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REVIEW

Graft-versus-host disease and dry eye

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Abstract

Graft-versus-host disease (GVHD) is an important problem of hematopoietic stem cell transplantation. Dry eye disease (DED) is one of the most common complications of ocular GVHD, and patients experience symptoms such as blurred vision, photophobia, sand stinging, pain, burning, and redness. DED can progress to keratopathy, ulceration, and visual loss if treatment is delayed or appropriate treatment cannot be arranged. Treatment of people with GVHD needs a multidisciplinary approach to ensure early diagnosis and to recognize all clinical signs of GVHD and to define disorder category and severity. The aim of the treatment is to improve the quality and quantity of tears, to protect the corneal epithelial integrity, and to reduce the inflammation on the ocular surface to reduce the severity of the symptoms and prevent their progression. In conclusion, patients with GVHD should be evaluated ophthalmologically very carefully, especially the condition of the ocular surface and the findings of DED before and after transplantation, and it is important to carry out ophthalmological examinations and follow-up of these patients at regular intervals. Thus, early diagnosis, prevention of possible complication, and correct planning of treatment, when necessary, are very important before serious, perhaps permanent, and life-threatening consequences are experienced.

Keywords: Dry eye disease; graft-versus-host disease; ocular surface.

Graft-versus-host disease (GVHD) is an important problem of hematopoietic stem cell transplantation (HSCT).[1] The incidence of GVHD varies depending on the donor source, age, sex, presence of other systemic diseases, and degree of histocompatibility, among other factors.[2] While acute GVHD primarily affects the liver, skin, and gastrointestinal system,[3,4] it has been shown that there is a high rate of ocular complication in chronic GVHD (cGVHD).[5,6] In cGVHD, 60–90% of patients complain of ocular symptoms such as stinging, burning, watering, blurred vision, and discomfort.[5,6] Dry eye disease (DED) is one of the most common complications of ocular GVHD, and patients experience symptoms such as blurred vision, photophobia, sand stinging, pain, burning, and redness. Ocular GVHD does not usually cause permanent vision loss and its clinical course is stable,[7] but this ocular discomfort condition significantly reduces the quality of life of patients.[8,9] The degree of ocular surface disease correlates with the level of damage to tear film components.[10] The ocular findings are summarized in Table 1. DED can progress to keratopathy, ulceration, and visual loss if treatment is delayed or appropriate treatment cannot be arranged.[11] It is thought that the reason for the detection of ocular findings in patients with acute GVHD may be related to the interaction

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Table 1. Ocular findings in GVHD

Conjunctiva	Cornea	Eyelids	Posterior segment
Hyperemia	Punctate keratopathy	Scar	Central serous chorioretinopathy
Chemosis	Neovascularization	Trichiasis	Serous retinal detachment
Pseudomembrane	Secondary corneal infection	Ectropion	Posterior scleritis
Symblepharon	Perforation	Entropion	Infectious retinitis
Cicatricial conjunctivitis	Painful erosions	Lagophthalmus	Endophthalmitis
Superior limbic keratoconjunctivitis	Filament formation	Floppy eyelids	Intraocular lymphoma
Keratinization	Sterile stromal necrosis	Lacrimal punctal stenosis	Optic disc inflammation

of donor lymphocytes with host tissue compatibility antigens.[5] T lymphocytes known to originate from the donor have been demonstrated in patients with pseudomembranous conjunctivitis associated with acute GVHD. Conjunctival hyperemia, chemosis, and pseudomembrane development are commonly seen in patients with acute GVHD.[12] The deterioration of the ocular surface in cGVHD patients was thought to be due to dryness of the ocular surface due to apoptosis and fibrosis of the conjunctiva as well as the lacrimal gland.[13] Dry eye accompanied by meibomian gland dysfunction and chronic blepharitis is the most common ocular finding of cGVHD.[14] Corneal epithelial alterations such as punctate keratopathy, conjunctival subepithelial fibrosis, filament formation, aching erosions, and secondary corneal diseases may develop due to this. Less commonly, sterile corneal stromal necrosis and perforations may also be seen. In addition, atrophy and irregularity may develop on the eyelid margins, and complication such as entropion or ectropion development, loss of eyelashes, and lacrimal punctal stenosis may occur as a result of keratinization of the tarsal conjunctiva and structural changes on the ocular surface.[15] Palpebral and subtarsal conjunctival scarring is realized in some people and may cause cicatricial lagophthalmos.[16] Approximately half (47.8%) of cGVHD patients have significant meibomian gland dysfunction.[17] This dysfunction causes increased evaporation of the tear layer, leading to further deterioration of the ocular surface. In cGVHD, fibrotic processes usually affect the lacrimal gland, reduce its secretory power, and even cause extensive stasis with obliteration of the duct lumen.[8] Histological examinations showed an increase in CD34+ stromal fibroblasts accompanied by mild lymphocytic infiltration, destruction of tubuloalveolar glands and ducts in the lacrimal gland, tissue atrophy, and fibrosis.[8] Wang et al.[18] found that corneal sensitivity decreased and the rate of meibomian gland obstruction increased in all patients after HSCT, in a study examining patients with cGVHD, post-HSCT without DED, and healthy control groups. Tabbara et al.[16] retrospectively evaluated 620 patients after allogeneic HSCT in a large series they performed and observed eye involvement in 80 patients, although cGVHD developed in only 34 patients. They reported DED with or without cGVHD as the most common ocular complication. It has been suggested that the development of aqueous insufficiency in individuals who do not develop cGVHD may be due to immunosuppression, body irradiation, or both. They observed that vernal or atopic keratoconjunctivitis developed in four patients after allogeneic HSCT from atopic donors. They reported corneal ulcers in 15 patients, involving bacterial corneal ulcer (10), herpetic keratitis (1), and sterile epithelial defect (4). They observed that an ocular cicatricial pemphigoid-like clinical finding developed in five patients with cGVHD. It should also be kept in mind that ocular opportunistic infections may develop due to immunosuppression therapy.[16] Cataract development, mostly posterior capsular cataract, is seen in patients with GVHD, which is thought to be related to steroid use. However, it has been reported that GVHD alone is not an independent risk factor for cataract development.[19] Posterior segment involvement, including microvascular retinopathy, central serous chorioretinopathy, serous retinal detachment, posterior scleritis, optic nerve edema, infectious retinitis, endophthalmitis, and intraocular lymphoma, has also been reported in GVHD.[20]

Risk Factors

Skin and mouth involvements are among the risk factors for the development of ocular GVHD.[21] Human leukocyte antigen (HLA) incompatibility or an unrelated donor, advanced age of the patient and donor, female donor for male recipient, previous acute GVHD are also shown as risk factors.[22] The severity of ocular symptoms is generally proportional to the severity of systemic findings.[23] Conjunctival involvement in acute GVHD can be divided into degrees (Table 2). There is no ocular surface disease in Stage 0, and conjunctival hyperemia is present in Stage 1. In Stage 2, hyperemia accompanies chemosis. Chemosis may be the effect of liquid inequity (from concomitant systemic fluid

Table 2. Staging of conjunctival findings in acute GVHD[25]

Stages	Findings
Stage 0	There is no ocular surface disease
Stage 1	Conjunctival hyperemia
Stage 2	Hyperemia and chemosis
Stage 3	Pseudomembranous conjunctivitis
Stage 4	Corneal epithelial loss and pseudomembrane formation

overload in steroid-suppressed patients) or ocular GVHD. Although the definitive diagnosis of ocular GVHD can be made by conjunctival biopsy, it is important to carry out a detailed systemic examination of the patients, to question the drugs used, and to exclude conditions such as hyponatremia and hypoalbuminemia as an aid to the diagnosis. Pseudomembranous conjunctivitis seen in 12–17%[24] of patients with acute GVHD is classified as Stage 3 and is known as a marker of systemic involvement associated with poor prognosis. Stage 4 is known as corneal epithelial loss and pseudomembrane formation.[25] One study identified an increased expression of ICAM1 in the conjunctival epithelium of people with ocular cGVHD and was also thought to be a possible marker of its progression.[26] Ophthalmologic examination should be performed before allo-HSCT to evaluate for ocular surface deformities, conjunctival scarring, and inflammation, and patients should be informed about this. This may be useful for detecting ocular involvement in the early period after transplantation and to prevent possible complication, and is important for improving the quality of life of patients.[27]

Treatment

Treatment of people with GVHD needs a multidisciplinary approach to ensure early diagnosis and to recognize all clinical signs of GVHD and to define disorder category and severity. If proper diagnosis and treatment cannot be performed, irreversible complication may occur in patients and their quality of life may be seriously impaired. Today, the use of corticosteroids is an indispensable treatment option for both acute and cGVHD[28] as well as the frequency of recurrence and complication[29] has made it necessary to bring different treatment options to the agenda. The aim of the treatment is to improve the quality and quantity of tears, to protect the corneal epithelial integrity, and to reduce the inflammation on the ocular surface to reduce the severity of the symptoms and prevent their progression.[30] Patients are generally managed according to DED treatment guidelines, partly because few studies have evaluated the efficacy of topical treatments for ocular GVHD. Preservative-free artificial tears should be used to relieve ocular surface dryness and reduce inflammation.[31] In the occurrence of filamentary keratitis, topical N-acetylcysteine (5–10%) should be used alongside artificial tears due to its mucolytic and an-

Table 3. Treatment options in DED due to GVHD

Treatment	Advantages	Disadvantages
Preservative-free artificial tears	Elimination of ocular dryness, suppression of inflammation[31]	
Topical N-acetylcysteine	Mucolytic and anti-collagenolytic in the presence of filamentary keratitis[32]	
Topical or systemic tetracycline or macrolide	Treatment of blepharitis[33]	Side effects related to the gastrointestinal tract and genitourinary system, hypersensitivity reaction[34]
Punctal plugs	Temporarily increasing tear volume[35]	Worsening of inflammation with chronic use[35]
Topical corticosteroids drops	Suppression of inflammation[36]	Topical corticosteroids are contraindicated in the presence of corneal epithelial defects, stromal thinning, or infiltrates[36]
Topical nonsteroidal anti-inflammatory drops	Suppression of inflammation[40]	Cytotoxicity, delayed healing, corneal melts[40]
Topical cyclosporine	Suppression of inflammation[37]	
Topical tacrolimus	Suppression of inflammation[38]	
Topical autologous serum	Preservation of the ocular surface epithelium, epithelial healing[39]	There is no standard for the preparation conditions Contamination and risk of infection[41]
Contact scleral lens	Relief of symptoms and healing of corneal erosions[42]	High cost

ti-collagenolytic properties.[32] In the presence of blepharitis, eyelid hygiene and warm compress application and, if necessary, topical or systemic tetracycline or macrolide use should be recommended depending on the severity of blepharitis. Due to the matrix metalloproteinase inhibiting effect of azithromycin and tetracyclines, it is used as an anti-inflammatory in the treatment of blepharitis.[33] However, it is known that these agents have side effects on the gastrointestinal and genitourinary system, and may also cause a hypersensitivity reaction.[34] Temporary punctal plugs and punctal occlusion are among the treatment options that can be applied.[35] Topical nonsteroidal anti-inflammatory and topical corticosteroid drops are classically used to suppress ocular inflammation.[36] Topical steroid use should be applied carefully because of possible side effects and patients should be followed closely. Topical cyclosporine therapy is also an important treatment option in ocular GVHD due to its anti-inflammatory effects and improvement of tear quality.[37] In addition to these, topical tacrolimus treatment is an option that is approved and can be used in the medication of DED.[38] There are studies in the literature reporting that the application of autologous serum in the form of topical drops is also effective and safe.[39] Treatment options, along with their advantages and disadvantages, are summarized in Table 3.

Conclusion

The patients with GVHD should be evaluated ophthalmologically very carefully, especially the condition of the ocular surface and the findings of DED before and after transplantation, and it is important to carry out ophthalmological examinations and follow-up of these patients at regular intervals. Thus, early diagnosis, prevention of possible complication, and correct planning of treatment, when necessary, are very important before serious, perhaps permanent, and life-threatening consequences are experienced.

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