

Diagnosis and Management of Limbal Stem Cell Deficiency

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The corneal epithelium is a continuously regenerating surface that is replenished by a stem cell supply located in the basal epithelial layer of the limbus. The importance of these stem cells is most apparent when their numbers are decreased. With a reduced ability to repopulate the corneal epithelium and an unstable ocular surface, patients with limbal stem cell deficiency (LSCD) can have ocular pain from corneal erosions and decreased vision from stromal scarring or epithelial irregularity.

LSCD is often misdiagnosed, especially during its early stages. Patients may present with nonspecific complaints that are common to many ocular surface disorders, and clinical examination is often nonspecific as well.

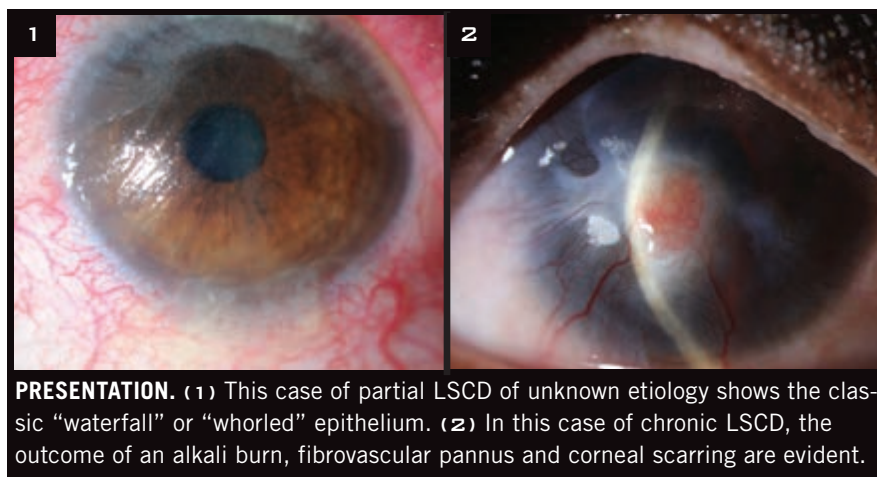
Etiology

LSCD can be caused by any process that diminishes the number of stem cells or disturbs the stem cell environment.¹ With the exception of some congenital conditions and neoplasia, each of the disorders listed in the table, next page, is associated with significant ocular surface inflammation.

Diagnosis

Presentation. Patients complain of blurry vision, a foreign-body sensation, photophobia, tearing, and pain.

Clinical examination. The slit-lamp exam reveals a dull and irregular reflex from the conjunctivalized corneal surface.² A classic “waterfall” or



PRESENTATION. (1) This case of partial LSCD of unknown etiology shows the classic “waterfall” or “whorled” epithelium. (2) In this case of chronic LSCD, the outcome of an alkali burn, fibrovascular pannus and corneal scarring are evident.

“whorled” epithelium is often present, along with the loss of limbal palisades of Vogt (Fig. 1).³

Fluorescein staining will show a stippled pattern when the conjunctival epithelium has encroached on the corneal surface.² Unhealthy epithelial cells have poor adhesion to the basement membrane and cause recurrent erosions, which can lead to persistent epithelial defects. These defects, in turn, may result in corneal ulceration and perforation.¹ In advanced LSCD, fibrovascular pannus and corneal scarring predominate (Fig. 2).²

In a series of 44 eyes with LSCD, the most common signs were corneal epithelial haze, superficial neovascularization, stromal scarring, and conjunctival hyperemia.⁴

Diagnostic testing. Although the diagnosis of LSCD is typically based on the patient history and the slit-lamp exam, certain diagnostic tests facilitate

narrowing the differential.

Corneal impression cytology, in which cellulose acetate paper is applied to the corneal surface to remove cells for histologic analysis, can be used to detect goblet cells. Goblet cells are a hallmark for the presence of “conjunctivalization” of corneal epithelium and can confirm the diagnosis of LSCD. However, in advanced cases, such as those arising from severe chemical injury or Stevens-Johnson syndrome (SJS), goblet cells are often absent.³

In vivo confocal microscopy also can be used to confirm the diagnosis. Imaging of the limbus in patients with the condition demonstrates loss of limbal architecture, cystic changes in the epithelium, and subepithelial fibrosis; and it is often concordant with impression cytology findings.⁵ Moreover, unlike impression cytology, in vivo confocal microscopy provides information about both the superficial and deeper

zones of the limbal area, and it does so in a noninvasive manner.⁵

Treatment

Partial LSCD. This entity can be treated conservatively with frequent ocular lubrication and topical steroid therapy. With increased corneal conjunctivalization, and in the presence of some remaining corneal stem cell tissue, repeated scraping of the conjunctivalized epithelium to allow regrowth of normal corneal epithelium in its place may be performed.⁶ Amniotic membrane transplantation with sutures or fibrin glue as an adjunctive procedure has a high success rate.^{3,7}

Complete LSCD. This condition is challenging, as no stem cells are available to repopulate the corneal surface.

In cases of unilateral complete LSCD, a contralateral conjunctival limbal autograft may be performed.^{3,7} Although this procedure confers no risk for rejection, the process of creating the graft leaves the contralateral donor eye at risk for LSCD. This risk is low when fewer than four to six clock-hours of limbal tissue are transplanted.²

Treatment of bilateral cases most often involves a keratolimbal allograft procedure from a cadaveric source coupled with systemic immunosuppression.^{3,7} However, this procedure carries the risk of rejection. Another disadvantage is that corneoscleral donor discs obtained from an eye bank have little or no rim of conjunctival tissue. With little tissue, conjunctival

reapproximation is difficult during the procedure.³ Occasionally, a limbal allograft may be taken from a living related donor who is HLA compatible, thus decreasing rejection risk.⁶

Surface restoration. Corneal transplantation can be performed either simultaneously with limbal grafting or after a limbal grafting procedure has proved successful. The latter is more common. In either case, a good tear film layer is important to support the corneal graft. Restoration of the ocular surface environment, especially the tear film, may be achieved with aggressive lubrication, use of autologous serum, epilation of trichitic lashes, partial tarsorrhaphy, punctal occlusion, symblepharon lysis, and fornix reconstruction.³

Use of a keratoprosthesis. As is often the case in patients with LSCD, the tear film is not adequately restored, and the resulting dryness contributes to the failure of traditional corneal transplantation. In this scenario, a keratoprosthesis is the only option.⁷ These patients have improved vision postoperatively, but they may develop glaucoma and retroprosthetic membranes.

In a review of eyes with LSCD having undergone a Boston type I keratoprosthesis implantation, those with immune-mediated LSCD (as seen with cases due to SJS) had higher complication rates and lower keratoprosthesis retention rates than did those with non-immune-mediated LSCD (as in cases related to aniridia). Complica-

tions included persistent epithelial defects and sterile stromal necrosis.⁸

Stem cell research. Recently, ex vivo growth of stem cells in culture has been used to create grafts. A biopsy of healthy limbus from the contralateral eye, cadaveric donors, or even autologous oral mucosal epithelial cells can be grown on various substrates and transplanted onto the affected eye.¹ Although there are no antigen-presenting cells in the ex vivo cultured stem cell graft, systemic immunosuppression is still required for allografts.¹

Conclusion

Exciting new developments in both the diagnosis and treatment of LSCD have occurred in recent years. With the advent of new imaging modalities such as confocal microscopy, the corneal surface of a patient with LSCD can be examined noninvasively at a microstructural level. Treatment options are no longer dependent on available donor tissue; instead, stem cells can be expanded ex vivo from ocular or non-ocular sources, such as autologous oral mucosal epithelium.

Further research into the complexities of corneal stem cells will be necessary to allow for a better understanding of the diseases affecting this tissue and to guide more targeted therapy. ■

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Causes of LSCD

Autoimmune	Stevens-Johnson syndrome Ocular cicatricial pemphigoid
Traumatic	Chemical injury Thermal injury Chronic contact lens wear
Iatrogenic	Multiple surgeries, cryotherapy, etc.
Infectious	Extensive corneal/ocular surface infection
Congenital	Aniridia Dominantly inherited keratitis Ectodermal dysplasia
Neoplastic	Limbal tumors

Adapted from Lim et al.¹