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Superior Limbic Keratoconjunctivitis-like Inflammation in Patients with Chronic Graft-Versus-Host Disease

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Abstract

Purpose—Describe the presentation and management of superior limbic keratoconjunctivitis (SLK-like inflammation and secondary limbal stem cell dysfunction in the setting of ocular chronic graft-versus-host disease (cGVHD).

Methods—Retrospective observational case series in a multicenter clinical practice. Participants were 13 patients (26 eyes) with ocular cGVHD and SLK-like inflammation presenting to the University of Illinois at Chicago and Boston Foundation for Sight between January 1, 2009 and July 1, 2013.

Main outcome measures—1) Reversal or worsening of SLK, and 2) development of limbal stem cell dysfunction.

Results—All eyes showed evidence of SLK-like inflammation and superior limbal stem cell dysfunction manifested by conjunctival injection and superior conjunctival and corneal staining. In addition to aggressive lubrication, management strategies for SLK included topical steroids (20/26), punctal occlusion (18/26), topical cyclosporine (24/26), autologous serum tears (12/26), therapeutic soft contact lens (13/26 eyes) and scleral lenses (4/26 eyes). SLK and limbal stem cell dysfunction were reversed in 23/26 eyes. Three eyes of two patients with long-standing disease demonstrated frank limbal stem cell deficiency (LSCD) and corneal pannus, with one patient requiring multiple reconstructive surgical procedures.

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Dr. Jacobs works for Boston Sight®, which makes and distributes the PROSE device. The other authors have no commercial or proprietary interest in any concept or product discussed in this article.

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Conclusions—SLK-like inflammation is an under-recognized condition in patients with severe dry eyes secondary to ocular cGVHD. Untreated SLK can potentially lead to permanent LSCD over time. Early recognition and management of SLK in ocular cGVHD can improve vision, reverse signs, and may prevent these long-term consequences.

Keywords

Limbal stem cell dysfunction; ocular chronic graft-versus-host disease; prosthetic replacement of the ocular surface (PROSE); superior limbic keratoconjunctivitis

I. Introduction

Superior limbic keratoconjunctivitis (**SLK**) is an ocular surface condition characterized by inflammation of the superior tarsal and bulbar conjunctiva, staining of the superior conjunctiva, superior corneal filaments, and disturbance to the superior limbal epithelium.^{1,2} The pathogenesis of SLK is unclear. One theory suggests SLK is caused by repetitive microtrauma between the tarsal and superior palpebral conjunctiva, which may be exacerbated by conditions such as dry eye and a tight upper lid.³

Although there is an established association between SLK and idiopathic dry eye and thyroid eye disease, the incidence of SLK among secondary dry eye conditions has not been well studied. Specifically, the ocular form of chronic graft-versus-host disease (cGVHD) is among the most severe forms of secondary dry eye conditions. The course of ocular cGVHD is similar to that of other forms of autoimmune-mediated ocular surface disease, which involves inflammatory damage to the lacrimal glands, meibomian glands, cornea, and conjunctiva.^{4,5} This, in turn, leads to increased frictional forces between conjunctival surfaces, leading to the repetitive microtrauma that can predispose to SLK-like inflammation.

The true incidence of SLK in cGVHD is unknown and requires further study. To our knowledge, there is only one published report that mentions SLK in cGVHD patients, which stated an incidence of 8.8%.⁶ However, in our anecdotal experience, SLK-like inflammation is a frequent comorbid feature in patients with severe ocular cGVHD. Due to the potential for permanent morbidity from undiagnosed SLK in this vulnerable population, all eye care providers should be aware of the signs of SLK so that therapeutic intervention can be instituted promptly. Herein, we describe our experience of SLK-like inflammation in 26 eyes with cGVHD and describe their clinical characteristics, course and response to treatment.

II. Methods

Approval was obtained from the University of Illinois at Chicago Institutional Review Board and the New England Institutional Review Board, both of which granted waivers of informed consent. All research adhered to the tenets of the Declaration of Helsinki.

A retrospective review was performed of all patients with a history of allogeneic stem cell transplant with subsequent cGVHD-related dry eye and clinical features consistent with SLK. Patients were evaluated at the University of Illinois Eye and Ear Infirmary or Boston

Sight® between January 1, 2009 and December 31, 2013. The diagnosis of cGVHD was established by the referring hematologists based on the National Institute of Health Consensus development project on criteria for clinical trials in GVHD.⁷ The diagnosis of SLK was made based on the presence of at least two of the following criteria: 1) Presence of injected and redundant superior bulbar conjunctiva; 2) presence of whorl-like fluorescein staining in the superior cornea; and 3) presence of rose bengal staining in the superior conjunctiva. Patients with pre-existing ocular surface disease were excluded.

Patient records were reviewed to obtain demographic information, including age, sex, indication for allogeneic stem cell transplant, other systemic GVHD manifestations, and ocular and systemic medications. Specific details of each patient's ocular history and examination, including visual acuity, intraocular pressure, Schirmer tear production (without anesthesia), slit lamp exam findings and fluorescein/rose bengal staining patterns, were also recorded.

When available, the results of ocular surface impression cytology were analyzed. Impression cytology samples were obtained by placing a dry tear test strip into contact with the superior cornea for 10–15 seconds. Care was taken not to allow the test strip to touch any conjunctival surface. The test strip was then peeled off with forceps. Any adherent cells were immediately transferred by sandwiching the test strip between two coated glass slides and smearing the strip against the slides.⁸ The cells attached to the glass slides were then stained with Periodic Acid Schiff (PAS) and examined with light microscopy.⁹

III. Results

Twenty-six eyes of 13 patients met inclusion criteria. Demographic characteristics are summarized in Table 1. The mean age was 55.1 ± 12.9 years (range 25–75 years), and 8 of the 13 patients were male. All patients had a history of an allogeneic hematopoietic stem cell transplant for the treatment of a hematologic malignancy. The patients presented at a mean of 50 months after undergoing stem cell transplantation (range: 3–245 months). At presentation, all patients had been diagnosed with chronic systemic GVHD with involvement of at least one other major organ system. Initial best-corrected visual acuity ranged from 20/20 to 20/400. Schirmer testing without anesthesia was documented in 24 eyes and revealed significantly decreased tear production (<5 mm tear production in 5 min) in 23 of 24 tested eyes (95.8%; mean 1.4 mm; range 0–12 mm).

A. Anterior Segment Examination

All 26 eyes demonstrated superior conjunctival injection and superior corneal/conjunctival staining with fluorescein and/or rose bengal at presentation (Figures 1–4). Likewise, all eyes showed evidence of superior limbal stem cell dysfunction with superior corneal epithelial staining in a wave/whorl-like pattern (Figure 1). Eleven eyes of six patients demonstrated recurrent corneal filaments. Three eyes of two patients showed evidence of frank limbal stem cell deficiency (**LSCD**) with conjunctivalization and opacity of the superior cornea (Figures 4 and 5). Other clinical characteristics are summarized in Table 2.

B. Impression Cytology

Impression cytology of the superior cornea was performed in both eyes of one patient (Patient 9 in Tables 1 and 2). Although there was no conjunctivalization of the cornea evident on slit lamp examination, Periodic Acid Schiff staining histologically confirmed the presence of squamous metaplasia with rare goblet cells in the superior cornea.

C. Management

Figure 6 summarizes the treatment algorithm and clinical response of all treated eyes. All 26 eyes were treated on presentation with aggressive lubrication using preservative-free artificial tears. Twenty-four eyes were either already using topical cyclosporine A 0.05% 2–4 times a day or this treatment was initiated upon presentation. Early treatment (within 3 months of presentation) also included topical corticosteroids in 20 eyes of 10 patients. Eighteen eyes of 10 patients had either previously had punctal occlusion or underwent this procedure within 3 months of presentation. Autologous serum tears were initiated in 12 eyes of 6 patients. With the use of these conservative treatments alone (lubrication, topical cyclosporine A, topical corticosteroids, punctal occlusion and serum tears) the symptoms and signs of SLK improved in 10 of 26 eyes, as evidenced by increased comfort and reduction in superior corneal staining with vital dyes and decreased corneal filament formation, respectively.

In the 16 remaining eyes, there was a poor response to these conservative measures alone. Twelve of these eyes (Patients 1, 2, 7, 8, 10 and 11) were treated with 14 mm-diameter daily wear therapeutic soft contact lenses to help manage their dry eye symptoms. Of these 12 eyes, 8 eyes of 4 patients (Patients 2, 7, 8 and 11) tolerated the lenses well with improvement of subjective dry eye symptoms and stable to improved superior epitheliopathy. The remaining 4 eyes of 2 patients (Patients 1 and 10) were unable to tolerate a therapeutic soft contact lens and were switched to either scleral (Jupiter Scleral Lens, Visionary Optics, Front Royal, VA) or PROSE lenses (Boston Sight®, Needham, MA), with significant improvement in their symptoms. One patient (Patient 13) was treated with PROSE lenses at presentation and experienced significant improvement in subjective dry eye symptoms. In all eyes in which a scleral lens was used, the superior epitheliopathy was noted to be significantly reduced, whereas eyes with PROSE lenses experienced complete resolution of their epitheliopathy.

One patient (Patient 4 in Tables 1 and 2), who had a history of ocular cGVHD for over 20 years, presented with advanced disease. At the time of presentation to us, the patient had evidence of superior LSCD in both eyes with conjunctivalization encroaching on the visual axis. Despite aggressive lubrication and topical anti-inflammatory therapy, the conjunctivalization progressed and required a superficial keratectomy and amniotic membrane transplant (Figure 4). This patient also had cicatrizing changes of the palpebral conjunctiva bilaterally that required multiple eyelid and fornix reconstruction procedures. This patient's left eye has developed recurrent superior LSCD with a final best-corrected visual acuity of 20/100 despite multiple ocular surface reconstruction procedures and cataract extraction with intraocular lens placement. A conjunctival-limbal allograft from the patient's bone marrow donor has been recommended for the management of the LSCD.

D. Visual Outcomes

After a mean follow-up of 16.0 months (range: 2–47), visual acuity was improved 2 or more Snellen lines in 6 eyes (23.0%) and stable within one Snellen line in 11 eyes (57.6%) compared to visual acuity at presentation (Table 2). The remaining 5 patients (19.2%) lost two or more Snellen lines of vision with one patient experiencing a significant loss of vision due to LSCD (Patient 4).

IV. Discussion

Ocular cGVHD can significantly limit quality of life in patients who have already survived a life-threatening hematologic malignancy.¹⁰ Previously reported ocular consequences of poorly controlled cGVHD include keratoconjunctivitis sicca, lacrimal gland dysfunction, and cicatricial conjunctivitis.¹¹ Our observations suggest that in addition to severe dry eye symptoms, cGVHD can produce an SLK-like condition and limbal stem cell dysfunction, which, if unrecognized, can potentially result in permanent LSCD. However, the classic SLK findings of superior corneal fluorescein staining and superior conjunctival injection are easily missed in a patient with cGVHD-related dry eye, who may already have extensive corneal staining and diffuse injection. It is therefore important for all eye care providers to be aware of the possibility of comorbid SLK-like disease in ocular cGVHD patients so that the diagnosis is made promptly and the proper treatment initiated.

Prior studies have established the contribution of mechanical injury to the conjunctiva in the pathogenesis of SLK.^{3,11,12} Specifically, Cher et al proposed that “SLK arises from soft tissue microtrauma: (i) between tarsal and bulbar surfaces; and (ii) between conjunctival stroma and sclera.”³ Predisposing factors for this repetitive microtrauma include a tight upper lid, tear deficiency states, and other conditions that result in increased frictional forces between the tarsal and bulbar conjunctiva.^{3,12,13} Mucin, which is produced by conjunctival goblet cells, is essential for reducing frictional forces in a normal blink cycle.¹⁴ Goblet cell loss is a key histologic finding in cGVHD and may be another way in which this condition predisposes to the development of SLK-like disease.¹⁵

Tear film optimization is the first step in the treatment algorithm for management of both classic and cGVHD-related SLK. This includes punctal occlusion, artificial tears, and autologous serum tears in addition to topical anti-inflammatory agents. All of the patients in our study were treated with lubrication and topical anti-inflammatory agents with a large percentage also utilizing serum tears and punctal occlusion. Although it is difficult to ascertain the effectiveness of these treatments in isolation since patients were generally on multiple therapies at once, these measures were at the very least well-tolerated and sufficient to control SLK-like symptoms in 10 of 26 eyes or 38.4%.

Reduction of frictional forces on the vulnerable superior bulbar conjunctiva has also been a major strategy for treatment of SLK. Contact lenses, which prevent the repeated rubbing of the upper lid on the superior conjunctiva, as well as pharmacological therapy aimed at increasing goblet cell production, have both been effective in treating SLK symptoms.^{16,17} Although one prior study has described extended wear of 13.8-mm silicone hydrogel soft lenses in the treatment of ocular cGVHD, the presence or absence of SLK was not

mentioned.¹⁸ In our study, 12 eyes of 6 patients were treated with 14-mm therapeutic contact lenses. Two of these patients could not tolerate these lenses, but the remaining four patients showed both subjective and objective improvement in their ocular cGVHD symptoms. In the two patients (4 eyes) that were intolerant of 14-mm bandage soft contact lenses, treatment was advanced to large-diameter rigid gas-permeable (**RGP**) scleral lens or PROSE treatment, which were generally used as a last resort. PROSE treatment was also used as a primary therapeutic lens option for both eyes of one patient with advanced disease. In all 6 eyes treated with rigid gas-permeable scleral lenses or PROSE treatment, marked improvement was noted in both the symptoms and signs of SLK.

Large-diameter rigid gas-permeable scleral lenses and the devices used in PROSE treatment have a mechanical advantage over conventional soft contact lenses in that they fully protect the superior cornea from the overriding bulbar conjunctiva and do not contact the cornea at all. Two studies of their use in patients with severe ocular GVHD show that they improve dry eye symptoms, visual acuity, and overall quality of life.^{19,20} These lenses are thought to exert their effect in part by creating a stable and abundant precorneal tear film and protecting the ocular surface from the shearing forces of the eyelids.²⁰ In the case of ocular cGVHD with SLK, these lenses provide a physical barrier to both the frictional forces from the upper eyelid and the redundant, inflamed superior conjunctiva overriding the cornea. It is therefore no surprise that the subset of patients in our study with ocular GVHD and SLK-like inflammation treated with scleral lenses all showed significant improvement in their symptoms. As this repetitive microtrauma is thought to be the main pathogenic mechanism in SLK, we propose that large-diameter rigid gas permeable scleral lenses or PROSE treatment are the options of choice for patients with severe SLK-like symptoms including advanced limbal stem cell dysfunction.

Although not specifically studied herein, we have anecdotally observed that frequent blinking and blepharospasm are commonly seen in patients with cGVHD and SLK. This possible association is consistent with the mechanical theory of SLK pathogenesis from repetitive eyelid trauma. In addition to RGP scleral lenses and PROSE treatment, injection of Botulinum Toxin A to the pre-tarsal orbicularis muscle has also been reported as an effective treatment for SLK.²¹ This treatment has not previously been reported in the setting of cGVHD-related SLK, but it may be another option for treatment in recalcitrant cases.

Although the therapeutic utility of contact lenses was supported by the findings of this study, other classic SLK treatments such as conjunctival cautery and/or resection would likely be of no benefit, and possibly some detriment, in cGVHD-related SLK. For example, resection of the superior bulbar conjunctiva has been reported to resolve or improve symptoms in non-cGVHD related SLK in up to 80% of eyes.² Similarly, chemical or thermal cautery of the superior bulbar conjunctiva has been reported as an effective treatment for SLK, likely by inducing scarring and shrinkage of the conjunctiva.²² However, patients with cGVHD already suffer from a severe form of inflammatory dry eye with a generalized loss of goblet cells.¹⁵ In this subset of patients, conjunctival resection or cauterization may further reduce the critically low population of goblet cells and actually exacerbate dry eye and SLK-like symptoms.

V. Conclusion

LSCD has been reported as a rare complication of cGVHD.²³ We postulate that repetitive frictional microtrauma to the limbal stem cells in an already inflamed environment leads to limbal stem cell dysfunction. This is evident by the whorl-like staining of the superior cornea. We documented the presence of goblet cells on the superior corneal surface in one patient who demonstrated only the whorl-like staining without frank conjunctivalization, suggesting that subclinical limbal stem cell dysfunction may exist in such patients. We believe that prompt recognition and management of SLK in patients with ocular cGVHD is critical for preventing progression to overt LSCD, as was seen in this study (Patients 4 and 10).

The limitations of this study are its retrospective nature and lack of strict objective diagnostic criteria for either SLK-like inflammation or ocular cGVHD. Further study should be directed toward gaining a better understanding of the pathogenesis of both ocular cGVHD and SLK so that treatments can be better directed at the root cause of these diseases rather than alleviation of their symptoms.

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Figure 1.

Slit lamp photograph shows the fluorescein staining pattern of the left eye of Patient 5. Note the superior corneal staining indicative of SLK-like inflammation and limbal stem cell dysfunction. This is in addition to the band of interpalpebral dry-eye related staining in the inferior half of the cornea.

Figure 2. Right (A) and left (B) eyes of Patient 1 showing sectoral superior conjunctival injection consistent with SLK-like inflammation. Treatment with scleral contact lenses led to significant improvement in the ocular surface and subjective symptoms.

Figure 3.
Superior conjunctival injection and corresponding rose bengal staining in the left eye of patient 7.

Figure 4. Slit lamp photograph of the left (A) and right (B) eyes of Patient 4. The patient developed severe superior limbal stem cell dysfunction due to untreated superior limbic keratoconjunctivitis. This subsequently led to permanent limbal stem cell deficiency and corneal vascularization.

Figure 5.

Slit lamp photographs with (A) and without (B) fluorescein staining of the left eye of Patient 10 showing frank superior limbal stem cell deficiency with superior corneal neovascularization and pannus. This patient was initially evaluated at our clinic 3 years earlier and was noted to have SLK-like inflammation in both eyes (left worse than right), with superior corneal staining but no neovascularization. Patient was subsequently lost to follow-up and returned with frank limbal stem cell deficiency in the left eye.

Figure 6. Summary of response to treatment of eyes with superior limbic keratoconjunctivitis-like inflammation and chronic graft-versus-host disease. SLK: superior limbic keratoconjunctivitis. cGVHD: chronic graft-versus-host disease.

Table 1

Patient Demographic Characteristics

Patient	Age	Sex	Indication for BMT	Time from BMT to presentation (months)	Other GVHD-affected organs systems
1	52	F	AML	9	Skin, lungs
2	25	F	ALL	10	Lungs
3	75	M	MDS	22	Skin
4	60	M	NHL	228	Skin, gastrointestinal
5	72	F	AML	23	None
6	60	M	AML	3	Skin, gastrointestinal
7	47	M	CLL	29	Skin, gastrointestinal
8	46	M	Lymphoma	12	Skin, lung
9	65	M	NHL	33	None
10	56	M	NHL	245	None
11	58	M	ALL	14	Gastrointestinal
12	64	F	AML	11	Skin, gastrointestinal
13	49	F	MM	15	Skin, gastrointestinal

BMT: Bone marrow transplantation; GVHD: Graft versus host disease; AML: Acute Myelogenous Leukemia; ALL: Acute Lymphocytic Leukemia; MDS: Myelodysplastic Syndrome; NHL: Non-Hodgkins Lymphoma; CLL: Chronic Lymphocytic Leukemia; MM: Multiple Myeloma; OD: Right eye, OS: Left eye

Table 2

Clinical characteristics of patients with chronic graft versus host disease and concurrent superior limbic keratoconjunctivitis.

Patient	BCVA at Presentation	Dense superior corneal fluorescein staining	Superior Rose Bengal conjunctival staining	Corneal Filaments	Frank limbal stem cell deficiency	Schirmer without anesthesia (mm)	Length of Follow-up (mo)	BCVA at Last Follow-up
1	OD: 20/25 OS: 20/30	+	+			OD: 1 OS: 1	12	OD: 20/40 OS: 20/30
2	OD: 20/30 OS: 20/25	+	+			OD: 2 OS: 1	11	OD: 20/25 OS: 20/25
3	OD: 20/40 OS: 20/60	+	+	+		OD: 0 OS: 0	29	OD: 20/20 OS: 20/20
4	OD: 20/60 OS: 20/50	+	+		+	OD: 1 OS: 1	47.5	OD: 20/60 OS: 20/100
5	OD: 20/30 OS: 20/30	+	+	+		OD: >12 OS: 1	39	OD: 20/40 OS: 20/40
6	OD: 20/20 OS: 20/25	+	+	+		OD: 0 OS: 0	5	OD: 20/30 OS: 20/25
7	OD: 20/40 OS: 20/40	+	+			OD: 0 OS: 0	2	OD: 20/25 OS: 20/30
8	OD: 20/40 OS: 20/20	+	+			OD: 1 OS: 4	3	OD: 20/20 OS: 20/20
9	OD: 20/20 OS: 20/30	+	+	+		OD: 0 OS: 1	10	OD: 20/30 OS: 20/40
10	OD: 20/25 OS: 20/60	+	+		+	OD: 1 OS: 1	5	OD: 20/40 OS: 20/70
11	OD: 20/20 OS: 20/20	+	+	+		Not performed	15	OD: 20/25 OS: 20/25
12	OD: 20/50 OS: 20/20	+	+	-		OD: 1.5 OS: 1.5	18	OD: 20/30 OS: 20/25
13	OD: 20/30 OS 20/400	+	Not performed	+		OD: 2 OS: 1	12	OD: 20/25 OS: 20/40

BCVA: Best Corrected Visual Acuity; CF: Counting fingers