Ocular Graft-Versus-Host Disease After Allogeneic Transplantation

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Ocular graft-versus-host disease (GVHD) is a common complication that occurs after allogeneic transplantation. It can cause severe dry eyes that are described as having a burning, gritty, and painful sensation. Ocular GVHD can affect quality of life by causing pain and photophobia, limiting activities of daily living (e.g., reading, watching television), compromising safety while driving, and permanently damaging vision. Pre- and post-transplantation evaluations by an ophthalmologist are recommended. Routine assessments using the National Institutes of Health eye score should be administered to patients at each follow-up visit to their transplantation physician. Treatment options include lubricating eye drops, immunomodulator and steroid drops, and punctal occlusion. Relieving symptoms is difficult, and although multiple treatment options exist, many are ineffective. The Boston Foundation for Sight’s scleral lens is an available option that promotes corneal healing and symptom relief. The current article discusses treatment options and supportive care measures for patients with ocular GVHD aimed at relieving symptoms and preventing complications.

50-year-old man named M.E. had chronic graft-versus-host disease (GVHD) in his eyes, skin, and gastrointestinal tract. He received a matched, unrelated allogeneic transplantation six years ago that included total body radiation. He did not receive prophylactic treatment for GVHD prior to transplantation and, within 30 days, he experienced acute GVHD symptoms that resolved within six months post-transplantation. Two years after the transplantation, M.E. began feeling burning and scratching symptoms in his eyes and experienced pain and difficulty keeping his eyes open. His physician treated him with lubricating eye drops, topical and oral steroids, and cyclosporine eye drops. He also was taking immunomodulators, including tacrolimus and mycophenolate mofetil, as systemic therapy for GVHD. Those treatment options did not improve his ocular manifestations. His physician referred him to an ophthalmologist who specialized in ocular GVHD. He was treated with punctual plugs one year after his ocular symptoms began, but they repeatedly fell out. As the symptoms worsened, his eyes often appeared very red and swollen. He had great difficulty driving to and from work because of the bright lights, burning sensations, and frequent need to administer lubricating eye drops. M.E. struggled daily with the severity of his symptoms until his local optometrist suggested that he should go to the Boston Foundation for Sight to be evaluated for scleral lenses. Four years post-transplantation, M.E. was seen and fitted with the lenses, and he reported relief within 48 hours. He remained in Boston for two weeks to be trained to apply the scleral lenses. When he returned home, he was able to enjoy things that he had been unable to do or had suffered through for two years. Scleral lenses improved M.E.’s quality of life by relieving his photophobia and eye pain and improving overall functional status.

Ocular Graft-Versus-Host Disease

Patients are surviving hematologic malignancies (e.g., leukemia, lymphoma, multiple myeloma) because of the increased use of hematopoietic stem cell transplantation (Fraser et al., 2006). Despite the advances in treatment, patients receiving allogeneic transplantations may experience major complications (e.g., GVHD) that can significantly affect quality of life and become life threatening. GVHD, the most common complication, occurs because the hematopoietic stem cells do not recognize the host’s tissues and begin to attack like an exaggerated immune response (Choi, Levine, & Ferrara, 2010). In contrast to
what happens in a solid organ transplantation, the organ attacks the host in GVHD. A graft-versus-leukemic or graft-versus-tumor benefit exists in that the immune response also destroys any remaining malignant cells (Choi et al., 2010).

Chronic GVHD usually occurs at more than 100 days post-transplantation and can last a lifetime, but timing does not influence the diagnosis. Chronic GVHD can occur in one or more organs in the host’s body, most commonly occurring in the skin, eyes, mouth, gastrointestinal tract, female genitalia, lungs, musculoskeletal system, and immune system. Chronic GVHD is the most common complication in long-term survivors and is the main cause for treatment-related mortality after allogeneic transplantation (Choi et al., 2010; Filipovich et al., 2005). The incidence of chronic GVHD increases if the patient had prior acute GVHD, is of older age, is a male recipient receiving a transplantation from a female donor, received a donor lymphocyte infusion, or had a peripheral blood stem cell transplantation (Choi et al., 2010; Filipovich et al., 2005). It occurs in about 30% of matched sibling transplantations and in 60%–70% of mismatched and unrelated transplantations (Choi et al., 2010). Although the pathogenesis of chronic GVHD is poorly understood, it may be associated with alloreactive T cells, alloantigens, autoantigens, T-cell subsets, B cells, and interaction with chemokines and cytokines (Choi et al., 2010). The manifestations are similar to an autoimmune disease and are believed to have similar pathophysiology (Choi et al., 2010). Treatments are targeted toward the immune system and supportive care, but no treatments approved by the U.S. Food and Drug Administration exist for chronic GVHD (Inamoto & Flowers, 2011).

Ocular GVHD is when GVHD targets the ocular tissue (Wang et al., 2010). The ocular manifestations that occur are considered distinctive signs and symptoms of chronic GVHD by the National Institutes of Health (NIH) and can be used for diagnosis (Filipovich et al., 2005; Westeneng et al., 2010). Ocular symptoms (e.g., dry eyes) may indicate chronic GVHD (Dignan et al., 2012; Inamoto et al., 2012). Multiple studies have shown that ocular GVHD is a major complication that affects more than 50% of patients who have received an allogeneic transplantation for a hematologic malignancy (Allan et al., 2011; Dietrich-Ntoukas et al., 2012; Sabti, Halter, Braun Fränkl, & Goldblum, 2012; Westeneng et al., 2010). The most common manifestation is keratoconjunctivitis sicca (i.e., dry eyes syndrome) (Tabbara et al., 2009), which usually begins to develop six months after transplantation and can progress rapidly (Ogawa & Kuwana, 2003). Ocular GVHD damages the eye and can permanently impair the eye’s ability to lubricate and protect itself, causing severe pain, photophobia, and disability (Jacobs & Rosenthal, 2007; Takahide et al., 2007; Wang et al., 2010; Westeneng et al., 2010). Ocular GVHD causes significant morbidity and decreased quality of life, affects activities of daily living, and may cause temporary or permanent vision loss (Westeneng et al., 2010). The purpose of the current article is to increase understanding of ocular GVHD, promote early recognition, and provide information to guide clinical decision making.

Pathogenesis

The pathophysiology of ocular GVHD is not fully understood. Studies have shown that fibrotic and atrophic changes are seen in the conjunctiva and the cornea (Ban et al., 2011; Riemens, Stoyanova, Rothova, & Kuiper, 2012; Wang et al., 2010). The inflammatory process appears to play a major role in ocular GVHD. Pro-inflammatory cytokines (e.g., interferon, interleukin-6) were found to be elevated in the tear fluid of patients with ocular GVHD. Riemens et al. (2012) proposed that interferon is elevated in the beginning stages, and interleukin-6 is elevated in later stages and correlates with the severity of the disease. Interferon and interleukin-6 also are involved in the pathogenesis of systemic GVHD and its severity (Coghill et al., 2011). Patients with severe dry eyes related to ocular GVHD also may have systemic chronic GVHD, supporting similar pathological processes between the two (Wang et al., 2010).

Donor-derived stromal fibroblasts are present in the lacrimal glands of patients with dry eyes after allogeneic transplantation (Ogawa & Kuwana, 2003), which suggests that fibroblasts function as antigen-presenting cells. This leads to increased production of pro-inflammatory cytokines, fibrosis of the lacrimal glands, and worsening dry eyes.

Meibomian glands are sebaceous glands that secrete lipids onto the ocular surface to lubricate the eyes during blinking and decrease tear evaporation rate (Ban et al., 2011). Meibomian gland dysfunction occurs in ocular GVHD, leading to ocular surface changes and increased tear evaporation rate (Ban et al., 2011; Riemens et al., 2012; Wang et al., 2010). Increased tear evaporation rate accompanied by a decrease in aqueous tear production from lacrimal gland fibrosis exacerbates dry eye manifestations. Total body irradiation used in the conditioning regimen for transplantations can worsen lacrimal and meibomian gland dysfunction (Tabbara et al., 2009; Wang et al., 2010). A decrease in goblet cells that secret mucous to protect and lubricate ocular surfaces on the conjunctiva may occur in ocular GVHD (Wang et al., 2010). Patients with severe dry eyes and decreased goblet cells also showed high grades of squamous metaplasia. The aqueous, lipid, and mucous layers make up the tear film, and dysfunction can lead to severe dry eyes that could result in ocular surface disease and chronic inflammation (Filipovich et al., 2005) (see Figure 1).

FIGURE 1. Cross-Section of the Eye
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Risks

Multiple risk factors exist that can increase the likelihood of developing ocular GVHD. Chronic GVHD occurs more often in peripheral stem cell transplantation when compared to bone marrow transplantation, so the risk for developing ocular GVHD also is increased (Filipovich et al., 2005). Ocular GVHD has been shown to coincide with GVHD involvement of the skin, serous, and mucous membranes (Filipovich et al., 2005; Westeneng et al., 2010). Westeneng et al. (2010) noted that patients who did not receive antithymocyte globulin, a medication that suppresses T cells and is used for GVHD prophylaxis during conditioning regimens, were at an increased risk for developing ocular GVHD. Risk factors for developing ocular GVHD include patients who are more likely to have chronic systemic GVHD with skin and oral involvement and who did not receive prophylaxis with antithymocyte globulin during the conditioning regimen.

Assessment

A pretransplantation evaluation by an ophthalmologist to establish a baseline assessment and detect and treat any underlying conditions may improve post-transplantation patient outcomes if symptoms of ocular GVHD develop (Dietrich-Ntoukas et al., 2012). Preexisting ocular diseases could worsen after a transplantation. Healthcare providers should perform routine screenings at follow-up visits. The NIH eye score is a one-item scale ranging from 0–3 that has been validated as an appropriate measure to evaluate the severity of ocular GVHD and patients' responses to treatment (Filipovich et al., 2005; Inamoto et al., 2012) (see Table 1). The NIH eye score effectively evaluates clinician- and patient-reported symptoms, has demonstrated sensitivity to reported symptom change when compared to other scales, and takes less than 15 seconds to complete (Inamoto et al., 2012). Nurses can use the NIH eye score to easily assess patients for ocular GVHD, and it does not require special equipment or training. Patients are recommended to schedule post-transplantation ophthalmology examinations every 3–12 months for five years following hematopoietic stem cell transplantation (Couriel, 2008). Because most ophthalmologists are not familiar with ocular GVHD, patients experiencing signs and symptoms should be referred to an ophthalmologist with a specific interest in the disease (Dignan et al., 2012; Inamoto et al., 2012). Adherence to those recommendations may allow healthcare providers to detect manifestations of ocular GVHD and offer earlier treatment that could prevent ocular damage and negative effects on quality of life.

Signs and Symptoms

Patients with ocular GVHD most commonly present with symptoms related to keratoconjunctivitis sicca and complaints of dry, gritty, painful, irritated, itchy, burning, or foreign body sensation of the eyes (Filipovich et al., 2005). Patients often have photophobia, blurred vision, or difficulty opening their eyes in the morning because of mucous secretions (Filipovich et al., 2005). Specific signs may include redness, periorbital hyperpigmentation, erythema, and edema of the eyelids (i.e., blepharitis). Inflammation of the cornea or conjunctival scarring may be present in later stages (Tabbara et al., 2009).

Diagnosis

Early recognition is critical for optimal outcomes (Inamoto et al., 2012; Tabbara et al., 2009). Early diagnosis can be made with Schirmer's test, where filter paper is placed in the lower lid of the eye to test whether the eye produces enough tears to keep itself moist (Lusby, 2013). A normal result is greater than 10 mm of moisture noted on the test filter paper after five minutes. In addition to clinical signs and symptoms, a Schirmer's test is necessary for diagnosis of ocular GVHD. The NIH has recommended a diagnosis of ocular GVHD based on new onset of dry eyes and a score of 5 mm or greater on Schirmer's test or a new onset of keratoconjunctivitis sicca by slit-lamp examination and a mean score of 6–10 mm in both eyes (Filipovich et al., 2005). Corneal staining, slit-lamp examination, tear evaporation rate, and tear film breakup time performed by an ophthalmologist also are useful in diagnosing ocular GVHD (Dietrich-Ntoukas et al., 2012). Brush cytology and impression cytology are minimally invasive and easily repeated procedures that assist in viewing inflammatory cells and ocular surface epithelium, and they are useful in monitoring the pathological progress (Wang et al., 2010). Other potential causes of dry eyes, such as medications with anticholinergic side effects or a history of total body irradiation and chemotherapy, should be considered (Couriel, 2008). Microbial swabbing may be performed along with fundoscopy to rule out infectious disease or complications in the posterior portion of the eye (Dietrich-Ntoukas et al., 2012).

Treatment

Early ocular GVHD treatment is focused on preventing irreversible damage, fibrosis, and possible vision loss (Wang et al., 2010). Treatment aims to increase lubrication, decrease ocular
inflammation, control drainage, and decrease tear evaporation (Couriel, 2008) (see Figure 2). Because the pathogenesis is not completely understood, most treatment is directed toward symptom management and supportive care (Riemens et al., 2012). Preservative-free eye drops usually are the first line of treatment when symptoms develop. The eye drops can be used as needed; however, when patients need to use them more than three times per day, additional treatment options should be explored. Eye drops provide lubrication to the ocular surface when inadequate tear production or increased evaporation occurs. Selective muscarinic agonists (e.g., pilocarpine, cevimeline) taken orally also may increase lubrication by elevating aqueous tear production (Dietrich-Ntoukas et al., 2012). Cyclosporine 0.05% eye drops, when used four times per day for one month in patients with ocular GVHD, may decrease ocular surface inflammation and improve dry eye symptoms (Wang et al., 2008). Cyclosporine eye drops typically can be administered two times per day and increased, if needed, to three or four times per day. Patients should be aware that effects are delayed, and treatment must be continued for weeks before results are evident (Dietrich-Ntoukas et al., 2012). Topical steroids also may be given for short-term use to decrease inflammation. However, patients should take caution, and ophthalmologists should follow up closely because using topical steroids increases the risk for ocular hypertension, cataracts, glaucoma, and infections (Couriel, 2008; Dietrich-Ntoukas et al., 2012). Topical steroid administration prevents systemic side effects and increases steroid concentrations on the ocular surface. Rimeloxone and fluoromethalone are preferred over prednisolone acetate because of the lower risk for secondary glaucoma (Dietrich-Ntoukas et al., 2012). Immunomodulators and corticosteroids may be associated with secondary complications and should be used cautiously (Sabti et al., 2012). Autologous serum eye drops have been used for ocular GVHD to improve tear breakup time and decrease corneal sensitivity (Ogawa et al., 2003). A small amount of the patient’s blood is collected and centrifuged, then the collected serum is combined with saline and an antibiotic. Autologous serum eye drops contain vitamins, growth factors, and fibronectin that promote corneal and conjunctival integrity (Ogawa et al., 2003). Patients also may require punctal plugs, which are silicone plugs placed by an ophthalmologist in the inferior or superior punctum (i.e., opening of the lacrimal duct) to occlude the tear drainage pathway and allow the few tears that are produced to remain on the ocular surface for a longer period without draining (Sabti et al., 2012). Treatment with autologous tears and punctal plugs is recommended because the plugs should increase the amount of time the autologous tears are on the corneal surface and provide additional benefit (Ogawa et al., 2003). Punctal plugs improve subjective symptoms and corneal staining may decrease (Sabti et al., 2012). However, punctal plugs fall out in more than 50% of patients and require replacement (Sabti et al., 2012). If this occurs repeatedly, permanent punctal occlusion with thermal cautery is a possibility (Couriel, 2008). Some controversy exists regarding punctal occlusion because pro-inflammatory cytokines that are present in the tear film may remain on the ocular surface and cause damage (Sabti et al., 2012). Ophthalmologists should consider this before providing the treatment. Systemic treatment with immunomodulators and corticosteroids also may be used (Dietrich-Ntoukas et al., 2012; Ogawa & Kuwana, 2003). However, they are recommended only when ocular GVHD involves other organs. Ocular GVHD appears to improve when systemic GVHD improves (Westeneng et al., 2010). When systemic treatment is tapered, an exacerbation of ocular GVHD that requires topical treatment may occur (Dietrich-Ntoukas et al., 2012).

Additional research is needed to discover effective treatment options for ocular GVHD because many conventional therapies fail (Couriel, 2008; Jacobs & Rosenthal, 2007; Ogawa & Kuwana, 2003). Multiple research studies have used the U.S. Food and Drug Administration–approved scleral lens as supportive care for patients with severe dry eyes related to ocular GVHD and reported improvements in pain and photophobia as well as restored ability to perform activities of daily living, which indicate improved overall quality of life (Fraser et al., 2006;
The scleral lens sits between the cornea and holds artificial tears that provide a “liquid bandage” or precorneal tear film to protect and lubricate the cornea and relieve symptoms of dry eyes (Rosenthal & Croteau, 2005). Three studies used the scleral lens made by Boston Foundation for Sight called PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) treatment (Jacobs & Rosenthal, 2007; Rosenthal & Cotter, 2003; Takahide et al., 2007) (see Figure 3). PROSE treatment uses custom-made and custom-fitted scleral lenses that provide an oxygenated aqueous environment maintained at neutral pressure and protect the cornea and epithelium from evaporation, air, and friction that occurs during blinking, and they may assist with corneal healing (Jacobs, 2008; Rosenthal & Cotter, 2003; Takahide et al., 2007). Use of the scleral lens is contraindicated in patients with visible corneal edema, and a trial placement should be considered (Rosenthal & Croteau, 2005; Takahide et al., 2007). Patient cost of the lenses is high when not covered by insurance, and only 11 medical centers nationwide and 5 worldwide provide PROSE treatment (Boston Foundation for Sight, 2012). Boston Foundation for Sight is a nonprofit organization and may provide financial assistance. Additional information can be found at www.bostonsight.org.

Implications for Nursing

Nurses should educate patients to avoid using preservative- or phosphate-containing eye drops because they are cytotoxic to the ocular surface and can lead to corneal calcifications (Bernauer et al., 2006; Dietrich-Ntoukas et al., 2012). Environmental controls, such as avoiding low-humidity environments and wearing moisture chamber goggles, may relieve symptoms of ocular GVHD (Couriel, 2008; Dietrich-Ntoukas et al., 2012). Warm compresses promote meibomian gland output of the oil layer in the tear film (Couriel, 2008). Adequate hydration is essential to prevent dehydration and decreased tear production. Emphasis should be placed on hand hygiene when performing any eye care to prevent infections. Nurses administering the NIH eye score to patients should encourage them to notify their physicians with new or changing ocular symptoms. Nurses can be patient advocates and suggest alternative treatment options to healthcare providers to help improve patient quality of life.

Conclusion

Ocular GVHD is a condition that can occur after allogeneic transplantation and significantly affects patients’ ability to perform activities of daily living because of pain, photophobia, and vision loss. These patients no longer have cancer but continue to suffer this consequence of treatment. Early detection and treatment are important in preventing ocular discomfort, damage, and vision loss. Assessing for ocular GVHD is crucial, and patients with new onset of symptoms should be referred to an ophthalmologist specializing in GVHD. Providing education on pharmacologic and nonpharmacologic management may improve distressing symptoms and promote healing.

References


FIGURE 3. Boston Foundation for Sight PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) Scleral Lenses


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