Surgical Management of Bilateral Limbal Stem Cell Deficiency

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ABSTRACT Limbal stem cell deficiency (LSCD) is now established as a distinct entity with a spectrum of clinical manifestations. Bilateral LSCD presents a unique set of challenges to the clinician dealing with ocular surface disease, due to the underlying causes, clinical presentation, and adnexal status, as well as lack of a source of autologous limbal stem cells. Various surgical modalities have been described to achieve visual rehabilitation in patients with bilateral LSCD. These can primarily be divided into cell-based therapies and implantation of keratoprostheses. In this review, the surgical options for management of bilateral LSCD, including autologous and allogeneic cell-based therapies and different types of keratoprostheses are described and classified. The indications, prerequisites, technique, results and complications of each modality are discussed. Based on the status of the ocular surface, an algorithm for choosing appropriate surgical management for vision restoration in bilateral LSCD has been proposed.

KEY WORDS Boston KPro, cultivated oral mucosal epithelial transplantation, keratoprosthesis, limbal stem cell deficiency, limbal stem cell transplantation, LVP KPro, osteo-odonto keratoprosthesis

I. INTRODUCTION

The corneal epithelium is the first point of contact of the eye with the external environment. Normal corneal epithelium is of a non-keratinizing stratified squamous type, and a healthy epithelium is vital to preservation of corneal transparency. Thoft and Friend provided early insights into corneal epithelial homeostasis decades ago, when they proposed their elegant 'XYZ hypothesis.' The essence of their premise was that ongoing loss of corneal epithelial cells is balanced by proliferation of basal cells and centripetal migration of peripheral cells.[1] Based on keratin expression data, Schermer et al proposed a model for corneal epithelial maturation, placing the location of corneal epithelial stem cells at the limbus.[2] Over the decades, evidence from multiple laboratory and clinical studies has firmly established that the corneo-scleral limbus is the repository of stem cells, which replenish the loss of corneal epithelial cells in health and disease.[2-10] In addition, the limbus acts as a barrier, preventing conjunctival epithelium from growing over the corneal surface. The pigmented palisades of Vogt, easily visible on slit lamp examination, denote the location of limbal stem cells.

II. LIMBAL STEM CELL DEFICIENCY (LSCD)

Limbal stem cells are critical to the renewal of corneal epithelium, which suffers ongoing loss of surface cells. In the relative or absolute absence of limbal stem cells, this replenishment of corneal epithelium is impaired, a condition known as limbal stem cell deficiency **(LSCD)**.[11] This can be primary or acquired. Primary LSCD is found in association with conditions such as aniridia, multiple endocrine deficiency, and congenital erythrokeratodermia. Acquired LSCD is much more common, and can be a consequence of ocular surface chemical or thermal burns, infections, ocular surface squamous neoplasia, surgeries at the limbus,

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irradiation, or contact lens wear.[12,13] Prolonged inflammation at the limbus, as in vernal keratoconjunctivitis, can also cause LSCD.[14,15] Immune-mediated diseases causing profound ocular surface inflammation and cicatrization, such as Stevens-Johnson syndrome (**SJS**) and ocular cicatricial pemphigoid (**OCP**), can lead to LSCD that is particularly challenging to manage.[16-18]

Clinical features of LSCD include absence of pigmented limbal palisades and a lusterless corneal surface. Epithelial healing problems manifest as persistent epithelial defects. Vascularization of the cornea is accompanied by growth of thick, translucent or opaque conjunctival epithelium across the limbus — a phenomenon known as conjunctivalization of the cornea. In severe cases, a fleshy fibrovascular pannus may completely obscure the cornea, and in severely dry eyes, the surface may even resemble skin, known as dermalization of the ocular surface (Figure 1). The clinical diagnosis of LSCD can be confirmed by techniques such as impression cytology and in vivo confocal microscopy.[11,19,20] Histopathology shows conjunctiva-like epithelium with goblet cells over the cornea, and immunohistochemistry can be used to look for specific markers of corneal, conjunctival, or limbal stem cell markers.[10,21]

A. Unilateral LSCD

LSCD can be categorized as partial or total, based on the extent of limbal involvement. In partial LSCD, observation may be acceptable management if the central cornea is clear with good vision. In cases where vision is affected, surgical options include sequential removal of conjunctival epithelium from the corneal surface and removal of pannus with amniotic membrane application to provide a scaffold for growth of corneal epithelium from the remaining healthy limbus.[22-26] Long-term results suggest that LSCD tends to recur in a majority of cases treated with amniotic membrane application.[27] Cell-based therapy, in the form of direct or cultivated limbal stem cell transplantation (**LSCT**) provides long-term stabilization of the ocular surface with significant improvement in visual acuity.[28]

For unilateral, total LSCD, autologous limbal tissue containing limbal stem cells from the healthy eye is transplanted to the affected eye after excision of fibrovascular pannus. Limbal autografts have been shown to be successful in restoring an avascular, stable corneal surface in eyes with unilateral LSCD.[29,30] Iatrogenic LSCD at the donor site is a potential complication in this form of direct LSCT, as the amount of tissue harvested is substantial.[31] Ex vivo cultivation of epithelium from a small amount of limbal tissue, followed by transplantation onto the affected surface minimizes the chances of inducing LSCD at the donor site. Autologous cultivated LSCT has been found to provide excellent long-term success rates in terms of ocular surface restoration and improvement in visual acuity.[32-35]

Depending on the amount of stromal corneal scarring, a keratoplasty may be required in addition to LSCT to restore vision.[36,37] Cultivated LSCT can be safely repeated in case LSCD recurs, and success rates of repeat transplantation have been reported to be similar to those for a primary LSCT.[38] The primary drawback of cultivated LSCT is that it requires a laboratory for ex vivo expansion of cells, which drives up the cost and limits availability of this procedure. Recently, a single-stage technique has been described, in which a minimal amount of limbal tissue is harvested, cut into small pieces, and transplanted directly onto the affected

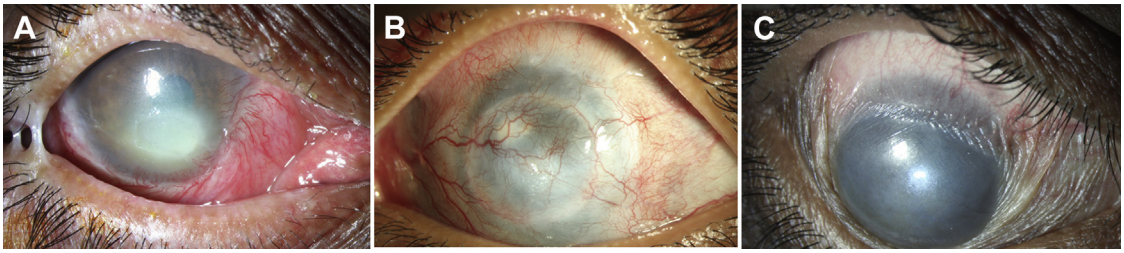

Figure 1. Clinical features of LSCD. A. Clinical photograph showing a persistent epithelial defect (PED). B. Clinical photograph showing total LSCD following chemical injury with conjunctivalization and wet surface. C. Clinical photograph showing total LSCD sequelae of Stevens-Johnson syndrome with dermalized dry surface.