Novel Association of a Familial \textit{TGFBRI} Mutation in Loeys-Dietz Syndrome with Concomitant Hematologic Malignancy

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Concomitant Loeys-Dietz syndrome (LDS) and hematologic malignancies are exceptionally rare. This is the first report of a patient operated on for aortic root dilation who had been previously diagnosed with LDS and B-cell-lymphoma. After completion of chemotherapy and complete remission, an elective valve-sparing aortic root replacement (using the David-V method) was performed. Due to the positive family history, pre-operative genetic counseling was conducted, and revealed LDS with a \textit{TGFBRI} (transforming growth factor beta receptor type I) mutation in 6 probands of the family, albeit in 1 of them posthumously. This missense mutation has been previously described in relation to aortic dissection, but a causative relationship to malignancy has so far neither been proposed nor proven.

\textbf{Key words:} 1. Loeys-Dietz syndrome  
2. B-cell lymphoma  
3. Aortic aneurysm, thoracic

\section*{Case report}

A 54-year-old man was referred to our clinic to undergo elective surgery for an aortic root dilation measuring 54 mm in diameter (Fig. 1A). Routine echocardiography had been performed as a screening examination due to newly diagnosed sleep apnea/hypopnea syndrome 6 months previously and revealed aortic root dilation with a concomitant mild aortic regurgitation. The diagnosis was confirmed by means of a subsequent aortic computed tomography (CT) scan. The otherwise asymptomatic patient revealed a positive familial history of 2 female second-degree cousins. Both cousins had been previously diagnosed with Loeys-Dietz syndrome (LDS) with a heterozygous missense mutation, c.759G>A, p(Met253Ile), in exon 4 of the transforming growth factor beta receptor type I (\textit{TGFBRI}) gene. Unfortunately, the first cousin was diagnosed only postmortem after passing away from a ruptured aortic root aneurysm at the age of 30, just hours after giving birth to triplets. The other cousin (sister of the deceased) underwent genetic counseling, which revealed exactly the same mutation as well as clinical signs of arachnodactyly, dolichocephaly, scoliosis, and hypermobility, thus establishing the diagnosis of LDS. Furthermore, the
triplets of the deceased sister were subsequently screened and 2 of them were detected to have the same missense mutation and various concomitant clinical manifestations, ranging from general hypermobility, hypermobile fingers, and arachnodactyly to mild cerebral palsy in 1 of them. Targeted genetic counseling of our patient also revealed the above-mentioned mutation in the \textit{TGFBR1} gene, as well as mild scoliosis, dolichocephaly, and arachnodactyly. Therefore, LDS type 1 was diagnosed. Moreover, one of the patient’s offspring (a 25-year-old son) also tested positive for the same mutation. Noteworthy, all probands were negative for \textit{FBN1} gene mutations.

Prior to the writing of this case report, the patient was verbally informed and he declared his willingness for his case to be published.

While on the waiting list for elective surgery of the aortic root, the patient presented to the emergency unit of our hospital with an unclear swelling of the left axilla and left arm. Consecutive CT imaging of the chest revealed a pronounced left axillar and infraclavicular lymphadenopathy, with conglomerates of lymph nodes measuring up to 33 mm (Fig. 1B). Lymph node biopsy revealed diffuse large-cell B-cell lymphoma in stage IIA (according to the Ann Arbor staging classification, aaIPI [low risk]). A pre-phase treatment with vincristine/prednisolone and 1 course of the R-CHOP protocol (rituximab, doxorubicin, mesna, cyclophosphamide, vincristine, and pegfilgrastim) were initiated. After receiving a total of 6 courses of the R-CHOP protocol within 5 months, complete clinical and imaging remission was established.

Two months after completing the R-CHOP protocol, an elective aortic root operation was performed, using a standard median sternotomy approach. Inspection of the aortic root showed symmetrical root dilatation combined with a significant thinning of the aortic wall tissue. The aortic valve consisted of 3 cusps without signs of calcific degeneration or any other structural deterioration. Valve-sparing aortic root replacement (using the David-V method) was conducted with subsequent reimplantation of both coronary ostia. Intraoperative transesophageal echocardiography showed a competent aortic valve. The entire postoperative course was uneventful and the patient was discharged on postoperative day 9.

The postoperative management of the patient included \(\beta\)-blockers and an angiotensin-receptor antagonist (losartan). The latter category of medications is beneficial due to their effects on the TGF-\(\beta\) signaling cascade. Moreover, exercise restrictions to reduce stress on the aortic and arterial tissue included avoidance of competitive sports and isometric exercises.

**Discussion**

Since its first description, LDS has been the subject of intense research due to its deleterious cardiovascular manifestations, such as aortic dissection and cerebral hemorrhage [1,2]. It may present with diverse craniofacial, skeletal, cardiovascular, and cutaneous clinical features [1]. The majority of LDS patients die of aortic dissection and cerebral hemorrhage, at a very early mean age of 26 years [1]. However, the survival of affected individuals can be improved by early detection, surveillance, and early treatment [3]. Since LDS represents a rather new genotypic and phenotypic entity, the spectrum of concomitant multisystemic manifestations is still a
topic of research. Furthermore, to date, little is known about potential associations of LDS with malignancies.

Transforming growth factor-beta receptor I and II (TGFBR1 and TGFBR2) mutations were the first genetic abnormalities diagnosed in LDS, which were later expanded to include other genes, such as SMAD3 and TGFBR2, which were also found to cause LDS [3]. However, significant phenotypic variability within and between individuals affected 4 LDS have been reported [3]. Due to the multisystemic manifestations of LDS, along with its aggressive clinical course and the need for intense life-long surveillance, an interdisciplinary team approach is strongly recommended in the care of these patients. Moreover, aortic dimensions alone are not a good predictor of adverse aortic events in LDS patients, as aortic dissection has been reported to occur in aortas with a diameter of less than 4.0 cm [1]. This is quite different from patients presenting with Marfan syndrome, in whom aortic risk increases significantly as aortic root dimensions exceed 5.0 cm. Surgical correction by means of valve-sparing root surgery is a very reasonable treatment option for LDS patients, which distinguishes LDS patients from those presenting with vascular Ehlers-Danlos syndrome, who are prone to fatal perioperative complications [4]. Although there are many overlapping features between patients with Marfan syndrome and those with LDS, patients with LDS most often present with cardiovascular features first, while this is not the case for Marfan syndrome.

The concomitant occurrence of LDS and malignancy is a very rare manifestation, and no systematic data exist regarding such an association. Reports of concomitant LDS and hematologic malignancies are exceptionally rare, which furthermore hinders the possibility of establishing a causative relationship between both phenomena. To the best of our knowledge, this is the first report of a clinically apparent association between LDS and B-cell lymphoma. Furthermore, this particular mutation has been previously found in a family with several individuals affected by aortic dissection [5], but the possibility of a causative relationship with malignancies has not yet been established. Although the life-long risk of malignancy in LDS patients has not been well established, TGF-β signaling has been proposed to play a role in the initial stage of oncogenesis, as well as in the later stages, by promoting tumor progression and metastasis formation [6]. Our patient was diagnosed with a heterozygous missense mutation, c.759G>A, p.(Met253Ile) in the TGFBR1 gene. The index patient is indicated by an arrow. n.a., no DNA available; Wt, wild type (no mutation detected); TGFBR1, transforming growth factor beta receptor type I.

Fig. 2. Pedigree of a family with Loeys-Dietz syndrome associated with c.759G>A p.(Met253Ile) in the TGFBR1 gene. The index patient is indicated by an arrow. n.a., no DNA available; Wt, wild type (no mutation detected); TGFBR1, transforming growth factor beta receptor type I.
sentative of all known family members with this mutation, which in part may explain the singular occurrence of such a malignancy in the analyzed family. Six family members who were tested for this mutation were diagnosed positive (Fig. 2). Considering the high penetrance and the variable expression of the genetic defect in this family, along with the documented aggressive clinical course of LDS and the excellent long-term results of valve-sparing root surgery, increased alertness and timely aortic root intervention should be strongly considered in patients who test positive for this TGFBR1 mutation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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