ONLINE FIRST

Multiple Facial Milia in Patients With Loeys-Dietz Syndrome

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Background: Loeys-Dietz syndrome (LDS) results from mutations in the TGFBR1 or TGFBR2 genes and is known to cause aggressive cardiovascular disease, including aortic aneurysms and dissections at an early age. Currently, craniofacial, skeletal, and cardiovascular findings play an important role in early recognition of the disease. While many patients do have recognizable cutaneous features of LDS, little information about associated skin findings has been reported.

Observations: Four unrelated patients with LDS due to a mutation in the TGFBR2 gene were observed to have numerous facial milia. All 4 patients reported that the milia had been present since early childhood and had increased in number with time. In some cases, affected relatives were reported to have similar findings.

Conclusions: To our knowledge, the association of LDS and facial milia has not been previously reported. Recognition of LDS is important because the aggressive aortic and arterial disease warrants early surgical therapy. Facial milia and other cutaneous findings may possibly differentiate LDS from Marfan syndrome and other related disorders, thereby facilitating early diagnosis. Interestingly, each of the 4 patients with LDS and facial milia had a mutation in TGFBR2 despite widespread variability in other features of the disease.

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LOEYS-DIETZ SYNDROME (LDS) is a recently described autosomal dominant disorder that is caused by mutations in TGFBR1 or TGFBR2 (transforming growth factor-β [TGF-β]-receptor) genes. Patients with LDS have widespread manifestations that may include arterial tortuosity, aortic aneurysms and dissections, craniosynostosis, hypertelorism, cleft lip, bifid uvula, bluish sclera, arachnodactyly, pectus deformities, and translucent skin. Some authors have further classified patients with LDS into type I (those with more severe craniofacial abnormalities) and type II (those with vesiculobullous and translucent skin, resulting in easily visible veins), but there is considerable overlap.

Abnormalities in TGF-β signaling are known to be associated with Marfan syndrome and other aneurysm syndromes. Marfan syndrome is characterized by mutations in the fibrillin-1 gene (FBN1), which produces structural defects in the extracellular matrix as well as increased TGF-β signaling. Both structural and regulatory abnormalities are thought to contribute to the pathogenesis. In LDS, the mutation occurs in TGFBR1 or TGFBR2, producing a different phenotype with some overlapping features but with much more aggressive cardiovascular disease.

Numerous cardiovascular and skeletal manifestations of LDS have been described in several case series. The only reported cutaneous findings to date include velvety and translucent skin, easy bruising, varicose veins, and atrophic scars. The facies of LDS are characterized by malar hypoplasia, retrognathia, deformities and asymmetry resulting from craniosynostosis, bluish sclera, and hypertelorism. Other common skeletal abnormalities include arachnodactyly, pectus deformity, scoliosis, cervical spine abnormalities, talipes equinovarus, camptodactyly, and joint laxity.

To date, our institution follows up 25 individuals with LDS, each with a mutation in TGFBR1 or TGFBR2. We describe 4 patients from this population with LDS who have numerous facial milia that have been present since early childhood. To our knowledge, this finding has not previously been reported in patients with TGFBR1 or TGFBR2 mutations outside of a brief oral communication, which included 1 of our 4 patients. We also report other potentially relevant cutaneous findings in these patients in an attempt to summarize known skin manifestations of LDS.

REPORT OF CASES

CASE 1

An 18-year-old man with LDS presented with numerous facial milia, most notably
in a periocular distribution (Figure 1). Detailed history from his mother indicated that his facial milia had been present since early childhood and had increased in number. The lesions had been “scraped off” numerous times in childhood, only to recur within a short time. Examination of his head and face revealed an abnormal cranial structure consistent with craniosynostosis, hypertelorism, malar hypoplasia, and retrognathia (Figure 2), and inspection of his oral cavity showed a high-arched palate and bifid uvula.

His cardiovascular findings included aneurysms of his aortic root and left subclavian artery, which had been repaired surgically. Numerous other tortuous cervicocranial vessels had been identified radiographically. He had also undergone surgical correction of the talipes equinovarus and pectus excavatum. Other significant skeletal abnormalities included kyphoscoliosis, arachnodactyly, camptodactyly, and joint laxity.

Before LDS was described in 2005, this patient had been incorrectly diagnosed as having Shprintzen-Goldberg syndrome. The correct diagnosis of LDS was confirmed in 2005 by the identification of a \textit{TGFBR2} mutation (p.Arg537Gly). His father, who had a surgically repaired aortic aneurysm, was also diagnosed as having LDS at that time. The father was not known to have facial milia.

**CASE 2**

A 24-year-old woman with LDS due to a mutation in \textit{TGFBR2} (p.Arg528His) presented with numerous facial milia in the orbital area, including the eyelids (Figure 3). Milia had also developed at sites of scarring, including within and around her wide atrophic sternotomy scar. She reported that the facial milia had been present since early childhood.

Physical examination revealed prominent malar atrophoderma vermiculatum (Figure 4). Other facial features included hypertelorism and retrognathia. The oral cavity was notable for a high-arched palate and a broad uvula. The patient had undergone surgical resection of an ascending aortic aneurysm as well as replacement of both the aortic and the mitral valves. She had enlargement of the pulmonary artery and marked tortuosity of the carotid and vertebral arteries as well. Other skeletal findings included scoliosis, arachnodactyly, camptodactyly, and joint laxity (Figure 5). She also had undergone multiple operations to repair skeletal defects, including a cleft palate, pectus excavatum, and talipes equinovarus, and had suffered a spontaneous uterine rupture that was not related to pregnancy and required an emergency hysterectomy.
CASE 3

A 36-year-old woman with LDS presented with numerous facial milia. She reported that the milia had been present since early childhood. She also reported that her father, who had suffered a fatal aortic rupture, had similar facial lesions. She has 2 children with LDS, one of whom has facial lesions consistent with milia.

Examination of her oral cavity was notable for a high-arched palate. She did not have a noticeably broad or bifid uvula. Skeletal abnormalities included mild arachnodactyly and joint laxity. She had velvety skin and easily visible veins. She also had suffered a type A aortic dissection and had undergone surgical repair of an aortic root aneurysm and replacement of her aortic valve. She subsequently required resection of a descending aortic aneurysm. She had been diagnosed as having Marfan syndrome until analysis in our institution revealed a mutation in exon 5 of TGFBR2 (p.Phe442Leu).

CASE 4

A 37-year-old woman with LDS presented with numerous facial milia. She reported that the milia had been present since early childhood. Inspection of her skin revealed numerous striae. Examination of her oral cavity revealed a high-arched palate and a bifid uvula. Her cardiovascular surgical history consisted of an aortic root replacement. She also had mitral valve prolapse and mild tortuosity of her cervical vessels.

Her skeletal abnormalities included pectus excavatum, scoliosis, and hyperflexibility. She had experienced numerous joint dislocations. She also had been diagnosed as having Marfan syndrome until evaluation in our institution identified a TGFBR2 mutation (p.Arg537Cys).

COMMENT

It is imperative to diagnose LDS correctly because it is associated with very aggressive vascular disease. Also, because LDS may be confused with other familial aneurysm syndromes, including Marfan syndrome, vascular Ehlers-Danlos syndrome, and Shprintzen-Goldberg syndrome, it is important to identify the features that differentiate these conditions. Besides craniofacial defects such as hypertelorism, bifid uvula, and cleft palate, certain cutaneous features may be very helpful in suggesting and confirming the diagnosis of LDS. Facial milia, which have not been specifically reported in other familial aneurysm syndromes, may be specific to LDS. More research is needed to verify this point, but facial milia may contribute to the proper recognition of LDS.

Because we believe that facial milia may represent a phenotypic manifestation of LDS, we herein report 4 cases of LDS with facial milia that were seen in our institution. We would add facial milia to velvety and translucent skin, easy bruising, varicose veins, and atrophic scars as recognizable cutaneous features of LDS.
Further studies, examining a larger population of affected patients, may demonstrate that other skin findings, including atrophoderma vermiculatum and striae and milia formation at sites of trauma, are associated with LDS.

In our population of patients with LDS, milia were present in 4 out of 25 patients. The genetic defect was identified in all 25 patients, and each family studied had a unique mutation. In our population, the presence of milia did not correlate with a specific genetic defect or with other clinical findings in LDS. Approximately two-thirds of our patients with LDS had a mutation in TGFBR2, and one-third had a mutation in TGFBR1. It is interesting that all 4 of our patients with milia harbored a TGFBR2 mutation, but the phenotypes observed in these patients were otherwise quite variable. There is widespread phenotypic variability among all patients with LDS, patients were otherwise quite variable. There is wide-

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