STEVENS-JOHNSON SYNDROME (SJS) AND ITS MORE severe form, toxic epidermal necrolysis (TEN), are on a spectrum of immune-mediated, mucocutaneous diseases triggered by medications and, less commonly, infections.\(^1,2\) SJS/TEN is typified by an acute febrile illness associated with prodromal target lesions, followed by skin detachment and involvement of at least 2 mucous membrane sites.\(^3\) Ocular surface involvement occurs in 50%-78% of SJS/TEN cases and can result in significant long-term ocular sequelae, with 35% of survivors of SJS/TEN experiencing permanent vision loss.\(^4,5\)

Long-term medical and surgical management of patients with severe ocular surface disease, as can occur after SJS/TEN, is complex. One form of nonsurgical management is the use of therapeutic contact lenses.\(^6-9\) Clinicians may hesitate to consider therapeutic contact lenses in SJS/TEN patients because of assumptions that cicatricial conjunctival changes may be a barrier to achieving satisfactory fit. Additionally, these patients might be excluded as candidates because of ocular comorbidities such as aqueous tear deficiency and limbal stem cell deficiency that together would put patients in a high-risk category for epithelial breakdown and superinfection.

Prosthetic replacement of the ocular surface ecosystem (PROSE) is a treatment approach developed by Boston Foundation for Sight (BFS), Needham, Massachusetts, that uses a custom-designed and fitted, FDA-approved, rigid gas-permeable scleral lens prosthetic device to support ocular surface functions. The devices used in PROSE treatment vault the cornea and limbus and rest on sclera. They are filled with sterile saline at the time of application, worn on a daily-wear basis, and removed for sleep (Figure 1).\(^10,11\) PROSE treatment is also used in the management of corneal ectasia (ECT),\(^11,12\) a degenerative disorder that manifests as progressive corneal thinning and steepening. The resultant irregular astigmatism, myopia, and irregular corneal surface can lead to impaired vision and can require surgical intervention.\(^13\) The most common of the corneal ectasias is keratoconus (KC). KC is also the most common condition requiring scleral lens wear.\(^12\) Scleral lenses have been shown to improve visual acuity and comfort in patients with KC.\(^14\) However, when scleral lenses and other treatment options fail, PROSE treatment has been shown to significantly improve vision and visual function,\(^5,11,15\) which may delay and perhaps eliminate the need for surgical intervention with its inherent risks and unpredictability.
In the course of a medical records review of patients with SJS/TEN, we noticed several patients who also had a diagnosis of ECT. This coincidence was striking, given the rarity of each condition. We present a review of 9 such cases here. Though the literature addresses corneal pathophysiology in SJS/TEN and ectatic disorders individually, to our knowledge, there are no reports of the prevalence, pathogenesis, and management of these entities as associated disorders.

METHODS

THIS STUDY WAS CONDUCTED ACCORDING TO THE DECLARATION OF Helsinki, was compliant with the Health Insurance Portability and Accountability Act (HIPAA), and was determined to be exempt from review by the New England Institutional Review Board. A manufacturing database of PROSE patients from January 1, 2002 to December 31, 2014 at BFS was searched to identify patients with diagnoses of both SJS/TEN and ECT. Referral to BFS occurred for management of poor or worsening visual function. All cases of ectasia were first diagnosed by the referring ophthalmologist and independently confirmed at BFS at the time of consultation. For this study, the diagnosis of ECT was confirmed by reviewing clinical examination notes and videokeratography. The Krumeich staged clinical classification of KC was used to stage the level of disease.16 Though the accuracy of videokeratographic data in SJS/TEN is unknown, generation of central 3-mm simulated keratometry (sim K) values was designated as a reliable measurement of keratometry values for Krumeich classification. Other relevant data were extracted from the medical records, with visual acuity recorded in Snellen format and then converted to logarithm of the minimum angle of resolution (logMAR) for analysis. Statistical analysis was performed using the InStat statistical package by GraphPad Software, Inc (La Jolla, California, USA) with the level of statistical significance set at .05.

RESULTS

TWO HUNDRED FIFTY PATIENTS WITH A DIAGNOSIS OF SJS/TEN were identified in the BFS database of patients for whom prosthetic devices were manufactured between 2002 and 2014. Seventeen eyes in 9 of these patients had been coded with a secondary diagnosis of ECT. Review of referral letters, notes, and records revealed that in each of these 9 cases, the diagnosis of ECT was made after acute SJS/TEN, with a range of 1–33 years.

### TABLE 1. Clinical Classification of Patients With Stevens-Johnson Syndrome and Corneal Ectasia by Stage Using the Krumeich Classification of Keratoconus

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Number of Eyes at Each Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eccentric steepening, induced myopia and/or astigmatism of ≤5.00 D, K-reading ≤48.00 D, Vogt lines, typical topography</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Induced myopia and/or astigmatism of 5.00 to ≤8.00 D, K-reading ≤53.00 D, Pachymetry ≥400 μm</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Induced myopia and/or astigmatism of 8.00 to ≤10.00 D, K-reading ≥53.00 D, Pachymetry 200–400 μm</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Refraction not measurable, K-reading ≥55.00 D, Central scars, Pachymetry ≤200 μm</td>
<td>6</td>
</tr>
</tbody>
</table>

D = diopters. Pachymetry is measured at the thinnest site of the cornea.

16 Adapted from Krumeich et al.16

Stage is determined if 1 of the characteristics applies.
Sixteen of 18 eyes had clinical and slit-lamp findings of an ectatic disorder, with videokeratography on record for 14 eyes of 7 patients. Thirteen of these eyes had sufficient videokeratographic data to generate 3-mm sim K values, which were used for keratoconus staging using the Krumeich classification (Table 1). Table 2 presents demographic and clinical data on these patients. In 1 eye of 1 patient (Patient 4) there were rigid gas-permeable corneal contact lens data available from which corneal curvature was derived as 48.00 diopters (D). Sim K values from videokeratography reveal keratometries of 43.2 D to 52.1 D with a mean of 47.65 D, suggesting that sim K values are valid representations of steepness in these patients. For 2 eyes of 1 other patient (Patient 8) there are Scheimpflug imaging data supporting diagnosis of ectasia.

Figure 2 illustrates the slit-lamp and videokeratography findings of Patient 6.

Based on use of a commonly cited KC prevalence rate of 54.5 per 100 000 population, with videokeratography on record for 14 eyes of 7 patients. Thirteen of these eyes had sufficient videokeratographic data to generate 3-mm sim K values, which were used for keratoconus staging using the Krumeich classification (Table 1). Table 2 presents demographic and clinical data on these patients. In 1 eye of 1 patient (Patient 4) there were rigid gas-permeable corneal contact lens data available from which corneal curvature was derived as 48.00 diopters (D). Sim K values from videokeratography reveal keratometries of 43.2 D to 52.1 D with a mean of 47.65 D, suggesting that sim K values are valid representations of steepness in these patients. For 2 eyes of 1 other patient (Patient 8) there are Scheimpflug imaging data supporting diagnosis of ectasia.

**DISCUSSION**

The prevalence of ECT among SJS/TEN patients in the BFS manufacturing database as compared with that of the general population was statistically significant (P < .0001, Fisher exact test). It was not possible to determine progression, if any, of ECT in the SJS/TEN patients compared with that in the general population owing to limited data points.

The median visual acuity at the initial visit, in habitual correction, was 20/200 (range, count fingers to 20/20; logMAR 1.0), whereas the median visual acuity at completion of customization was 20/30 (range, 20/60–20/15; logMAR 0.1761, P < .0025, McNemar test). All eyes that underwent PROSE treatment attained best-corrected visual acuity of ≥20/60 (P = .002), with most eyes attaining 20/30 vision or better (P = .008). Vision with PROSE treatment was maintained in all patients, with a median duration of follow-up of 14 months (range, 0.5–120 months), consistent with findings among SJS/TEN patients in general with PROSE treatment.

The interval between diagnosis of ECT and initial consultation for PROSE treatment ranged from 0 to 33 years, with a mean of 9 years, and did not correlate to final BCVA (r = 0.1432; P = .6253, Pearson correlation) or to the severity of ECT at the time of initial consultation (r = 0.0132, P = .9693, Pearson correlation).

The Oxford scheme was used to assess dry eye state at the time of consultation in 8 of 18 eyes. There was a tendency for higher initial Oxford scheme scores to correlate with higher KC stage, but this was not statistically significant (r = 0.6054; P = .1491, Pearson correlation). Post-PROSE Oxford scheme scores are not available.
eyelid margin keratinization, and lipid tear deficiency. These changes can lead to corneal complications from blink-related microtrauma.19 However, there are no reports in the literature directly addressing a relationship between microtrauma in SJS/TEN and ECT. Data from Dogru and associates suggest that tear function disturbance and ocular surface disease contributes to the progression of KC.20 They propose that abnormal eyelid–cornea interactions may contribute to ECT via altered tear film stability, loss of goblet cells, and subsequent squamous metaplasia, possibly from matrix metalloproteinase (MMP) expression by metaplastic epithelial cells. All of these ocular changes have been demonstrated in SJS/TEN eyes, although their significance in the development of ECT has not been researched.1,19 Future studies might look for correlation between eyelid pathology and presence or extent of ECT.

Other studies postulate that the defect in KC may lie in extracellular matrix degradation in the cornea.20 Though there are varying reports in the literature and no consensus, the potential role for degradative enzymes, including MMPs, tissue inhibitor of metalloproteinases-1 (TIMP-1), and cytokines, in the pathogenesis of KC have been reported. Elevated levels of MMPs, particularly collagenases and gelatinases, have been demonstrated in KC eyes, along
with decreased levels of TIMP-1. Particular MMPs demonstrated to be elevated in KC eyes include MMP-1, MMP-3, MMP-7, MMP-9, and MMP-13. MMP-2 has also been implicated by virtue of elevated levels of membrane-type MMP in KC eyes, which can in turn activate MMP-2.\textsuperscript{13,20–27} Some of these MMPs have also been demonstrated to be elevated in the tears of SJS/TEN patients. This elevation combined with a decrease in MMP regulation may predispose SJS/TEN patients to corneal remodeling. In 1 study of tears of SJS/TEN patients, MMP-8, MMP-9, and myeloperoxidase were all found to be significantly elevated, with lesser increases in MMP-2 and MMP-3.\textsuperscript{28} Future studies on MMPs and other effectors in the subset of SJS/TEN patients with coexisting ECT are indicated to further elucidate the putative relationship between the 2 diseases.

Elevated MMPs have been found to be elevated in general ocular surface disease, including dry eye,\textsuperscript{29–31} and may be a contributory factor in the mechanism of ECT in SJS/TEN patients. A case series by de Paiva and associates suggested that chronic desiccation may produce inferior corneal steepening and that this can be reversed with lubrication.\textsuperscript{32} A pilot study by Carracedo and associates demonstrated that KC patients have reduced goblet cell density and tear volumes, have higher ocular surface disease index scores, and suffer greater symptoms of dry eye than control subjects.\textsuperscript{33} Whether a dry eye state precedes the development of KC or vice versa is unclear.

We note that that each one of our patients with SJS and subsequent ECT developed SJS in the first, second, or third decade of life. Keratoconus tends to progress in the second and third decades. Further analysis and a larger sample would be required to determine if age is protective against subsequent ECT in SJS.

Though it was not statistically significant, we did find a correlation between higher Oxford scheme score for dry eye and higher ectatic stage, using the Krumeich classification. PROSE treatment significantly improved BCVA in all patients. It is unknown whether PROSE treatment can reverse topographic changes. Longitudinal studies would be needed to study the effect of PROSE on ECT in SJS/TEN.

Management of ECT typically is stepwise, starting with glasses, rigid gas-permeable contact lenses, collagen cross-linking, and/or intracorneal ring segments, and then as required, to lamellar or full-thickness keratoplasty, each with high rates of success.\textsuperscript{34,35} The coexistence of SJS/TEN with ECT complicates management, as ocular surface disease interferes with successful wear of corneal rigid gas-permeable lenses and healing after any corneal surgery. The development of ECT during the chronic phase of SJS/TEN represents a particularly difficult therapeutic challenge.

PROSE treatment has been shown to be a cost-effective and cost-beneficial means of improving visual acuity, visual function, ocular surface comfort, healing, and quality of life in patients with irregular corneas and with ocular surface disease,\textsuperscript{8,36} including the specific subsets of patients with SJS/TEN\textsuperscript{18,37,38} and KC.\textsuperscript{11,12} PROSE treatment appears especially well suited to patients in whom ECT and SJS/TEN are associated.

Limitations of our study include its retrospective design, low sample size, and lack of a control group. Our use of steepest sim K values as support for diagnosis of ectasia can be challenged, as patients with keratoconjunctivitis sicca may have reversible topographic corneal steepening. Pachymetry mapping, not available when most of these patients were first seen in consultation and not generally used for PROSE treatment, would be useful for better characterization of the ECT in these SJS patients. Additional data points over time would be useful to assess progression of ECT. Because patients with coexisting SJS/TEN and ECT may be more likely to be referred for PROSE treatment, the apparent association of these 2 disorders may represent a bias of ascertainment.

This first report of the association of ECT with SJS/TEN patients should be of interest to researchers studying either condition. Furthermore, the rehabilitation of SJS/TEN and ECT as coexisting disorders with PROSE treatment should be of interest to clinicians. Further studies are warranted to characterize the apparent association of ECT with SJS/TEN.

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