THE OCULAR MANIFESTATIONS OF GVHD

Know the complications of this disease and the treatment options for the best patient outcomes.

BY BITA ASGHARI, OD, FAAO, FSLS

The effect of ocular graft-versus-host disease (GVHD) on a patient's quality of life is profound, and the ocular surface manifestations of the condition can be severe and difficult to manage, necessitating a multimodal, collaborative approach to treatment. Patients with GVHD commonly present with sensitivity to light; difficulty opening their eyes; dense blepharitis (Figure 1A); meibomian gland dysfunction (MGD) (Figure 1A, Figure 2); diffuse corneal and conjunctival staining, including filamentary keratitis (Figure 1B); and conjunctival cicatricial changes (Figure 3).[1-3] Periocular hyperpigmentation is also common.[3] The ophthalmic care of patients with GVHD focuses on controlling inflammation and sustaining ocular surface lubrication; however, it is directly influenced by the state of their systemic GVHD.[1,3]

This article provides a look at the ocular manifestations of this condition and the different treatment options available for managing these complications.

GVHD IN A NUTSHELL

Hematopoietic stem cell transplantation (HCT) is administered in patients with bone marrow or immune system dysfunction to restore blood cell production.[4] The indication for HCT, sometimes referred to as a bone marrow transplant, includes both malignant and nonmalignant conditions. In the United States alone, it is estimated that 20,000 HCTs are performed annually.[5] Following HCT, the activation of donor T cells can result in a marked inflammatory reaction,

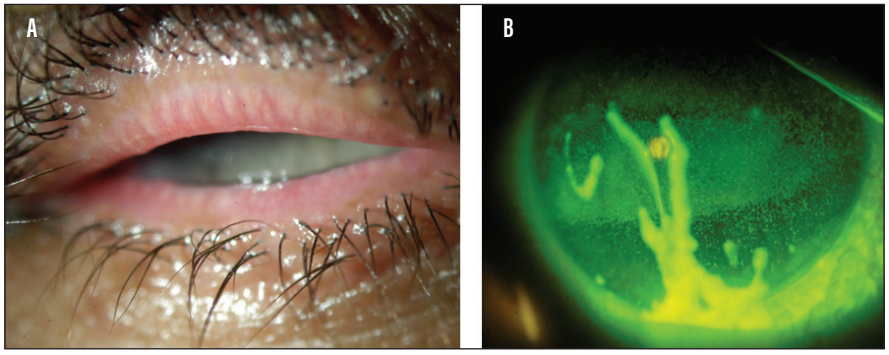

Figure 1. Patient with ocular GVHD, including severe blepharitis, MGD, difficulty opening their eyelids (A), and filamentary keratitis (B).

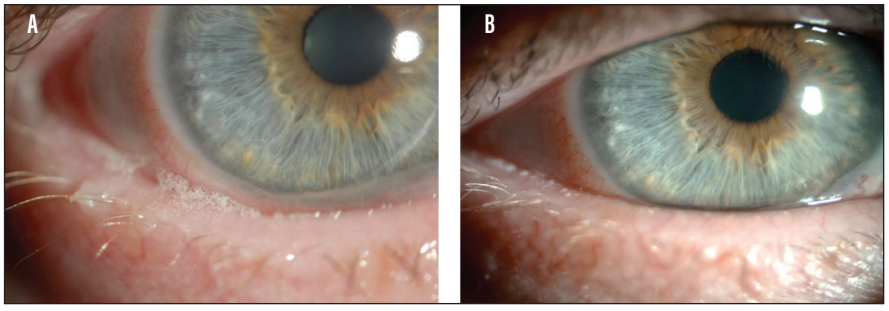

Figure 2. Lid margin frothing in a patient with MGD and ocular GVHD before (A) and after (B) implementation of twice-daily hypochlorous acid eyelid cleanser.

affecting and damaging normal host tissue and organs.[4] This inflammatory response of the host from the grafted stem cells is known as GVHD, and can be acute (onset < 100 days following HCT) or chronic (onset > 100 days following HCT).[1,2,4]

COMPLICATIONS

Complications of chronic GVHD are generally more complex, with extensive fibrosis and atrophy of tissues involving the skin, lungs, and mucous membranes of the body, including the eyes.[3] Although ophthalmic complications can manifest in both the acute and chronic states of GVHD, ranging in prevalence from 20% to 90%, they are considered more common and severe in chronic GVHD.[2]

Dry eye is the most common complication of ocular GVHD, affecting 40% to 76% of patients.[3] Ocular GVHD generally manifests in the setting of systemic GVHD, but it can present as an initial sign of systemic GVHD.[3] Ophthalmic manifestations of ocular GVHD present as a spectrum, including keratoconjunctivitis sicca and ocular surface inflammation, which affect the conjunctiva, lacrimal gland, and accessory tear glands.[1] In severe cases, keratoconjunctivitis sicca may progress to corneal epithelial defects (Figures 4, 5, and 6), corneal stromal melt (Figure 4), or perforation, necessitating penetrating keratoplasty (Figure 4). Conjunctival cicatrization can also occur, leading to fibrosis and keratinization and further increasing the risk of severe corneal complications. Posterior segment involvement is rare in ocular GVHD.

TREATMENT CONSIDERATIONS

Treatment of systemic GVHD is focused on reducing the immune response, with oral steroids used as first-line therapy.[6] Other immunomodulating therapies, such as methotrexate, rituximab, and mycophenolate mofetil, may also be considered.[6] Oral, fungal, bacterial, and

AT A GLANCE

- Ocular graft-versus-host disease (GVHD) is a major long-term morbidity in patients, and its negative effect on quality of life is significant. The ocular manifestations of GVHD can be debilitating and blinding.
- Dry eye is the most common complication of ocular GVHD, affecting 40% to 76% of patients.
- Treatment of ocular GVHD requires a multifactorial approach because patients commonly have severe aqueous deficiency secondary to lacrimal and mucous dysfunction, as well as evaporative dry eye manifestations secondary to meibomian gland dysfunction.
- The positive therapeutic utility of scleral lenses, particularly larger diameter designs, in patients with ocular GVHD is well documented in the literature; however, the modality is underused and often delayed in utility for the treatment of this condition.

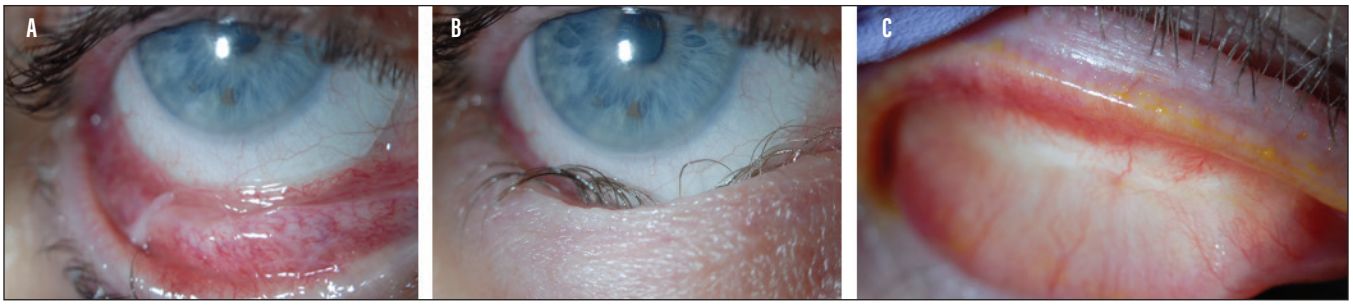

Figure 3. Inferior fornix shortening with palpebral fibrosis (A), resulting in entropion with trichiasis of the lower lid (B) of the right eye in a patient with ocular GVHD. The scleral lens serves as a protective barrier from lid/lash microtrauma (A, B). Superior palpebral conjunctival fibrosis is also evident (C).

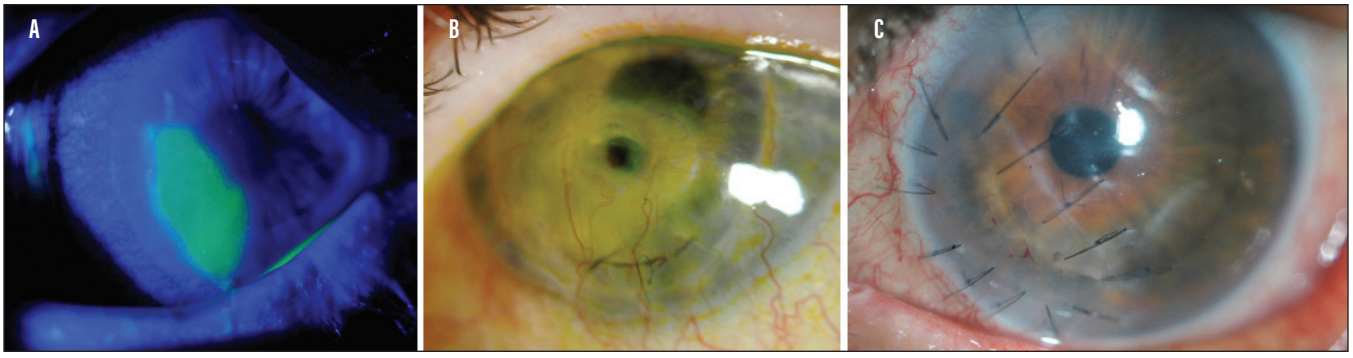

Figure 4. Complications of ocular GVHD. Peripheral persistent epithelial defect (A). Apical round clear zone in area of stromal melt with resultant descemetocele on a corneal graft (B). Peripheral patch graft for treatment of peripheral corneal melt (C).

viral prophylaxis are prescribed as part of supportive care.[6] It's important to note that the chronic use of oral steroids often results in elevated IOP, cataract formation, and increased risk of infectious keratitis.[3]

As oral steroids are tapered, focus must be given to ophthalmic flares. With increased ocular surface inflammation, topical steroids may be necessary to control conjunctival inflammation and prevent cicatricial conjunctival changes. Communication with a patient's managing GVHD specialist is essential in cases of ocular GVHD, and in severe cases of GVHD, collaborative care with a corneal specialist is often necessary, as patients are at an increased risk for corneal melt/perforation, which can be recalcitrant to conventional therapies.

Treatment of ocular GVHD requires a multifactorial approach because patients commonly have severe aqueous deficiency secondary to lacrimal and mucous dysfunction, as well as evaporative dry eye manifestations secondary to MGD. Management of evaporative dry eye in ocular GVHD is like that for patients with non-GVHD and includes eyelid hygiene (Figure 2), warm compresses, oral antiinfectives (ie, tetracyclines), and manual gland expression. The utility of intense pulsed light therapy has also been studied and found to be helpful in improving ocular symptoms in some patients with both GVHD and MGD.[7] Autologous serum tears and cyclosporine may reduce ocular surface inflammation. Punctal occlusion is also commonly used. Patients with ocular GVHD often require multiple doses of artificial tears and should always use preservative-free formulations to avoid preservative toxicity.

Cryopreserved amniotic membranes can be used for severe cases, namely those with corneal ulceration or epithelial defects; however, they do not address the chronic inflammatory nature of ocular GVHD. Multi-layer amniotic membrane transplantation may be of benefit to these patients as well. Peripheral corneal patch grafts (Figure 4C) or penetrating keratoplasty (Figure 4B) may be necessary in patients with severe corneal thinning. For patients with severe disease who are at risk of progressive corneal melt or thinning, tarsorrhaphy should be considered (Figure 5).

Therapeutic contact lenses can be considered in ocular GVHD to reduce pain and support the ocular surface. The use of a bandage soft contact lens (BSCL) can also be considered but with caution. The immunocompromised state of patients with ocular GVHD, coupled with the chronic use of topical steroids, elevates their risk for ocular infections, particularly in the context of continuous BSCL wear. Concomitant use of prophylactic topical antibiotics and timely lens replacement is imperative to mitigate risk of infectious keratitis. With continued dosing of steroid and

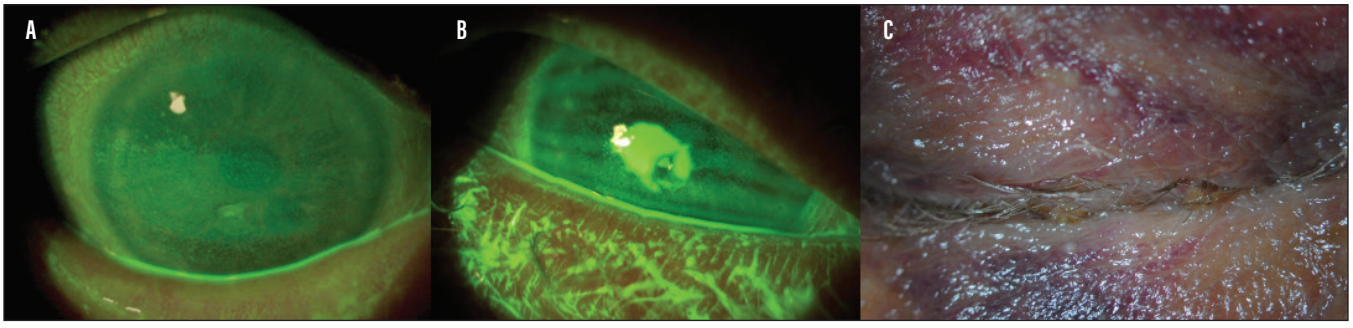

Figure 5. GVHD with severe staining and notable central apical thinning at baseline (A), which progressed to a persistent epithelial defect (B) recalcitrant to all therapies including amniotic membrane and scleral lens wear. Tarsorrhaphy was performed (C) and will be sustained until improved control of systemic GVHD is demonstrated.

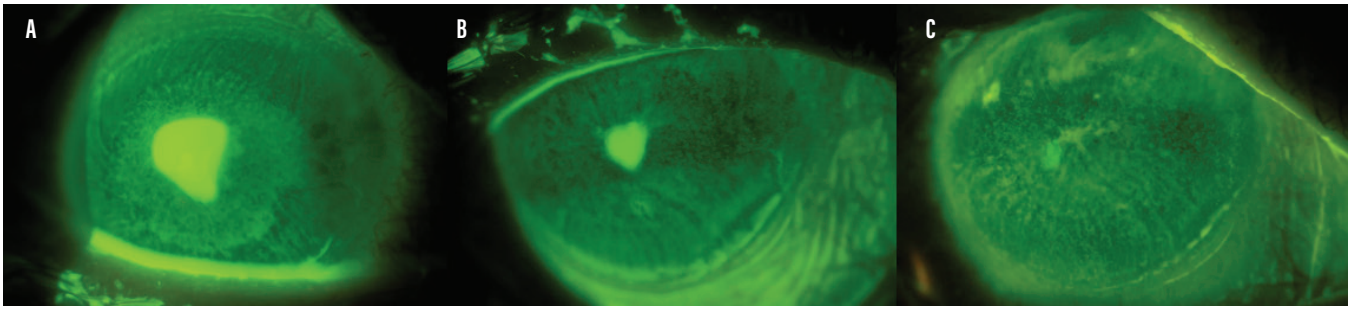

Figure 6. Persistent epithelial defect recalcitrant to all prior therapies, ranging from lubrication to amniotic membrane (A). Progressive healing with daily scleral lens wear and nighttime ointment at day 6 (B) with complete healing by day 13 (C).

antibiotic drops, particular focus and attention must be given to the potential development of fungal keratitis.

The positive therapeutic utility of scleral lenses, particularly larger diameter designs, in patients with ocular GVHD is well documented in the literature.[1,8-12] Each scleral lens is applied in the morning and removed in the evening, with nightly disinfection. The continued lubrication of the ocular surface by virtue of the post-lens tear reservoir (filled with preservative-free saline) and rigid lens shape helps to sustain lubrication of the cornea and prevent corneal microtrauma from inflamed/keratinized lid margins (Figures 3 and 6). Scleral lens wear in one ocular GVHD cohort had a 90% rate of continuation of wear, averaging over 32 months.[12] Still, this lens modality is underused and often delayed in use for the treatment of ocular GVHD. In a 2021 study by Bligdon et al, 89% of patients reported an improvement in overall quality of life with scleral lens wear, 94% reported improvement in dryness/grittiness of the eyes, and 56% wished the lenses had been recommended to them sooner.[13]

SILVER LINING

Ocular GVHD is a major long-term morbidity in patients following HCT. Its negative effect on quality of life is significant. The ocular manifestations of GVHD can be debilitating and blinding. With timely intervention of appropriate therapeutic interventions and collaborative care, patients with this condition can find relief from ocular pain to regain visual function. ■

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BITA ASGHARI, OD, FAAO, FSLS
- Associate Director of Clinical Education, BostonSight, Needham, Massachusetts
- bashari@bostonsight.org; Instagram @cornealove
- Financial disclosure: Employee (BostonSight)

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