (A); measuring 6.4 × 6.2 mm (B).



**Figure 5** Post-balloon angioplasty of the right coronary artery with resulting TIMI 2 flow to the posterior descending artery.

## Conclusion

Heritable thoracic aortic aneurysm disease encompasses a wide variety of genetically distinct aneurysm conditions with different complications and thus differing natural history. Patients may have overlapping clinical features with Marfan syndrome. Timely genetic diagnosis is essential. Patients with LDS can have aneurysms anywhere throughout their vascular tree and thus surveillance differs from Marfan syndrome. The presence of coronary artery aneurysm in LDS patients is rare but can occur. This patient likely suffered coronary aneurysm due to a combination of LDS plus atherosclerotic risk factors. We believe this case highlights the possibility of coronary involvement in patients with LDS and the need for close monitoring and surveillance, particularly in those with additional risk factors for coronary artery disease.

Documented coronary artery involvement in LDS is rare. There are two case reports of coronary artery dissection—one in a patient with a *TGFBR2* mutation<sup>5</sup> and one in a patient with a *TGFBR1* mutation, both following prior aortic root replacement.<sup>6</sup> Similarly, coronary aneurysms or pseudoaneurysms in this population have been rarely described and only diagnosed following aortic root replacement.<sup>3,7</sup> This is the first report of a patient with a *TGFBR1* mutation presenting with coronary artery aneurysm without antecedent aortic replacement. This patient did have other risk factors for coronary aneurysm, including atherosclerosis and a history of significant tobacco abuse, which may have also contributed to CAA formation.

## Lead author biography



Dr Jennifer Nickol, DO is a graduate of Lincoln Memorial University-DeBusk College of Osteopathic Medicine (USA). She completed residency at Magnolia Regional Health Center (USA). She served as Assistance Professor of Medicine at Florida State University in the department of Internal Medicine. She is currently a cardiology fellow at the University of Nebraska Medical Center (USA).

## Supplementary material

[Supplementary material](#) is available at *European Heart Journal—Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** Written informed consent was obtained in accordance with COPE guidelines from the patient for publication of this case report.

**Conflict of interest:** None declared.

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## Data availability

No new data were generated or analyses in support of this research.

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