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Case Report

Bilateral Corneal Perforation in a Patient with Chronic Ocular Graft-Versus-Host Disease: A Case Report and Literature Review

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Academic Editor: Nidhi Sharma

Special Issue: Haploidentical Stem Cell Transplantation

OBM Transplantation
2022, volume 6, issue 3
doi:10.21926/obm.transplant.2203164

Received: June 17, 2022
Accepted: July 27, 2022
Published: August 02, 2022

Abstract

Graft-versus-host disease (GVHD) is a serious complication that may occur in patients receiving allogeneic hematopoietic stem cell transplant (HSCT). GVHD occurs because of the immunological reaction between the donor's T cells and the recipient's antigens; GVHD may develop in different tissues, including the eye. Corneal perforation is an uncommon but vision-threatening manifestation of GVHD. We reported the case of a 65-year-old male patient who developed corneal perforation sequentially in both eyes 3 years after receiving HSCT. Conservative treatment with topical steroids and lubricants, bandage contact lens, and lacrimal punctal occlusion surgery resulted in the successful resolution of the corneal perforation with satisfactory visual recovery in the right eye. Therefore, corneal perforation can occur as the presenting manifestation of ocular GVHD. Regular ophthalmological

examinations are recommended after HSCT to enable the early diagnosis of ocular GVHD and prompt treatment initiation.

Keywords
Graft-versus-host disease; ocular graft-versus-host disease; allogeneic stem cell transplant; hematopoietic stem cell transplant; bone marrow transplant; dry eye; corneal perforation

1. Introduction

Hematopoietic stem cell transplant (HSCT) is the standard of care for a wide spectrum of hematological diseases, solid tumors, and immune disorders [1, 2]. However, despite undergoing immunoprophylaxis, patients receiving allogeneic HSCT often have the complication of graft-versus-host-disease (GVHD), which affects up to 70% of such patients and is the major cause of late morbidity and mortality. GVHD is a complex interplay of immune-mediated reactions caused by the recognition of recipient antigens by the donor immune cells. The most accepted conceptual model of GVHD involves three phases: recipient tissue damage from the pretransplant conditioning regiment with the activation of antigen-presenting cells; donor T-cell activation and differentiation; and target tissue damage and fibrosis [3, 4].

Ocular GVHD primarily affects the ocular surface, which is a complex morpho-functional unit consisting of the surface and glandular epithelia of the cornea, conjunctiva, eyelid margin, and lacrimal and meibomian glands. Ocular GVHD results in meibomian gland loss, symblepharon formation, cicatricial conjunctivitis, limbal stem cell deficiency, corneal epithelial defects leading to ulceration, neovascularization, conjunctivalization, corneal scar, and corneal opacification. In severe cases, the ocular surface impairment can lead to corneal blindness [5-7]. Dry eye disease (DED) is the clinical hallmark of this condition; however, the clinical manifestations of ocular GVHD can be heterogenous and can infrequently include corneal perforation, microvascular retinopathy, scleritis, and intraretinal and vitreous hemorrhage [8-15].

We reported an atypical case of ocular GVHD presenting with sequential bilateral corneal perforation without any previous ocular signs or symptoms. The patient provided his verbal and written consent for the publication of his data anonymously.

2. Case Report

A 65-year-old male patient with a history of allogeneic HSCT for myelodysplastic syndrome 3 years prior presented to our Cornea clinic (Department of Ophthalmology, University “Magna Græcia,” Catanzaro, Italy) with acute onset of ocular pain and blurring of vision in the right eye. The patient had no prior history of DED, and previous ophthalmological examinations were unremarkable. Upon presentation, the patient’s visual acuity (VA) was limited to counting fingers at 1 foot. Slit lamp examination revealed severe inferior corneal ulceration associated with perforation (Figure 1A). Anterior segment optical coherence tomography (AS-OCT) confirmed full-thickness perforation with complete iridocorneal adhesion and a flattened anterior chamber (Figure 1C). The slit lamp examination of the left eye was unremarkable, except for mild conjunctival hyperemia. Oral doxycycline (20 mg twice a day), topical dexamethasone eye drops (four times a day), and

topical lubricants were prescribed. A bandage contact lens was applied, and lacrimal punctal occlusion surgery was performed to improve tear retention. Both clinical picture and ocular symptoms improved gradually over the following weeks. However, 3 months from the initial presentation, the patient presented at the clinic with pain and blurry vision in the contralateral eye. The VA of the left eye was limited to hand motion, and the slit lamp examination revealed a corneal perforation involving the visual axis (Figure 1B). AS-OCT revealed marked corneal thinning and a shallow anterior chamber (Figure 1D).

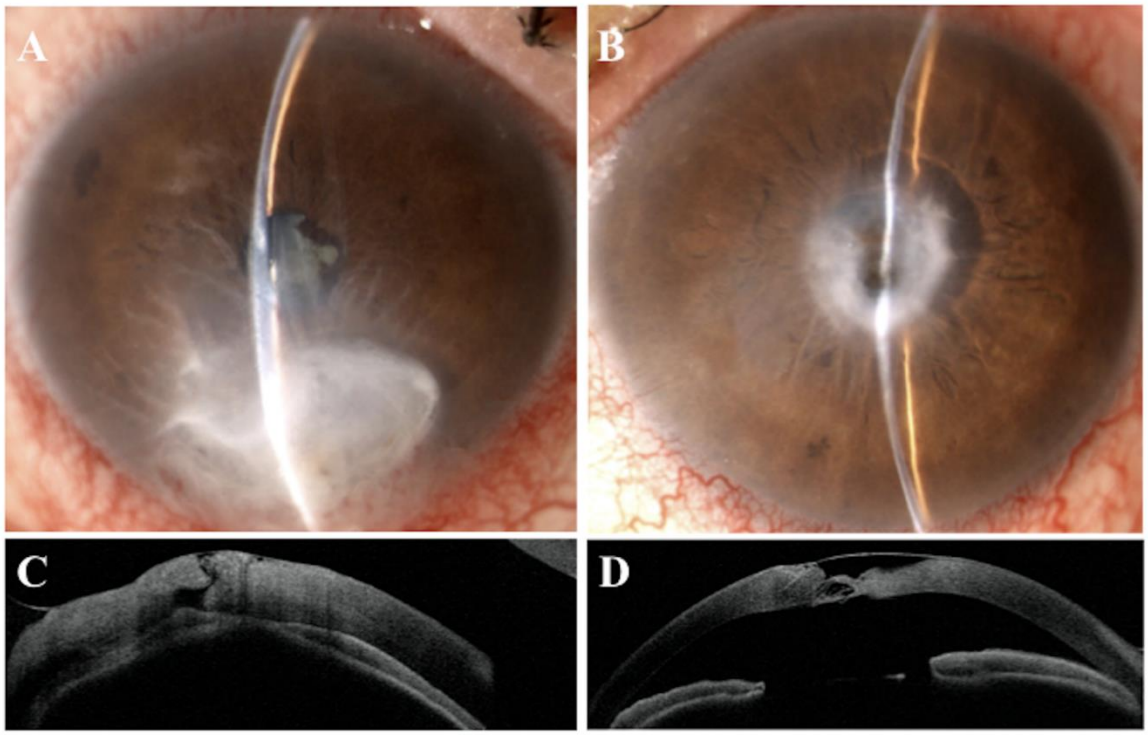

Figure 1 A. Slit lamp image of the right eye revealing inferior corneal perforation. B. Slit lamp image of the left eye revealing central corneal perforation. C. AS-OCT of the right eye revealing a full-thickness perforation with complete iridocorneal adhesion and a flattened anterior chamber. D. AS-OCT of the left eye revealing marked corneal thinning with a shallow anterior chamber.

The aforementioned treatment was also prescribed in the left eye and resulted in gradual spontaneous healing. Doxycycline was suggested to be taken for 6 months, whereas topical dexamethasone was tapered off in 12 months until discontinuation. At the last follow-up 12 months after the initial presentation, the VA was 20/50 in the right eye and counting fingers at 1 foot in the left eye (Figure 2).

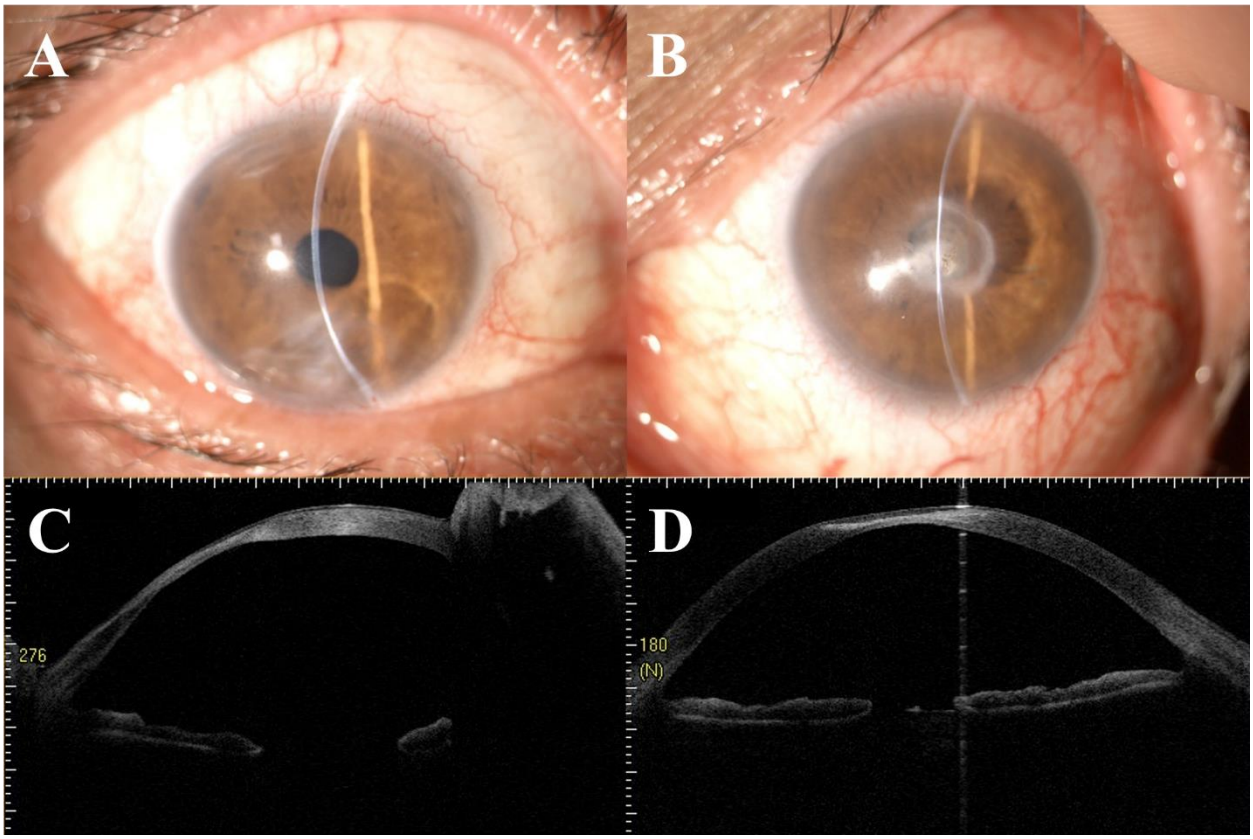

Figure 2 12-month follow-up visit. A. Slit lamp image of the right eye revealing healed corneal perforation. B. Slit lamp image of the left eye revealing healed central corneal perforation. C. AS-OCT of the right eye. D. AS-OCT of the left eye.

3. Discussion

We described a case of severe ocular GVHD initially presenting with spontaneous corneal perforation in one eye, which rapidly progressed to corneal perforation in the other eye. The patient did not present with the typical manifestations of GVHD or any other ocular symptoms. This severe and atypical presentation indicates the importance of periodical hematological and ophthalmological examinations in patients who have undergone HSCT to promptly diagnose GVHD and initiate appropriate treatment.

Corneal perforation is a rare and severe complication of ocular GVHD, resulting not only in functional visual impairment but also in the loss of the globe [16]. In a large retrospective case series conducted by Lin et al. (n = 249), Stevenson et al. (n = 243), and Pellegrini et al. (n = 283), the rates of corneal perforation in patients with GVHD were exceedingly low, ranging from 0.7% to 1.2% [17-19] (Table 1). A few cases of bilateral corneal perforation, usually associated with advanced chronic ocular GVHD, have been reported in the literature [20-23]. Lin et al. described one case of bilateral corneal perforation secondary to infectious keratitis in which penetrating keratoplasty was ultimately required [17]. Mohammadpour et al. reported a case of recurrent corneal perforation in both eyes in a patient with severe DED secondary to chronic GVHD. Corneal perforation recurred twice in the patient following cyanoacrylate gluing and amniotic membrane transplant, and penetrating keratoplasty was eventually performed [24]. Yoshida et al. described the occurrence of sequential bilateral corneal perforations in a patient with severe chronic GVHD [25].

Table 1 Large case series on ocular GVHD.

First Author, Year	Design	Population	No. patients	Ocular GVHD (%)	Corneal ulcer (%)	Corneal perforation (%)
Pellegrini, 2021	Retrospective	Post-HSCT	283	141 (49.7)	11 (3.9)	2 (0.7)
Berchicchi, 2018	Prospective observational	Post-HSCT	269	149 (51.9)	n.s	n.s.
Sinha, 2021	Retrospective cohort	Chronic GVHD	405	405 (100)	n.s.	15 (3.7)
Stevenson, 2013	Retrospective observational	Ocular GVHD	243	342 (100)	4 (1.6)	2 (0.8)
Lin, 2015	Retrospective observational	Systemic GVHD	249	49 (19.7)	3 (1.2)	3 (1.2)
Westeneng, 2010	Prospective observational	Post-HSCT	101	54 (54)	n.s.	n.s.
Ivanir, 2013	Cross-sectional	Post-HSCT	111	41 (37)	2 (1.8)	1 (0.9)
Shikari, 2016	Retrospective observational	Ocular GVHD	179	179 (100)	n.s.	n.s.

HSCT: Hematopoietic stem cell transplant; GVHD: Graft-versus-host disease.

The National Institutes of Health diagnostic criteria were developed in 2005 and revised in 2014 to standardize the diagnosis and grading of chronic GVHD. The diagnosis of GVHD requires either one diagnostic clinical sign or one distinctive manifestation confirmed by pertinent biopsy or other relevant tests, including biopsy or laboratory confirmation in the skin or another organ. According to these criteria, ocular involvement alone is not sufficient to confirm chronic GVHD [1]. Nevertheless, because eye involvement is common, patients with ocular manifestations alone might not fit these diagnostic criteria. Therefore, Shikari et al. and Ogawa et al. have suggested that the presence of ocular GVHD should be sufficient to establish a diagnosis of chronic GVHD [26, 27]. In 2007, the International Chronic Ocular GVHD Consensus Group proposed alternative diagnostic criteria specifically for ocular GVHD on the basis of the Ocular Surface Disease Index score, Schirmer test, corneal staining, and conjunctival redness. However, ocular GVHD can manifest with a wide range of presentations that may not meet these diagnostic criteria. As demonstrated by the present case, corneal ulceration and perforation can occur in the absence of ocular surface symptoms or other manifestations of systemic GVHD [20, 28]. Thus, ophthalmologists should maintain a high degree of suspicion for ocular GVHD in patients who have undergone HSCT.

Corneal perforation management in the setting of GVHD includes different medical and surgical treatments, such as topical anti-inflammatory drugs, autologous serum tears, bandage contact lenses, amniotic membrane transplant, cyanoacrylate gluing, and tectonic keratoplasty [29-37]. Systemic immunosuppression plays an important role in multisystemic GVHD; however, the risk-to-benefit ratio in localized diseases remains undetermined [29-33]. Oral doxycycline is particularly highly effective in inhibiting pro-inflammatory cytokines, including matrix metalloproteinases (e.g., MMP-6 and MMP-9); such cytokines typically infiltrate epithelial and stromal matrix in eyes with ocular GVHD [22, 38, 39]. Previous studies have reported the successful use of cyclosporine eye drops for the treatment of noninfectious corneal ulcers [40]. Because of its ability to reduce the number of activated T cells on the ocular surface, topical cyclosporine may represent a valid option for the treatment of corneal ulceration in patients with ocular GVHD [14].

Our patient was managed conservatively with a bandage contact lens, topical dexamethasone, lubricants, lacrimal punctal occlusion surgery, and oral doxycycline. This approach resulted in the successful resolution of the corneal perforation with satisfactory visual recovery in the right eye. Some authors have reported that compared with patients receiving nonsurgical interventions, patients receiving keratoplasty exhibit superior visual rehabilitation [35, 36]; however, keratoplasty results in an overall poor prognosis in eyes with intense inflammation, dryness, and neovascularization [41]. Therefore, we reserve keratoplasty for nonhealing corneal perforations following failed medical treatment or for late visual rehabilitation once the ocular surface status has improved.

In conclusion, corneal perforation is a rare but vision-threatening manifestation of ocular GVHD. In the presented patient, the perforation occurred sequentially in both eyes without any prior evidence of ocular GVHD. Therefore, regular ophthalmological examinations are recommended following HSCT to enable the prompt diagnosis, prevention, and appropriate treatment of GVHD and ocular complications. Conservative medical treatment resulted in the successful resolution of the corneal perforation with satisfactory visual recovery.

Author Contributions

All authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

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