Original Article

Evaluation of Medically Reversible Limbal Stem Cell Deficiency

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Abstract

Objectives: To evaluate the clinical characteristics and treatment strategies of limbal stem cell deficiency (LSCD) patients managed with medical therapy.

Materials and Methods: The study included 29 eyes of 21 patients with LSCD who were managed medically at Ege University Faculty of Medicine, Department of Ophthalmology between May 2013 and May 2023. LSCD stages before and after medical treatment were recorded according to the LSCD staging system published by the International LSCD Working Group. The medical records of patients showing improvement in LSCD stage with medical treatment without surgical intervention were evaluated.

Results: The mean age was 35.5±23.8 years (range, 5-71 years) with a male-to-female ratio of 6:15. The primary etiology of LSCD was ocular rosacea in 12 patients (57.1%), marginal keratitis in the setting of blepharitis in 8 patients (38.1%), and topical medication toxicity in 1 patient (4.8%). The mean baseline best corrected visual acuity (BCVA) was 0.25±0.26 logarithm of the minimum angle of resolution (logMAR) (range, 0-1 logMAR). Pre-treatment LSCD stage was stage 1A in 5 eyes (17.2%), stage 1B in 12 eyes (41.4%), stage 1C in 4 eyes (13.8%), stage 2A in 4 eyes (13.8%), and stage 2B in 4 eyes (13.8%). Complete regression of LSCD was achieved in 6 eyes (20.7%) with medical treatment addressing the primary etiology. In the remaining eyes, after medical treatment, the severity of LSCD decreased below the surgical threshold, which is considered stage 2B. The mean final BCVA was 0.07±0.1 logMAR (range, 0-0.4 logMAR).

Conclusion: This study highlights that LSCD can be completely or partially reversible with appropriate management, especially in cases with underlying limbal niche dysfunction, where inflammation plays a significant role. Although limbal stem cell transplantation is considered the main treatment approach for LSCD, localized and early-stage LSCD can be effectively managed medically without the need for surgical intervention.

Keywords: Limbal stem cell deficiency, marginal keratitis, ocular rosacea

Introduction

The limbus is a specialized region that hosts pluripotent limbal stem cells and forms a physical barrier between the avascular cornea and vascular conjunctiva. A healthy limbus is essential to the regeneration of the corneal epithelium and preservation of corneal transparency.[1,2] Limbal stem cell deficiency (LSCD) is characterized by limbal stem cell damage and impaired limbal barrier function. It may occur due to genetic (e.g., aniridia), acquired (e.g., chemical burns, vernal and atopic keratoconjunctivitis, contact lens use), or immunological (e.g., drug toxicity, ocular surface infection, ocular rosacea) causes.[3]

Limbal stem cell transplantation, the process of transplanting healthy limbal stem cells to the damaged limbal region, is considered the main treatment approach to LSCD. However, localized (i.e., early-stage) LSCD can be treated without surgical intervention.[4] This is especially true in cases where limbal niche function is impaired due to chronic ocular surface inflammation. Therefore, according to the current consensus regarding LSCD, it has become clear that cases associated with limbal niche dysfunction are partially or completely reversible with elimination of the causative factor and correct medical treatment.[3,5,6]

The aim of this study was to perform LSCD staging using the classification system defined by the International LSCD Working Group and evaluate the clinical characteristics and treatment strategies of patients in whom LSCD stage regressed with medical treatment.

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Materials and Methods

Approval for this retrospective, cross-sectional study was obtained from the Ege University Faculty of Medicine Medical Research Ethics Committee (decision number: 24-4T/25, date: 04.04.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The study included 29 eyes of 21 LSCD patients managed medically in the Cornea Unit of Ege University Faculty of Medicine, Department of Ophthalmology between May 2013 and May 2023. The demographic and clinical characteristics of patients with improved LSCD stage after medical treatment without surgical intervention were evaluated from their medical records. Age, sex, laterality (unilateral/bilateral) and primary etiology of LSCD, medical treatment approach, and best corrected visual acuity (BCVA) before and after treatment were recorded.

Two different researchers evaluated the patients' anterior segment photographs and recorded the LSCD stages. LSCD stage before and after medical treatment was determined according to the global consensus on LSCD staging published by the International LSCD Working Group in 2019.[5] According to this staging system, LSCD was divided into 3 main groups based on the degree of corneal epithelial damage: stage 1, normal corneal epithelium in the central 5 mm area; stage 2, epithelial damage in the central 5 mm area; and stage 3, damage to the entire corneal epithelium. Stages 1 and 2 were also subdivided based on the extent of limbal involvement (A, B, and C for stage 1; A and B for stage 2) (Table 1).[5]

Patients who had a history of ocular trauma, underwent surgical treatment for LSCD, or had incomplete medical records were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics 25.0 package program (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.). The significance level was determined as $p<0.05$ for all analyses. Descriptive statistics of the data were given as mean, standard deviation, median, range, frequency, and percentage values.

Table 1. Global consensus on limbal stem cell deficiency staging published by the International LSCD Working Group in 2019[5]

Main stages		Subgroups	
Stage 1	Normal corneal epithelium in the central 5-mm zone	**A**	<50% limbal involvement
		B	≥50% to 100% limbal involvement
		C	100% limbal involvement
Stage 2	Corneal damage in the central 5-mm zone	**A**	<50% limbal involvement
		B	≥50% to 100% limbal involvement
Stage 3	Damage to the entire corneal surface		

LSCD: Limbal stem cell deficiency

Results

The mean age was 35.5±23.8 years (range, 5-71 years) and the male-to-female ratio was 6:15. LSCD was unilateral in 13 patients (62%) and bilateral in 8 patients (38%). The primary etiology of LSCD was ocular rosacea in 18 eyes of 12 patients (57.1%), blepharitis-related marginal keratitis in 10 eyes of 8 patients (38.1%), and drug toxicity in 1 eye of 1 patient (4.8%). The mean BCVA before treatment was 0.25±0.26 logarithm of the minimum angle of resolution (logMAR) (range, 0-1 logMAR). Pre-treatment LSCD stage was stage 1A in 5 eyes (17.2%), stage 1B in 12 eyes (41.4%), stage 1C in 4 eyes (13.8%), stage 2A in 4 eyes (13.8%) eyes, and stage 2B in 4 eyes (13.8%).

The mean BCVA after treatment was 0.07±0.1 logMAR (range, 0-0.4 logMAR). With etiology-targeted local and systemic medical treatment, LSCD resolved completely in 6 eyes (20.7%). The distribution of post-treatment LSCD stages in the other eyes was as follows: stage 1A in 16 eyes (55.2%), stage 1B in 4 eyes (13.8%), stage 1C in 1 eye (3.4%), and stage 2A in 2 eyes (6.9%) (Table 2).

Table 2. Demographic data and clinical findings of the patients

Demographic and clinical data	Results
Mean age (years), mean ± SD (range)	35.5±23.8 (5-71)
Sex (patients), n (%)	
Female	15 (71.4%)
Male	6 (28.6%)
Laterality (patients), n (%)	
Unilateral	13 (62%)
Bilateral	8 (38%)
Primary etiology (patients), n (%)	
Ocular rosacea	12
Blepharitis-related marginal keratitis	8
Medication toxicity	1
Medical treatment modality (eyes), n (%)	
Conservative treatment (topical steroid, antibiotic, lubrication)	9 (31%)
Topical cyclosporine	6 (20.7%)
Systemic treatment	14 (48.3%)
Pre-treatment LSCD stage (eyes), n (%)	
Stage 1A	5 (17.2%)
Stage 1B	12 (41.4%)
Stage 1C	4 (13.8%)
Stage 2A	4 (13.8%)
Stage 2B	4 (13.8%)
Post-treatment LSCD stage (eyes), n (%)	
Complete resolution	6 (20.7%)
Stage 1A	16 (55.2%)
Stage 1B	4 (13.8%)
Stage 1C	1 (3.4%)
Stage 2A	2 (6.9%)

SD: Standard deviation, LSCD: Limbal stem cell deficiency

Combined treatment with conservative measures (e.g., eyelash base cleaning, warm compress), lubrication support with preservative-free artificial tears (Eyestil single dose, Sifi, Italy), topical antibiotic (moxifloxacin 0.5%, Moxai, Abdi İbrahim, Türkiye), and topical corticosteroid (loteprednol etabonate 0.5%, Dolte, Abdi İbrahim Pharmaceuticals, Türkiye) resulted in improved LSCD stage in 9 eyes (31%; 7 with marginal keratitis, 2 with ocular rosacea). In another 6 eyes (20.7%) with ocular rosacea, improved LSCD stage was achieved by adding topical cyclosporine (cyclosporine A 0.05%, Depores, Deva, Türkiye) to this treatment. Systemic therapy was required for 13 (44.9%) eyes that did not respond to medical treatment (3 with marginal keratitis, 10 with ocular rosacea). Of these, 8 regressed with oral doxycycline (Tetradox, Teva Pharmaceuticals, Türkiye) and 5 regressed with oral azithromycin (Azitro, Deva Pharmaceuticals, Türkiye) (Figure 1). In 1 patient who developed LSCD due to topical antiglaucoma medication toxicity (0.5% betaxolol; Betoptic-S; Novartis; Alcon), the LSCD stage decreased from 2A to 1C after discontinuation of the preserved topical agents and treatment with topical corticosteroid, autologous serum, and oral doxycycline.

The mean follow-up period of the patients was 5.3±3 months (range, 1-13 months).

Discussion

The presence of healthy and functional limbal stem cells is critical for regeneration of the corneal epithelium and lifelong maintenance of ocular surface homeostasis. Limbal stem cells are found in the limbus region, and damage to this area from various etiologies results in LSCD, characterized by corneal vascularization, recurrent epithelial erosions, and corneal opacification. LSCD occurs as a result of limbal stem cell loss or dysfunction. The underlying mechanism varies according to the primary etiology.[7,8] Direct physical damage to the limbal region, as in chemical burns, Steven-Johnson syndrome, microbial keratitis, and contact lens use, may cause limbal stem cell aplasia. Alternatively, LSCD may develop due to impaired limbal stem cell function resulting from an abnormal microenvironment or insufficient stromal support, as in aniridia, peripheral inflammatory diseases, chronic limbitis, and neurotrophic keratopathy.[3]

The treatment approach in LSCD also varies according to the primary etiology and associated pathogenesis. Although there are different medical and surgical treatment approaches, until recently there was no clear consensus on the definitive surgical indication.[9,10,11] The International LSCD Working Group recently defined an LSCD staging system, and a global consensus on the diagnosis and treatment algorithm of LSCD was formed based on this system.[5,6] According to this consensus, a more conservative approach including medical therapy is recommended as initial treatment for asymptomatic and early-stage (stage 1 and 2A) LSCD cases. The primary goal of treatment is to provide ocular surface optimization, tear film stabilization, inflammation control, and sustained epithelial regeneration.[6] With the global consensus on the LSCD treatment algorithm, the importance of adopting a stepwise treatment approach has been emphasized.[6] There are a few studies in the literature showing that especially in early-stage LSCD secondary to inflammatory etiologies, elimination of the triggering factor and treatment with ocular surface lubrication, topical anti-inflammatory therapy, and systemic tetracycline leads to LSCD regression. However, data are scarce regarding the effectiveness of medical treatment in LSCD and what treatment algorithm to follow in such cases.[12,13,14] The present study showed that, in light of the recently published consensus on LSCD staging, LSCD can regress with appropriate medical treatment, especially in the early stages.

Another problem is that LSCD diagnosis and stage are determined using different criteria. LSCD staging is mostly based on clinical findings, which introduces the potential for subjectivity and bias when assessing treatment response.[14,15,16] In contrast, pre-treatment and post-treatment LSCD stages in our study were determined according to the global consensus on LSCD classification. This classification, defined by the

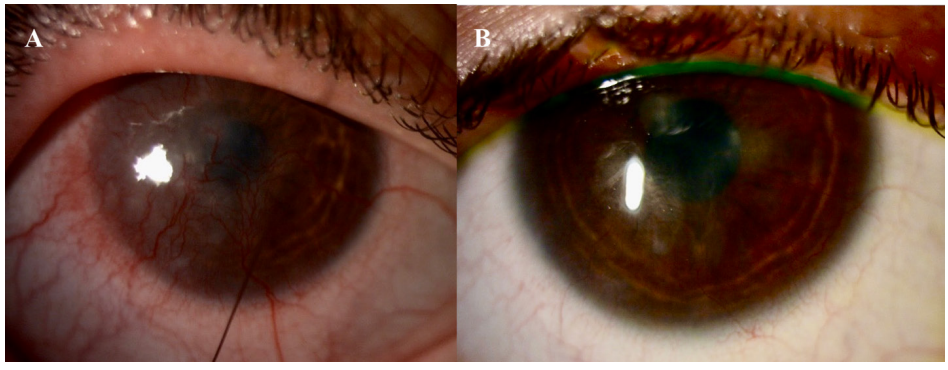

Figure 1. A 14-year-old girl diagnosed with ocular rosacea presented with redness and blurred vision. (A) On initial examination at the time of admission, 270 degrees of limbal insufficiency and central corneal opacity were observed. LSCD stage was recorded as 2B. The patient was treated with topical artificial tears (Eyestil single dose, Sifi, Italy), topical antibiotic (moxifloxacin 0.5%, Moxai, Abdi İbrahim, Türkiye), topical corticosteroid (loteprednol etabonate 0.5%, Dolte, Abdi İbrahim İlaç, Türkiye), topical cyclosporine A (0.05%, Depores, Deva, Türkiye), and oral doxycycline (Tetradox, Teva İlaç, Türkiye). (B) LSCD stage decreased to 1B after 6 months of treatment
LSCD: Limbal stem cell deficiency

International LSCD Working Group in 2019, aims to prevent the use of different parameters and subjective evaluations in determining LSCD severity.[5,6] Therefore, using this current and well-defined system for LSCD staging can provide a more objective interpretation when evaluating treatment response.

With appropriate patient selection and the right treatment algorithm, ocular surface healing can be achieved in LSCD patients without surgical intervention. The first step in medical treatment is to eliminate possible triggering factors such as contact lenses and preserved topical medications. Providing ocular surface lubrication to protect and support residual limbal stem cells is very important. Another step of treatment is controlling ocular surface inflammation with anti-inflammatory agents (e.g., topical corticosteroid, topical cyclosporine, oral tetracycline, systemic immunomodulators). When planning medical treatment, a stepwise treatment approach should be preferred, taking into account factors such as the primary etiology of LSCD, the condition of the ocular surface, and degree of LSCD.[6,17,18] In this study, medical treatment taking all of these parameters into account brought about regression in LSCD stage. The fact that most patients in the study (86.2%) had stage 2A or lower LSCD, in line with global consensus recommendations, may be a factor that increased the success of treatment. However, the 4 eyes (13.4%) with stage 2B LSCD also had an improved LSCD stage with medical treatment.

In advanced LSCD unresponsive to medical treatment, surgical treatment is unavoidable to ensure corneal homeostasis and healthy corneal epithelial regeneration. Limbal stem cell transplantation, the process of transplanting healthy limbal stem cells to the area of damage, is considered the main treatment approach for advanced LSCD.[2,3] According to the treatment algorithm established by the International LSCD Working Group in 2020 based on the LSCD staging system, limbal stem cell transplantation is recommended for stage 2B or higher LSCD.[6] However, our observation that LSCD stage regressed with medical treatment in 4 eyes with advanced (stage 2B) LSCD highlights the importance of medical treatment in advanced-stage patients as well. Therefore, in eyes with advanced-stage LSCD that indicates surgery, progression can be prevented with medical treatment until surgery. In these patients, medical treatment should be regarded as preparation for surgery, keeping in mind that it may contribute to ocular surface stability until limbal stem cell transplantation is planned.

In addition to the stage of LSCD, it is also important to recognize the etiologies of LSCD that can regress with medical treatment. Limbal niche dysfunction is the main pathogenetic factor in LSCD of inflammatory etiologies.[19] Pajoohesh-Ganji et al.[20] reported that limbal niche dysfunction due to trauma and inflammation caused goblet cell migration to the cornea. Tear film stabilization and inflammation control restore the limbal microenvironment, thereby helping to restore limbal niche function. Kim et al.[14] reported that LSCD could be managed with medical treatment alone in 22 eyes that developed LSCD due to contact lens wear, benzalkonium chloride toxicity, and idiopathic causes. Our study showed that LSCD stage regressed with medical treatment and conservative measures in patients who developed LSCD due to ocular rosacea, blepharitis-related marginal keratitis, and drug toxicity, which are inflammatory causes of LSCD.

Rosacea is a chronic skin disease, and approximately 58-72% of patients have ocular involvement. Ocular rosacea manifests with increased inflammation in the eyelids and ocular surface. The most common ocular effects are dry eye, conjunctivitis, and meibomian gland dysfunction. However, corneal involvement occurs in approximately 30% of patients with ocular rosacea. Increased ocular surface inflammation in untreated ocular rosacea cases causes loss of limbal niche and limbal stem cells. This can result in corneal neovascularization, recurrent epithelial defect, and corneal opacity.[21,22] In addition to conservative measures, artificial tear therapy, systemic and topical anti-inflammatory agents, and topical antibiotherapy are recommended when necessary. Kim et al.[14] showed that LSCD regressed with conservative measures plus a combination of topical corticosteroid, topical cyclosporine, and oral doxycycline in 3 eyes with ocular rosacea and soft contact lens use. In our study, 12 patients diagnosed with ocular rosacea developed LSCD without a history of contact lens use, and all of them exhibited regression of LSCD stage with medical treatment.

Contact lens wear itself is an important cause of LSCD due to chronic trauma to the ocular surface. Eliminating this factor alone often leads to dramatic improvement.[23] Martin[13] showed that whorl-like epitheliopathy in contact lens users responded to medical treatment. Because cases of contact lens-associated LSCD were usually followed up and treated on an outpatient basis in our clinic and resolved with modification of contact lens use without the need for aggressive medical treatment, these patients were not included in this study.

Increased bacterial flora at the lid margin and associated chronic inflammation play a major role in the pathogenesis of blepharitis-related marginal keratitis. In untreated cases, increased ocular surface inflammation leads to limbal niche dysfunction and secondary LSCD. Although the pathogenesis of secondary LSCD is common to both diseases, less aggressive treatment is generally sufficient for clinical regression in marginal keratitis compared to ocular rosacea.[3] In the present study, the majority of eyes diagnosed with marginal keratitis (70%) recovered without the need for systemic treatment, whereas most eyes with ocular rosacea (88.9%) required topical cyclosporine and systemic doxycycline therapy.

Drug toxicity is a relatively uncommon cause of LSCD. Iatrogenic causes account for approximately 5.5-7.3% of LSCD cases, and approximately 30% of them are due to drug toxicity. Drug toxicity-associated LSCD is especially associated with long-term use of topical agents containing preservatives.[12,24,25,26]

In this study, there was a history of long-term use of 3 anti-glaucomatous medications in the patient who developed LSCD due to drug toxicity. Discontinuing the preserved agents and providing supportive treatment resulted in regression of LSCD findings.

Study Limitations

The main limitations of this study include its retrospective design and the relatively small number of patients. There is a need for prospective studies that include more participants and compare different patient groups.

Conclusion

While chemical injuries or severe autoimmune reactions cause severe LSCD, certain pathological conditions such as ocular rosacea, blepharitis-related marginal keratitis, and medication toxicity give rise to a clinical picture of LSCD with limbal niche dysfunction. Consistent with the literature, the present study demonstrated that inflammation has a fundamental role and that LSCD is fully or partially reversible with correct management in cases with limbal niche dysfunction. With etiology-targeted local and systemic medical treatment, LSCD completely resolved in 6 eyes (20.7%) and in all other eyes regressed in severity to below stage 2B, which is the threshold for surgical treatment. Therefore, in the early stages and with the right indications, LSCD can be treated medically, without surgical intervention. Although limbal stem cell transplantation is the main treatment approach in eyes with advanced LSCD, medical treatment administered before surgery may contribute to ocular surface stabilization.

Ethics

Ethics Committee Approval: Ege University Faculty of Medicine Medical Research Ethics Committee (decision number: 24-4T/25, date: 04.04.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.P., S.E., A.Y., Concept: M.P., Ö.B.S., Design: N.F.E., Ö.B.S., Data Collection or Processing: İ.K., N.F.E., Analysis or Interpretation: S.E., A.Y., Literature Search: İ.K., Writing: İ.K.

Conflict of Interest: Sait Eğrilmez, MD, is an Associate Editor of the Turkish Journal of Ophthalmology. He was not involved in the peer review of this article and had no access to information regarding its peer review. The other authors have no disclosures.

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