Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

Ocular Graft Versus Host Disease

Oküler Graft Versus Host Hastalığı

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation is an important therapeutic procedure for the treatment of hematologic malignancies. Graft-versus-host disease is a common cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. Severe systemic form of graft-versus-host disease may become life threatening. Ocular involvement of graft-versus-host disease remains the most common cause of long-term morbidity.

In this review article, the etiology, pathophysiology, clinical features, and treatment modalities of ocular graft-versus-host disease are presented.

Key words: Ocular Graft Versus Host Disease, dry eye

ÖZET

Allojenik hematopoetik kök hücre nakli , hematolojik malignitelerin tedavisinde önemli bir terapötik yöntemdir. Graft-versus-host hastalığı, allojenik hematopoetik kök hücre nakli sonrası morbidite ve mortalitenin sık görülen bir nedenidir. Graft-versus-host hastalığının ciddi sistemik formu hayatı tehlit edebilir. Graft-versus-host hastalığının göz tutulumu ise uzun dönemdeki morbiditenin en yaygın nedenidir.

Bu derleme makalede, oküler graft-versus-host hastalığının etyolojisi, patofizyolojisi, klinik özellikleri ve tedavi seçenekleri sunulmaktadır.

Anahtar kelimeler: Oküler Graft Versus Host hastalığı, kuru göz

Introduction

Allogeneic hematological stem cell transplantation (allo-HSCT) from human donors is a potentially curative treatment modality for hematologic diseases. Donor cells can be

harvested from bone marrow, peripheral blood and placental cord blood. Graft-versus-host disease (GVHD) is mediated by donor-derived T cell recognition of host antigens as foreign and that is a major restriction for widespread use of allo-HSCT. Incidence of GVHD varies from 10-90% of patients receiving allo-HSCT and depending on the source of donor tissue, gender, age, underlying disease, and degree of histocompatibility [1-5]. The most often immunologic targets at GVHD are the skin, gastrointestinal tract, and liver [4,6].

Recent improvements in the treatment modalities of patients with GVHD have led to the recognition of ocular problems in a high percentage. The ocular complications of GVHD and treatment methods are the topic of this communication.

Ocular Manifestations of GVHD

Ocular symptoms are very common in patients receiving allo-HSCT, 40-60% of patients affects[7-9]. Ocular surface problems can be seen in patients with no findings of systemic GVHD. Dry eye is most common ocular manifestation of GVHD and may be even the presenting symptom[10,11]. Acute conjunctival inflammation, pseudomembranous and cicatrial conjunctivitis also can be seen in these patients[9,12]. In advanced cases, persistent corneal epithelial defects may progressed to corneal ulcer, melting, perforation, and loss of vision[8,13,14].

Ocular surface and lacrimal glands are immunological targets in GVHD with histologically similar to those seen in cutaneous GVHD[5]. Dyskeratosis, lymphocyte exocytosis, and epithelial cell necrosis have been demonstrated in conjunctival specimens which are characteristic for GVHD[9,14].

Ocular GVHD can be classified as acute (within the first 3 months after allo-HSCT) or chronic (ongoing from 3 months after transplantation). In general, ocular manifestations are uncommon in acute GVHD, but when it occurs the severity of ocular findings correlates with the severity of systemic disease[9,15].

Beside of dry eye, other manifestations of ocular GVHD are eyelid position abnormalities (entropion or ectropion, lagophthalmos) and rarely retinal vascular occlusive disease[15]. That was reported the anterior uveitis can occur in the wake of acute exacerbation of chronic GVHD after allogeneic HSCT[16].

The pathogenesis of keratoconjunctivitis sicca in ocular GVHD is not clear. That was not demonstrated any infiltration of inflammatory cell into lacrimal gland, whereas epithelial cell flattening of duct and acini has been shown[8].

A complete ophthalmologic examination including tear function tests should be performed in suspected cases. The Schirmer test is the most commonly used test for evaluation of tear secretion. A Whatman filter paper strip is placed over the conjunctival sac at the junction of the medial and lateral third of lower lid without anesthesia. The wetting of the paper is measured after 5 minutes. Symptoms accompanied by a Schirmer score of ≥5 mm at 5 minutes in the presence of another affected system, fulfill the diagnostic criteria for chronic ocular GVHD [17]. Schirmer test is helpful for quantitative assessment of tear volume, whereas tear-film break up time test gives valuable information about quality of tear. Tear-film break up test measures tear film stability which may be most the important and practical test for dry eye diagnosis. At this test, a fluorescein dye-impregnated paper strip is wetted with artificial tear and placed in the lower conjunctival sac, asking the patient to blink, and measuring the interval between a complete blink and first appearing dry spot. The time interval should be at least 10 second for healthy tear film. Fluorescein dye also used for assessing of corneal epithelial integrity and punctate staining of cornea indicates severe dry eye (Figure 1).

Ocular disease generally do not affect visual acuity, but impair quality of life of patients [18]. National Institutes of Health worked on dry eye and its relation with activities of daily living, and consequently that was reached a consensus on defining a staging system of chronic GVH (Table 1) [17]. According to this system the daily activities almost completely limited because of dry eye symptoms at stage 3.

Another clinical grading system has also been described for conjunctival changes in acute and chronic ocular GVHD in a range from 0 to 4 (Table 2) [14,19].

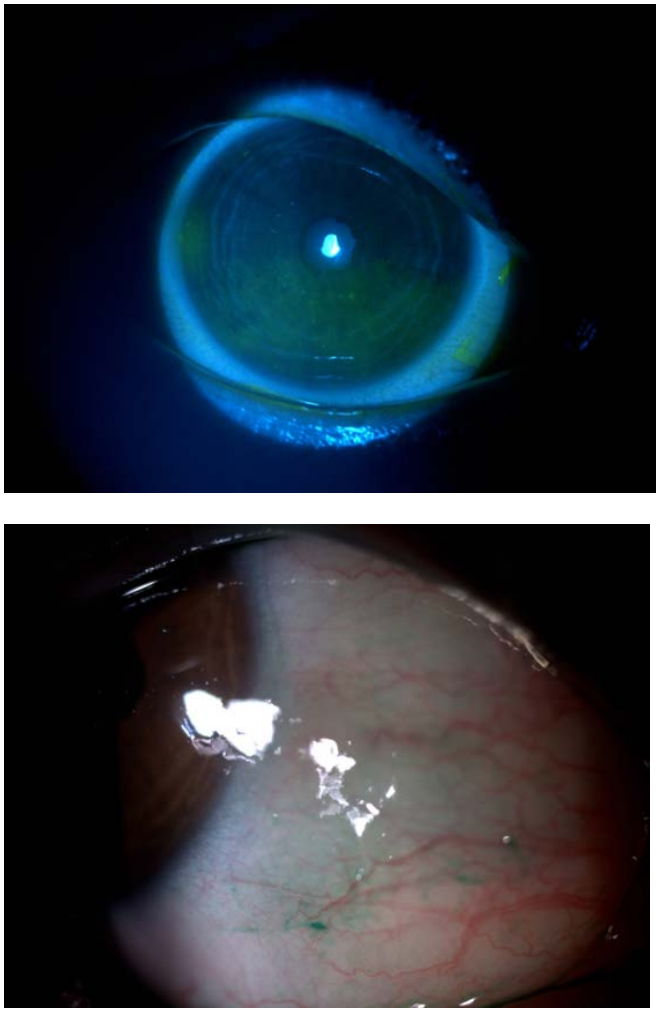

Figure 1a,b. A 13 years-old boy with Thalassemia major. Allo-HSCT had been performed 3 years before. Slit-lamp photography of right eye, punctate staining of cornea and conjunctiva with fluorescein (a) and lissamine green (b) dyes are shown. Vital dyes stain the areas with tear distribution problem and epithelial defects. Schirmer I test was 6 mm at this eye.

According to this grading system, grade 1 means the presence of mild conjunctival hyperemia, whereas pseudomembranous conjunctivitis with corneal epithelial sloughing is seen in grade 3. In most cases, the pseudomembranous conjunctivitis indicates systemic involvement and poor prognosis [14,15].

Table 1. National Institutes of Health Defined Ocular Scoring System for Patients with Chronic Graft-versus-Host Disease [17]

Grade	Symptoms
0	No dry eye symptoms
1	Mild dry eye symptoms not affecting ADL (requiring eye drops ≤ 3x per day) or asymptomatic signs of keratoconjunctivitis sicca
2	Moderate dry eye symptoms partially affecting ADL (requiring drops > 3x per day or punctual plugs) without vision impairment
3	Severe dry eye symptoms significantly affecting ADL (special eye-ware to relieve pain) or unable to work because of ocular symptoms or loss of vision caused by keratoconjunctivitis sicca

ADL: Activities of daily living

Table 2. Clinical grading of conjunctival changes in Acute and Chronic GVHD [14,19]

Grade	Acute GVHD	Chronic GVHD
0	None	None
1	Hyperemia	Hyperemia
2	Hyperemia with serosanguinous discharge	Palpebral conjunctival fibrovascular changes with or without epithelial sloughing
3	Pseudomembranous conjunctivitis	Palpebral conjunctival fibrovascular changes involving 25-75% of total surface area
4	Pseudomembranous conjunctivitis with corneal epithelial sloughing	Involvement of 75% of total surface area with or without cicatricial entropion

GVHD: Graft-versus-host disease

Treatment of Ocular GVHD

The effectiveness of treatment is limited in cases with a late stage of the disorder[20]. Treatment modalities for ocular GVHD including; lubrication, inflammation control, and support of epithelial health. In these patients, aqueous deficiency plays a major role in dry eye pathogenesis. Non-preserved artificial tears is usually preferred option for replacement treatment. Lubrication of ocular surface with frequent use artificial tear can dilute the inflammatory mediators present at the ocular surface[21]. Punctum occlusion (reversible or irreversible) may be helpful to preserve tear in selected patients. Ocular surface and lacrimal gland inflammation are another challenge at the management of dry eye. Topical cyclosporine A (CsA) inhibits T-cell proliferation and activation, that have been shown as effective to control of ocular surface inflammation in patients with chronic ocular GVHD[22,23]. Systemic immunosuppression is only indicated in patients who can not be controlled with topical treatment.

Persistent epithelial defect is another problem in dry eye. Autologous serum had been shown that promoted epithelialization and improve tear score in many studies[24,25]. Autologous serum contains many essential factors for epithelial health, which are epitheliotropic growth factors, cytokines, nerve growth factor, fibronectin, and transforming growth factor beta.

Severe ocular surface problems in ocular GVHD may need surgical intervention. Amniotic membrane transplantation may be helpful in patients with persistent epithelial defect[26]. In advanced cases, auto- or allo-limbal stem cell implantation can be combined with amniotic membrane transplantation[27]. Progressive corneal melting and perforations need penetrating keratoplasty.

Conclusion

Recent advances in HSCT technologies brought out to increase the life expectancy of patients, consequently ocular symptoms has been seen more common in long-term follow–up. Primary targets of ocular GVHD are conjunctiva and lacrimal glands, so dry eye is major clinical presentation. Fortunately, vision threatening complications very rare in these patients and early disease can be controlled with topical treatment. Multimodal and interdisciplinary approach should be tailored for each patients individually.

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