DOI 10.5935/0034-7280.20190016

Graft-versus-Host Disease: Review

Doença do Enxerto-versus-hospedeiro ocular: Revisão

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ABSTRACT

Graft-versus-host Disease (GVHD) is a major complication with high morbidity and mortality rates on patients undergoing hematopoietic stem cell transplantation. The ocular involvement, named ocular GVHD, may affect all structures of the eyes, but the lacrimal unit (lacrimal glands and ocular surface) is the main target of the inflammatory response mediated by the donor T cells. The development of dry eye disease is the main clinical ocular manifestation, and the association of a variety of therapeutics options is necessary. The aim of the review is to describe the clinical manifestations, diagnostic criteria, impact in quality of life, the current treatment and future perspectives of this disease that demands a multidisciplinary follow-up.

Keywords: *Graft vs Host Disease; Dry eye syndromes; Keratoconjunctivitis sicca; Corneal diseases; Conjunctival diseases; Lacrimal apparatus*

RESUMO

Doença do Enxerto-versus-hospedeiro (do inglês Graft-versus-Host Disease - GVHD) é uma complicação importante e com altas taxas de morbidade e mortalidade nos pacientes submetidos ao transplante alogênico de células-tronco hematopoiéticas. O acometimento ocular, denominado GVHD ocular, pode acometer todas as estruturas dos olhos, porém a unidade lacrimal (glândulas lacrimais e superfície ocular) é o principal alvo da resposta inflamatória mediada por células T doadas. O desenvolvimento de doença do olho seco grave é a principal manifestação clínica ocular, e a associação de diversas opções terapêuticas se faz necessário. O objetivo desta revisão é descrever as manifestações clínicas, os critérios diagnósticos, o impacto na qualidade de vida, o tratamento atual e as perspectivas desta doença, que precisa de um acompanhamento multidisciplinar.

Descritores: Doença enxerto-hospedeiro; Síndromes do olho seco; Ceratoconjuntivite seca; Doenças da córnea; Doenças da túnica conjuntiva; Aparelho lacrimal.

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The authors declare no conflicts of interests.
Received for publication 17/07/2018 - Accepted for publication 10/12/2018.

Introduction

Over the past few decades, allogeneic transplant of hematopoietic stem cells has been a treatment for a variety of benign and malignant hematological disorders.[1] Donor cells can be collected not only from the bone marrow, but also from the peripheral blood and the umbilical cord.[1] Patients' accessibility to treatment along with improved techniques and adequate support for the procedure such as immunosuppression and prophylaxis against infections are important processes to increase the survival of the patients affected by the disease.[1,2] However, a complication called Graft-versus-host disease (GVHD) has restricted the dissemination of the procedure, being an important cause of morbidity and mortality among patients undergoing treatment.[1-3]

GVHD is lymphocytic response mediated by donor T cells directed against host tissues considered as foreign.[1-4] Its incidence varies in 10 - 90% of patients undergoing allogeneic transplant.[1,3] The target organs are mainly the skin, the gastrointestinal system, the lungs, the oral mucosa, the liver and the eyes.[2,5]

In the past, GVHD was classified as acute or chronic according to the time of disease onset. Cases occurring within the first 100 postoperative days were classified as acute GVHD, whereas cases occurring after the same period were chronic GVHD. This classification, considering only the onset time of the disease, failed to represent the patients' actual clinical condition. Currently, the consensus of the National Institutes of Health (NIH) considers clinical and histopathological aspects as well as systemic and ocular complications to determine the condition as acute or chronic.[1] Acute GVHD usually affects the oral mucosa, the gastrointestinal system, the skin and the liver, whereas chronic GVHD mainly affects the lungs, eyes, and intestines.[6,7] Risk factors for the development of both forms of GVHD include: advanced age of recipient, female donor for male recipient, incompatible donors, and peripheral blood donor cells.[8,9]

The pathophysiology of GVHD is considered multifactorial, and the immune response between donor and recipient is mediated by complex interactions between adaptive and innate immunity. T cells derived from the donor are considered to be primarily responsible for the pathogenesis of the disease.[1,3]

Acute GVHD arises when an exaggerated inflammatory response of donor lymphocytes generates the so-called "cytokine storm" which occurs in 3 distinct phases: activation of antigen-presenting cells; activation, proliferation, differentiation, and migration of donor T cells; and destruction of target tissues.[10] In the case of chronic GVHD the pathophysiology is not fully understood, and it is believed that the loss of immune regulation in general may cause deficiency of donor T cell activity.[1,10]

Ocular manifestations occur more frequently and severely in the chronic form of the disease, and are present in 60-90% of the patients affected.[1,3,11,12] The ocular condition resembles the manifestations of other autoimmune diseases, and there are no clinical signs or specific symptoms of ocular GVHD.[1,3,13] The development of ocular disease may precede systemic disease, besides being an indicator of higher mortality. (14) Involvement of the skin, oral mucosa, gastrointestinal system, and liver are risk factors for the onset of ocular GVHD.[15,16]

Structures of the anterior segment are the most affected ones, mainly the tear and meibomius glands, the conjunctiva, and the cornea. Dry eye is the most common ocular finding, being present in up to 90% of cases.[1,3,13] Typical signs and symptoms include conjunctival hyperemia, foreign body sensation, epiphora, photophobia, visual blur, and burning sensation.[17]

The lacrimal glands are important targets of the inflammatory process in ocular GVHD. Lymphocyte infiltration and fibrotic activity severely reduce their secretory capacity, and almost obliterates the lumens of their ducts generating severe aqueous insufficiency on the ocular surface.[1,3,17] In addition, there is progressive and extensive involvement of the function of the meibomius glands and goblet cells, contributing to the dysfunction of the tear film.[1,3,13] Therefore, all layers of the tear film and lacrimal unit structures are compromised, resulting in the onset of severe keratoconjunctivitis sicca. As a result, other manifestations appear as diffuse punctate keratitis, filaments, recurrent corneal erosions, infections, and even perforations in the cornea due to ocular surface conditions.[1,3,17-19]

The conjunctival involvement can manifest in a condition of sterile conjunctivitis with hyperemia, chemosis, serosanguineous secretion, formation of pseudomembranes and consequent corneal epithelial defect.[6] It is related to a higher mortality rate of up to 89.5% when compared to patients without conjunctival involvement.[12]

The development of cataracts, especially the posterior subcapsular one, is mainly a result of systemic exposure to corticosteroids which is decreasing due to the development of immunosuppressive therapies.[1,20] Facectomy in these patients is shown to be safe, provided that the ocular surface is subjected to aggressive anti-inflammatory treatment in the pre- and postoperative periods.[21]

Although affected to a lesser extent, the posterior segment is affected in 12.8% of patients, and may present alterations including serous retinal detachment, papilla edema, posterior scleritis, and endophthalmitis.[1,3,11,22]

As described before, the pathophysiology of GVHD is primarily caused by the infiltration of donated T cells, causing an inflammatory response and fibrosis in the affected tissues. However, we believe that other cells are also present in these tissues, and their functions are compromised due to the intense inflammatory stimulus. In addition to T cells, macrophages have also been identified in abundance in the ocular tissues of patients with ocular GVHD.[23, 24] Recently, the presence of neutrophilic activity in the tears of these patients was also identified, evidencing the action of another cellular type on the ocular surface.[25] Four enzymes secreted by neutrophils had expressive concentrations in the tears of the patients involved, and one of them - neutrophil elastase - reached a concentration 250 times higher than in controls. This is the main enzyme secreted by neutrophils, and has a high capacity for degradation of several mucins of the ocular surface contributing to the establishment of the chronic inflammatory process.[25]

The quality of life related to vision in patients with the disease in question is severely compromised. Several daily activities are impacted, and dependence on others increases due to chronic ocular surface condition.[26] Ocular pain is the main symptom described by patients with ocular GVHD. It is known that there is a strong correlation between ocular symptomatology when checked with the Ocular Surface Disease Index (OSDI) questionnaire and vision-related quality of life.[26] Thus, this questionnaire is considered an objective and rapid tool to follow up these patients. Regarding clinical signs, only punctate keratitis seems to correlate with quality of life related to vision.[26]

Diagnostic Criteria

According to the NIH, for the diagnosis of chronic ocular GVHD the involvement of chronic GVHD in another organ other than the eyes is necessary, and it should be followed by: [1] a new condition of keratoconjunctivitis sicca documented with a bilateral mean Schirmer test ≤ 5 mm in 5 minutes, or [2] a new condition of keratoconjunctivitis sicca with bilateral mean Schirmer test between 6 - 10 mm, not from other causes.[27] Therefore, it is not currently considered the other clinical signs and symptoms for the diagnosis of ocular GVHD, besides that ocular involvement alone does not characterize the presence of systemic GVHD. Aiming for a more complete definition and classification for the disease, and at the same time considering ocular GVHD as sufficient signal for the diagnosis of systemic GVHD, the International Chronic Ocular Graft-versus-Host Disease Group proposes that the diagnostic criteria include: (1) OSDI, (2) Schirmer's test without anesthesia, (3) punctate keratitis, and (4) conjunctival injection.[28] A prospective, multicenter study is being developed to validate the proposal.

The NIH diagnostic and staging group developed an organ graduation system for GVHD, and for the eyes it is based on: presence of keratoconjunctivitis sicca diagnosed by an ophthalmologist, frequency of instillation of lubricating eyedrops per day, and the impact of keratoconjunctivitis sicca in daily activities (Table 1).[27]

Table 1
National Institute of Health (NIH) Ocular Screening for Chronic Graft-versus-Host Disease

0. Absence of symptoms
1. Dry eye symptoms do not affect daily activities (daily requirement of lubricants up to 3 times a day) or asymptomatic signs of dry eye
2. Dry eye symptoms partially affect daily activities (daily need for lubricants greater than 3 times a day or use of lacrimal canaliculus occluders) without visual acuity involvement due to dry eye
3. Dry eye symptoms severely affect daily activities (need for ocular device for pain relief) or unable to work due to symptoms or loss of visual acuity due to dry eye

Source: Translated and adapted from Shikari H, Antin JH, Dana R. Ocular graft-versus-host disease: a review. Surv Ophthalmol. 2013;58(3):233–51. [1]

Treatment

Topical medications play a critical role in the treatment of ocular GVHD, contributing to the reduction of local symptoms and inflammation. The treatment must be multifactorial, because in addition to the extreme aqueous deficiency there is lipid and mucosal deficiency. There are several options for topical treatments, such as: topical corticosteroids, cyclosporine, tacrolimus, autologous serum, eye drops and lubricating ointments, among others. The use of scleral contact lenses and surgical procedures such as lacrimal punctum occlusion and tarsorrhaphy are often required. Despite all this therapeutic arsenal, the control of ocular surface inflammation is sometimes not achieved.[1,13] Corneal epitheliopathy assessed through punctate keratitis and ocular symptoms are the main indicators of response to treatment in ocular GVHD.[29]

Lubrication is a crucial factor in treating the disease. As previously described, patients may have the lacrimal glands totally fibrous and nonfunctional generating minimal or absent lacrimal production. [30] Thus, the use of lubricants is mandatory, especially those without preservatives. In addition to intolerance, preservatives may provide epithelial toxicity and punctate keratitis, which with the use of preservative-free lubricants may decrease.[31,32] Temporary or permanent occlusion of lacrimal puncta is frequently used to reduce excessive use of lubricants, especially intolerant patients with reduced lacrimal production. However, continuous verification of signs and symptoms is necessary due to the risk of concentration of inflammatory factors in the tear after occlusion of the lacrimal channels.[33-35] In addition, measures to increase local and environmental humidity such as humidifiers and wet-chamber goggles are used by patients with exuberant symptomatology and who are exposed to windy and dry environments.

The use of warm compresses, palpebral hygiene, and oral use of tetracyclines help treatment and symptomatology of the involvement of the Meibomius glands with consequent improvement of the tear film.[6]

The anti-inflammatory treatment of the ocular comprises a variety of drugs with different mechanisms of action. Acute phase control is mainly done by corticosteroids to reduce the immune response by inhibiting cell migration and phagocytosis. [36] However, the low dose therapeutic response appears to be lower in patients with ocular GVHD when compared to patients without the disease.[37] These medications should be carefuly used due to the side effects from their use such as glaucoma, cataracts, and corneal infections.[3,30]

Cyclosporin A is an immunomodulatory agent to inhibit T cell activity by inhibiting the enzyme calcineurin and suppressing the release of numerous inflammatory cytokines, mainly interleukin 2.[38] Since its main mechanism of action is the inhibition of T cells, cyclosporin A is a relevant option for the reduction of ocular GVHD inflammatory activity. This drug at concentrations of 0.05% or 0.1% has already demonstrated efficacy in reducing punctate keratitis, releasing inflammatory enzymes, and symptomatology, as well as increasing lachrymal production in ocular GVHD.[1,3,9,14,39,40]

Tacrolimus is also an immunomodulatory agent with the same mechanism of action as cyclosporin A, but is 10 to 100 times more potent than the same.[38] Different drug concentrations were tested with efficacy in inflammatory and symptom reduction.[41-44] At the concentration of 0.05%, it was more effective than a corticosteroid in reducing corneal epitheliopathy during 10 weeks of treatment, in addition to similarly reducing symptomatology.[30] In addition, it significantly increased tear film rupture time, demonstrating improved goblet cell function, whereas at cellular level it significantly reduced the expression of inflammatory markers (HLA-DR and ICAM-1) on the ocular surface.[30] At concentrations of 0.02% and 0.03%, the drug was also efficient in reducing corneal epithelial disease and improving symptomatology, in addition to increasing tear production.[41-44] The major limiting factor for the use of topical tacrolimus is its tolerability, mainly due to burning sensation after instillation. Several vehicles are used in the preparation of the drug, but there is still no consensus on which is the most effective and/or most tolerated.[30]

Other anti-inflammatory agents have been tested, but more restrictively so far. Anakira 2.5% is an antagonist of the interleukin 1 receptor, and achieved reduction in corneal epitheliopathy and symptomatology in patients with keratoconjunctivitis sicca, which may be an option for the treatment of ocular GVHD.[45] Recently, association of Janus Kinase and splenic kinase tyrosine, a T cell inhibitor, at concentration of 0.5% also reduced punctate keratitis in a randomized pilot study.[46]

Thinking about support and health of the corneal epithelium, autologous serum becomes a valid option. It consists of epithelial and neural growth factors, fibronectin, vitamin A, cytokines, and transforming growth factor β, besides not having preservatives.[47,48] It promotes lubrication, healing of the corneal and conjunctival epithelium, and helps maintain the integrity of the ocular surface.[1,47,48] In patients with ocular GVHD, it has demonstrated efficacy with the improvement of corneal sensitivity and symptoms, besides its use being considered safe.[1, 47]

Scleral lenses play a determinant role in the treatment of patients with ocular GVHD. These large diameter gas-permeable rigid lenses are capable of promoting protection, lubrication, and reduction of symptoms.[35, 36, 49-51] There is evidence of almost immediate improvement of pain and photophobia in patients with ocular GVHD.[53] They also protect the corneal and conjunctival epithelia against abrasions by palpebral friction, reduce ocular surface exposure to the environment, and improve visual acuity due to a healthier surface.[52] In addition, its efficiency can be proven by the continuous high use rate (90%) during 32 months of follow-up.[52]

Surgical interventions are the last therapeutic option, and are generally used for severe cases that do not respond to clinical therapy. Tarsorrhaphy has an important role in reducing ocular exposure, and helping corneal re-epithelization, whereas the amniotic membrane can be used in recurrent epithelial defects and difficult to heal.[53]

Final Comments

Due to the increasing number of patients undergoing allogeneic transplant of hematopoietic stem cells, the number of patients affected by ocular GVHD will also increase. Ophthalmologists will play an increasingly important role in the multiprofessional team needed to follow up and treat these patients. The treatment of the ocular surface requires experience and association of several therapeutic options to better control the persistent inflammatory activity. As the life expectancy of these patients tends to increase with the new immunomodulatory therapies, more robust prospective studies and evidence-based protocols may be studied to better understand the disease.

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