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Thymoma Associated with Loeys-Dietz Syndrome Type 1

Timomanın Eşlik Ettiği Loeys-Dietz Sendromu Tip 1

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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. *(Marmara Medical Journal 2012;25:103-6)*

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

Özet

Loeys-Dietz sendromu kardiovasküler, kraniofasiyal ve iskelet sisteminin tutulduğu nadir bir otozomal dominant hastalıktır. Esas etyoloji, transforming growth faktör beta-reseptör tip 1 ve 2 genlerindeki mutasyonlardır. Günümüzde, Loeys-Dietz sendromu kraniofasiyal bulguların varlığına göre iki alt gruba ayrılmıştır. Aort genişlemesi olan hastalar diseksiyon ve rüptür açısından risk taşırlar. Sonuçta, tanıdaki gecikme kötü prognoz ile sonuçlanabilir. Timomanın eşlik ettiği ve Loeys-Dietz tip 1 sendromu tanısı konulan yeni bir vakayı sunduk. Ayrıca, vaka sunumu literatürde bir tümörün eşlik ettiği ilk Loeys-Dietz sendromudur. *(Marmara Üniversitesi Tıp Fakültesi Dergisi 2012;25:103-6)*

Anahtar Kelimeler: Loeys-Dietz sendromu, Timoma, Aort kökü anevrizması, Aort dilatasyonu

Introduction

Loeys-Dietz syndrome (LDS) is a newly identified genetic disorder of the connective tissue, described by Loeys et al. in 2005[1]. Th diagnostic triad of the syndrome is the following: 1) arterial tortuosity, aneurysms or dissections 2) hypertelorism and 3) bifid uvula or cleft palate[1-3]. 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 3p24[4]. Affected individuals exhibit a variety of features, mainly involving the musculoskeletal, cardiovascular and central nervous systems. The clinical findings of the musculoskeletal system includes symptoms such as arachnodactyly, joint laxity, pectus deformity, scoliosis, dolichosternomelia, talipes equinovarus, camptodactyly and cervical spine instability[4]. 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 defects[4]. Up to now, two subtypes of LDS have been delineated[4]. The patients with LDS type 1 have both craniofacial

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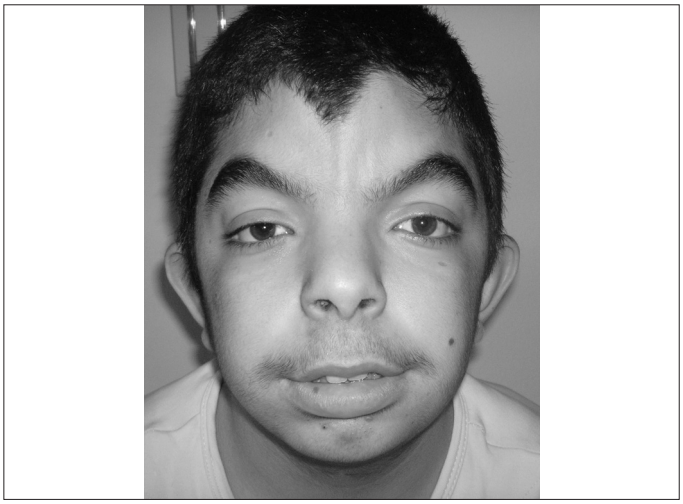
and cardiovascular disorders. The most common characteristic of craniofacial clinical features are hypertelorism and cleft palate or bifid uvula[1-4]. In contrast, patients with LDS type 2 may have a bifid uvula but do not have a cleft palate, craniosynostosis or hypertelorism[4]. Additional manifestations of LDS include malar hypoplasia, exotropia, blue sclera and retrognathia[4]. The phenotypes of patients with LDS closely resemble Marfan, Shprintzen-Goldberg, Beals, Larsen or vascular Ehlers-Danlos syndromes[1,2]. 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 steneous 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.



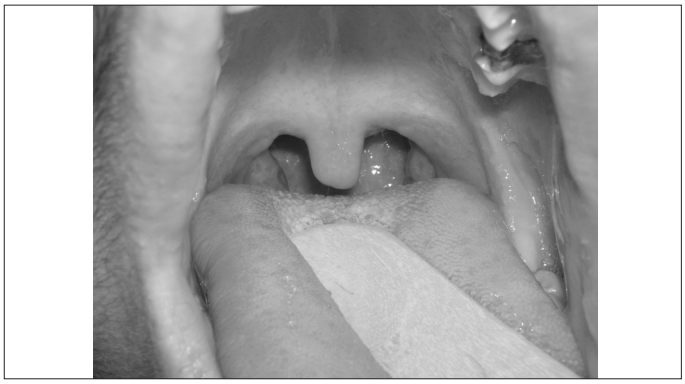


Figure 1a, b. (a) Dolichocephaly, hypertelorism and malar hypoplasia, (b) bifid uvula and high-arched palate

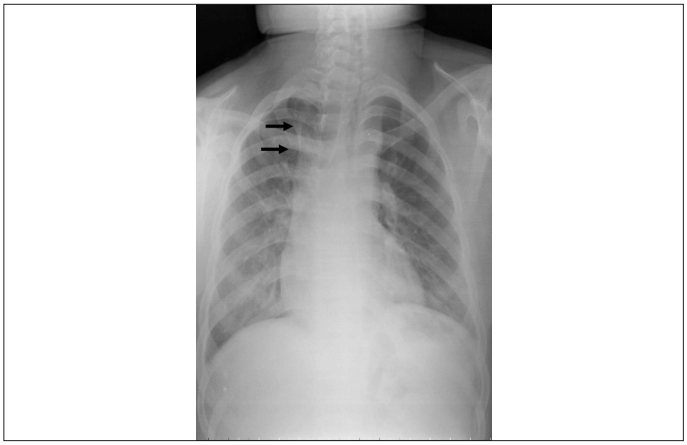


Figure 2. Expansion of the superior mediastinum due to thymoma on the chest radiography

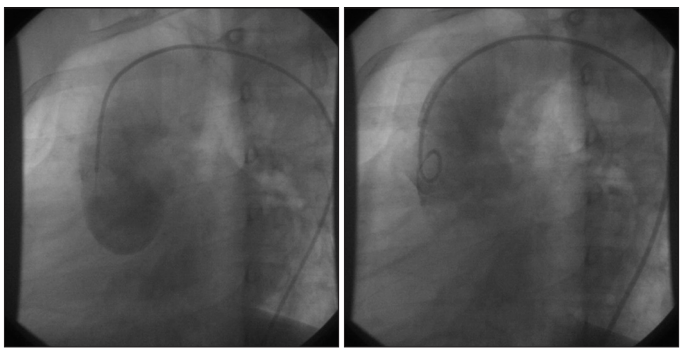


Figure 3a, b. (a) Bicuspid aortic valve and wide aorta with the diameters of root 44 mm, (b) arcus 43 mm and descending 40 mm respectively on diagnostic cardiac catheterization

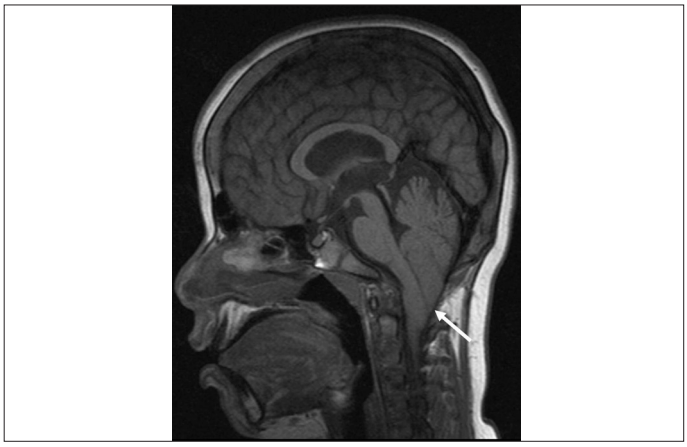


Figure 4. Chiari 1 malformation on magnetic resonance imaging

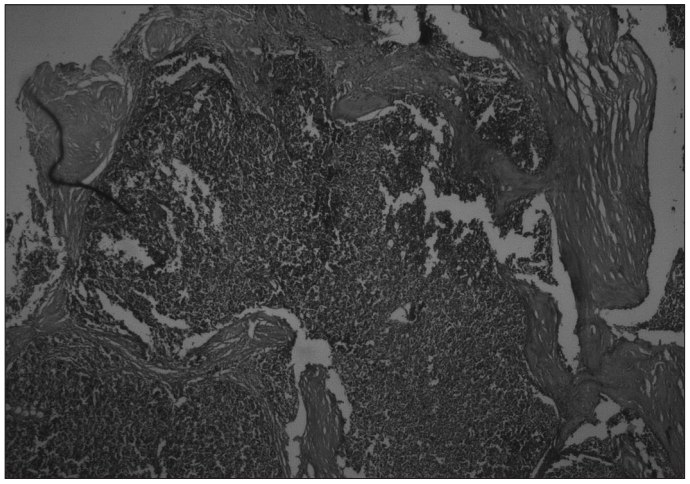


Figure 5. Magnetic resonance imaging of the thorax demonstrated a well-defined superior mediastinal mass

Table I. Comparison of clinical and laboratory findings of LDS type 1 described by Loeys et al. and of our patient

	Loeys et al.[1]	Patient
Cardiovascular		
Aortic root aneurysm	98%	+
Craniofacial		
Hypertelorism	90%	+
Cleft palate/bifid uvula	90%	+
Malar hypoplasia	60%	+
Craniosynostosis (dolichocephaly)	48%	+
Skeletal system		
Arachnodactyly	70%	+
Camptodactyly	38%	+
Neurocognitive		
Chiari 1 malformation	10%	+
Mental retardation	15%	+

[1]Loeys BL, Chen J, Neptune ER et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development causes by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275-81.

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[3,5].

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 risc 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[1,2,4,5,10,13,14]. Physicians should have been alerted by the expansion on superior mediastinum which may be

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[2].

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

1. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development causes by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275-81.
2. Williams JA, Loeys BL, Nwakanma LU, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg 2007;83:757-63.
3. Rodrigues VJ, Elsayed S, Loeys BL, Dietz HC, Yousem DM. Neuroradiologic manifestations of Loeys-Dietz syndrome type 1. AJNR 2009;30:1614-9.
4. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788-98.
5. LeMaire SA, Pannu H, Tran-Fadulu, V Carter SA, Coselli JS, Milewicz DM. Severe aortic and arterial aneurysms associated with a TGFBR2 mutations. Nat Clin Pract Cardiovasc Med 2007;4:167-71. doi:10.1038/ncpcardio0797
6. Kosaki K, Takahashi D, Udaka T, Kosaki R, Matsumoto M, Ibe S. Molecular pathology of Shprintzen-Goldberg syndrome. Am J Med Genet A 2006;140:104-8. doi: 10.1002/ajmg.a.31006
7. Hecht F, Beals RK. New syndrome of congenital contractural arachnodactyly originally described by Marfan in 1896. Pediatrics 1972;49:574-9. doi: 10.1542/peds.1972-1800
8. Larsen LJ, Schottsstaedt ER, Bost FC. Multiple congenital dislocations associated with characteristic facial abnormalities. J Pediatr 1950;37:574-81. doi: 10.1016/S0022-3476(50)80268-8
9. Kiel EA, Frias JL, Victorica BE. Cardiovascular manifestations in the Larsen syndrome. Pediatrics 1983;71:942-6. doi: 10.1542/peds.1983-1844
10. Drera B, Ritelli M, Zoppi N, et al. Loeys-Dietz syndrome type l and ll: clinical findings and novel mutations in two Italian patients. Orphanet J Rare Dis 2009;2:24. doi: 10.1186/1750-1172-4-24
11. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol 2010;5:260-5. doi: 10.1097/JTO.0b013e3181f1f62d
12. Rajan A, Giaccone G. Targeted therapy for advanced thymic tumors. J Thorac Oncol 2010;5:361-4. doi: 10.1097/JTO.0b013e3181f21114
13. Onrat ST, Emmiler M, Sivaci Y, Söylemez Z, Ozgöz A, Imirzalioğlu N. A patient with ascending aortic dilatation, similar to phenotypes of connective tissue disorders. Genet Mol Res 2009;8:426-34.
14. Tug E, Loeys B, De Paepe A, Aydin H, Gideroglu K. A Turkish patient of typical Loeys-Dietz syndrome with a TGFBR2 mutation. Genet Couns 2010;21:225-32.