Prevalence of Persistent Corneal Epithelial Defects in Chronic Ocular Graft-Versus-Host Disease

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• PURPOSE: To establish the prevalence, clinical characteristics, and risk factors for persistent corneal epithelial defects (PED) in patients with chronic ocular graft-versus-host disease (oGVHD) and to determine visual outcomes after healing.

• DESIGN: Retrospective cohort study.

• METHODS: A chart review was conducted of patients in whom chronic oGVHD was diagnosed between January 2011 and December 2018 and their demographic and clinical characteristics were collected. Data were analyzed to determine prevalence of PED, and multivariate logistic regression was performed to determine the risk factors associated with it.

• RESULTS: A total of 405 patients at a mean age of 60 ± 13 years in whom chronic oGVHD was diagnosed; 58% were men. The prevalence of PED was 8.1%. The median time for PED development after hematopoietic stem cell transplantation was approximately 24 months. Median time to PED resolution was 4.5 weeks after starting therapy. The mean best-corrected visual acuity declined by 2 lines post-PED resolution. The prevalence rates of corneal ulcer and perforation were 6.2% and 4.0%, respectively, over 8 years. Logistic regression analysis, used to determine factors associated with PED, showed diabetes ($P = .006$), limbal stem cell deficiency (LSCD) ($P = .02$), filamentary keratitis ($P = .02$), subconjunctival fibrosis ($P = .02$), and a higher National Institutes of Health (NIH) oGVHD score ($P = .01$) were significant risk factors for PED development.

• CONCLUSIONS: The study found the prevalence rate of PED, corneal ulceration, and corneal perforation in chronic oGVHD to be 8.1%, 6.2%, and 4%, respectively. Analysis showed that oGVHD patients with diabetes, LSCD, filamentary keratitis, subconjunctival fibrosis, and a high NIH score were at higher risk of developing severe corneal disease. (Am J Ophthalmol 2020;218: 296–303. © 2020 Elsevier Inc. All rights reserved.)

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ADVANCEMENTS IN THE FIELD OF ALLOGENEIC HEmatopoietic stem cell transplantation (HSCT) have facilitated the management of various malignant and nonmalignant hematologic diseases. As outcomes improve, the frequency of these procedures continues to increase.[1,2] Graft-versus-host disease (GVHD) is a significant and potentially life-threatening complication of allogeneic HSCT.[3] Following stem cell transplantation, donor-derived T cells recognize host antigens as foreign and may subsequently mount a response against host tissues, including ocular tissue.[4] Ocular GVHD (oGVHD) occurs in 40%-60% of patients undergoing HSCT and can have a significant negative impact on patient quality of life.[5–7]

Although ocular manifestations may be observed in acute GVHD, pathological changes are more commonly associated with chronic GVHD.[8] Dry eye or keratoconjunctivitis sicca is one of the most common manifestations of chronic oGVHD.[9] It results from the lymphocytic destruction of lacrimal glands, meibomian glands, and goblet cells, and damage to the epithelium of the conjunctiva and cornea.[10] A persistent epithelial defect (PED) is defined as a corneal epithelial defect lasting more than 2 weeks without improvement, despite conventional treatments such as artificial tears or extended-wear soft contact lenses.[11,12] oGVHD and dry eye may contribute to the pathophysiology of PED through the presence of proinflammatory immune cells and cytokines and the depletion of several vital components of the tear film (including vitamins A and E, epidermal growth factor, transforming growth factor-β, platelet-derived growth factor, hepatocyte growth factor, and pigment epithelium-derived factor) that are involved in the proliferation and migration of the corneal epithelium.[13–16] PED is associated with severe sequelae including corneal ulceration, scarring, and even perforation, all of which may lead to irreversible vision loss.[17] Current management strategies for PED include aggressive lubrication, surgical debridement, bandage contact lenses, amniotic membrane, autologous serum, and other blood-derived products. The management of PED is often challenging, requiring frequent clinic visits and, in some cases, surgical interventions including tarsorrhaphy and even keratoplasty for treatment of corneal ulcers or perforations.[18–21]

The underlying pathological mechanisms that lead to corneal complications such as PED, corneal ulceration, and perforation in patients with oGVHD are not entirely

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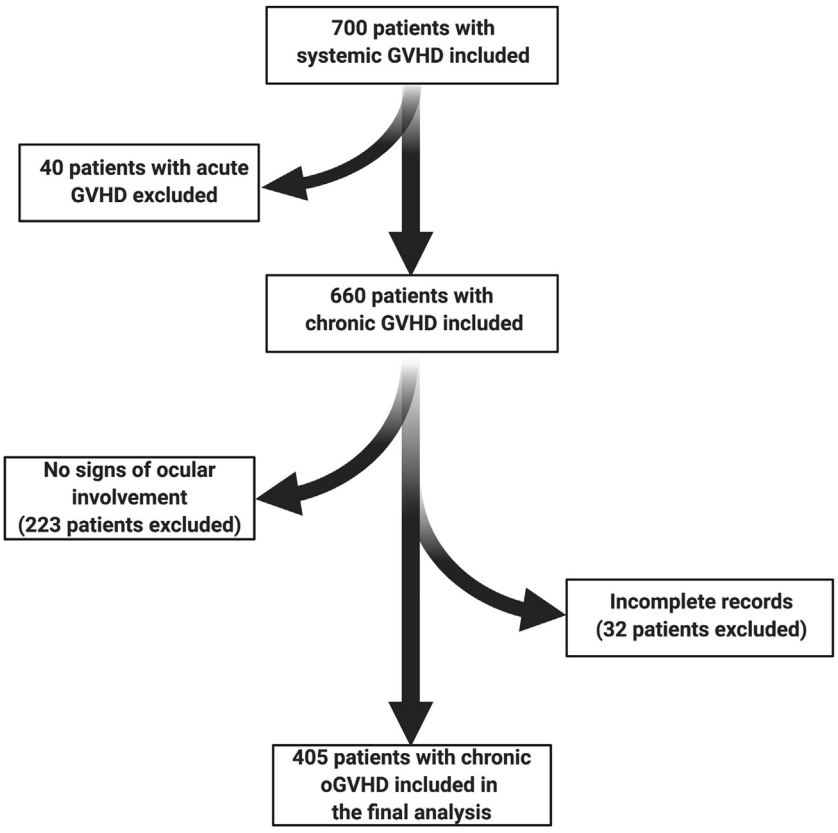

FIGURE 1. Flow chart of 405 patients with chronic ocular graft-vs-host disease included in the final analysis.

understood.[22] PED has been associated with certain risk factors such as corneal hypesthesia, neurotrophic keratopathy, diabetic keratopathy, limbal stem cell deficiency (LSCD), dry eye disease, and exposure keratopathy.[10,23] Healing of epithelial defects may be delayed in patients with oGVHD due to their compromised ocular surface defenses such as eyelid and palpebral conjunctival abnormalities, decreased tear production, abnormal tear film, and chronic ocular surface inflammation.[10] Although PED has been reported to be one of the clinical manifestations of oGVHD in the current medical literature, there are no studies reporting its prevalence and characteristics in oGVHD.[24–26] Therefore, this study was conducted to find the prevalence of PED in patients with oGVHD and to determine the associated risk factors, clinical characteristics, treatment methods, and the visual consequences of PED.

SUBJECTS AND METHODS

APPROVAL WAS OBTAINED FROM THE INSTITUTIONAL REview Board/Ethics Committee at the Massachusetts Eye and Ear. The study was conducted in compliance with the Health Insurance Portability and Accountability Act of 1996 and adherence to tenets of the Declaration of Helsinki. A retrospective review was conducted of the clinical charts of all patients whose diagnosis included chronic oGVHD at the Massachusetts Eye and Ear between January 2011 and December 2018.

A total of 700 subjects were identified with systemic GVHD from the electronic patient record database, using International Classification of Disease (ICD) codes 9 (279.50) and 10 (D89.813) for unspecified GVHD and codes 9 (279.52) and 10 (D89.811) for chronic GVHD. Patients with acute GVHD (n = 40), absence of dry eye symptoms (n = 198), absence of signs of ocular surface disease (n = 25), and incomplete records (n = 32) were excluded (Figure 1). All 405 patients met the following diagnostic criteria for chronic oGVHD: 1) they had a history of allogeneic HSCT; 2) they had exclusively post-HSCT onset of dry eye symptoms that required treatment with frequent topical lubricants or anti-inflammatory eye drops; 3) they had signs of ocular surface disease which included any 2 of the following: decreased Schirmer test (≤5 mm; without anesthesia); presence of corneal fluorescein staining (National Eye Institute grading system),[27] and decreased tear break-up time (≤10 seconds).[5] oGVHD severity was scored from 0 to 3 according to the National Institutes of Health (NIH) scoring criteria for chronic oGVHD.[28] For this study, PED was considered a corneal epithelial defect persisting for at least 2 weeks according to previous recommendations.[11,12]

TABLE 1. Demographic Characteristics of Patients with Chronic Ocular GVHD

Characteristics	N = 405
Mean ± SD age, y	60 ± 13
Age range, y	23-81
Gender (%)	
Males	236 (58)
Females	169 (42)
Ocular GVHD NIH scores: n (%)	
1	15 (4)
2	314 (78)
3	76 (19)
Types of transplants (%)	
Allo PBST	374 (92)
Allo BMT	31 (8)

Allo = allogeneic; BMT = bone marrow transplant; GVHD = graft-versus-host-disease; NIH: National Institutes of Health; PBST = peripheral blood stem cell transplant; SD = standard deviation.

TABLE 2. Ocular Manifestations in Patients with Chronic Ocular Graft-Versus-Host Disease

	N = 405	%
Persistent epithelial defect	33	8.1
Meibomian gland dysfunction	240	59.3
Filamentary keratitis	124	30.6
Blepharitis	103	25.4
Confluent punctate epithelial erosions	99	24.4
Conjunctivochalasis	90	22.2
Telangiectasia	83	20.5
Trichiasis	52	12.8
Subconjunctival fibrosis	14	10.1
Corneal ulcer	25	6.2
Culture-positive	13	
Culture-negative	12	
Corneal perforation	16	4

The data acquired from patient files were recorded in a standardized database in the Research Electronic Data Capture software (REDCap, Vanderbilt University, Nashville, Tennessee). Data acquired included demographics (age, sex); transplantation characteristics (allogeneic peripheral blood stem-cell transplantation or allogeneic bone marrow transplantation; systemic factors (diabetes mellitus); ocular (past or present herpetic keratitis) comorbidities; underlying hematologic disorder; oGVHD severity scores; systemic and topical medications; ocular examination findings including the presence or absence of PED, corneal ulcers, perforations, LSCD (limbal flattening, corneal neovascularization and/or whorled vortex pattern of epithelium), meibomian gland dysfunction, conjunctivochalasis, filamentary keratitis, lagophthalmos, trichiasis, subconjunctival fibrosis, and symblepharon. Patients were divided into PED and non-PED groups for statistical analysis, and data were analyzed to determine the prevalence of PED, characteristics of patients with PED, and any associative factors.

• **STATISTICAL ANALYSIS:** Kaplan-Meier survival curve analysis was performed to determine the time course of PED presentation in oGVHD patients after transplantation by using GraphPad version X.5.3 software (Prism, LaJolla, California) for Macintosh (Cupertino, California). Statistical analyses were performed using R version 3.4.3 software (Vienna, Austria) by using descriptive statistics for continuous variables (mean, standard deviation, median, range) and calculated percentages of categorical variables. Data normality was determined using the Shapiro-Wilk test. The Fisher exact test was used for comparing categorical variables between the PED and non-PED groups in terms of demographics and transplant characteristics, oGVHD NIH scores, and comorbid conditions including diabetes mellitus and LSCD. The Mann-Whitney *U* test was used for comparing continuous variables. Multivariate stepwise logistic regression analysis was performed with PED as the dependent variable. Factors analyzed included age, sex, underlying disease, type of transplant, NIH oGVHD score, diabetes mellitus, herpetic keratitis, LSCD, treatment with topical steroids, and other clinical manifestations of oGVHD, including meibomian gland dysfunction, trichiasis, confluent punctate epithelial erosions, subconjunctival fibrosis, symblepharon, conjunctivochalasis, telangiectasia, filamentary keratitis, trichiasis, and lagophthalmos in a multivariate logistic regression analysis of PED development. After optimal model selection (Akaike information criteria for model selection), the redundant variables were removed. A *P* value of less than or equal to .05 was considered statistically significant

RESULTS

A TOTAL OF 405 PATIENTS FULFILLED THE PREDETERMINED inclusion criteria for the study. Subjects had a mean age of 60 ± 13 years (range, 23-81 years), and 236 (58%) were men and 169 (42%) were women. The majority of patients (97%) had an NIH oGVHD score of 2 (78%) or 3 (19%). Within the cohort, 374 patients (92%) underwent an allogeneic peripheral blood stem-cell transplantation, and 31 (8%) underwent allogeneic bone marrow transplantation (Table 1).

The ophthalmic findings in patients with oGVHD are summarized in Table 2. Epithelial defects were observed in 43 patients (10.6%). The defects healed within 2 weeks after therapy was initiated in 10 of these 43 patients. The remaining patients developed PED at a prevalence rate of

TABLE 3. Characteristics of Patients with Persistent Epithelial Defects

BCVA, LogMAR	
Mean ± SD pre-PED	0.27 ± 0.24 (range: 0-0.8)
Mean ± SD post-PED healing	0.50 ± 0.38 (range: 0.1-1.8)
Time to heal, weeks	
Median (IQR)	4.5 (2.3, 8.5)
Location of PED (n = 36)	
Central, central 4 mm of cornea	23
Peripheral	13
Mean ± SD time since transplant, mo (median [IQR])	24 (14, 18)
<2 y	12
2-5 y	21
>5 y	3

BCVA =best-corrected visual acuity; LogMAR =logarithm of the minimum angle of resolution; IQR = interquartile range; SD = standard deviation; PED = persistent corneal epithelial defects.

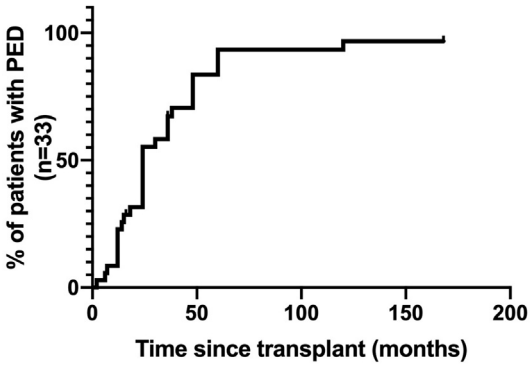

FIGURE 2. Kaplan-Meier analysis of persistent corneal epithelial defects presentation in patients with ocular graft-vs-host disease.

8.1% (n = 33) over 8 years. The 10 patients whose epithelial defects healed within 2 weeks had a clinical presentation similar to that of the patients with PED in terms of age, type of transplantation, time since transplantation, and systemic management. However, only 1 patient (10%) compared to 12 patients (36%) in the PED group had a more severe NIH oGVHD score of 3. Three patients (30%) were taking topical steroids (loteprednol) in the group (n = 10) with healed epithelial defects, compared to 23 (70%) in the PED group (14 taking loteprednol and 9 taking preservative-free prednisolone). Although there were significantly more patients taking steroids in the group that did not heal within 2 weeks compared to the group that did heal (chi-square test result = 5.06; $P = .02$), the logistic regression analysis did not find an association between topical steroid use and PED. Three of the 33 patients had PED in both eyes, and the remainder (n = 30) had unilateral PED. Although most patients had unilateral PED, 63% of the contralateral eyes (n = 19) had epithelial abnormalities (diffuse punctate epithelial erosions, filamentary keratitis), and 27% (n = 8) had stromal abnormalities (corneal thinning, ulcer, or scar). PED was more commonly located in the central cornea (<4-mm diameter) than in the peripheral cornea (Table 3). PEDs in the peripheral cornea were superior (n = 4), inferior (n = 4), nasal (n = 3) and temporal (n = 2) in location.

Of the 405 patients with oGVHD in the cohort, 25 patients (6%) had corneal ulceration. Twelve patients had culture-negative ulcers, and 13 patients had culture-positive ulcers (bacterial, n = 8; fungal, n = 3; and herpetic, n = 2). The prevalence of corneal perforation in the cohort of oGVHD was found to be 16 of 405 (94%). Corneal perforations were recorded in 8 patients at initial presentation, whereas 8 other patients developed corneal perforation from stromal ulcers (4 from culture-negative ulcers and 4 from culture-positive ulcers).

The clinical characteristics (timeline and clinical presentation) of those patients who developed PED are summarized in Table 3. Kaplan-Meier survival analysis showed that the median time of PED presentation in the cohort was 24 months. (Figure 2) Approximately one-third of the eyes developed PED within the first 2 years (n = 12), and half of the eyes (n = 18) developed PED between 2 and 5 years after HSCT. Few eyes (n = 5) developed PED more than 5 years after transplantation. In the cohort, PED was diagnosed in 36 eyes of 33 patients. PED healed in 30 eyes in a median period of 4.5 weeks; however, it progressed to stromal ulceration and eventually perforation in 5 eyes, and 1 patient was lost to follow-up. The median size of the PED was 6.0 mm^2 and was found to have no correlation to the time required to heal. For PED management, 9 patients were prescribed bandage contact lenses, amniotic membrane (Prokera; Biotissue, Miami, Florida) was applied in 3 patients, 2 patients underwent lateral tarsorrhaphy, and the remaining patients were managed with aggressive lubrication, including autologous serum tears. Eight patients with PED developed corneal ulcers (4 culture-negative and 4 culture-positive), of which 5 eyes eventually progressed to perforation. Of note, the mean best-corrected visual acuity declined by 2 lines following PED resolution.

To evaluate potential risk factors for PED development, oGVHD patients with PED (n = 33) were compared with those without PED (n = 372) (Table 4). Age ($P = .01$), NIH oGVHD score ($P = .03$), diabetes mellitus ($P = .01$), and LSCD ($P = .009$) were significantly associated with PED. Among the cohort, a significantly higher number of patients taking topical steroids and topical antiglaucoma medications had PED ($P < .01$). However, there were no significant differences between the proportions of

TABLE 4. Characteristics of Chronic oGVHD Patients with and without Persistent Epithelial Defects

Characteristics	Patients with PED (N=33)	Patients without PED (N=372)	*P* Value[a]
Mean ± SD age, y	66 ± 10	60 ± 13	.01
Age range, y	36-81	23-80	
Gender (%)			.10
Males	24 (73)	212 (57)	
Females	9 (27)	160 (43)	
HLA matching, %			.79
Fully matched	29 (88)	317 (85)	
Partially matched	2 (6)	20 (5)	
Unknown	2 (6)	35 (9)	
Donor relation (%)			.39
Related	5 (15)	94 (25)	
Unrelated	26 (79)	246 (66)	
Unknown	2 (6)	32 (9)	
Ocular GVHD NIH scores, %			.03
1	0 (0)	15 (4)	
2	21 (64)	293 (79)	
3	12 (36)	64 (17)	
Comorbidities, %			
Diabetes Mellitus	13 (39)	73 (20)	.01
Limbal stem cell deficiency	9 (27)	39 (11)	.009

HLA = human leukocyte antigen; NIH = National Institutes of Health; oGVHD = ocular graft-versus-host disease; PED = persistent epithelial defect; SD = standard deviation.

[a]A *P* value <.05 was considered statistically significant.

TABLE 5. Ocular Surface Parameters for Chronic oGVHD Patients with and without PED

Outcomes	Patients with PED (N = 33)	Patients without PED (N = 372)	Z	*P* (Mann–Whitney U test)
Corneal fluorescein staining				
Mean ± SD	9 ± 5.4	6 ± 4.4	−2.582	.009
Schirmer tear secretion score (mm)				
Mean ± SD	2.6 ± 3.8	3.3 ± 3.4	0.828	.406
Tear film break-up time (secs)				
Mean ± SD	0.1 ± 0.5	1.5 ± 2.2	2.464	.013

oGVHD = ocular graft-versus-host disease; PED = persistent epithelial defect; SD = standard deviation.

P < .05 was considered to be statistically significant.

patients taking topical immunomodulatory drops (cyclosporine and lifitegrast) in the 2 groups. The patients with PED showed significantly worse clinical signs of ocular surface disease (corneal fluorescein staining scores and tear break-up times) (Table 5). The factors and conditions associated with PED according to logistic regression are shown in Table 6. oGVHD patients with diabetes mellitus (P = .006), LSCD (P = .02), filamentary keratitis (P = .02), subconjunctival fibrosis (P = .02), and a higher NIH oGVHD score (P =.01) were approximately 3 times more likely to have PED than those oGVHD patients without these conditions.

DISCUSSION

OGVHD AND ITS VARIED CLINICAL MANIFESTATIONS remain a major cause of visual impairment and morbidity in patients undergoing allogeneic HSCT and greatly impair vision-related quality of life.[7,29] Dry eye or keratoconjunctivitis sicca is the most common manifestation of chronic oGVHD, and changes to the ocular surface associated with oGVHD are attributed to the direct interactions between donor lymphocytes and host histocompatibility antigens.[30] These interactions lead to an inflammatory environment that damages the cornea and conjunctiva

TABLE 6. Multivariate Logistic Regression Exploring Factors Related To PED in Chronic oGVHD

Variable	Odds Ratio	*P* Value	95% CI for Odds Ratio	
			Lower	Upper
NIH oGVHD eye score	2.81	.01	1.22	6.45
Diabetes Mellitus	3.15	.006	1.37	7.21
LSCD	3.06	.02	1.12	7.93
Filamentary Keratitis	2.68	.02	1.20	6.04
Subconjunctival Fibrosis	3.20	.02	1.15	8.32

CI = confidence interval; LSCD = limbal stem cell deficiency; NIH =National Institutes of Health; oGVHD = ocular graft-versus-host disease; PED = persistent epithelial defect.
P <.05 was considered to be statistically significant.

and causes destruction and fibrosis of the conjunctiva and lacrimal glands, which leads to a tear-deficient state that further exacerbates damage to the ocular surface.[31] Additionally, dry eye may be amplified as a consequence of pretransplantation total body irradiation and/or chemotherapy.[10,32] Proteomic studies in patients with oGVHD have reported elevated levels of inflammatory cytokines and matrix metalloproteinases, which are implicated in the degradation of extracellular matrix components and lead to impaired corneal wound healing.[33–36] Together, these inflammatory and biomechanical changes may predispose to corneal sequelae such as punctate corneal erosions, sterile or infectious corneal ulcers, and, as investigated here, PED.[9]

Epithelial defects can persist despite standard therapies in the presence of certain risk factors, such as dry eye disease, corneal hypoesthesia, diabetic keratopathy, limbal stem cell deficiency, and certain keratopathies.[23] In addition to dry eye and compromise of ocular surface defense mechanisms, reduced corneal sensation may also contribute to the pathophysiology of PED in oGVHD. Many studies have established that corneal sensation is important for supplying neuropeptides, such as substance P and calcitonin gene-related peptide, which function as growth factors for the corneal epithelium.[37] In a study by Tarnawska and associates,[24] the authors studied 11 eyes in 9 patients with chronic GVHD and stromal opacities and found that all eyes had reduced corneal sensation. Systemic GVHD has also been shown to have an association with peripheral neuropathy in some case reports.[38]

In the present study, the demographic and clinical characteristics of patients with oGVHD were analyzed and factors were identified that were associated with the development of PED in oGVHD patients. Although many previous studies have reported PED to be an ocular manifestation of GVHD, this is the first study to report its prevalence rate in patients with oGVHD.[22,39] The present study also represents the largest sample size of patients in whom oGVHD was diagnosed reported from a single center. The prevalence of PED in patients with oGVHD was found to be 8.1% (n = 33). Although most patients had PED unilaterally, 90% of contralateral eyes had epithelial or stromal abnormalities indicating bilateral involvement, highlighting the systemic nature of GVHD.

Among the 43 patients who developed epithelial defects in the setting of oGVHD, in 33 patients (approximately 77%), healing failed within the first 2 weeks, despite treatment with conventional regimens. The median duration for PED healing in this study was 4.5 weeks. Corticosteroids are commonly used in oGVHD patients, and although these drugs suppress the expression of inflammatory mediators that are cytotoxic to corneal epithelial cells and nerves, they can also suppress epithelial regeneration and tissue healing.[40,41] Their application can limit severe inflammatory responses that retard healing, and they are widely prescribed in settings such as in chemical burns and Stevens-Johnson syndrome.[42] Although corticosteroids are often used in oGHVD, their association with PED has not been studied in this population. In the present study, although 70% of patients with PED developed the defect while taking topical steroid therapy and significantly more patients in the PED group were taking topical steroids than in the non-PED group, logistic regression analysis did not find an association between topical steroid use and PED. Similar results have been reported in studies conducted by Sugar and associates[43] and Yulek and associates[44], who showed that topical steroid use has no direct effect on corneal wound healing. These data may be confounded by the fact that steroids are often prescribed in patients with more severe inflammatory disease, where epithelial healing is more problematic.

The present study found that the relative risk of diabetes mellitus is approximately double in patients with PED (~40%, n = 13 of 33) compared to patients without PED (~20%, n = 73 of 372). Multivariate analysis also showed that oGVHD patients with diabetes mellitus are 3 times more likely to develop PED than those without diabetes mellitus, which is suggestive of a potential neuropathic

component in these patients. Data from this study also demonstrate that LSCD is significantly associated with the development of PED. Logistic regression analysis shows a 3-fold higher likelihood of PED in oGVHD patients with LSCD. The study also found that the presence of filamentary keratitis, subconjunctival fibrosis, and a higher NIH oGVHD score, all of which are associated with increased inflammation and disease severity, were significant risk factors for the development of PED. Although these clinical findings have been previously reported to occur in patients with oGVHD,[39,45] no study has yet shown their association with the development of PED. In a previous study, these authors demonstrated that subtarsal fibrosis in patients with oGVHD is associated with more severe ocular surface epitheliopathy. This effect was attributed to fibrosis-induced microtrauma on the corneal epithelium occurring during each blink.[46] The association of subconjunctival fibrosis with PED in the present study could potentially be explained by the same hypothesis.

The present study also found that patients with PED had a worse outcome in terms of visual acuity, as there was an average decline of 2 lines of best-corrected acuity after the healing of PED. Although PED in patients with oGVHD can lead to complications such as corneal ulceration and perforation, even if these complications do not develop, PED patients are still at risk for a decline in visual acuity and quality of life.

Finally, as a retrospective study, the current study has its limitations. The possibility of neurotrophic changes in the cornea could not be ruled out due to the absence of corneal sensation assessment. Moreover, the diagnosis of LSCD was not confirmed by diagnostic tests such as impression cytology or in vivo confocal microscopy but was based on clinical findings, which could be nonspecific in complex eyes with oGVHD. Future prospective studies with an objective assessment of neurotrophic keratitis and LSCD may be warranted to help determine specific causes and mechanisms of PED in patients with oGVHD.

In conclusion, this study found the prevalence of corneal PED, ulcer, and perforation in patients with chronic oGVHD to be 8.2%, 6.2%, and 4%, respectively. Although these numbers are small, their impact can be significant in terms of visual compromise. Patients with diabetes, LSCD, filamentary keratitis, subconjunctival fibrosis, and a high NIH GVHD score are at a higher risk of developing a PED as determined by multivariate analysis. Prompt and aggressive management of ocular surface disease in GVHD patients is mandatory, with careful attention given to patients with these risk factors, to prevent severe corneal complications and associated vision loss.

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