ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

# Surgical Management of Bilateral Limbal Stem Cell Deficiency

# Abordagem Cirúrgica da Deficiência de Células Límbicas Bilateral

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**Acta Med Port 2023 Oct;36(10):679-682** ▪ https://doi.org/10.20344/amp.18960

**ABSTRACT**

At the age of 43 years-old, a man was left with bilateral limbal stem cell deficiency after an ocular alkaline burn with lime, which resulted in corneal opacification. After multiple unsuccessful surgical attempts to restore vision, including penetrating keratoplasties and Boston keratoprosthesis, visual acuity was counting fingers in the left eye. At 73 years of age, the patient underwent another surgery in his left eye. Cauterization of neovessels and removal of the vascular pannus were followed by partial excision of Tenon's capsule. Penetrating keratoplasty was followed by an intrastromal injection of anti-VEGF (vascular endothelial growth factor), and the ocular surface was covered with amniotic membrane. Postoperatively, the graft was clear with no signs of inflammation; vision improved to 20/50 and remained stable throughout the following two years. Herein we describe some adjunctive procedures that might have delayed failure and rejection of the corneal graft. This case demonstrates the difficulties in treating bilateral limbal stem cell deficiency in a tertiary eye care center with no capacity to perform stem cell therapy.
**Keywords:** Corneal Diseases/surgery; Epithelium, Corneal; Eye Burns/complications; Limbus Corneae; Ophthalmologic Surgical Procedures; Prosthesis Implantation; Stem Cells

**RESUMO**

Um doente do sexo masculino foi vítima de uma queimadura ocular com cal aos 43 anos, da qual resultou opacificação corneana bilateral e acuidade visual de perceção luminosa à direita e conta-dedos à esquerda. Foram feitas múltiplas tentativas para restaurar a visão, incluindo queratoplastias penetrantes e queratoprótese de Boston. Aos 73 anos, uma das abordagens cirúrgicas ao olho esquerdo do doente incluiu cauterização dos neovasos e remoção do *pannus* vascular, peritomia e excisão parcial da cápsula de Tenon. Seguidamente fez-se queratoplastia penetrante e injeção intraestromal de anti-VEGF (*vascular endothelial growth factor*), e a superfície ocular foi recoberta com membrana amniótica. No pós-operatório, o enxerto do olho esquerdo apresentava-se transparente, sem sinais de inflamação e a visão melhorou para 20/50, mantendo-se estável ao longo dos dois anos seguintes. Com este caso clínico pretendemos demostrar alguns procedimentos perioperatórios adjuvantes à queratoplastia penetrante que foram eficazes para aumentar a sobrevida do enxerto corneano, num centro terciário sem capacidade para fazer cultura e transplantação de células estaminais límbicas.
**Palavras-chave:** Células-Tronco; Doenças da Córnea/cirurgia; Epitélio Corneano; Implantação de Prótese; Limbus Corneae; Queimaduras Oculares/complicações

## INTRODUCTION

Limbal stem cells (LSC) are adult stem cells residing in the corneal limbus.[1] They play a role in corneal epithelium renewal and serve as an obstacle to the advancement of conjunctival cells onto the cornea, thus maintaining its transparency.[1] Limbal stem cell deficiency (LSCD) is a congenital or acquired corneal disease that can lead to severe visual impairment. Due to a lack of normal epithelium healing, patients with LSCD experience recurrent corneal erosions, chronic surface inflammation and conjunctivalization of the cornea, and often complain of pain, photophobia, and severely decreased vision.[2] When the condition is bilateral, there are few management options to restore vision but the results are still modest even with LSC transplantation.[2-4] We report the results of a surgical technique in a case of a patient with bilateral LSCD treated at a tertiary center with no resources to perform LSC therapy.

## CASE REPORT

We report a case of a man who at 43 years old suffered a bilateral chemical burn with lime, which resulted in adhesions of the bulbar and palpebral conjunctiva (symblepharon) and a vascularized corneal scar (leucoma) in the right eye (OD), as well as vascularization and corneal opacification in the other eye (LSCD Stage III) (Figs. 1 and 2).[1] Visual acuity (VA) was light perception with good projection in the OD and counting fingers (CF) at 2 m in the left eye (OS). The patient underwent multiple treatments and surgical procedures over the years, starting with symblepharon surgery of the OD, which consisted of transplantation of autologous oral mucosa. Cataract phacoemulsification and corneal transplant (penetrating keratoplasty) (PK) were undertaken in the OD at 63 years of age, but this was later rejected and failed. Three years later, the implantation of a Boston Keratoprosthesis type 1 (Boston K-Pro) was attempted in the OD, with VA improving to 20/63 (Fig. 3). Unfortunately, two years later, corneal melting ensued, causing extrusion of the Keratoprosthesis, which had to be replaced with a new PK. A corneal abscess developed once again, causing corneal melting, and vision decreased to hand motion. The patient was forced to undergo a third PK, but VA did not

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**Recebido/*Received*:** 12/08/2022 - **Aceite/*Accepted*:** 28/11/2022 - **Publicado *Online*/*Published Online*:** 07/02/2023 - **Publicado/*Published*:** 02/10/2023

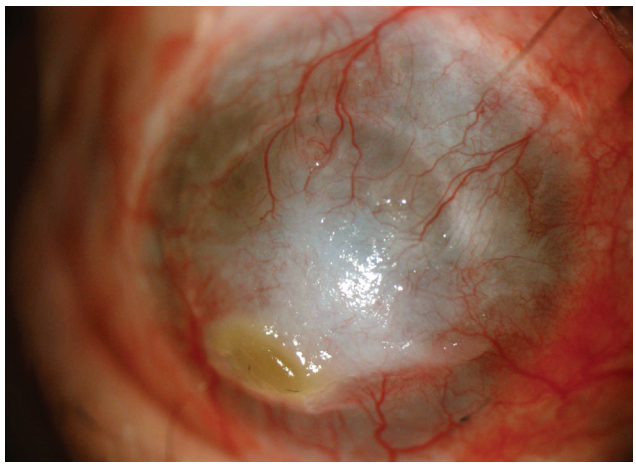

Figure 1 – Biomicroscopic photograph of the right eye, 23 years after the chemical injury and two years after the first penetrating keratoplasty. Conjunctivalization of the cornea, neovessels and inferior melting can be seen in the graft.

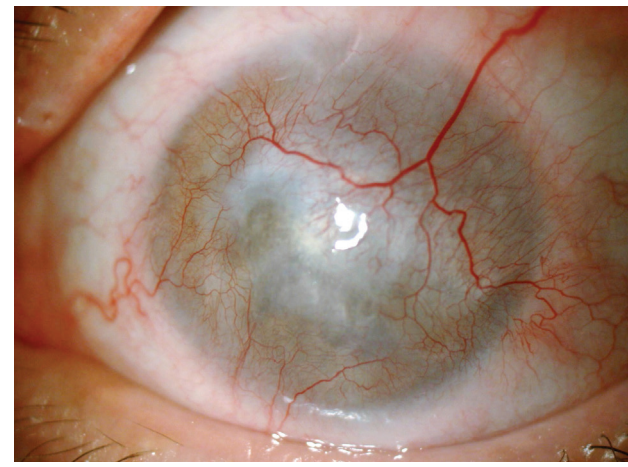

Figure 2 – Preoperative biomicroscopic photograph of the left eye. Conjunctivalization of the cornea with severe superficial and deep neovascularization is visible.

improve beyond CF.

At 73 years of age, immunosuppression treatment was initiated with oral cyclosporine (2 mg/kg daily) and tacrolimus ointment (0.2 mg/g) three times daily (tid) and autologous serum drops in the OS. Three months later, surgery was attempted in the OS (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18960/15054). Firstly, diathermy of neovessels and complete removal of the vascular pannus were performed, followed by a 360° conjunctival peritomy (an incision made at the limbus to reflect the conjunctiva and expose the Tenon's capsule) and partial excision of Tenon's capsule. Then, PK was performed and intrastromal injection of an anti-vascular endothelial growth factor (anti-VEGF) treatment (0.1 mL of ranibizumab, 10 mg/mL) was given in the periphery of the recipient's cornea. Finally, the transplant was fully covered with one layer of amniotic membrane, theepithelium was placed side up and the stromal side in contact with the ocular surface. The patient was kept under medical treatment with tacrolimus ointment tid, dexamethasone (1 mg/mL) tid, autologous serum drops and oral cyclosporine. Vision in the OS improved from CF at two meters to 20/50, and the graft was clear with no signs of vascularization (Fig. 4). Vision remained stable for two years, during which the patient was very satisfied with his quality of life. Two years after the procedure, intrastromal injection of ranibizumab, a new PK and cataract phacoemulsification were performed in the OS due to transplant rejection.

The patient is currently on fluorometholone 1 mg/mL tid, autologous serum drops and tacrolimus ointment. Visual acuity of the OS is 20/100 and the graft remains transparent with no epithelial defects or neovascularization.

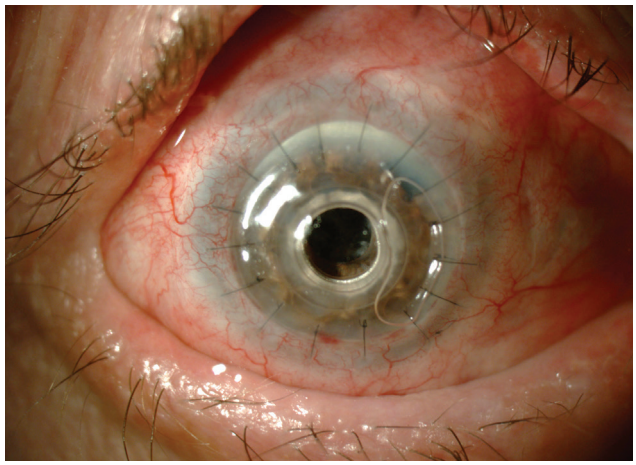

Figure 3 – Biomicroscopic photograph of the right eye after Boston type 1 keratoprosthesis implantation

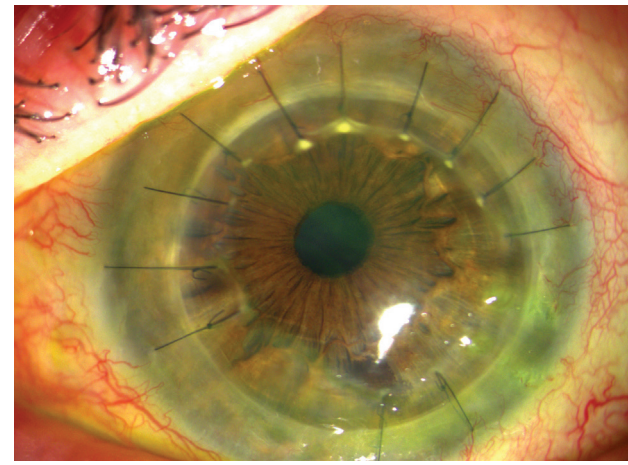

Figure 4 – Biomicroscopic photograph of the left eye, nine months after surgery. The cornea has a regular epithelium and there are no neovessels.

## DISCUSSION

We presented a case of bilateral chemical burn that resulted in LSCD in both eyes. Allogenic limbal grafts are the mainstay for the treatment of bilateral total LSCD, such as kerato-limbal allograft (cadaveric donor) and living related conjunctival limbal allograft (with some risk of causing LSCD in the donor's eye).[5,6] Like ours, most ophthalmology centers do not have the technology to perform LSC culture and transplantation, which would have been a good option for our patient.[7] Nevertheless, there are limitations of LSC transplantation, particularly in bilateral LSCD cases, as both techniques require immunosuppression, and success rates vary between 33% to 77%.[5,8] Holoclar®, a stem-cell treatment, requires healthy cells from the patient's limbus.[6] Other non-limbal autologous sources of grafts include cultivated oral mucosal epithelial transplantation and autologous conjunctival epithelial transplantation, but both have been associated with corneal neovascularization. More studies are necessary to ascertain the safety and efficacy of mesenchymal stem cells as an LSC niche.[5,6] Finally, keratoprostheses do not require immunosuppression and lead to a fast visual recovery, although more than half of patients suffer from complications, such as glaucoma.[6,9] In this clinical case, attempts to restore vision in the OD with PK and Boston-KPro were unsuccessful and of limited value.

Regarding treatment of the OS, we managed to control inflammation and hence reduce the chances of graft rejection by improving the stability of the ocular surface, with autologous serum drops and systemic and topical immunosuppressants (tacrolimus and cyclosporine), effective perioperative treatments in LCSD.[2,3] During OS surgery, we performed partial removal of Tenon's capsule. Subconjunctival fibrosis and scar formation are mediated by human Tenon's fibroblasts, which modulate the deposition of collagen and accumulation of extracellular matrix[10]; also, they exhibit VEGF production upon IL-1β stimulation and further contribute to neovascularization and fibrosis.[11,12] Therefore, the partial removal of Tenon's capsule might have contributed to the transparency of the graft.

Chronic ocular inflammation plays a key role in the pathophysiology of corneal neovascularization.[1,5] In an attempt to halt neovessel growth in the graft, vessel diathermy and intrastromal injection of anti-VEGF treatment were performed, similarly to other LSCD cases.[13,14] Amniotic membrane release anti-angiogenic and anti-inflammatory factors and have shown good results in promoting epithelization of the corneal surface, while also reducing inflammation and neovascularization in partial LSCD.[15] Furthermore, there is a decline in immune function in elderly individuals and the patient's age and immunologic state should also be taken into consideration.

This report demonstrated the difficulties of treatment of bilateral LSCD in a center that does not have the resources to perform LSC therapy. Preoperative treatment with systemic immunosuppression, optimization of the ocular surface, and prevention of inflammation and neovascularization with tenectomy, intrastromal anti-VEGF and vessel diathermy before PK, might have been crucial to delay failure and rejection. In summary, a few surgical adjunctive techniques to PK provided satisfactory results for two years, a relatively short period of time, but which led to a significant change in the patient's quality of life.

## AUTHOR CONTRIBUTIONS

RP: Data acquisition and analysis, draft of the paper, critical review.

JQG: Patient care, critical review and approval of the final version.

MJQ: Conception and design of the work, patient care, critical review and approval of the final version.

JM: Critical review and approval of the final version.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## PATIENT CONSENT

Obtained.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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