Valve-sparing aortic root replacement in Loeys-Dietz syndrome and a novel mutation in TGFBR2

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Introduction

Loeys-Dietz syndrome (LDS) is a rare, multisystemic, autosomal dominant connective tissue disease coursing with a progressive aortic root aneurysm. Despite the lack of definitive criteria, LDS is characterized by the triad of arterial tortuosity/aneurysm, hypertelorism, and bifid uvula or cleft palate, and shows genetic heterogeneity. In previous studies, mutations of the *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2* genes have been reported in LDS. Mutations in these genes cause dysregulation of the TGFB pathway (1, 2).

Presently described is a novel *TGBFR2* gene mutation that was detected in a child with a giant aortic aneurysm, which was treated with valve-sparing aortic root replacement.

Case Report

A 12-year-old male patient with a murmur and pectus carinatum was referred to the hospital. There was no consanguinity and the family history was negative. He had dysmorphic features of dolichocephaly, down-slanting palpebral fissures, micrognathia, thick and bifid uvula, significant pectus carinatum, arachnodactyly, and scoliosis.

Despite normal tricuspid morphology, there was severe regurgitation of the aortic valve due to dilatation and a lack of coaptation observed in the echocardiographic evaluation. Mitral valve prolapse and mild mitral regurgitation were demonstrated. Fusiform dilatation of the aortic root and the ascending aorta was detected. The annulus was measured at 32 mm (Z-score: +10.5), sinus of Valsalva at 90 mm (Z-score: +12.6), and the ascending aorta at 51 mm (Z-score: +8.3) (Fig. 1a). The left ventricle end-diastolic and end-systolic diameter was 68 mm (Z-score: +4.77) and 49 mm (Z-score: +5), respectively.

A computed tomography (CT) evaluation revealed aneurysmatic dilatation from the aortic root to the right truncal brachiocephalic branch, 90 mm from the level of the sinus of Valsalva (Fig. 1b, 1c). *TGFBR2* gene analysis was planned with the suspicion of LDS.

A heterozygous missense p.Leu305Phe (c.913C>T) mutation was detected in the *TGFBR2* gene. The parents were found to be wild type (Fig. 2).

The patient was operated on with 34°C hypothermia. Valve-sparing aortic root replacement (reimplantation technique with 28-mm Valsalva graft-David operation) and ascending aorta graft replacement were performed (Fig. 3a, 3b). Cardiopulmonary bypass time was 130 minutes, and the mean aortic cross-clamp time was 110 minutes. The patient was discharged at the end of the first postoperative week without any complication. There were no significant symptoms during 6 months of follow-up in which echocardiographic findings revealed only mild to moderate aortic insufficiency with an ejection fraction of 56% and a shortening fraction of 30%.

Discussion

The new mutation missense p.Leu305Phe (c.913C>T) mutation in the *TGFBR2* gene detected in our patient, to the best of our knowledge, has not been reported before. The in silico prediction tools (Alamut, MutationTaster, PolyPhen-2, and SIFT) classify this mutation as a highly probable pathogenic mutation, as it is located within a highly conserved region.

LDS is characterized by cardiovascular, skeletal, and ocular system abnormalities, and diagnosis should be confirmed with molecular tests, as there are no specific clinical criteria for diagnosis. While some of the known mutations are aggressive, others usually have a mild course. In previous reports, authors have emphasized that a 4-cm intervention was appropriate in LDS patients with more lethal mutations, but they also highlighted that even among these patients who have a more aggressive phenotype and particularly bad acting mutations, it would be beneficial to proceed with a root replacement at diameters of around 2 cm (3). In another report, it was suggested that at centers with experienced staff and the ability to perform a valve-sparing procedure, surgery should be considered for young children, especially in cases of aggressive phenotypes, once the maximal dimension of the ascending aorta exceeds the 99th percentile and the diameter of the aortic annulus exceeds 1.8 cm (1). The progressive increase in aortic root Z-scores of our patient up to +10 might be an indicator of the aggressive nature of the recently diagnosed mutation.

Overall, aggressive connective tissue disorders such as LDS require earlier than usual surgical intervention in the cardiovascular system. Reports suggest a comprehensive, multidisciplinary, aggressive approach to the surgical treatment of aortic disease in patients with LDS. During follow-up,

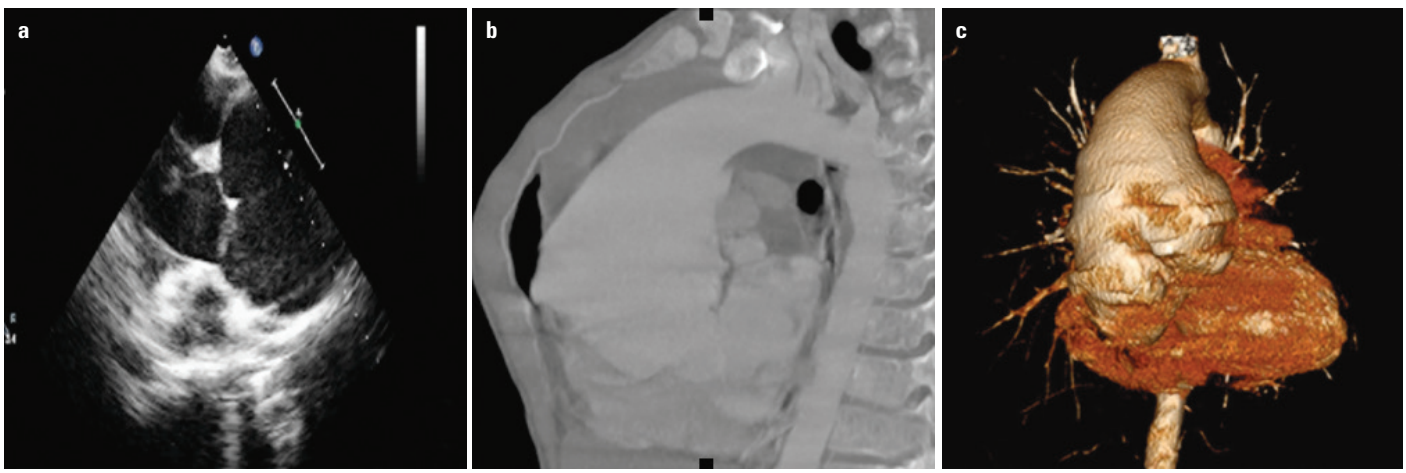

Figure 1. (a) The fusiform dilatation of the sinus of Valsalva in echocardiographic evaluation. (b, c) The aneurysmatic dilatation of the aortic root and arcus aorta on computed tomography angiographic images

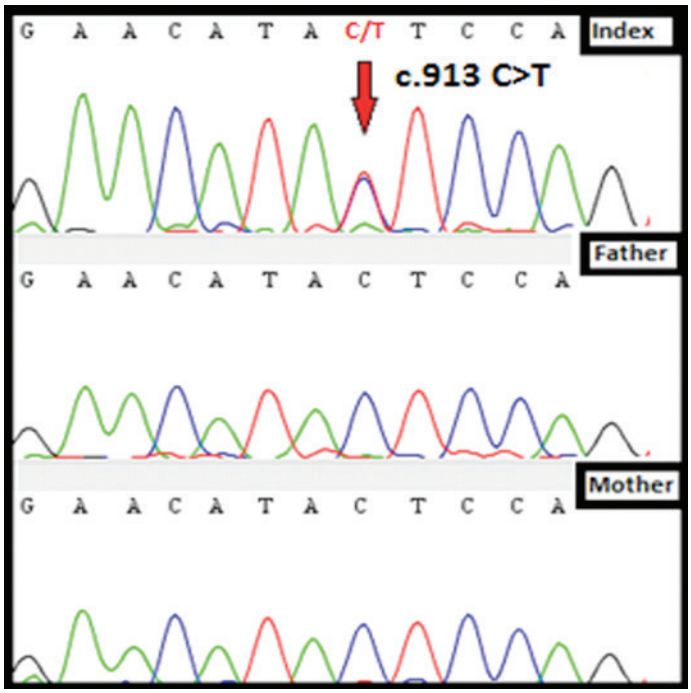

Figure 2. Sequence images of exon 4 in the TGFBR2 gene

one-quarter of the patients are expected to require surgical reintervention due to the nature of this inherent disorder (3, 4).

Valve-sparing root replacement has become a safe and reliable option for LDS patients with a low risk of mortality and need for reoperation of the aortic root (3, 4). Valve-sparing root replacement can be performed in all but patients with acute dissection and unstable hemodynamics, bicuspid aortic valves with extensive calcification, severe leaflet fenestration, or leaflet asymmetry (3). Unlike the increased risk of aortic dissection at or above the 5.0 cm aortic root dimension in Marfan syndrome, dissections have occurred in individuals with LDS type I, II, or III at aortic dimensions of 3.9 cm to 4.0 cm, and have been reported in LDS type IV at a dimension <5.0 cm (1, 5, 6). The dimensions of the aortic root of our patient were already greater than the specified indications for surgery. As our patient was very young, to prevent complications of the prosthetic valve and coumadization, valve-sparing surgery was preferred.

Conclusion

The novel p.Leu305Phe (c.913C>T) mutation in the *TGBFR2* gene determined in the present case, which exhibited a malignant course, contributes additional data to the unknown spectrum of mutations in LDS. We believe that much earlier aggressive treatment is needed in selected patients with aggressive mutations.

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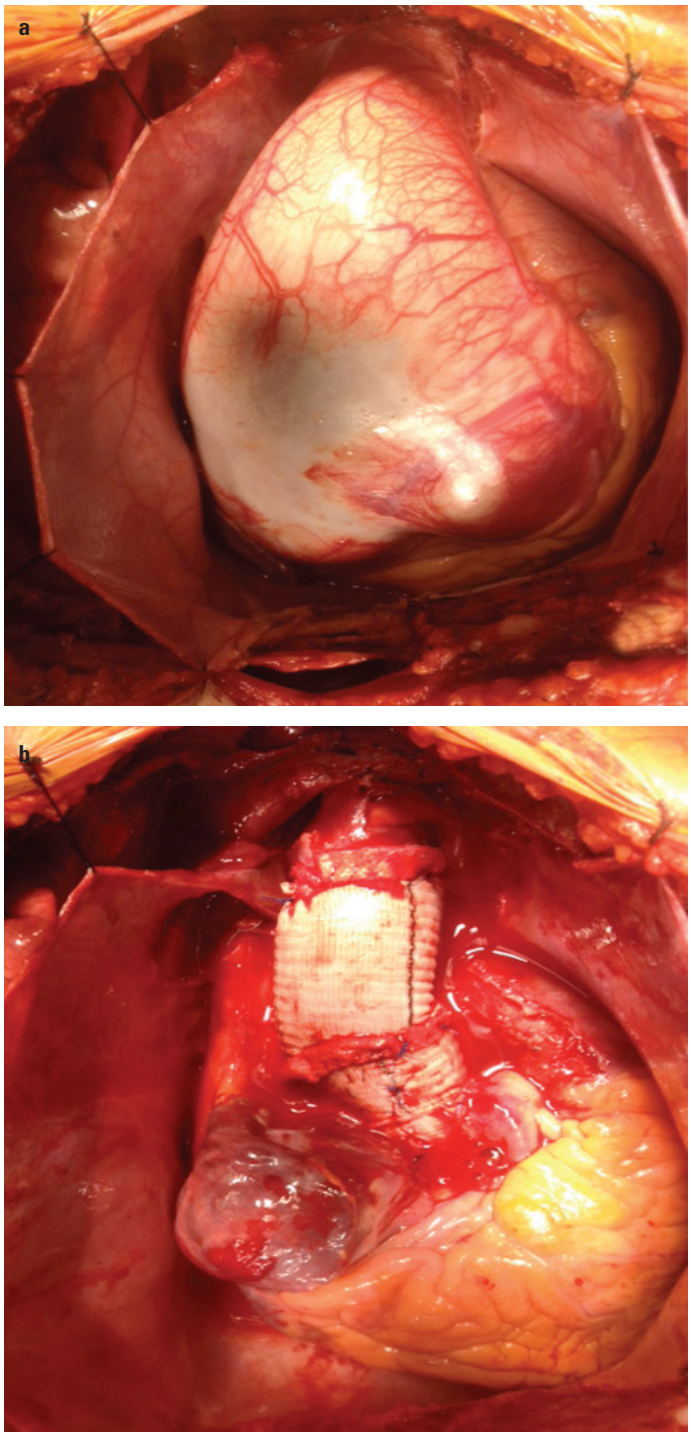

Figure 3. (a) Preoperative and (b) postoperative view of the aortic root

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