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

Kavitha R. Sivaraman, MD,[1] Renu V. Jivrajka, MD,[1] Ketki Soin, MD,[1] Charles S. Bouchard, MD,[2] Asadolah Movahedan, MD,[1] Ellen Shorter, OD,[1] Sandeep Jain, MD,[1] Deborah S. Jacobs, MD,[3,4] and Ali R. Djalilian, MD[1]

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 BostonSight® 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. 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.**

KEY WORDS **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

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From the [1]Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, IL; [2]Loyola University, Department of Ophthalmology, Maywood, IL; [3]BostonSight®, Needham Heights, MA; and [4]Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA.

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Single-copy reprint requests to Ali R. Djalilian, MD (address below).

Corresponding author: Ali R. Djalilian, MD, 1855 W. Taylor St M/C 648, Chicago, IL 60612. Tel: 312-996-8937. Fax: 312-355-4248. E-mail address: adjalili@uic.edu

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OUTLINE

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 BostonSight® 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 the13 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.