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Case report

Ocular surface reconstruction of Steven Johnson syndrome / toxic epidermal necrolysis affected eye - A case report

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ABSTRACT

Introduction: Toxic epidermal necrolysis (TEN), also known as Steven Johnson syndrome (SJS), is a devastating disease. Patients develop blindness and symblepharon despite multiple reconstructive surgeries. We report a case of SJS/TEN with ocular involvement where treatment with hyperbaric oxygen therapy (HBOT) resulted in a significant improvement in the visual acuity after surgery.

Case presentation: A woman with SJS/TEN with severe ocular complication (SOC) had limbal stem cell deficiency and symblepharon of the superior and inferior fornix. Pannus grew over her cornea, reducing the vision to counting finger. The symblepharon produced shortening of the fornix, causing entropion. The in-turned eyelid caused her eyelashes to rub against the cornea, causing great damage to the ocular surface. Limbal stem cell deficiency led to the loss of normal corneal morphology and invasion of the pannus onto the central visual axis, resulting in poor vision. She experienced ocular inflammation for 3 months before transfer to our hospital for admission. Ophthalmic examination showed bilateral corneal opacity with conjunctivalization, and inferior and superior fornix shortening. Symblepharon-lysis with amniotic membrane transplantation was attempted but the outcome was poor, with recurrence of superior scaring and symblepharon. She finally underwent major reconstructive surgery with allogeneic limbal stem cell transplantation with her sister as the donor, autologous minor salivary gland transplantation, and oral buccal mucosa flap transplant. HBOT was given daily post-surgery for supporting the

Abbreviations: AMT, amniotic membrane transplantation; CLAL, conjunctival limbal allograft; HBOT, Hyperbaric oxygen therapy; LSCD, Limbal stem cell deficiency; CLAU, conjunctival limbal autograft; lr-CLAL, living-related conjunctival limbal allograft; HLA typing, human leucocyte antigen typing; SJS, Steven Johnson syndrome; SOC, severe ocular complication; TEN, toxic epidermal necrolysis; CLET, Cultivated limbal epithelial transplantation.

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grafts and suppressing inflammation. After 17 HBOT sessions and 3 months of autoserum drops, her left eye vision increased from the initial counting finger to 0.4 due to the successful growth of the corneal epithelium from the donor corneal limbal cell line. When a scleral contact lens which vaulted over the corneal limbal area was fitted, her vision improved to 0.8 due to redressal of high order aberration and astigmatism from the cornea scar.

Conclusion: After major reconstruction of the ocular surface with multiple cell type transplants, including limbal stem cells, minor salivary gland acinar cells, and oral mucosa cells, HBOT proved

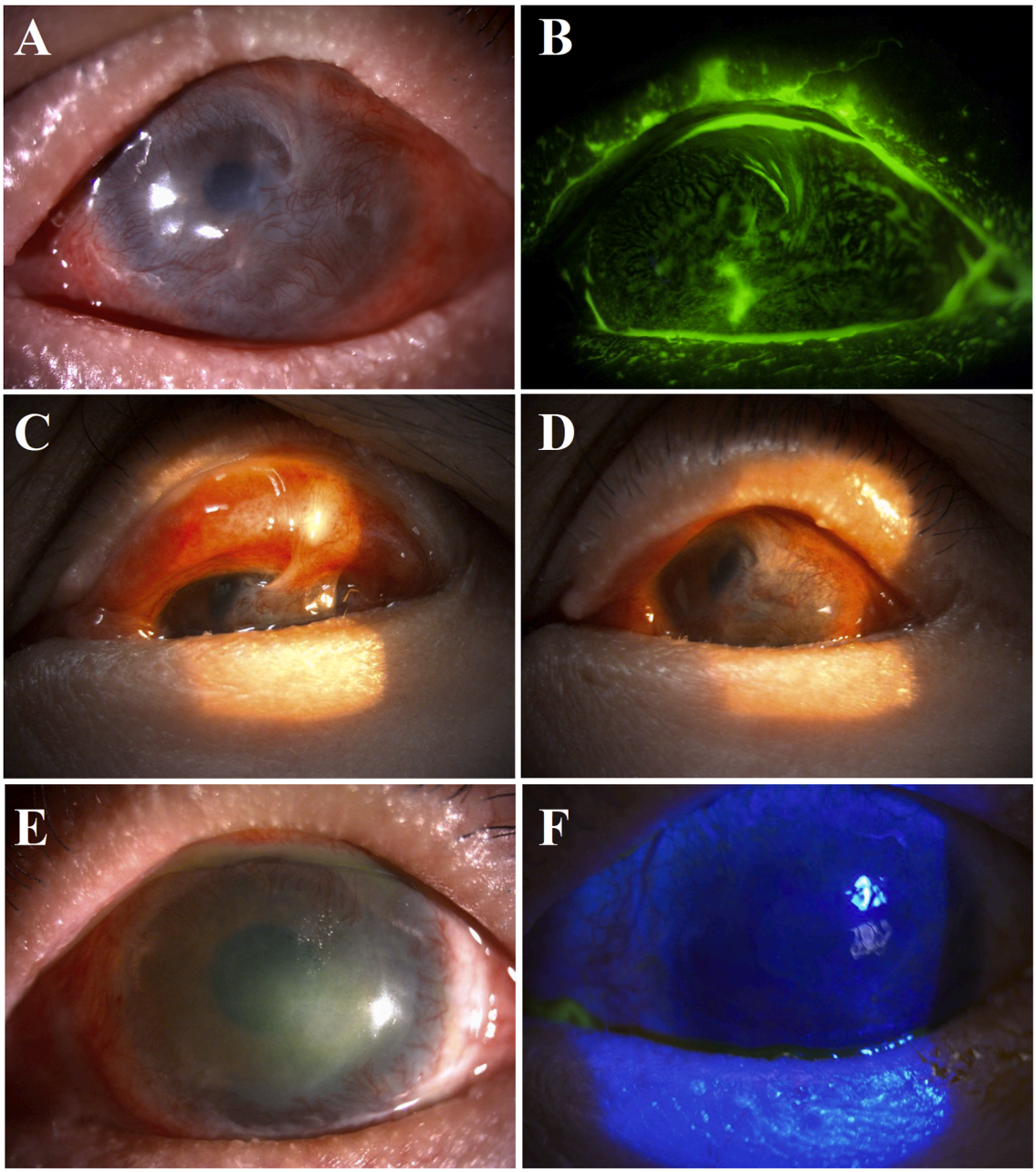

Figure 1. Profound pannus ingrowth onto the cornea after limbal stem cell deficiency (LSCD) [A] and fluorescence revealed bizarre ocular surface in her left eye [B]. Symblepharon causes superior fornix shortening [C] and vision occlusion by pannus formation [D]. After surgical procedure of allogeneic limbal stem cell transplantation (LSCT) with living-related conjunctival limbal allograft (lr-CLAL) & simple limbal epithelial transplantation (SLET), combined with 17 times of HBOT. Postoperative 4-month image showing a stable well-epithelialized ocular surface with mild neovascularization, a faint residual deep stromal scarring as seen in the left eye [E], fluorescence staining of the same eye shows no cornea epithelium defect and stable tear film [F].

useful in supporting the graft uptake and oxygenation of the donor tissues, enabling fast recovery of the grafts and cell functioning, with eventual return of the working vision of the patient.

1. Introduction

Steven Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is a potentially fatal mucocutaneous adverse drug reaction, characterized by extensive epithelial cell necrosis and shedding, and a high mortality rate [1]. Our patient had SJS/TEN with severe eye involvement, and was treated with an oral mucosal graft, minor salivary gland transplant, and limbal stem cell transplant. Postoperatively, hyperbaric oxygen therapy (HBOT) was started to support wound healing. HBOT is given by placing the whole body in a hyperbaric chamber, applying pressure greater than 1.4 absolute atmospheric pressure, and inhaling 100% pure oxygen directly or indirectly. Studies have confirmed the usefulness of HBOT in diabetes-related wounds, as it promotes wound healing and enhances the effect of antibiotics [2]. In ophthalmology, HBOT has demonstrated a beneficial effect in ocular diseases such as central retinal arterial/venous occlusion, branch retinal venous occlusion, and recurrent pterygium by mitigating hypoxia, facilitating wound healing, and reducing inflammation [3, 4]. In this case report, we have described the impact of SJS/TEN on the eye, along with the surgical management and HBOT. We have also reviewed literature to discuss the mechanism of HBOT in corneal wound healing and its benefits in complicated grafts.

2. Case presentation

2.1. Patient history

A 30-year-old woman was referred for SJS/TEN with ocular involvement caused by an adverse reaction to lamotrigine for her seizure disorder. She initially had a progressive red rash and blisters on her mouth, nose, trunk, and extremities plus severe ocular complications. She was admitted to the intensive care unit due to profound skin necrosis and an ophthalmology consultation was immediately sought for sight-threatening complications of both eyes. She received lubricants, anti-inflammatory eyedrops, and an amniotic membrane device (Prokera®); however, her condition deteriorated. Due to the persistent corneal epithelial defect, corneal haze, and symblepharon, she was referred to our tertiary hospital after three months.

2.2. Clinical examination

The initial slit lamp examination showed a total epithelial defect with severely engorged vessels, inflamed eye, corneal neovasculature pannus, and symblepharon with loss of the fornix in both eyes (Figure 1A). The visual acuity (VA) in both eyes was decreased to counting finger (less than 0.01). She underwent debridement surgery with symblepharon-lysis and amniotic membrane transplantation (AMT) twice in her left eye. Although the epithelial defect subsequently improved, her condition fluctuated with poor epithelial growth, whorl-like epitheliopathy with fluorescein pooling, abnormal epithelial opaque deposition, recurrent neovascularization, and prominent pannus ingrowth onto the central cornea (Figure 1A-D); the poor corneal condition was attributed to

Table 1
Biomarker human leucocyte antigen (HLA)typing of the patient and her sister.

Pharmacogenetics (the patient)	the result	Pharmacogenetics (the donor)	the result
HLA-B*15:02	Negative	HLA-B*15:02	Negative
HLA-B*58:01	Negative	HLA-B*58:01	Negative
HLA-B*13:01	Negative	HLA-B*13:01	Negative
HLA-B*57:01	Negative	HLA-B*57:01	Negative
HLA-A*31:01	Negative	HLA-A*31:01	Negative
A Locus Serology	2, 24	A Locus Serology	2, 24
A Locus Molecular	02, 24	A Locus Molecular	02, 24
B Locus Serology	38, 56	B Locus Serology	38, 60
B Locus Molecular	38, 56	Bw Locus Serology	4, 6
C Locus Serology	1, 7	C Locus Serology	7
C Locus Molecular	01, 07	C Locus Molecular	7
Bw Locus Serology	4, 6	B Locus Molecular	38, 40
DR Locus Serology	15, 16		
DQ Locus Serology	5, 6	HLA-DR, DQ typing	
DRw Serology	51, -	DR Locus Serology	14, 16
DRB1 Locus Molecular	15, 16	DQ Locus Serology	5
DRB3 Locus	Negative	DRw Serology	52, 51
DRB4 Locus	Negative	DRB1 Locus Molecular	14, 16
DRB5 Locus	Positive	DRB3 Locus	Positive
DQB1 Locus Molecular	05, 06	DRB4 Locus	Negative
HLA-ABC	*	DRB5 Locus	Positive
HLA-DR, DQ typing	*	DQB1 Locus Molecular	5

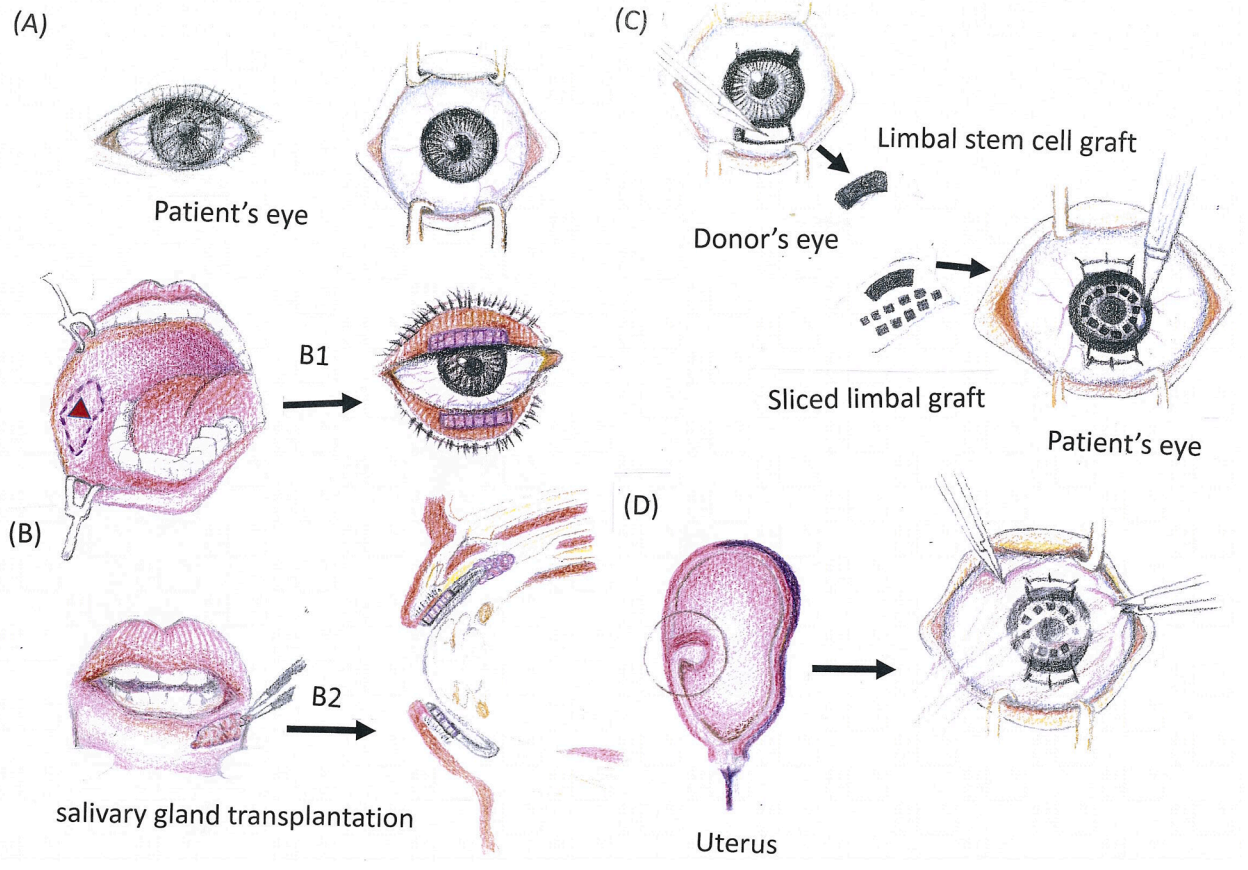

Figure 2. Illustration of surgical procedure. A. Pannus removal from disease eye of bulbar conjunctiva and Palpebral conjunctiva. B. Buccal mucosal flap and minor salivary gland transplantation.B1. Oral buccal mucosa taken from patient's right cheek, sliced into 2 pieces, then transplanted to the patient's upper and inferior palpebral conjunctiva. B2. Minor salivary gland taken from patient's left labial area transplanted to diseased eye's superior conjunctiva and superior fornix. C. Lr-CLAL (living related conjunctiva limbal allograft) + SLET (Simple Limbal Epithelial Transplantation). The limbal stem cell within the conjunctiva limbal graft is taken from her sister's donor eye, suture to the patients' superior and inferior limbus area, extra limbus tissue was sliced into small pieces, and then transplanted to patient's central denuded cornea vie fibrin glue (Artiss®). D. Amniotic membrane, taken from uterus, was grafted over the patient's cornea, bulbal conjuncitiva, upper and lower fornix, palpebral conjunctiva.

limbal stem cell deficiency (LSCD). Despite two additional AMT patch grafts, her vision soon deteriorated to only light perception in the right eye and hand-motion in the left eye. Total limbal stem cell deficiency (LSCD) was diagnosed. Her Ocular Surface Grading Score (OSGS) was (C3N3O2K0S2U2L2:T14) and the results of Schirmer's test without anesthesia was 0 mm in 5 min before surgery, After considering the vision-threatening consequence, she agreed to undergo major ocular reconstruction surgeries to salvage her eyesight.

2.3. Therapeutic intervention

The surgeries included allogeneic conjunctival-limbal stem cell transplantation (CLAL), autologous buccal and labial mucosal flap with minor salivary gland transplant, and amniotic membrane transplantation (AMT) patch graft in the left eye. The patient's sister was identified as an appropriate donor after HLA-typing evaluation of her close family members (Table 1). To study for pharmacogenetics reason of the SJS/TEN and immune compatibility for limbal stem cell transplantation, the patient's HLA typing was performed before surgery, her HLA typing were as listed (Table 1). Our laboratory has specifically looked for HLA-B*13:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01, HLA-A 31*01 and HLA-B*27 alleles, but these show up negative. According to her Serology typing of HLA-B locus which is 38, 56, she should also be negative for HLA-B 46:01. The patient underwent symblepharon-lysis with all kerato-conjunctival pannus removal. Conjunctiva-limbal allograft was obtained from the upper and lower limbus with a size of 5 × 7 mm from her sister, and transferred to the patient at the approximate location. Simple limbal epithelial transplantation (SLET) was also performed by gluing extra limbal tissues onto the central denuded cornea with fibrin glue (Artiss®). Simultaneously, minor salivary gland transplantation from labial and buccal area, mucous membrane graft from the patient's oral buccal mucosa, and AMT patch graft over the SLET and conjunctiva limbal graft were performed (Figure 2).

Due to the complicated situation and multiple at-risk grafts, we administered HBOT as an adjunctive therapy to promote graft survival, cornea limbal epithelium healing, and minor salivary gland and mucosa graft uptake. Pre-procedure, it was decided that HBOT should comprise a daily session with bottom depth of 10 m (2.0 ATA) and bottom time of 75 min with a 5-minute air-break in between to avoid seizure relapse. She was placed in a hyperbaric chamber with the applied pressure greater than 1.4 absolute

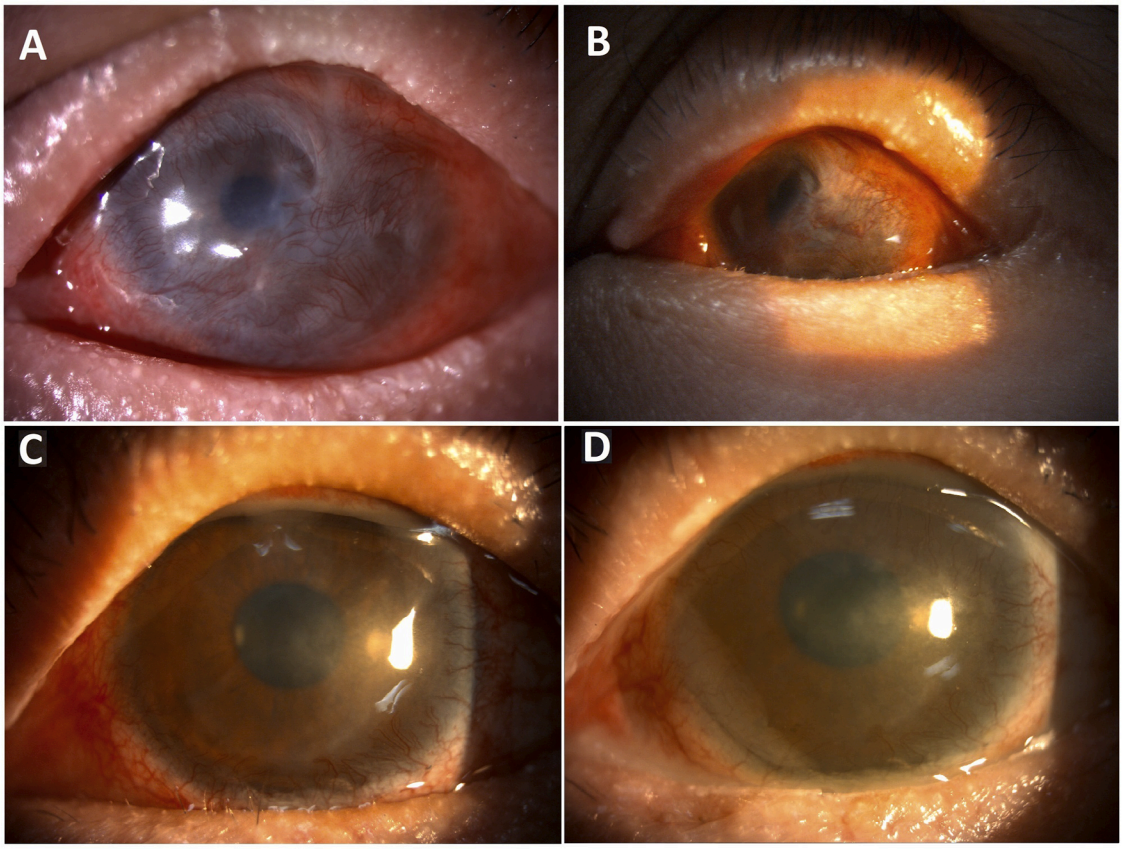

Figure 3. Ocular Surface Grading Score (OSGS) and images of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) patient. C, conjunctivalization; N, neovascularization; O, opacification; K, keratinization; S, symblepharon; U, upper conjunctival sac shortening; L, lower conjunctival sac shortening; T, total OSGS. (A–B) Pre-operation surgery OSGS status: pre-operation (C3,N3,O2,K0,S2,U2,L2:T14), (C) Post operation 4 months OSGS status: (C1,N1,O1,K0,S0,U0,L0: T3). (D) Post op 12 months OSGS status: (C2,N1,O1K0,S0, U0, L0: T4).

atmospheric pressure, and 100% pure oxygen was inhaled directly. The patient had no HBOT-associated side effects and endured the pressure transection with ease. Meanwhile, supportive ophthalmologic treatments such as frequent lubricant, topical steroid, and autoserum were continued. After 17 sessions of HBOT, complete re-epithelialization of the eye was noted at one-month follow-up. The ocular surface was wet with mucoidal secretion from her upper fornix, showing minor salivary gland activation. The mucosa flap was noticeably viable with vasculation and attachment to the tarsal plate, and no visible synechia of the conjunctiva to the cornea. At the 3-month visit, uncorrected VA in her left eye had improved to 0.4, with additional scleral lens correction, VA of (0.8) could be obtained. Slit-lamp examination revealed smooth corneal epithelium and a faint corneal scar at the site of the original corneal pannus along with para-central haze induced by an epithelium defect from trichiasis (Figure 1E, F). Four month after operation, her Ocular Surface Grading Score (OSGS) improvement to T3, (C1,N1,O1,K0,S0,U0,L0:T3) (Figure 3A-D) and the results of Schirmer's test without anesthesia was 6 mm in 5 min. Post op 12 months OSGS status deteriate slightly to T4, (C2,N1,O1K0,S0,U0,L0:T4).

3. Discussion

Regarding the pharmacogenetics risk of having Steven Johnson syndrome with severe ocular complications SOC in our patient, we have tried to investigate her HLA typing, but no significant correlation can be founded. According to Ma et al. [16], he collected 26 diagnosed SJS/TEN patients with severe ocular complications (SOC) in Taiwan, the HLA-A*02:07 carrier gene frequency was found to be significant ($p = 0.049$). In SJS/TEN patients with SOC, HLA-A*02:07 carrier frequency was higher ($p = 0.016$), as was allele frequency ($p = 0.001$). The HLA-B*46:01 allele frequency was significantly higher in SJS/TEN patients with SOC ($p = 0.008$). Therefore, the HLA-A*02:07 and HLA-B*46:01 alleles are significantly correlated with the SOC of the Han SJS/TEN patient. But in our case, our patient's HLA typing was HLA-A 02, 24; HLA-B 38,56; HLA-C 01, 07, therefore she was negative for HLA-B*13:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01, HLA-B* 27 and HLA-B*46:01 alleles. Since her HLA-A typing were 02,24, she can probably be a HLA-A* 0207 but unfortunately, our hospital facility cannot differentiate the last two digits. On limbal stem cell deficiency (LSCD), the normal transparency of the corneal epithelial surface is maintained by Limbal stem cells (LSC) [5], which are located in the basal layer of the limbal area [6]. This area is a protective environment called the niche in the border between the sclera/conjunctiva and cornea [3, 7]. LSCD is a condition where insufficient number of functional LSCs reach the cornea surface, and can be caused by many pathologies, such as genetic defects, systemic immune-mediated diseases, or a secondary injury to the LSC niche and its microenvironment [5]. LSCD impairs the ability of the corneal epithelium to repopulate itself, leaving the denuded cornea to be overrun by invading conjunctiva and fibrotic tissues. Therefore, LSCD after SJS/TEN usually has a poor visual outcome [8]. Patients with LSCD often experience redness, irritation, photophobia, and decreased vision from corneal opacity and irregular astigmatism. Initially, the epithelium becomes wavy, irregular, hazy, and eventually progressing to persistent corneal epithelial defects, stromal scarring, ulceration, and even corneal perforation. Conservative treatment, such as intensive use of nonpreserved lubrication and topical corticosteroids only provides temporary remission, the condition will deteriorate over time if LSCs are not replenished.

For treatment of LSCD with SOC, surgical options include the removal of corneal conjunctivalization, with or without concurrent AMT and different types of reconstruction with LSCs to restore the normal corneal structure and function [9]. Ocular surface reconstruction for LSCD involves limbal stem cell transplantation (LSCT) with transplantation of the normal conjunctiva plus limbus graft in conjunctival limbal autograft (CLAU) from the contralateral healthy eye, or allograft from a cadaver/living donor (keratolimbal allograft (KLAL)/conjunctival limbal allograft (CLAL) [7] when there is no healthy contralateral eye available. Other options are cultivation of autologous limbal epithelial transplantation (CLET) if sufficient laboratory facility is available [10]. Simple limbal epithelial transplantation (SLET), a modified form of CLAU, reportedly has a better success rate in the treatment of unilateral LSCD induced by chemical burns, and is more tissue saving for the donor eye [11]. A systemic review by Ganger et al. found that although the anatomical success rates were similar among SLET, CLET, CLAL, and KLAL (63.65%–79.8%), the functional outcome in terms of the gain in the post-operative VA was better with KLAL and SLET than CLET [12]. Hence, we selected a combination of CLAL and SLET. To ensure successful limbal epithelium regrowth, a wet environment suitable for the survival of LSCs and transient amplifying cornea epithelium cells must be created; and aqueous, mucin must be replenished. Accordingly, we transplanted the minor salivary gland, mucosa flap graft, and amniotic membrane patch graft along with LSCT. Postoperatively, the wounds may experience hypoxia due to the breakdown of the ocular surface circulation. As the cornea is avascular, it normally acquires oxygen directly from the atmosphere. In our patient, after amniotic membrane patch graft and LSC coverage, a reduction in the atmospheric oxygen supply was likely to impair the corneal physiology and function. According to previous studies, hypoxia impairs the integrity of the corneal cell junctions and causes neovascularization [13]. Zieske et al. also found that the cornea becomes vascularized with pannus formation due to hypoxia during disease or trauma [14]. However, evidence has been controversial regarding LSC survival, with one cell-based study showing that human corneal epithelium stem cells cultured in hypoxic conditions may exhibit a quiescent stem cell phenotype and survive longer [15]. The hypoxia related vicious cycle may impede and damage the self-healing process of the ocular surface due to matrix protein deposition and focal adhesion protein loss, leading to re-epithelialization failure and decreased surgical success rate [17, 18]. Apart from the controversy regarding LSCs, other at risk graft transplantations are well documented to benefit from HBOT induced hyperoxygenation [19]. We therefore used HBOT to increase the survival rate of the multiple grafts in the SJS/TEN compromised environment based on following assumptions. First, HBOT improves oxygenation of the graft directly by immersing the graft in 100% oxygen, whereas the normal environment is only 20% oxygenated. This allows survival until the graft develops its own blood supply from the scleral/conjunctiva bed [20]. Second, oxygen upregulates a number of cytokines and growth factors, such as transforming growth factor-1 and platelet-derived growth factor, which facilitate corneal re-epithelialization [4]. Third, HBOT stimulates angiogenesis and reduces wound edema by an osmotic effect, thus promoting oxygen diffusion and wound healing [4]. Fourth, HBOT is known to have an anti-inflammatory effect [21], which may reduce the recurrence of symblepharon or fornix

shortage. An animal study on chemical burns in the cornea showed that oxygen therapy improved prelimbic conjunctiva ischemia and promoted corneal epithelial healing [22]. Therefore, in corneal hypoxia and contact lens wearing incidents, HIF-1α, IL-8, IL-6 and angiopoietin are restricted. The expression of 12-HETE, 12-HETrE and VEGF increased during contact lens wear. As in other tissues, the corneal hypoxic response causes an imbalance of pro- and anti-angiogenic mediators. IPAS domain proteins, endostatin, angiostatin, PEDF, and erythropoietin are candidates for important mediators of anti-angiogenesis. Therefore, when hyperbaric oxygen therapy is applied with 2.0ATA for 75 min, sufficient oxygen obtained by the corneal cells can obtain partial pressure of oxygen are 1500 mmHg, which is about 15 times the original partial pressure of oxygen, so the corneal vascular hyperplasia will be decreased [23]. We administered HBOT to our patient based on past experience and literature, normally hyperbaric oxygen therapy is a very safe treatment method, but there may still be some side effects and complications, such as following symptoms: ear barotrauma, dizziness, dyspnea, palpitations, and cold sweats. The incidence of the above-mentioned possible complications is low and most of them are reversible. The more serious complications include: Oxygen toxicity, seizures, pneumothorax, cardiac arrhythmia, but rarely happen. All above complications was not seen in our patient, we speculate that the wound-healing mechanism of HBOT in our patient worked as follows: A minimum of 20 mmHg partial pressure of oxygen is required for wound healing, including fibroblast proliferation and collagen production; under hyperbaric oxygen conditions, the partial pressure of oxygen can be brought up to 280–350 mmHg, which enables proper cellular function and promotes wound healing [24]. Considering the successful recovery of our patient, HBOT seems to be effective and may be advocated as an adjuvant therapy for ocular surface reconstruction in SJS/TEN.

4. Conclusion

SJS/TEN can have serious systemic and ocular sequelae, including vision-threatening ocular complications and high mortality. Even with ocular reconstruction surgery, the success rates are often low. We highlighted an innovative method of combining simultaneous ocular surface reconstruction surgeries, including oral mucosa flap graft, minor salivary gland transplant, allogeneic conjunctival LSCT, and simple limbal epithelial transplantation in one setting, followed by postoperative HBOT as adjuvant treatment. This resulted in promising recovery of the vision and ocular surface.

Although we have achieved pre-mature success in this case, more clinical studies are needed to verify the benefits of HBOT for ocular surface reconstruction surgeries and long term follow up of the patient's ocular surface are needed.

Patient consent

The patient provided a written informed consent for inclusion of her clinical and imaging details in the manuscript for the purpose of publication.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

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