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A novel cultivated oral mucosal epithelial cell sheet transplantation (COMET) method using a commercially available regenerative product sheet originating from human ectopic autologous tissue

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ABSTRACT

BACKGROUND: We report the first case of cultivated oral mucosal epithelial cell sheet transplantation (COMET) using a commercial product from a different human tissue.

CASE PRESENTATION: An 80-year-old man presented with bilateral blurred vision secondary to corneal limbal stem cell deficiency (LSCD) caused by bilateral ocular cicatricial pemphigoid (OCP). The patient first noted the loss of visual acuity in his left eye at 56 years of age. He was referred to a local hospital and was diagnosed with uveitis. He was administered ten bilateral ocular sub-tenon injections of triamcinolone acetonide. The uveitis progressed to cataracts, requiring bilateral phacoemulsification with intraocular lens implantation. Although the uveitis gradually improved, his visual acuity deteriorated due to the LSCD caused by OCP. At 61 years of age, amniotic membrane transplantation was performed in the left eye. However, its effect was limited, and OCP continued progressing in both eyes. On referral to our hospital, he had only light perception on visual acuity testing. The COMET was performed in the right eye using a commercially available product sheet (Ocular®; Japan Tissue Engineering Co., Ltd., Aichi, Japan). Ten days postoperatively, epithelialization was observed in the cornea and conjunctiva. His visual acuity improved to 20/1000. The patient was discharged on the same day.

CONCLUSION: This is the first report on the use of a commercially available ectopic product (Japan Tissue Engineering Co., Ltd., Aichi, Japan) originating from different human tissues (oral mucosa) for COMET. COMET may be a radical treatment for corneal LSCD.

KEY WORDS: cultivated oral mucosal epithelial cell sheet transplantation (COMET), limbal stem cell deficiency (LSCD), ocular cicatricial pemphigoid (OCP), Ocular®, Japan Tissue Engineering Co., Ltd., Aichi, Japan

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INTRODUCTION

Ocular trauma or disease may result in severe corneal epithelial disorders and opacification of the epithelium and stroma [1]. Consequently, severe vision loss results from the damage of corneal epithelial stem cells [2]. Autologous stem tissue source transplantation is another maneuver for allograft transplantation without immunosuppression; however, it is impossible in eyes where bilateral disorders result in total corneal stem cell deficiency [3].

In eyes with completely absent corneal epithelial stem cells due to limbal disorders caused by thermal trauma or chemical trauma or eye disorders such as Stevens-Johnson syndrome or ocular cicatricial pemphigoid (OCP), the sources of corneal epithelial tissues are damaged, the peripheral conjunctival epithelium moves inward, and the corneal surface becomes damaged by conjunctival tissue [4]. Consequently, corneal opacification results in a severe loss of visual acuity. The abnormal condition is corneal limbal stem cell deficiency (LSCD) [5, 6].

Nishida et al. developed cell tissue sheets from autologous oral mucosal epithelium to serve as regenerative tissues for limbal tissue allografts for reconstructing corneal and limbal surfaces [1]. They elucidated these strategies based on regenerative medicine, from immunohistochemistry to physiological aspects. Sheets of tissue-engineered epithelial cells were successfully transplanted into the recipient's eyes and collected ex vivo from autologous oral mucosal epithelium. These maneuvers are reportedly useful for reconstructing the ocular surface condition and sustaining visual acuity, particularly in patients with bilateral stem cell deficiency.

Here, we report the first case of a patient who underwent cultivated oral mucosal epithelial cell sheet transplantation (COMET) using a commercially available ectopic product sheet originating from different human tissues (Oculal®; Japan Tissue Engineering Co. Ltd., Aichi, Japan).

CASE PRESENTATION

We report the case of an 80-year-old male with a history of bilateral uveitis, bilateral continuous myodesopsia physiologica, and hypertension. The patient presented with severe blurred vision secondary to corneal LSCD caused by bilateral OCP. He worked as a truck driver and noted the loss of visual acuity in his left eye while driving at 56 years of age. He was referred to a local hospital for gradually worsening blurring of his vision and was diagnosed with uveitis. He was administered ten sub-tenon triamcinolone acetonide injections in both eyes. The uveitis progressed to cataracts, thus requiring bilateral phacoemulsification with intraocular lens implantation at a local hospital. Both corneas were transparent, and the cataract surgery was successfully performed.

Although his uveitis gradually improved, his visual acuity deteriorated due to the LSCD caused by OCP. At 61 years of age, amniotic membrane transplantation was performed in the left eye. However, its effect was limited, and OCP continued progressing in both eyes.

He was referred to our hospital at 80 years of age, with only light perception elicited during visual acuity testing (Fig. 1A). COMET was performed in his right eye 69 days after visiting our hospital using a commercially available product sheet (Oculal®, Japan Tissue Engineering Co., Ltd., Aichi, Japan).

We removed the conjunctival scar tissue from the cornea 3 mm outward from the limbus to the corneal stroma (Fig. 2A–D). Next, the product sheet of the oral mucosal cells was put directly onto the naked intact stromal bed (Fig. 2F–G). The sheet was continuously sutured around the corneal limbs (Fig. 2H). The sheets, recipient sclera, and conjunctiva were sutured (Fig. 2I). The corneal surface of the graft was protected by a soft contact lens for wound healing.

After the surgical intervention, topical antibiotics (1.5% levofloxacin) and steroids (0.1% betamethasone) were used four times daily. For the first week after surgery, prednisolone (5 mg/day) was used orally to avoid severe inflammation. Preservative-free artificial tears were frequently used.

Ten days after surgery, epithelialization was observed in the cornea and conjunctiva (Fig. 1B). Moreover, the patient's best-corrected visual acuity improved to 20/1000. The patient was then discharged the same day. The observation period was 90 days after surgery, and the best-corrected visual acuity at the last examination was 20/1000.

DISCUSSION

Autologous limbal transplantation is a method of corneal surface reconstruction in eyes with unilateral LSCD [7]. However, autologous limbal transplantation requires a large limbal graft from the contralateral healthy eye, and tissue collection is associated with the risk of LSCD in the healthy

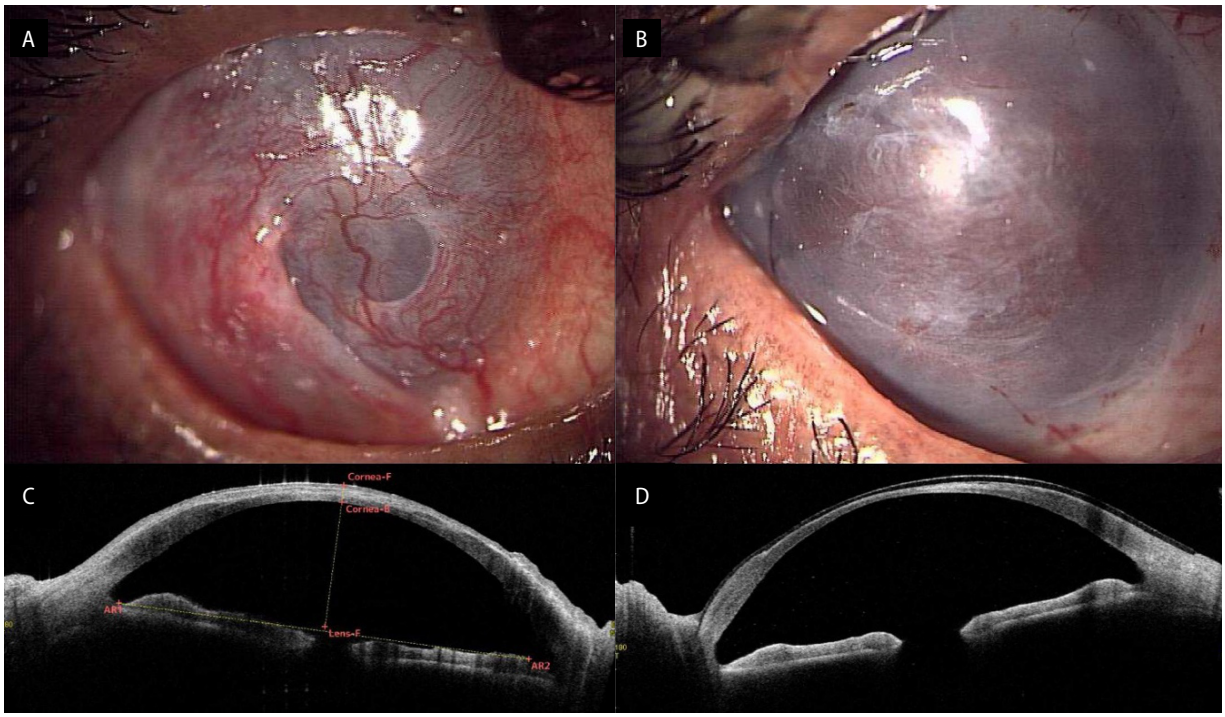

FIGURE 1. The anterior segment photograph (**A**) and anterior segment optical coherence tomography (AS-OCT) CASIA 2 (Tomey Corporation, Nagoya, Japan) examination (**C**) of the patient's right eye at the initial presentation (69 days before the cultivated oral mucosal epithelial cell sheet transplantation surgery). The anterior segment photograph (**B**) and AS-OCT examination (**D**) of the patient's right eye at the initial presentation (1 day after the cultivated oral mucosal epithelial cell sheet transplantation surgery)

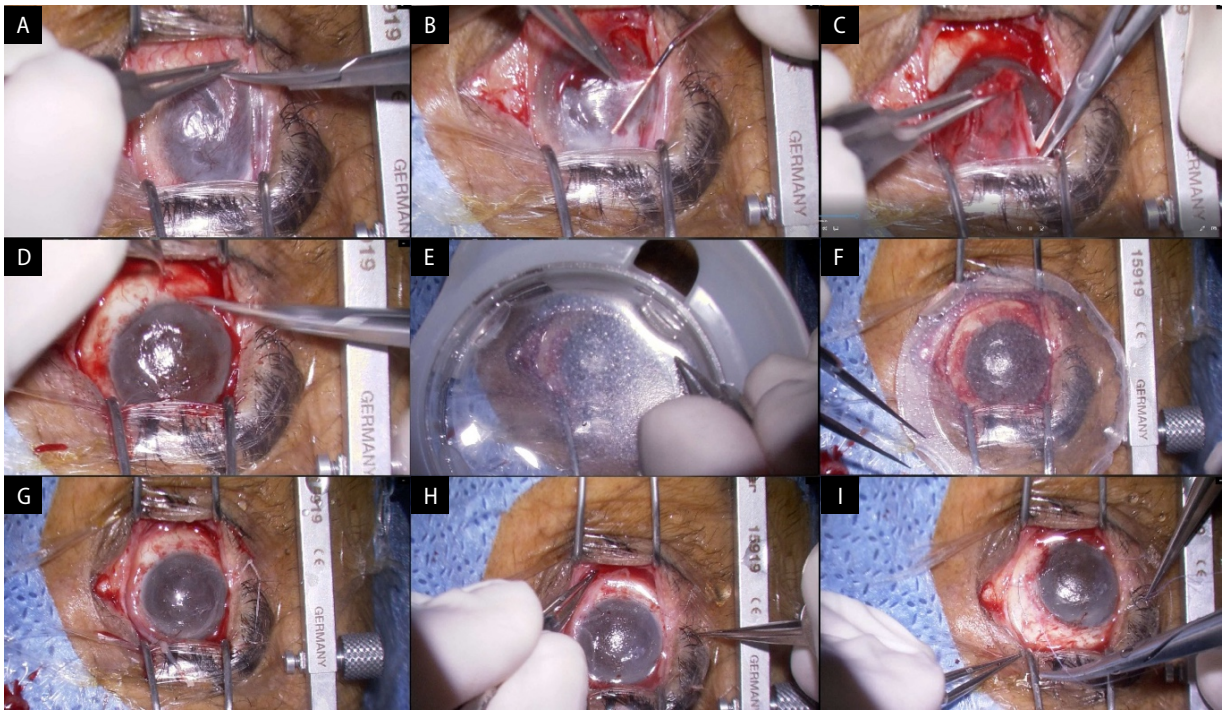

FIGURE 2. Transplantation procedures photograph for tissue-engineered autologous epithelial-cell sheets. The entire surface of the cornea was covered by conjunctival tissue with neovascularization (**A**). The conjunctival tissue over the cornea is surgically removed to expose the relatively transparent corneal stroma (**B**, **C**, and **D**). Subsequently, the sheet of tissue-engineered epithelial cells is placed on the stromal bed (**E**, **F**, and **G**). The sheet is continuously sutured around the corneal limbs (H), and finally, the sheets, recipient sclera, and conjunctiva are sutured (I).

eye [8]. In addition, this is impossible in patients with bilateral disorders [9]. Limbal allograft transplantation surgery is useful for the eyes with unilateral or bilateral disorders [10]. However, this surgical treatment requires long-term medical immunosuppression after surgery. It has risks of ophthalmologic severe or systemic disorders, including bacterial infection or iatrogenic systemic disorders, such as disorders in the liver or kidney [10]. In eyes with Stevens-Johnson syndrome and OCP, transplanted graft failure and severe dry eye is not rare, although heavy immunosuppression [11–13].

To minimize allograft rejection and achieve good long-term surgical outcomes, eyes with unilateral stem cell tissue deficiencies have been treated with corneal epithelial tissue grafts constructed from tissues collected by expanding autologous limbal stem cells cultivated from intact contralateral eyes. The tissues were harvested from cell carriers, such as amniotic membranes and fibrin gel [14–16]. However, these procedures cannot be used to treat bilateral total LSCD.

Nishida et al. developed cell tissue sheets from the oral mucosal epithelium of the patient as regenerative tissues for limbal tissue grafts in reconstructing corneal and limbal surfaces [1]. These strategies were elucidated based on regenerative medicine, from immunohistochemistry to physiological aspects. Sheets of epithelial cell tissues from autologous oral mucosa were successfully transplanted into the recipient's eyes. These maneuvers have been reported to be useful for reconstructing the ocular surface, especially in bilateral stem cell deficiency.

One ethical advantage of this therapy is that it does not require a donor. The oral mucosal epithelial cell sheet is autologous; therefore, donor corneas are unnecessary.

One possible disadvantage is that the long-term survival of the transplanted graft sheets is uncertain. In cases where the ability to proliferate in the transplanted cell sheet is insufficient compared to the original disease exacerbation, the scar tissue will re-enter the cornea; thus, the graft tissue will be replaced by the pathologic opaque tissue. Therefore, careful observation and use of topical treatment interventions are essential; however, the titer for topical treatment is limited.

Herein, we report the first case of a patient who underwent COMET using a commercially available ectopic product sheet originating from different human tissues (Ocular®, Japan Tissue Engineering Co., Ltd., Aichi, Japan).

The main limitation of this study is the small sample size and the retrospective design. The results need to be confirmed in a randomized, prospective, and blinded study. Nevertheless, these data suggest that examining a large cohort of patients, especially those with bilateral LSCD, including Stevens-Johnson syndrome or OCP, is vital to confirm the broad use of this commercially available product sheet (Ocular®, Japan Tissue Engineering Co., Ltd., Aichi, Japan) for epithelial disorders, including LSCD.

CONCLUSIONS

This is the first report to discuss the use of a commercially available ectopic product sheet (Ocular®; Japan Tissue Engineering Co., Ltd., Aichi, Japan) originating from different human tissues (oral mucosa) in COMET. Therefore, the COMET may be considered a radical treatment for corneal LSCD.

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Conflict of interests

The authors declare that the research was conducted in the absence of financial or commercial conflicts of interest.

Additional requirements

This study was registered (Registration number: UMIN000046037[2021/11/11]).

Author contributions

All authors had full access to all study data and were responsible for the integrity and accuracy of data analysis. H.F.: Study concept and design, statistical analysis, and supervision. H.F. and J.K: Data acquisition. H.F.: Analysis and interpretation of data and drafting of the manuscript. H.F.: Funding; J.K.: Administrative, technical, and material support.

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Patient consent

Consent was obtained for the publication of this case report. This report contains no personal information that could lead to patient identification.

Ethics approval statement

This observational retrospective study was approved by the Institutional Review Board of Kawasaki Medical School Hospital (approval number 3572-00). The study was conducted in accordance with the principles of the Declaration of Helsinki. All authors attest that they meet the current ICMJE criteria for authorship.

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