Ocular Problems after Hematopoietic Stem Cell Transplantation

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Abstract
Hematopoietic stem cell transplantation (HSCT) is a common treatment for many hematologic malignant and non-malignant disorders. Graft-versus-host disease (GVHD) is one of the major, unrelated with rejection, complications after HCT. Ocular involvement occurs in more than fifty percent of patients with GVHD after HSCT and ranges from mild conjunctivitis to severe cicatricial conjunctivitis and corneal perforation. Non-GVHD ocular complications after HSCT are uncommon and include: cataract, glaucoma, ocular infections, ocular involvement of malignancy, ischemic microvascular retinopathy, central vein occlusion, retinal hemorrhage, retinal detachment, ocular toxicities of medications. Both GVHD and non-GVHD ocular complications can cause prolonged morbidity affecting patients’ quality of life and function. We would like to present recent updates in ocular disorders after HSCT, to highlight the relevance of ophthalmological examination before and after HSCT and to stress the importance of collaboration between transplant physicians and ophthalmologists for optimal recipients care.

Keywords: Graft-Versus-Host Disease; Eye Complications; Dry Eye; Hematopoietic Cell Transplantation

Introduction
Hematopoietic Stem Cell Transplantation (HSCT), including bone marrow transplantation, peripheral blood stem cell transplantation and cord blood transplantation, has become the standard treatment for life-threatening neoplastic and non-neoplastic hematological disorders [1-12]. Improvements in human leucocyte antigen (HLA) matching, advances in pre- and post-transplant procedures and treatment increased the number of patients undergoing this therapy and have enhanced survival during post-transplant period [3-5,13-14]. However, the number of complications due to prolonged patients survival increased. Graft-versus-host disease (GVHD) is a leading, unrelated with rejection, cause (25 - 85% of patients) of morbidity and mortality after allo-HCST [3-5,8-9,11-215-16]. Ocular problems affect 40-60% of patients treated with HSCT. Ocular GVHD may be the only manifestation of the disease, though it is rather connected with other systemic manifestations; up to 90% patients with systemic GVHD also have ocular problems [3-4,12,16-19]. Moreover, pre- and post-transplant therapy, neutropenia, impaired cellular and humoral immunity are responsible for other ocular problems in patients after HSCT [4,9,19-21]. We would like to summarize updates in both GVHD and non-GVHD ocular complications after HSCT for better understanding the necessity of collaboration between transplant physicians and ophthalmologists to provide optimal patients’ care.

Graft-versus-host disease (GVHD)
In 1956 Barnes and Loutit demonstrated that irradiated mice after infusion of allogenic marrow and spleen cells recovered from irradiation injury and aplasia but died due to "secondary disease" (diarrhea, weight loss, skin changes, liver abnormalities). That was described as graft-versus-host disease. In 1966 Billingham proposed conditions necessary to recognize GVHD:

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- The transplanted graft must contain immunologically competent cells
- The recipient must be incapable of rejecting or eliminating transplanted cells
- The recipient must express tissue antigens that are not present in the transplant donor, thus the recipient antigens are recognized as foreign by donor cells [4-5,22].

Further studies revealed that lymphocytes T of the stem cells’ inoculum are immunologically competent cells responsible for GVHD [4-5,22-23].

Previously, the onset of symptoms defined GVHD as acute (before day 100 after transplantation) or chronic (beyond day 100). Now, we know that acute GVHD can occur after day 100. Recent National Institutes of Health classification include late acute GVHD (e.g., after cessation of immunosuppression or after donor lymphocyte infusion) or overlap syndrome of both acute GVHD and chronic GVHD. Therefore clinical findings and symptoms - not timing relative to HSCT - are used to classify acute and chronic syndrome [4-5,11,13,24-26]. The pathogenesis of acute GVHD consists of three steps: 1. activation of antigen-presenting cells by the tissue damage, 2. activation, proliferation and migration of donor lymphocyte T, 3. complex cascade (due to donor lymphocyte T) of cellular mediators and soluble inflammatory agents, amplifying local tissue destruction and further promoting inflammation and tissue damage [4-5,19,22]. The clinical changes of acute GVHD are observed in the skin, gastrointestinal tract and liver. In experimental studies acute GVHD was observed also in the lungs [4-5,19,22,27-28]. The pathophysiology of chronic GVHD is not completely clear. Experimental studies suggest: 1. thymus destruction with deficient selection of donor lymphocytes T, 2. regulatory T cell deficiency, 3. insufficient elimination in aberrant B cells, producing auto- and allo-antibodies, 4. development of sclerotic lesions in majority of organs [5,18-19,22,29-31]. There are some risk factors for both acute and chronic GVHD [4-6] table 1 to 4.

### Table 1: Risk Factors for Graft-versus-Host Disease (GVHD) [79].

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
</tr>
<tr>
<td>female donor previous pregnancy</td>
</tr>
<tr>
<td>high level of T cells in transplanted tissue</td>
</tr>
<tr>
<td>female donor/male recipient</td>
</tr>
<tr>
<td>HLA mismatch or unrelated donor</td>
</tr>
<tr>
<td>advanced age of donor/recipient</td>
</tr>
<tr>
<td>intensity of conditioning regimen(irradiation)</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
</tr>
<tr>
<td>previous acute GVHD</td>
</tr>
<tr>
<td>advanced age of donor/recipient</td>
</tr>
<tr>
<td>HLA mismatch or unrelated donor</td>
</tr>
<tr>
<td>female donor/male recipient</td>
</tr>
<tr>
<td>grafting with growth factor–mobilized blood cells</td>
</tr>
</tbody>
</table>

### Table 2: The Severity Grading System of NIH Consensus Group for GVHD.

<table>
<thead>
<tr>
<th>Score</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no symptoms</td>
</tr>
<tr>
<td>1</td>
<td>mild DES symptoms not affecting daily activities (eye drops not more than three times daily) or asymptomatic signs of KCS</td>
</tr>
<tr>
<td>2</td>
<td>moderate DES affecting daily activities (drops more than three times daily or punctal occlusion) without visual impairment</td>
</tr>
<tr>
<td>3</td>
<td>severe DES symptoms significantly affecting daily activities (special eyewear to reduce pain) or unable to work because of DES symptoms or impairment of visual acuity because of KCS</td>
</tr>
</tbody>
</table>


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<table>
<thead>
<tr>
<th>Score</th>
<th>Schirmer Test Without Anesthesia (Mm)</th>
<th>Corneal Fluorescein Score</th>
<th>Osdi Score</th>
<th>Conjunctival Injection Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>more than 15</td>
<td>0</td>
<td>less than 13</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>11-15</td>
<td>1</td>
<td>13-22</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>6-10</td>
<td>2</td>
<td>23-32</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>not less than 5</td>
<td>3</td>
<td>more than 32</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:** The Severity Grading System of the International Chronic Ocular Graft-Versus-Host Disease Consensus Group (ICGDCC).

<table>
<thead>
<tr>
<th>Systemic GVHD \ Diagnosis</th>
<th>None (Score)</th>
<th>Probable cGVHD (Score)</th>
<th>Definite cGCHD (Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0-5</td>
<td>6-7</td>
<td>more than 7</td>
</tr>
<tr>
<td>Present</td>
<td>0-3</td>
<td>4-5</td>
<td>more than 6</td>
</tr>
</tbody>
</table>

**Table 4:** Ocular criteria of chronic GVHD diagnosis, depending on the presence or the absence of systemic GVHD proposed by the ICGDCC.

(c)GVHD: (chronic) Graft-versus-Host Disease, ICGVHDCC: International Chronic Ocular Graft-versus-Host Disease Consensus Group.

**Ocular graft-versus-host disease (oGVHD)**

The term “ocular GVHD” describes a post-HSCT condition, causing a spectrum of ocular disorders connected typically with ocular surface and lacrimal glands [4,16,32]. Other complications, such as uveitis, episcleritis, posterior scleritis, microvascular retinopathy with cotton-wool spots, vitreous and/or intraretinal hemorrhages and central serous retinopathy were described in the literature, but they are exceedingly rare [4,18,32]. Moreover, some of those complications, as well as cataract, glaucoma, infections or retinal detachment could be secondary to immunocompromised status of patients after HSCT or their cancer treatment (i.e. chemotherapy, radiation, steroid administration) [32] figure 1 to 5.

**Figure 1:** Conjunctival Injection.

Figure 2: Keratoconjunctival Sicca: Corneal Epitheliopathy and Filaments (Fluorescein Staining).

Figure 3: Corneal Vascularization.

Figure 4: Persistent Epithelial Defect (PED) (Fluorescein Staining).

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Acute oGVHD occurs between 1st and 100th day after HSCT. Eyelid skin changes include maculopapular, erythematous exanthema. Conjunctival involvement ranges from mild erythema to hemorrhagic, ulcerative and/or pseudomembranous conjunctivitis with a tendency to cicatrization [4,11,18-33]. Corneal epithelial or filamentary keratitis are not direct cause or result of tissue reaction but they are secondary to conjunctival changes. Rare observed peripheral corneal melting may lead to corneal perforation [4,17-19,34]. In acute GVHD anterior uveitis and episcleritis were also described [18,34-35].

Conjunctival changes in acute GVHD may serve as a marker for the severity of the disease (worse disease) and may reflect the course of systemic GVHD (worse survival) [2,11,32-33].

Chronic oGVHD pertains problems beyond 100th day after HSCT and is the most common form of oGVHD. This form of the disease mimics other autoimmune/collagen vascular diseases and affects: eyelid and periorbital skin, conjunctiva, cornea, lacrimal system, sclera, uvea and retina, though changes in the posterior part of the eye are rare. Nonetheless, different ocular symptoms can be the first and the only presentation of GVHD [4,7-8,11,20,32,36-37].

Eyelid cutaneous manifestation of chronic GVHD include: dermatitis, lagophthalmos, ectropion, poliosis, madarosis and vitiligo [7,18,32]. Meanwhile keratinization of the tarsal conjunctiva may progress to entropion, trichiasis and Meibomian gland atrophy [7].

Noninfectious conjunctivitis is a common manifestation of oGVHD. Jabs et al. proposed its’ clinical staging:

Stage I: hyperemia without other changes, Stage II: hyperemia with chemosis and/or serosanguineous exudates, Stage III: pseudomembranous conjunctivitis, Stage IV: pseudomembranous conjunctivitis with corneal epithelial sloughing [4,32-33]. The description of pseudomembrane is adequate only during early phase of Stage III; in time membranous fibrovascular scar form on the tarsal conjunctiva that leads to cicatrical form of conjunctivitis. Moreover, stage IV – corneal epithelium sloughing, occurs only in the acute or hyperacute phase after HSCT [32,38]. To describe more precisely conjunctival changes in chronic oGVHD four-step scale of Robinson., et al. is proposed [4,39].

In literature we can find description of superior limbic keratoconjunctivitis associated with GVHD in patients with cicatrical conjunctival changes and decreased Schirmer score. It was more common for patients after peripheral stem cell transplantation compared with bone marrow recipients [39-40].

Dry eye syndrome, affecting almost 80% of patients with systemic GVHD, reveals as a result of lacrimal gland fibrosis, ductules and lumina cicatrization, Meibomian gland dysfunction, previous therapy (irradiation, chemotherapy) and active underlying disease [1-3,20]. It typically develops by six to nine month after HSCT. Patients complain about irritation, burning, redness, pain, photophobia, tearing, blurry vision, sensation of having foreign body in the eye [8,12]. Corneal changes include: punctate keratitis, corneal filaments, persistent epithelial defect, corneal neovascularization, corneal keratinization, ulcerations, melting of the cornea and ultimately corneal perforation. In most patients DES persists after the remission of GVHD [1-3,7,18-19,32,36]. As a most common ocular complication it is considered as a hallmark of chronic GVHD [8,19,33-35,41].

According to the National Institutes of Health (NIH) working group chronic GVHD requires: 1.distinction from acute GVHD and other possible diagnosis, 2.the presence of at least one diagnostic clinical sign of GVHD or the presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant test. Therefore, new onset of dry, gritty or painful eyes, cicatrical conjunctivitis, keratoconjunctivitis sicca, photophobia, difficulty with morning opening the eyes because of mucoid secretions or confluent areas of punctate corneal epitheliopathy are known as distinctive manifestation of chronic oGVHD. Decreased values of the Schirmer test without anesthesia confirmed diagnosis [7-8,13,18,29]. Further studies revealed the low reproducibility of the Schirmer test and the inter- and intra-rater variability in reporting severity of symptoms. That is why NIH prepared a simple, symptom-based scale to assess severity of oGVHD. Tab.2. Although NIH eye score is a easy, quick and non-sophisticated but it correlates well with both clinical and patient-reported symptom changes [7-8,10,18,36,41]. In 2013 the International Chronic Ocular GVHD Consensus Group (ICOGG) proposed diagnostic metrics to increase objectivity in diagnosis and follow-up of chronic oGVHD. The Schirmer test without anesthesia, corneal fluorescein staining, conjunctival injection and patient reported DES symptoms (Ocular Surface Disease Index – OSDI questionnaire) are used for evaluation. The presence of systemic GVHD impact the result of evaluation – patients without systemic changes have to get higher score to recognize disease [7,10,42]. Tab.3.4. DES is known as a distinctive manifestation of cGVHD, that is why validated, chronic ocular GVHD-specific metric, may be a valuable tool for early prophylaxis, diagnosis and treatment in recipients after HSCT.

Non-GVHD ocular complications

In post-HSCT patients are generally not common, but they are responsible for prolonged morbidity affecting activity and quality of life. In some cases they are the reason of visual acuity impairment or even loss [9,18,37,44-46].

Cataract

A progressive opacification of the lens – occurs from 11 to 100% in adults and from 4 to 76% in children after HSCT. It develops secondary to total body irradiation, preHSCT chemotherapy and/or prolonged steroid administration [9,47-48].

Infections

Pre-HSCT latent infections, post-HSCT neutropenia, impaired cellular and humoral immunity, development of GVHD and medical treatment are responsible for ocular infections after transplantation [9,49-50]. Both bacterial (Gram-pasitive and negative), fungal (Candida,Aspergillus), viral (cytomegalovirus, herpes simplex virus, varicella zoster virus, adenovirus) and protozoan (Toxoplasma gondii) infections (corneal ulcers, uveitis, retinitis) were observed after HSCT [9,43,50-55]. That is why candidates for HSCT should be tested for latent infections [9,49].

Ocular manifestation of malignancy

Relapsed disease after HSCT involving eyes was described, either de novo or together with central nervous system or systemic relapse [9,56-57].

Glucoma

Irradiation used in conditioning regimens, long-term used steroids (both systemic and topical administration) and infections are the reason of elevated intraocular pressure in patients after HSCT. No correlation between stem cells and glaucoma has been observed [9, 50, 58-59].

Ischemic microvascular retinopathy (IMR)

In long-term follow-up changes in retinal small vessels with endothelium loss, capillaries obstruction and microaneurysms may develop. Total body irradiation, cyclosporine treatment and conditioning regimens with busulfan or carmustine are potential risk factors for IRM. IRM presents with cotton-wool patches, retinal edema and hemorrhages, optic nerve edema and proliferative retinopathy. Patients symptoms vary from asymptomatic to sight threatening forms, one or both eyes can be affected [9,43,60-66].

Other complications

The review of the literature provides some more complications connected with the posterior eye segment. Two cases of central retinal vein occlusion (CRVO) has been reported. The pathophysiology of CRVO after HSCT is not fully understood, but hypertension, hyperlipidemia, hypercoagulability and hyperviscosity are possible factors associated with it [9,66]. Retinal hemorrhages and detachment reported after HSCT are usually connected with other disorders like infectious (e.g. viral, protozoan) retinitis or neovascularization due to ischemic retinopathy (e.g. IMR, CRVO) [9,43,61,66].

Analyzing ocular complication after HSC we have to remember about toxicity of used medications.

Both topical and systemic corticosteroids are responsible for elevation of intraocular eye pressure and cataract formation, moreover their topical prolonged use is associated with decrease of epithelial healing and infections. Locally administered ophthalmic corticosteroids may be also the reason of tear-film instability, epithelial toxicity, crystalline keratopathy, decreased wound strength, orbital fat atrophy, ptosis, limitation of ocular movement, inadvertent intraocular injection and reduction in endogenous cortisol [9,67]. Immunosuppressants (i.e. tacrolimus and cyclosporine) used in topical therapy can cause conjunctival injection, burning and stinging sensation. Farther, cyclosporine systemic treatment was described as a risk factor for IMR [9,60,62-62,68]. Voriconazole therapy is connected with the risk of blurred vision, photophobia, changes in visual acuity, disturbances of color perception, visual hallucinations [69]. Scopolamine patches (antiemetics after high-dose therapy) potentially led to pupil problems (anisocoria/mydriasis after contamination) [9,70]. Antipsychotics are responsible for reduced accommodation, mydriasis, pigmentation of conjunctiva, cornea, eye lids and retina. Selective serotonin reuptake inhibitors influence accommodation [71,72]. Antihistamines, anticholinergics, antidepressants, antihypertensives and mucolytics increase risk of DES [9,72-74]. cGMP-specific phosphodiesterase type 5 inhibitors (erectile dysfunction drugs: sildenafil, vardenafil, tadalafil, avanafil) cause increased light perception, blurred vision, blue tinge in color perception, nonarteritic ischemic optic neuropathy (NAION) [9,72,75]. Multidose, topical used drops (e.g. lubricants, contain preservatives, that influence ocular surface. The most common Benzalkonium chloride – BAK disrupts tear stability, causes corneal and conjunctival epithelium damage and induces inflammatory changes that depends on dose and time of use A comprehensive review of local administrated medicines and DES with the list of medicines and herbs has been prepared by Askeroglu., et al [73,76-78-80].

Conclusions

Within last years, HSCT have been accepted as a standard in many hematological disorders. Advances in both pre – and post-transplant diagnostic and therapeutic procedures prolonged recipients’ survival. Unfortunately, it means that the number of patients with complications increases. Ocular problems affect majority of treated patients and are important factors reducing their quality of life and day activity.
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For the most common, not related with rejection complication as GVHD is, ocular manifestation may be the only sign of the disease or as a distinctive manifestation helps to diagnose systemic form. Groups of experts working on HSCT and GVHD have appreciated the meaning of ophthalmological examination in recipients’ care. They suggest precise ophthalmological examination connected with additional tests (corneal staining, Schirmer test without anesthesia, grading of conjunctival injection) and questionnaires of patient-reported symptoms (e.g. OSDI, NIH eye score) before and after HSCT to detect early post-transplant disease. They also highlight the necessity of cooperation between transplant specialists and ophthalmologists to provide optimal, long-term postoperative care. Early identification of complications allows to start adequate therapy or to modify on-going treatment. Therefore, as they imply, a prospective study evaluating a comprehensive ophthalmic evaluation pre- and post-transplantation to diagnose new onset dry eye or other chronic ocular non-GVHD and GVHD-related complications is needed.

Bibliography


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