**Thymoma Associated with Loeys-Dietz Syndrome Type 1**

**Timomanın Eşlik Ettiği Loeys-Dietz Sendromu Tip 1**

Hayrullah ALP¹, Fatih ŞAP¹, Hakan ALTIN¹, Zehra KARATAŞ¹, Tamer BAYSAL¹, Sevim KARAASLAN¹, Sevgi PEKCAN²

¹Sub-Department of Pediatric Cardiology, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
²Sub-Department of Pediatric Pulmonology, Department of Child Health and Pediatrics, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey

**Abstract**

Loeys-Dietz syndrome is a rare autosomal dominant disorder characterized by the involvement of cardiovascular, craniofacial and skeletal systems. The main etiology of the disease is the mutation in the transforming growth factor beta-receptor type 1 and 2 genes. Today, Loeys-Dietz syndrome has been classified into two subtypes due to the presence of craniofacial involvement. These patients have progressive aortic enlargement which increases the risk of dissection and rupture. So, delay in the diagnosis may be associated with poor prognosis. We present a new case with thymoma diagnosed as Loeys-Dietz syndrome type 1. Also, this is the first report of a tumor in Loeys-Dietz syndrome according to the current literature review.

**Key Words:** Loeys-Dietz syndrome, Thymoma, Aortic root aneurysm, Aortic dilatation

**Introduction**

Loeys-Dietz syndrome (LDS) is a newly identified genetic disorder of the connective tissue, described by Loeys et al. in 2005¹. The diagnostic triad of the syndrome is the following: 1) arterial tortuosity, aneurysms or dissections 2) hypertelorism and 3) bifid uvula or cleft palate¹-³. It is caused by heterozygous mutations in the genes encoding type 1 or type 2, transforming growth factor beta-receptors traced to chromosomes 9q33-34 and 3p24⁴. Affected individuals exhibit a variety of features, mainly involving the musculoskeletal, cardiovascular and central nervous systems.

The clinical findings of the musculoskeletal system include symptoms such as arachnodactyly, joint laxity, pectus deformity, scoliosis, dolichosternomelia, talipes equinovarus, camptodactyly and cervical spine instability⁴. Chiari malformation and hydrocephalus are associated anomalies of the central nervous system. However, the life-threatening complications, which determine the prognosis, are the results of cardiovascular system findings including aortic root aneurysm, arterial tortuosity, aneurysms of other vessels, patent ductus arteriosus and atrial septal defects⁴. Up to now, two subtypes of LDS have been delineated⁴. The patients with LDS type 1 have both craniofacial
and cardiovascular disorders. The most common characteristic of craniofacial clinical features are hypertelorism and cleft palate or bifid uvula. In contrast, patients with LDS type 2 may have a bifid uvula but do not have a cleft palate, craniosynostosis or hypertelorism. Additional manifestations of LDS include malar hypoplasia, exotropia, blue sclera and retrognathia. The phenotypes of patients with LDS closely resemble Marfan, Shprintzen-Goldberg, Beals, Larsen or vascular Ehlers-Danlos syndromes. However, LDS is characterized by a unique constellation of clinical and pathologic manifestations. We have reported a case of LDS type 1 syndrome with thymoma. Current review of the literature suggested no case with a tumor in LDS.

**Case Report**

The patient was a 17-year old male who referred to our clinic for evaluation of cardiac murmur. He was born at term after an uncomplicated pregnancy from non-consanguineous parents. He had a mild developmental delay during infancy and childhood. He was operated for bilateral inguinal hernias at the age of five. His height and weight were 50-75th percentile and his head circumference was >97th percentile, respectively. On initial examination, he had dolichocephaly, hypertelorism, bifid uvula, high-arched palate and malar hypoplasia (Figure 1a, b). Other examination findings were bilateral foot and hand contractures characterized by camptodactyly with arachnodactyly. Also, there was a second degree cardiac murmur detected on physical examination. The chest radiography revealed an expansion on the superior mediastinum (Figure 2). Echocardiography showed that the bicuspid aortic valve and aortic root diameter measured 44 mm. Diagnostic cardiac catheterization displayed bicuspid aortic valve without stenous or aortic insufficiency and dilated aorta with the following diameters: root 44 mm, arcus 43 mm and descending 40 mm respectively (Figure 3a, b). On cardiac catheterization and magnetic resonance imaging, no dilatation was detected in other arteries. Due to the mild mental retardation, magnetic resonance imaging of the brain was performed and it revealed Chiari 1 malformation (Figure 4). Magnetic resonance imaging of the thorax demonstrated a well-defined superior mediastinal mass and normal lung regions (Figure 5). An ultrasonography guided biopsy of intrathoracic tumor was performed showing a thymoma type B1 (Figure 6), according to the World Health Organization (WHO) classification. Beta-blocker treatment was given for the unexpected complications, dissection and rupture, and he was referred to the department of thoracic surgery for the surgery of thymoma. Also, a signed permission form was taken from the parents for all images of the patient prior to publication.

![Figure 1a, b. (a) Dolichocephaly, hypertelorism and malar hypoplasia, (b) bifid uvula and high-arched palate](image1)

![Figure 2. Expansion of the superior mediastinum due to thymoma on the chest radiography](image2)

![Figure 3a, b. (a) Bicuspid aortic valve and wide aorta with the diameters of root 44 mm, (b) arcus 43 mm and descending 40 mm respectively on diagnostic cardiac catheterization](image3)
Discussion

Loeys-Dietz syndrome is a newly recognized genetic disorder\(^1\). We have demonstrated clinical features of this disorder including: dolichocephaly, hypertelorism, bifid uvula, high-arched palate, malar hypoplasia, camptodactyly and arachnodactyly with the radiographic findings; bicuspid aortic valve, wide aortic root, aortic dilatation and Chiari 1 malformation which were diagnosed in the present patient with LDS. Comparison of the key clinical features of LDS type 1, reported by Loeys et al. in 2005\(^1\) and the present case are given in Table I.

The sex predominance and prevalence of this genetic syndrome has not been established yet. LDS may be commonly misdiagnosed as Marfan, Shprintzen-Goldberg, Beals, Larsen or vascular Ehlers-Danlos syndromes.

Marfan syndrome is caused by mutations in the fibrillin-1 gene located on chromosome 15q21\(^2,5\). Symptoms are skeletal, ocular; especially ectopia lentis which are not associated with LDS; and cardiovascular manifestations in patients with Marfan syndrome\(^5,5\).

Shprintzen-Goldberg syndrome is one of the marfonoid craniosynostosis syndromes with skeletal, ocular, cranial and connective tissue defects. Also, this syndrome is not associated with cleft palate, arterial tortuosity or risk of the aneurysm or dissection other than of the aortic root\(^5,6\).

Beals syndrome, otherwise known as congenital contractural arachnodactyly occurs as a result of a mutation in the fibrillin 2 gene. This syndrome is not associated with cardiac or ocular pathologies as in LDS\(^7\).

Larsen syndrome is caused by mutations in the flaming B gene encoded in the 3p14 region. The characteristic clinical features are craniofacial findings and multiple joint dislocations\(^8\). However, cardiac and spine abnormalities in association with joint contractures can be present in Larsen syndrome\(^9\).

Vascular Ehlers-Danlos syndrome (type 4) is autosomal dominant in type 3 collagen and characterized by fragile skin with life-threatening complications\(^10\). This syndrome can overlap with the features of LDS type 2.

As the site of maturation for T-cells, the thymus plays a central role in adaptive immunity\(^11\). Although primary tumors of the thymus are rare, the most common histologic type is thymoma. The cause of thymoma is unknown\(^11\). Complete surgical resection is vital for the successful management of thymic malignancies and chemotherapy and radiation therapy play an important role in the management of recurrent disease\(^12\). Our patient was referred to the department of thoracic surgery for surgery of the thymoma. This is the first report of a tumor in LDS syndrome. However, due to the reported of no malignancy in these patients, it cannot be suggested that there may be a predisposition for tumors in LDS patients. Probably, the thymoma was detected coincidentally in LDS.

Aortic dilatation in patients with LDS may appear in various age groups and major complications of the disease are aortic dissection or rupture\(^1,2,5,10,13,14\). Physicians should have been alerted by the expansion on superior mediastinum which may be

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associated with aortic dilatation or malignancy, as in our case, on the chest radiography. However, it cannot be estimated whether aortic root dilatation occurs in early or late decades of life. So, to follow up these patients for unexpected complications is important. Surgery, such as valve-sparing root replacement, reconstruction of the descending thoracic or abdominal aorta may be performed.

In conclusion, LDS syndrome causes an aggressive aortic aneurism or in the other arteries, with a predisposition to rupture or dissection at younger ages. So, early true diagnosis and differentiation from other similar syndromes are the basis for optimal management and meticulous surveillance.

References


