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Brief Report

Corneal perforation in ocular graft-versus-host disease

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ABSTRACT

Purpose: Corneal perforation is a rare, vision-threatening complication of ocular graft-versus-host disease (GVHD) and is not well understood. Our objective was to examine the clinical disease course and histopathologic correlation in patients who progressed to this outcome.

Methods: This study is a retrospective case series from four academic centers in the United States. All patients received a hematopoietic stem cell transplant (HSCT) prior to developing ocular GVHD. Variables of interest included patient demographics, time interval between HSCT and ocular events, visual acuity throughout clinical course, corticosteroid and infection prophylaxis regimens at time of corneal perforation, medical/surgical interventions, and histopathology.

Results: Fourteen eyes from 14 patients were analyzed. Most patients were male (86%) and Caucasian (86%), and average age at time of hematopoietic stem cell transplant was 47 years. The mean interval between hematopoietic stem cell transplant and diagnosis of ocular graft-versus-host disease was 9.5 months, and between hematopoietic stem cell transplant and corneal perforation was 37 months. Initial best-corrected visual acuity was 20/40 or better in 9 eyes, and all eyes had moderate or poor visual outcomes despite aggressive management, including corneal gluing in all patients followed by keratoplasty in 8 patients. The mean follow-up after perforation was 34 months (range 2–140 months). Oral prednisone was used prior to perforation in 11 patients (79%). On histopathology, representative specimens in the acute phase demonstrated ulcerative keratitis with perforation but minimal inflammatory cells and no microorganisms, consistent with sterile corneal "melt" in the setting of immunosuppression; and in the healed phase, filling in of the perforation site with fibrous scar.

Conclusions: In these patients, an extended time interval was identified between the diagnosis of ocular graft-versus-host disease and corneal perforation. This represents a critical window to potentially prevent this devastating outcome. Further study is required to identify those patients at greatest risk as well as to optimize prevention strategies.

1. Introduction

In recent years, the number of allogeneic hematopoietic stem cell transplants (HSCT) has steadily increased. HSCT has become the standard of care for many hematologic cancers as well as certain metabolic diseases and solid malignancies.[1] Unfortunately, graft-versus-host disease (GVHD), which occurs when donor-derived T cells recognize host antigens as foreign and attack host tissue, continues to affect more than half of HSCT recipients.[2]

Ocular GVHD occurs in 40–60% of patients receiving allogeneic HSCT.[1,3] It commonly manifests within 3 years post-HSCT,[1] often with symptoms such as ocular irritation, foreign body sensation, burning,

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pain, and blurry vision.[1,4] Diagnostic criteria for ocular GVHD include new onset keratoconjunctivitis sicca and/or punctate keratopathy in the setting of post-HSCT.[5] Aside from increasing systemic immunosuppression, treatment is primarily supportive and includes aggressive ocular lubrication, decreasing ocular inflammation, and providing support for the corneal and conjunctival epithelial surfaces.[6] Artificial tears, topical and systemic cyclosporine, and topical steroids are commonly used, along with bandage soft contact lenses, therapeutic scleral contact lenses, antibiotics, and autologous serum tears.[2,6]

Despite treatment, ocular GVHD may progress to sight-threatening complications including corneal ulceration and corneal perforation.[1] The pathophysiology of non-infectious corneal ulceration and perforation as the result of ocular GVHD is not entirely clear, though it has been proposed that local inflammation and overexpression of inflammatory mediators similar to the mechanism behind autoimmune diseases such as rheumatoid arthritis and Sjögrens may play a major role.[6,7] Past studies have asserted that use of topical or systemic corticosteroids as well as use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) may correlate with corneal ulceration and perforation in patients with chronic GVHD.[4,7] Local immunosuppression may also increase the risk of infectious corneal ulceration. In addition, while factors such as total body irradiation and immunosuppressive therapy have been linked to dry eye symptoms in patients post-HSCT,[1] it is not known if these factors also contribute to the likelihood and rapidity of corneal perforation.

If the clinical course for corneal perforation were better described, then patients presenting with ocular GVHD could be assessed for their likelihood to progress to perforation and ideally managed to prevent this devastating event. Identifying patients at risk for ocular GVHD could be advantageous, as it has been noted that early treatment of ocular GVHD tends to be more effective, with patients less likely to progress to more serious disease manifestations.[8] The purpose of our study was to examine the presentation and outcomes of patients with corneal perforation in the setting of ocular GVHD. We examined the clinical features, associated histopathology, and duration, timing, and types of pharmacologic agents used in these patients.

2. Materials and methods

Study Design: Institutional review board approval was obtained to conduct a retrospective chart review on patients who developed corneal perforation as a complication of ocular GVHD following HSCT. Patients were identified via an electronic medical record search for ICD-10 codes D89.81 (graft-versus-host disease) or T86.01 (bone marrow transplant rejection), and CPT codes for penetrating or lamellar keratoplasty, corneal gluing, or ocular surface reconstruction with amniotic membrane transplantation (65710, 65730, 65750, 65755, 65780, 65286), yielding 7 patients who presented to Washington University in St. Louis between January 1, 1960 to April 1, 2019. Additional patients were similarly identified and their charts reviewed at the University of Minnesota (3 patients), Loyola University (2 patients), and Vanderbilt University (2 patients).

Patient Characteristics of Interest: We gathered data on patient sex, race, age at HSCT, indication for HSCT, use of systemic corticosteroids and infection prophylaxis regimens at time of corneal perforation, and incidence of lamellar or penetrating keratoplasty in the affected eye. We also calculated the time intervals in months from HSCT to ocular GVHD diagnosis, HSCT to first corneal perforation, and ocular GVHD diagnosis to first perforation, when such records were available. We used the first HSCT date for patients who underwent more than one HSCT. Outliers were determined by calculating interquartile range (IQR) and excluding values that fell outside the bounds set by Q3+1.5*IQR.

In addition, we extracted best-corrected visual acuity (BCVA) in the affected eye at initial presentation to ophthalmology, at time of corneal perforation, and at the most recent follow-up visit. For patients who underwent penetrating keratoplasty or evisceration, histopathological results were reviewed. Histologic sections of the corneal buttons were processed for staining with hematoxylin and eosin (H&E) and for immunohistochemistry and were reviewed by an ocular pathologist (G. J.H.).

3. Results

In total, 14 eyes of 14 patients who had developed corneal perforation in the setting of ocular GVHD following HSCT, and who were treated at these academic ophthalmology departments, were identified. Patient demographics and the indication for HSCT in this cohort are summarized in Table 1. The mean age at the time of HSCT was 47±13 years (standard deviation), and the majority of patients were male (12 patients, 86%) and Caucasian (12 patients, 86%). While this cohort had a variety of underlying hematologic malignancies, notably 7 patients (50%) had acute myeloid leukemia as an indication for HSCT.

Table 2 summarizes the time course of each patient, reporting the intervals between HSCT and initial ocular GVHD diagnosis, between HSCT and first corneal perforation, and between ocular GVHD diagnosis and first perforation. A number of cases had incomplete data pertinent to these categories, but in general the patients had long time intervals between ocular GVHD diagnosis and first perforation, with a mean interval of 24 months (range 5–47 months, with outlier exclusion). The mean interval between HSCT and the diagnosis of ocular GVHD was 9.5 months (excluding an outlier whose interval was 155 months), and the mean interval between HSCT and first corneal perforation was 37 months. Common presenting symptoms to ophthalmology included blurry vision, dry eye sensation, eye irritation, foreign body sensation, photophobia, and/or eye redness.

Table 3 shows the BCVA at various time points during the patients' clinical courses, the length of follow-up for each patient after corneal perforation, the number of corneal transplants performed in the affected eye, and the size of the initial corneal transplant after perforation. Most of the patients presented to ophthalmology with good visual acuity; BCVA was 20/40 or better at initial presentation in 9 of 14 patients (64%) in the eye that later perforated, with 6 out of 14 patients (43%) having 20/20 vision initially. At time of corneal perforation, BCVA was consistently poor, with the best BCVA being 20/150 and 4 patients having hand motion or worse. The ulcerations appeared generally translucent, without associated infiltrate, consistent with sterile corneal "melt," and none were culture positive for either bacteria or fungi. Finally, despite the long periods of follow-up for most patients (mean 34

Table 1
Patient demographics and underlying hematologic malignancies.

Case Number	Patient Sex	Patient Race	Indication for HSCT	Age at time of HSCT (years of age)
1	Male	Caucasian	CLL	57
2	Female	Caucasian	AML	60
3	Male	Caucasian	AML	51
4	Male	Caucasian	AML	21
5	Male	Caucasian	CML	40
6	Male	Caucasian	unknown	54
7	Male	Caucasian	MDS and AML	70
8	Male	Caucasian	Waldenstrom's macroglobulinemia and CLL	49
9	Male	African American	CML	34
10	Male	Caucasian	AML	52
11	Female	Caucasian	AML	55
12	Male	African American	MDS and AML	48
13	Male	Caucasian	Acute Promyelocyte Leukemia	30
14	Male	Caucasian	Burkitt lymphoma	41

Abbreviations: Acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS).

Table 2
Time courses leading up to ocular graft-versus-host disease diagnosis and corneal perforation.

Case Number	HSCT to ocular GVHD diagnosis (months)	HSCT to first corneal perforation (months)	Ocular GVHD diagnosis to perforation (months)
1	4	26	22
2	7	29	22
3	13	33	20
4	16	31	15
5	1	6	5
6	8	152	144
7	unknown	60	unknown
8	155	202	47
9	unknown	98	unknown
10	unknown	33	unknown
11	unknown	20	unknown
12	4	21	17
13	23	65	42
14	unknown	19	unknown

Abbreviations: hematopoetic stem cell transplant (HSCT), graft-versus-host disease (GVHD).
*All durations were calculated from the first of the month. The date of ocular GVHD diagnosis was not available for a subset of records.

months, range 2–140 months), only 5 patients (36%) had a final BCVA of 20/100 or better in the affected eye, and 7 patients (50%) saw hand motion or worse at the last visit. Eight patients in our series had penetrating keratoplasties (PKPs) performed in the affected eye, with PKP sizes ranging from 2.0 to 9.0 mm. Only one of these initial corneal transplant procedures also utilized amniotic membrane at the time of the procedure, and none had tarsorrhaphy performed at the time of transplant. Although final visual acuity results were highly variable, half of the patients with PKPs saw 20/90 or better compared to only 1 of the 6 patients who did not undergo corneal transplant.

Table 4 summarizes the oral and topical immunosuppressive drug use, as well as the infection prophylaxis regimens, by each patient in the 2 months prior to perforation. Notably, oral prednisone was used by 11 patients (79%) and topical steroid eye drops were used by 8 patients (57%). The oral prednisone dosage ranged from 5 mg/day to 50 mg/day. Systemic calcineurin inhibitors (cyclosporine, tacrolimus) or sirolimus were used by nine patients (64%). Nine patients (64%) were also on topical antibiotic eyedrops during this time period. Prior to and after corneal perforation, various other treatments were employed, including punctal plugs or punctal cauterization in 8 patients, bandage contact lenses or scleral lenses in 7 patients, tarsorrhaphy in 2 patients, topical cyclosporine or tacrolimus in 3 patients, and autologous serum tears in 2 patients.

Representative histopathology is shown for 2 patients who underwent corneal transplant or evisceration after corneal perforation (Fig. 1). Case 3 underwent evisceration due to expulsive hemorrhage and uveal prolapse resulting from acute corneal perforation. Histopathology (Fig. 1A) exhibited a wide perforation, partially filled with chronic inflammatory cells, granulation tissue, and heme, with iris tissue and pars plana prolapsing toward the perforation site. Adjacent to the perforation, there was calcific keratopathy and anterior stromal vascularization, but minimal acute and chronic inflammatory cells, consistent with corneal "melt" in the setting of chronic underlying immunosuppression. There was total endothelial cell loss. Gram and Gomori-methenamine-silver (GMS) stains were negative for microorganisms. Case 6 underwent multiple repeat penetrating keratoplasties for graft failure with healed perforations. Histopathology of a representative corneal button obtained from a re-graft procedure performed in the healed phase (Fig. 1B–E) demonstrated re-epithelialization over the antecedent perforation site, with an underlying wide gap in Descemet's membrane centrally. Most notably, there was total endothelial cell loss associated with a fibrous retrocorneal membrane, which in the central region at the prior perforation site replaced the entire stromal thickness, corresponding clinically to a dense central scar. Anterior to mid-stromal vascularization was also appreciated peripherally to mid-peripherally. Clinically, the healed corneal perforations often exhibited stromal neovascularization and opaque scarring, as in this representative photograph taken approximately 5 months after corneal gluing for acute perforation in case 5 (Fig. 1F). Such corneal scars may be visually significant due to central location and/or induced astigmatism, and once the disease has quieted, may be conducive to visual rehabilitation via therapeutic scleral lenses or keratoplasty.

4. Discussion

While ocular involvement is not uncommon in patients with chronic GVHD, progression to corneal perforation is infrequent and described in only a handful of case reports. Combining case series of ocular GVHD in which corneal perforation was identified at two large tertiary referral centers, only 5 out of 307 patients suffered this devastating sequela (1.6%), suggesting that the incidence in the overall GVHD population is presumably even lower.[4,9] Thus, studying this relatively rare complication can be challenging, and very little is currently known regarding

Table 3
Best-corrected visual acuities, length of follow-up following initial corneal perforation, and number of corneal transplants performed in affected eye.

Case Number	BCVA at first presentation to ophthalmology	BCVA at first corneal perforation	BCVA at last follow-up visit	Length of follow-up period after first perforation (months)	Number of corneal transplants in affected eye during follow-up interval	Size of corneal transplant graft (initial transplant after perforation)
1	20/20	Unknown	20/60	140	2	Unknown size of PKP
2	20/60	Hand motion	Bare light perception	66	0	N/A
3	20/20	20/300	N/A (evisceration)	48	0	N/A
4	20/20	Hand motion	Light perception	15	0	N/A
5	20/70	Count fingers at 4 feet	20/90	29	1	8.25 mm
6	20/35	Unknown	No light perception	31	2	8.25 mm
7	20/300	Unknown	20/400	31	3	8.25 mm
8	20/300	20/150	Hand motion	2	0	N/A
9	20/20	Light perception	Hand motion	20	3	9.50 mm
10	20/40	Unknown	20/70	41	1	4.00 mm
11	20/25	Unknown	20/70	4	1	2.00 mm
12	20/20	20/400	20/50	3	0	N/A
13	20/50	Hand motion	Light perception	45	3	9.00 mm
14	20/20	20/200	20/300	2	0	N/A

Abbreviations: Best-corrected visual acuity (BCVA), penetrating keratoplasty (PKP). All parameters refer to the eye with corneal perforation.

Table 4
Oral and topical immunosuppression and infection prophylaxis regimens in the 2 months prior to corneal perforation.

Case Number	Systemic steroid-sparing immunosuppression	Oral steroid use	Topical steroid use	Infection prophylaxis
1	None	Yes	Unknown	Valacyclovir, pentamidine
2	Tacrolimus	Yes	Yes	Doxycycline, vancomycin, trimethoprim-sulfamethoxazole, gatifloxacin, topical polymyxin B sulfate/ trimethoprim, tobramycin, fluconazole, valacyclovir
3	Tacrolimus	Yes	Yes	Acyclovir, ofloxacin, dapsone, fluconazole
4	Tacrolimus, mycophenolate mofetil, ruxolitinib	Yes	Yes	Ofloxacin, acyclovir, dapsone
5	Tacrolimus	Yes	Yes	Acyclovir, azithromycin, dapsone, posaconazole, trimethoprim-sulfamethoxazole, bacitracin/ polymixin B, topical moxifloxacin
6	Unknown	Unknown	Unknown	Unknown
7	None	Yes	Unknown	Fluconazole, acyclovir, trimethoprim-sulfamethoxazole
8	None	No	Yes	Valacyclovir, ofloxacin
9	Sirolimus	Yes	Unknown	Unknown
10	None	No	Yes	Topical moxifloxacin
11	Sirolimus, mycophenolate mofetil	Yes	None	Topical moxifloxacin, bacitracin
12	Tacrolimus	Yes	Yes	Valacyclovir, fluconazole, levofloxacin
13	Cyclosporine	Yes	None	Valacyclovir, topical moxifloxacin
14	Sirolimus	Yes	Yes	Acyclovir, trimethoprim-sulfamethoxazole, fluconazole, micafungin, moxifloxacin

what factors may result in more severe disease and subsequent corneal perforation. Whereas many patients with ocular GVHD can maintain good visual acuity long-term,[6] patients who suffer corneal perforation often have poor visual outcomes, demonstrating the importance of studying this condition.

The majority of patients in our cohort were male and Caucasian. It is unknown whether the higher incidence of male patients was due to biological or social factors (e.g. delay in seeking medical care). However, the wider population of patients who undergo HSCT and are subsequently seen by ophthalmology departments included in our study are predominantly Caucasian. Out of the patients for whom the underlying indication for HSCT was able to be ascertained, 50% had AML. This is also likely representative of the overall ocular GVHD cohort, as 58% of all ocular GVHD patients at one of our institutions have AML as the indication for HSCT (unpublished data, Washington University in St. Louis).

On average, patients were diagnosed with ocular GVHD 9.5 months after HSCT and with corneal perforation 37 months after HSCT. Similarly, other studies have shown averages of between 24 and 26 months between HSCT and corneal perforation.[4,7] The extended duration between HSCT and corneal perforation highlights the need for long-term follow-up. It also demonstrates the importance of early recognition and treatment of ocular GVHD-related complications, as the majority of our patients first presented with excellent vision in the eye that subsequently progressed to perforation. The presence of multisystem GVHD should also prompt referral to ophthalmology, as the majority of the patients in this cohort had additional non-eye organs affected by GVHD, consistent with other studies on ocular GVHD.[10,11]

The majority of patients (71%) were on steroid regimens (including topical, systemic, or both) in the 2 months leading up to corneal perforation. The use of topical steroids has been associated with corneal ulceration and perforation in Sjogren's syndrome.[12] However, topical and systemic steroids are frequently used to treat chronic GVHD, and thus prolonged steroid use may be an indicator of more severe or recalcitrant inflammatory disease already at higher risk of corneal melt. Steroids, as well as other forms of immunosuppression, may also predispose to infectious keratitis. Although none of the cases in our cohort had a positive culture or histopathologic evidence of infection, this does not definitively rule out an infectious etiology in all cases. Nonetheless, the role of steroids in the long-term management of ocular GVHD should be carefully assessed.

It is likely that corneal melt in severe ocular GVHD has a multifactorial pathogenesis characterized by a chronic sicca microenvironment awash in a pro-inflammatory milieu. In prior clinicopathologic reports of corneal perforation in ocular GVHD, histopathology has confirmed stromal infiltration by chronic inflammatory cells.[7,13–15] One report described stromal infiltration by $CD68^+$ macrophages at the corneal perforation edge, but no $CD8^+$ or $CD4^+$ T cells,[7] whereas another found stromal infiltration by $CD8^+$ (but not $CD4^+$) T cells.[15] The former report also showed epithelial and stromal matrix metalloproteinase-9 (MMP-9), but not MMP-2, immunostaining at the perforation edge and also in the conjunctiva of GVHD patients.[7] Epithelial cell and keratocyte apoptosis has also been demonstrated.[16] Although these reports do not specifically comment on the degree of inflammation, their histologic photographs reveal a paucity of inflammatory cells, correlating with the clinically translucent appearance of the ulcerations, similar to the findings seen in our cases. Calcium deposition (a less common finding) and stromal vascularization have also been reported,[14] as we likewise demonstrated on histopathology in several of our cases. Additionally, we showed that the healed phase of these perforations involved replacement of previously ulcerated corneal stroma by thick fibroconnective scar tissue. Similar to GVHD-associated corneal perforations, immunohistochemical analyses of paracentral sterile perforating corneal ulcers in patients with both rheumatoid arthritis and severe aqueous tear deficiency also displayed stromal infiltration by macrophages and T cells.[17] The localization of these perforations in the central or paracentral cornea, similar to neurotrophic ulcers and persistent epithelial defects in limbal stem cell deficiency,[18,19] may signal a common pathway of chronic inflammation that could reveal promising molecular therapeutic targets.

Unfortunately, current interventions after corneal perforation in the setting of GVHD do not appear to be very effective with regard to long-term visual acuity. At last follow-up (on average 34 months after first perforation), only a third of patients had a final BCVA of 20/100 or better in the affected eye, and approximately half were hand motion or worse. Although results were mixed, patients who underwent corneal transplantation tended to have a better chance at visual rehabilitation compared with non-surgical intervention (i.e. corneal gluing only), perhaps due to visually-significant residual corneal scarring.

The limitations of this study include its retrospective design, as well

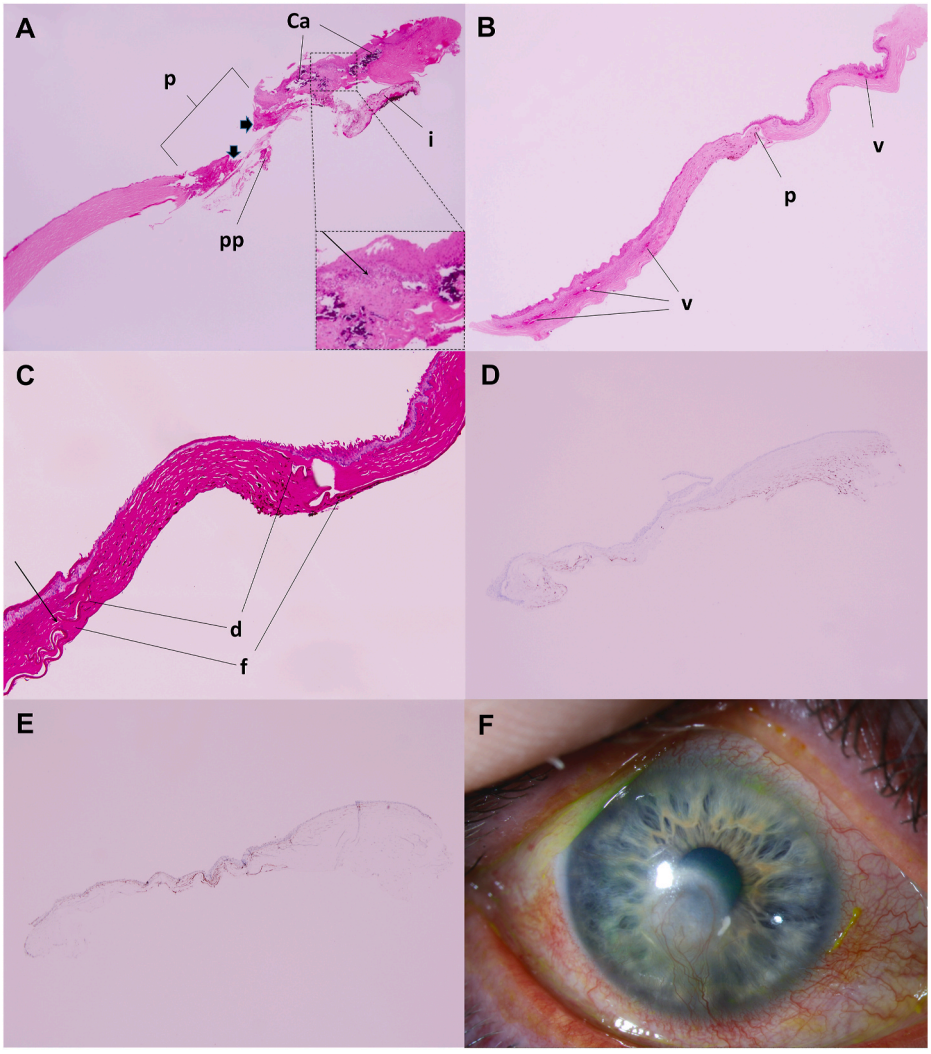

Fig. 1. *Histopathology of corneal buttons after corneal perforation in ocular graft-versus-host disease and clinical photograph of healed corneal perforation.*
Representative histopathology is presented for the acute phase of corneal perforation in case 3 (A) and the healed phase in case 6 (B–E).
A: The wide acute perforation site (p) is evident, partially filled with a mixture of chronic inflammatory cells, granulation tissue, and heme (block arrows), and with iris tissue (i) and pars plana (pp) prolapsing toward the perforation site. Adjacent to the perforation, calcific keratopathy is seen (Ca), along with anterior stromal vascularization associated with minimal inflammatory cells (arrow within magnified inset) (hematoxylin and eosin [H&E] stain, original magnification, ×20).
B: At low magnification, the healed perforation site (p) is identified by a narrow gap in the stroma. Anterior to mid-stromal vascularization (v) is appreciated peripherally to mid-peripherally (H&E stain, original magnification, ×40).
C: With periodic acid-Schiff (PAS) stain at higher magnification, the full width of the antecedent perforation site is identified by the broken ends of Descemet's membrane (d) paracentrally, and an additional break in Descemet's is also seen beyond the main perforation (arrow). A fibrous retrocorneal membrane (f) is appreciated, relatively thinner at the edges of the prior perforation, but centrally becoming so thick as to essentially replace the full thickness of the stroma. Foci of melanin pigment are evident within the fibrous membrane, presumably iris-derived (original magnification, ×100).
D, E: Immunostaining confirms the replacement of the central stroma by the fibrous retrocorneal membrane. In (D), CD34 immunostain (marker of normal keratocytes) exhibits positivity only peripheral to the central region, whereas in (E), smooth muscle actin immunostain (for myofibroblasts) exhibits full-thickness positivity in the central zone, confirming that the central portion of the stroma has been replaced with fibroconnective scar tissue (original magnification, ×40).
F: Representative clinical photograph of healed corneal perforation showing stromal neovascularization and opaque scarring, approximately 5 months after corneal gluing for acute perforation in case 5.

as incomplete medical record documentation pre-dating electronic medical records in some cases. As such, we were unable to comprehensively report on all medications such as systemic immunosuppression that may have impacted the patients' ocular outcomes. In addition, variation in documentation style by the different physicians prevented a standardized description of the eye exam for this retrospective study. While a relative strength is that the study included patients from four different institutions, all of these institutions are referral centers for tertiary ophthalmic care, so a selection bias may be present.

5. Conclusions

In summary, our study found that corneal perforation in the setting of ocular GVHD occurred an average of 3 years after HSCT, and that patients typically presented to the ophthalmologist prior to this event with good visual acuity. This demonstrates the importance of identifying at-risk patients and determining optimal prevention strategies, including regular ophthalmologic follow-up and patient education on signs and symptoms of ocular GVHD and its complications. We did not find evidence of infectious keratitis by culture or histopathology, which supports the hypothesis that these were predominantly sterile corneal ulcers that progressed to perforation. A role of steroids in pathogenesis remains unclear, but the use of steroids in the long-term management of ocular GVHD should be carefully considered. Our hope is that this study prompts further investigation of this rare but devastating entity.

Patient consent

Consent to publish the patient information in this brief report was not obtained. This report does not contain any personal information that could lead to the identification of the patients.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Authorship

All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the manuscript has been read and approved by all named authors.

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Declaration of competing interest

The following authors have no conflicts of interest to disclose: CZ, AF, GH, ES, JH, CB, CS, UT, AL, AH, GP.

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