It is believed that myelofibrosis results from a proliferation of polyclonal fibroblasts that is secondary to cytokines released from clonal megakaryocytes or platelets. The orbita is not a typical site for hematopoietic tumors arising in agnogenic myeloid metaplasia. It is commonly performed in patients with myelofibrosis, but the development of SEMHT is related to splenectomy. Although our patient developed orbital masses after splenectomy, it is not clear whether the formation of SEMHTs is related to splenectomy. Splenectomy may not be an important factor in the formation of SEMHTs. Moreover, splenectomy is commonly performed in patients with myelofibrosis, but the development of SEMHTs is relatively rare.

Figure 4. Immunostaining for factor VIII highlights megakaryocytes (original magnification ×600).

Despite the absence of a highly cellular marrow-like appearance and by the presence of a predominantly sclerotic background, it is believed that myelofibrosis may give rise to circulating stem cells. These findings suggest a benign disease. In summary, this is the first reported case, to our knowledge, of SEMHT in the orbita. Sclerosing extramedullary hematopoietic tumors can histologically and radiologically mimic other soft tissue neoplasms. History of a myeloproliferative disorder and a high index of suspicion are important in making the diagnosis. The clinical course is relatively benign, and aggressive local therapy does not seem to be mandatory.

Limbal Stem Cell Deficiency Associated With LADD Syndrome

The lacrimo-auriculo-dento-digital (LADD) syndrome is an autosomal dominant hereditary disease with variable expression. It was first described in 1967 by Levy as an isolated case of bilateral absence of the tear system, cup-shaped ears, dry mouth, and dental, arm, and digital abnormalities. Subsequently, new clinical findings such as renal anomalies, absent salivary glands, congenital hip dislocation, congenital hiatal and diaphragmatic hernias, sensory and conductive deafness, hypodontia, limb anomalies, xerostomia, and xerophthalmia were described associated with this syndrome. Thirty-five cases of LADD syndrome are described in the literature and most of them include ocular involvement. In particular, 71% showed hypoplasia or aplasia of the tear glands, hypoplasia or aplasia of...
64% showed tear deficiency, recurrent or chronic conjunctivitis, keratoconjunctivitis sicca, and corneal ulcerations related to the underlying tear gland aplasia.²,³

We describe, for the first time, limbal stem cell deficiency and corneal hypoanesthesia in 2 patients (mother and child) with LADD syndrome.

Report of a Case. In February 2002, a 30-year-old woman and her 9-year-old daughter were referred to our cornea and external disease center at the University of Rome "Campus Bio-Medical," Rome, Italy. They both came with a clinical diagnosis of LADD syndrome, on the basis of genetic counseling and radiographic and ultrasonographic examinations.

On physical examination, the patients had several digital abnormalities: syndactyly of the thumb and second finger and absence of the left third finger, as well as the left second toe. In addition, the mother showed agenesis of the central mandibular incisors and a history of extensive dental caries. Her nostrils appeared flared and both ears were small and cup-shaped. Moreover, signs of salivary insufficiency were present, such as fissures and ulcers of the tongue, oral mucosa, and lips.

On their ocular history, both described episodes of corneal ulceration with a more severe clinical evolution in the mother’s eyes (3 perforations, ocular dryness, and tear deficiency since the age of 10 years). The daughter had no symptoms of dry eye.

At slitlamp examination, they both showed haziness of the corneal epithelium with an irregular, gray appearance and superficial neovascularization (Figure 1A and Figure 2A). The central cornea was thinned, and small epithelial defects were present. Their visual acuities were partially reduced. In addition, the mother showed marked conjuncti-
val hyperemia and evident anatomical changes of the ocular surface in both eyes with fornix shortening and more pronounced corneal epithelial defects.

Corneal sensitivity, as tested by Cochet-Bonnet esthesiometer (Lu-neau Ophtalmologie, Chartres-Cedex, France) for each of the 5 corneal sectors (temporal, inferior, nasal, superior, and central), resulted in mild to marked corneal hypoesthesia. Reduced Schirmer tests, types 1 and 2, and break-up time, as well as squamous metaplasia and low density of conjunctival goblet cells, were present in the mother but not in the daughter (Table).

Two corneal swabs and routine hematological tests, including antinuclear antibody, extractable nuclear antibody, immunocomplex, and rheumatoid factor, were performed to exclude any infection or autoim-

### Table. Corneal Esthesiometry and Tear Function Tests

<table>
<thead>
<tr>
<th></th>
<th>Mother</th>
<th>Daughter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal esthesiometry (Cochet-Bonnet esthesiometer)</td>
<td>Right eye: marked hypoesthesia in all 5 corneal sectors (range, 0.5 to 1 of 6 cm)</td>
<td>Right eye: mild hypoesthesia in all 5 corneal sectors (range, 4 to 6 of 6 cm)</td>
</tr>
<tr>
<td></td>
<td>Left eye: complete anesthesia in all 5 corneal sectors (0 of 6 cm)</td>
<td>Left eye: mild hypoesthesia in all 5 corneal sectors (range, 3 to 6 of 6 cm)</td>
</tr>
<tr>
<td>Schirmer 1 test</td>
<td>Partially reduced in both eyes (range, 0-2 mm/5 min)</td>
<td>Normal in both eyes (&lt;20 mm/5 min)</td>
</tr>
<tr>
<td>Schirmer 2 test</td>
<td>Markedly reduced (0 mm/5 min) in both eyes</td>
<td>Normal in both eyes (range, 13-15 mm/5 min)</td>
</tr>
<tr>
<td>Break-up time</td>
<td>Markedly reduced (1 s) in both eyes</td>
<td>Normal (11 s) in both eyes</td>
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Figure 2. Clinical evaluation of the daughter’s right eye showed corneal epithelial haziness and neovascularization on the inferior corneal sector (A). Goblet cells (periodic acid–Schiff) (B) and cytokeratin K19 positive cells (immunohistochemistry) (D) were present on the inferior sector. Cytokeratin K3 positive cells (immunohistochemistry) (C) were present on the other sectors (original magnification ×20; digitally processed images).
associated with limbal stem cell deficiency. The impairment of corneal sensitivity is a new characteristic of LADD syndrome and the pathogenetic mechanism is unclear. Indeed, corneal hypoesthesia was also present in the child, with no presence of dry eye. It is possible that limbal stem cell deficiency and corneal hypoesthesia could both be contributing factors toward corneal changes found in this syndrome.

Our study suggests 2 additional clinical features of LADD syndrome, other than dry eye. Indeed, we found the presence of limbal stem cell deficiency and corneal sensitivity impairment in the absence of dry eye. These results have important therapeutic implications. In fact, to date, the therapeutic approach for the ocular manifestations of LADD syndrome was the treatment of the dry eye condition, based on tear substitutes and lacrimal punctum occlusion. These novel observations of LADD syndrome may introduce new therapeutic options; it would be interesting to evaluate if a limbal transplantation could be effective in improving the clinical manifestations of the disease, such as corneal anesthesia.

Comment. In this report, we describe 2 cases of LADD syndrome associated with limbal stem cell deficiency and corneal hypoesthesia. Limbal stem cell deficiency was diagnosed on the basis of clinical features (corneal epithelial erosions and neovascularization) and cytological findings (presence of goblet cells and specific cytokeratins of the corneal epithelium). Clinical ocular features of LADD syndrome, described as corneal erosions, neovascularization, and ulceration, were thought by authors to be clinical manifestations of the underlying dry eye condition. Based on the literature, we hypothesized that dry eye may also induce the development of limbal deficiency as well as corneal anesthesia. This hypothesis was at first confirmed by the mother's condition. However, the daughter showed an initial partial limbal deficiency and a history of corneal ulceration with no deficiency of tear production and without the anatomical changes related to dry eye. Therefore, it is possible that limbal deficiency could represent a genetically determined, clinical characteristic of LADD syndrome, adding this syndrome to the ever-increasing list of conditions associated with limbal stem cell deficiency.

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Correspondence: Dr Bonini, G. B. Bietti Eye Foundation, Via Livenza 3, 00196 Rome, Italy (s.bonini@unicampus.it).