

# Graft versus host disease: clinical evaluation, diagnosis and management

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Received: 7 November 2012 / Revised: 23 January 2013 / Accepted: 25 February 2013 / Published online: 17 March 2013  
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**Abstract** Graft versus host disease (GVHD) can be a devastating complication following bone marrow transplantation. Acute or chronic systemic GVHD can be lethal, and severe damage of different organs and tissues can occur with both types of GVHD. Ocular involvement, either in an acute or chronic presentation, may range from mild to severe with accompanying vision loss present in 60–90 % of patients. Chronic ocular GVHD, the most common form of GVHD, affects mainly the lacrimal gland, meibomian glands, cornea and conjunctiva, mimicking other immunologically mediated inflammatory diseases of the ocular surface without specific symptoms or signs. However, dry eye disease is the main manifestation of GVHD. The long-term treatment of ocular GVHD continues to be challenging and involves a multidisciplinary approach wherein the ophthalmologist plays a major role. Besides systemic immunosuppression and ocular lubricants, topical steroids and topical cyclosporine are commonly prescribed. Newer therapeutic interventions for moderate and severe ocular GVHD include the use of serum eye drops and scleral contact lenses. In this manuscript, we review the mechanisms, clinical findings, and treatment of ocular GVHD.

**Keywords** Dry eye · Ocular surface inflammation · Stem cells transplantation · Keratinization · GVHD

## Introduction

Allogeneic (genetically different, same species) hematopoietic stem cell transplantation (HSCT) is a curative therapy for a variety of hematological malignancies, autoimmune diseases, inherited disorders of metabolism, histiocytic disorders, and other malignant solid tumors [1–3]. The number of HSCTs continues to increase, with more than 30,000 procedures performed annually across the world [2]. The number of unrelated donors transplants, which are most commonly performed, is expected to double within the next 5 years due to improvements in techniques, including donor leukocyte infusions and isolation of umbilical cord stem cells [2, 3].

Syngeneic transplantation, between identical twins, represents the optimal form of HSCT and, unlike other allogeneic donors, does not carry risk of graft versus host disease (GVHD) [4]. Even with sibling donors, which are more likely than unrelated donors to be HLA-matched, 25–35 % of recipients develop GVHD [2, 4]. Despite HLA matching between a patient and donor (sibling or unrelated), substantial numbers of patients still develop GVHD because of differences in minor histocompatibility antigens that lie outside the matched HLA loci [2, 4].

GVHD remains the most frequent and serious complication limiting broader application of HSCT. Given the increasing number of transplant recipients, larger numbers of GVHD patients are expected in the near future. As many recipients of HSCT become long-term survivors, their quality of life and late complications have become increasingly important. Herein we review the mechanisms, clinical findings, and treatment of ocular GVHD.

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## Pathophysiology

### Sources of hematopoietic stem cells

Peripheral blood stem cells (PBSC) have largely replaced marrow for autologous and most allogeneic transplantations; unfortunately, peripheral-blood stem cells also contain T cells that increase the incidence and prolong the course of GVHD [2]. A process called apheresis or leukapheresis is used to obtain PBSCs for transplantation [2, 3].

Another source of hematopoietic stem cells is the umbilical cord blood [5]. In cases of urgent transplantation or if donors cannot be found, umbilical cord blood can be used. The establishment of a worldwide network for umbilical cord blood cell procurement, typing, and storage has resulted in a large collection and cryopreservation that has facilitated more than 7,000 unrelated transplants. Cord blood as a source of stem cells has several advantages: its transplantation requires less-stringent HLA matching than is required for that of peripheral blood or marrow, and mismatched cord-blood cells are less likely to cause GVHD [6, 7]. A recent study has reported that the incidence of dry eye was significantly higher in the recipients of peripheral blood stem cells than those receiving bone marrow or cord blood [8].

### Preparation of donor

For 4 or 5 days before apheresis, the donor may be given granulocyte colony-stimulating factor (G-CSF) to increase the number of stem cells in circulation. The stem cells are isolated from circulation based on the cell membrane expression of CD34+, a hematopoietic stem cell marker. These peripheral blood CD34+ stem cells are capable of forming colonies of granulocytes/macrophages, erythrocytes, and other multipotential or immature progenitors. The CD34+ stem cells are frozen until they are infused to the recipient.

### Preparation of recipient

Recipient first receives a conditioning regimen consisting of chemotherapy, which is often combined with radiotherapy and T-cell-depleting antibody designed to immunosuppress the host in order to decrease the possibility of graft rejection, and, when used to treat cancer, to reduce the number of malignant cells. This is followed by the infusion of donor cells [2].

### Basis for tissue damage

Whereas bone-marrow cells and G-CSF-mobilized PBSCs are both enriched with hematopoietic progenitors, they also

contain mature T cells that are responsible for graft rejection. [2] Three main strategies to deplete T cells and decrease the incidence of GVHD have been proposed: (1) selection of T cells ex-vivo before transplantation; (2) positive selection of CD34+ stem cells ex vivo by immunomagnetic separation [9]; and (3) antibodies against T cells in vivo [10]. These approaches showed substantial reduction of both acute and chronic GVHD. Unfortunately, reduced frequency of severe GVHD is offset by high rates of graft failure, relapse of malignant disease, infections, and Epstein-Barr virus-associated lymphoproliferative disorders. Moreover, overall survival has not significantly improved as compared with non-T-cell-depleted bone marrow [9, 10].

In contrast with acute GVHD (aGVHD), the pathophysiology of chronic GVHD (cGVHD) is not well understood. Current data suggests that Th1 subpopulation of cells play a critical role in the pathogenesis of aGVHD, whereas Th2 cells may be central in pathogenesis of cGVHD [11].

## Classification of GVHD

Graft versus host disease presents in an acute or chronic form. Historically, the acute and chronic forms were arbitrarily defined based on the time of onset since transplant (less than or more than 100 days, respectively) [2]. A clear distinction between acute and chronic forms of GVHD as originally described can no longer be delineated, given the alterations in the recipient's immunosuppression [2, 12]. Mindful of factors that produce clinical variability among transplant recipients, in 2005, a National Institutes of Health working group sought to standardize the definitions of acute and chronic GVHD (Table 1). Currently, the diagnosis of cGVHD is based on specific signs, degree of organ involvement (mild, moderate, severe), laboratory data, or histopathological confirmation, rather than time of onset since transplant (Table 2) [13].

### aGVHD

Despite prophylactic measures, the incidence of aGVHD is estimated to be 40–60 % among patients receiving transplants from HLA-identical sibling donors and 75 % in patients receiving HLA matched unrelated donors [14]. The sine qua non of aGVHD is selective epithelial damage of target organs [15] such as skin, liver, gastrointestinal tract within 14–42 days of infusion [12] (Fig. 1).

A “hyperacute” form of GVHD may occur within 14 days of infusion, in patients with severe HLA mismatched donor or in those that have received inadequate GVHD prophylaxis [12]. Hyperacute GVHD is manifested by high fever, severe cutaneous component (generalized erythema with

**Table 1** Categories of acute and chronic graft versus host disease (GVHD)

Category	Time of symptoms after hematopoietic cell transplantation (HSCT)	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic Acute GVHD	≤ 100 days	Yes	No
Persistent, recurrent, or late onset acute GVHD	> 100 days	Yes	No
Chronic GVHD			
Classic Chronic GVHD	No time limit	No	Yes
Overlap Syndrome	No time limit	Yes	Yes

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desquamation), in addition to hepatitis and intestinal symptoms; this form of GVHD may be rapidly fatal [13].

### cGVHD

The chronic form of graft versus host disease (cGVHD) has features resembling autoimmune disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Patients who have received stem cells/bone marrow from an HLA (human leukocyte antigen) mismatched related donor or from an HLA matched unrelated donor are at an increased risk of cGVHD [2]. Other factors that increase the risk of cGVHD include older recipients and those who have already experienced aGVHD [2].

Symptoms usually present within 3 years after allogeneic HSCT and are often preceded by a history of aGVHD [2, 4]. Manifestations of cGVHD may be restricted to a single organ or tissue or may be widespread. The diagnostic criteria are listed in Table 3. Dry eye is the most frequent ocular complication usually occurring approximately 6 months post-transplantation [16]. Chronic GVHD can lead to debilitating sequelae such as joint contractures, loss of sight, end-stage lung disease or mortality from profound chronic immune suppression induced life-threatening infections [2, 4].

**Table 2** Chronic graft versus host disease (GVHD) signs

<b>Skin:</b> Poikiloderma; lichen planus-like features; sclerotic features: morphea-like features, lichen sclerosus-like features; often areas of depigmentation: hypopigmentation or hyperpigmentation
<b>Nails:</b> Nails dystrophy or loss
<b>Hair:</b> Alopecia, scaling
<b>Mouth:</b> Xerostomia, restriction of mouth opening from sclerosis; mucosal atrophy; pseudomembranes and ulcers
<b>Muscle, fascia, joints:</b> Fasciitis, myositis, or joint contractures
<b>Gastrointestinal/Liver:</b> Anorexia, weight loss, esophageal web or strictures, Elevation of total bilirubin and liver enzymes
<b>Lungs:</b> Restrictive or obstructive defects on pulmonary function tests, bronchiolitis obliterans, pleural effusions
<b>Kidneys:</b> Nephrotic syndrome
<b>Heart:</b> Pericarditis
<b>Bone Marrow:</b> Thrombocytopenia, anemia, neutropenia

### Ocular surface manifestations

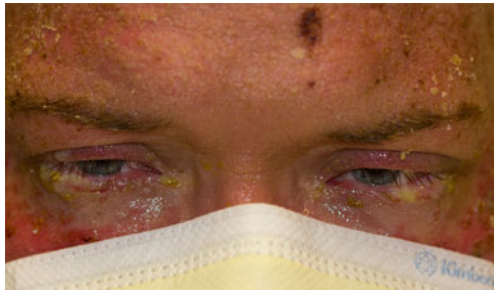
#### Symptoms and signs

Ocular cGVHD mimics other immunologically mediated inflammatory diseases of the ocular surface and there are no specific symptoms or clinical signs. Ocular manifestations, present in 60–90 % of patients with cGVHD, primarily affect structures of the anterior segment, mainly the lacrimal gland, meibomian glands, and conjunctiva [17] (Fig. 2). Typical symptoms of cGVHD are dry eye, photophobia, foreign body sensation, irritation, burning, epiphora, redness and blurriness (Table 4) [18, 19].

#### Target tissues

##### Lacrimal gland

The lacrimal gland is an important ocular target for the pathogenesis of GVHD [17, 20, 21]. Fibrotic processes often affect the lacrimal gland reducing its secretory capacity or even causing complete stasis with distended ductules and obliteration of ducts lumen, similar to bile duct damage seen in liver cGVHD [20]. Histological studies also showed extensive destruction, tissue atrophy and fibrosis of the



**Fig. 1** A 28-year-old male patient developed generalized skin pain and pruritus a month after allogeneic PBSC transplantation. Evaluation of periocular skin showed erythema with some areas of skin desquamation and bullae formation. Evaluation of lid margins showed areas of severe keratinization. A clinical diagnosis of acute graft versus host disease (aGVHD) was done based on the clinical findings

tubuloalveolar glands and ducts in the lacrimal gland with an increase in CD34+ stromal fibroblasts accompanied by mild lymphocytic infiltration [21].

#### *Meibomian glands*

Besides aqueous tear deficiency, progressive decline of conjunctival goblet cells and the dysfunction of meibomian glands contribute to the overall breakdown of the ocular tear film causing severe keratoconjunctivitis sicca [17, 22]. In vivo confocal microscopy shows destruction of the ductal epithelia due to lymphocyte infiltration, sloughing of epithelial cells, pseudomembrane formation, and subsequent excessive fibrosis around the orifice, ducts, ductules, and acini of the meibomian gland, all these findings together may explain the development of meibomian gland disease [23].

#### *Conjunctiva*

Pseudomembranous conjunctivitis can rarely occur in cGVHD and is partly considered as an acute variant of GVHD [22]. Sterile inflammatory conjunctival involvement is a common finding, which can be accompanied by formation of pseudomembranes, loss of lashes and stenosis or closure of the lacrimal punctum. Palpebral and subtarsal conjunctival scarring is seen in a number of patients, sometimes resulting in the formation of cicatricial lagophthalmos [22, 24] (Figs. 3 and 5).

**Table 3** Diagnostic Criteria for chronic graft versus host disease (cGVHD)

Distinction from acute GVHD
Presence of at least one diagnostic clinical sign of cGVHD
Presence of at least one distinctive manifestation confirmed by biopsy or other relevant tests
Exclusion of other possible diagnoses

#### *Cornea*

Corneal findings include punctate keratopathy, formation of mucus filaments, painful erosions and eventually secondary corneal infections [22, 24]. Figure 2 less frequently, sterile corneal stromal necrosis and perforations may occur [22, 24, 25]. Superior limbic keratoconjunctivitis in the setting of ocular cGVHD is believed to be more common in peripheral stem cell transplantation patients compared with bone marrow recipients [17] (Figs. 4 and 5).

#### Diagnostic evaluation

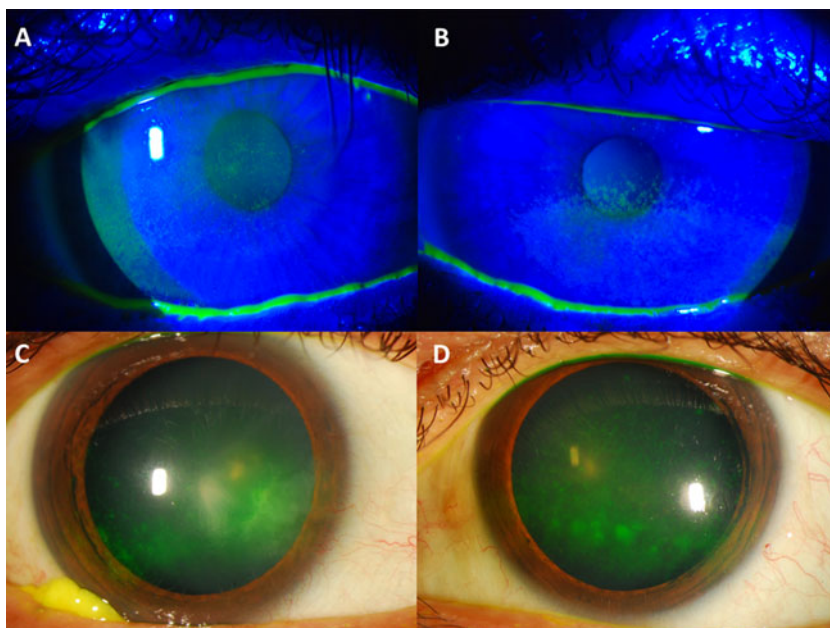
Vital staining using fluorescein, rose bengal or lissamine green needs to be performed. In the clinical setting, the staining profile of lissamine green is nearly identical to that of rose Bengal and they are considered to be interchangeable [26]. Fluorescein staining is usually used for cornea staining and rose Bengal or lissamine green for conjunctival staining. Additional tests for ocular surface examination include: tear break up time, schirmer test, tear evaporimetry, meibomian gland examination, conjunctival and corneal impression cytology, cornea sensitivity and other tests [26]. Schirmer score of less than 5 mm or new onset of dryness with a Schirmer of 6–10 mm is sufficient for a diagnosis of cGVHD if another organ is affected [13].

Wang et al. [27]. evaluated the baseline profiles of ocular surface and tear function alterations using tear evaporimetry, meibomian gland examination, impression cytology, and cornea sensitivity for a detailed ocular surface evaluation in patients with cGVHD, post-HSCT patients without dry eye disease, and healthy controls. They found decreased corneal sensitivity and an increased rate of meibomian gland obstruction in all post-HSCT patients. They also found that cGVHD-related mild and severe dry eyes showed significantly decreased goblet cell density compared with normal controls and post-HSCT without dry eye specimens. Moreover, high grades of squamous metaplasia and increased number of inflammatory cells with a decrease in number of goblet cell were found in the severe versus mild dry eye patients. as a form of posterior blepharitis, is the most common cause of evaporative-type dry eye disease. The authors speculated that the extent of the inflammatory process has a pivotal role in the outcome of cGVHD related dry eye disease with changes in tear evaporation, cornea sensitivity and goblet cell density acting as determinants of the ocular surface status, with MGD as a form of posterior blepharitis being the most common cause of evaporative-type dry eye disease [27].

Tabbara et al. reported the largest series of ocular involvement following allogeneic HSCT [24]. They retrospectively evaluated 620 patients that underwent allogeneic HSCT from bone marrow, peripheral blood and umbilical



**Fig. 2** Slit lamp examination in two different patients affected with chronic (c)GVHD following allogeneic bone marrow transplantation. **a** and **b** a mild form of corneal staining is noted, fluorescein staining is mostly localized to the interpalpebral area. A normal tear meniscus is noted. **c** and **d** a more severe form is shown. More diffuse and confluent staining in the interpalpebral zone is present. Tear meniscus is absent and mucus discharge noted



cord. Although only 34 of the 620 developed cGVHD, 80 of 620 patients (13 % of the total) developed some form of eye involvement. The most common ocular complication was dry eye syndrome with or without cGVHD. Twenty-nine of 34 patients with cGVHD had keratoconjunctivitis sicca. Patients with keratoconjunctivitis sicca who did not have cGVHD may have developed lacrimal deficiency secondary to immunosuppression, total body irradiation, or both. Four patients developed vernal or atopic keratoconjunctivitis after allogeneic HSCT from atopic donors.

Fifteen patients had corneal ulcers including bacterial corneal ulcers (10), herpetic keratitis (1), and sterile epithelial defects (4) [24]. Five patients with cGVHD developed ocular cicatricial pemphigoid-like clinical picture with evidence of conjunctival cicatrization, fornices obliteration, symblepharon, conjunctival keratinization and punctal occlusion [24]. It is important to realize that severe immunosuppression from treating cGVHD can lead to opportunistic

ocular infections, such as CMV retinitis or bacterial corneal ulcers [24].

In a prospective study of 101 patients [18], ocular GVHD developed in 54 patients manifesting combination of dry eyes in 42 %, conjunctivitis in 28 %, blepharitis in 26 %, and uveitis in 4 %. Chronic systemic GVHD developed in 45 of 101 patients and was strongly associated with the occurrence of ocular GVHD, specifically with dry eye. The severity of dry eyes and pseudomembranous conjunctivitis increased over time, although most patients were already treated for their ocular and systemic GVHD. It was interesting that the highest prevalence of ocular GVHD was observed in related donors (60 %) compared to matched unrelated donors (45 %). This might reflect the effect of antithymocyte globulin in the conditioning regimen for patients with matched unrelated donors, which causes T-cell depletion and consequently prevents GVHD.

Interestingly, Inamoto et al. reported that Schirmer test correlated poorly with both clinician-reported and patient-reported changes in cGVHD, demonstrating that Schirmer test is a poor diagnostic test of dry eye [28].

**Table 4** Ocular surface signs and symptoms in graft versus host disease (GVHD)

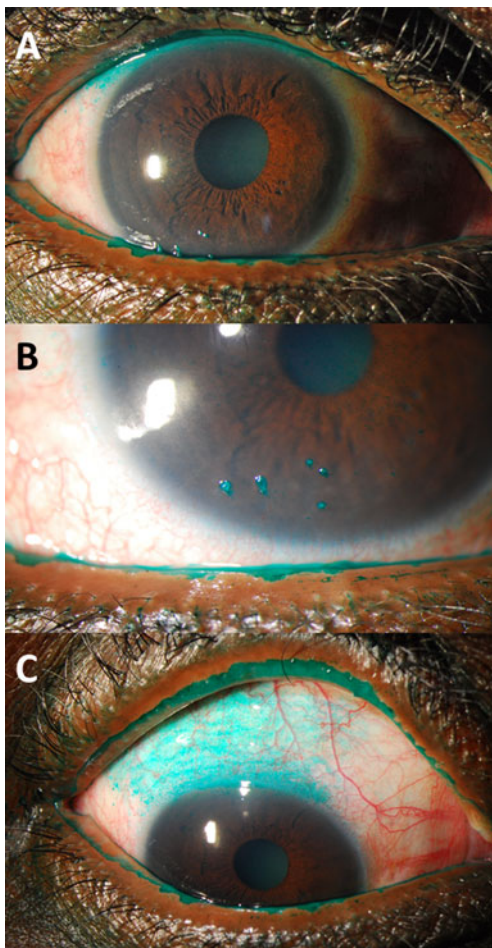
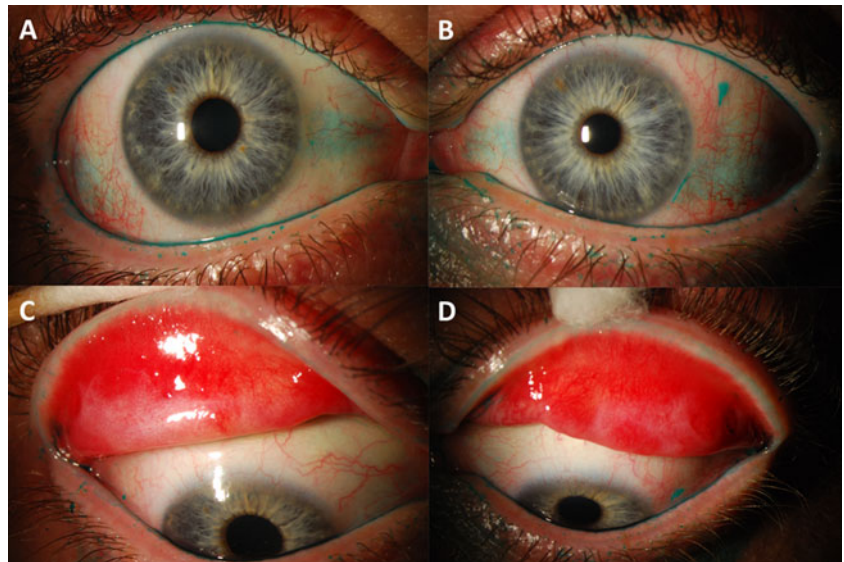
Acute ocular GVHD	Chronic ocular GVHD
Pseudomembranous conjunctivitis	Keratoconjunctivitis Sicca, Filamentary keratitis
Corneal ulcer	Meibomian gland dysfunction
Herpes keratitis	Corneal Melting
Lid margin ulceration	Superior limbal keratitis
	Episcleritis, Scleritis
	Conjunctival redness, conjunctival scarring
	Lid margin keratinization

### Treatment of systemic GVHD

#### Prevention of GVHD

Prevention of aGVHD by the use of pharmacologic prophylaxis is an integral component to the management of patients undergoing allogeneic HSCT [4, 12, 22]. A regimen based on methotrexate with a calcineurin inhibitor, a cytoplasmic enzyme important for activation of T cells, is standard practice and is recommended in different studies [14]. The

**Fig. 3** Slit lamp examination in a patient affected with cGVHD following allogeneic bone marrow transplantation. **a** and **b** a mild form of lissamine green staining in the cornea and conjunctiva is localized to the interpalpebral area. **A** decreased tear meniscus is noted. **c** and **d** evaluation of the tarsal conjunctiva shows subconjunctival fibrosis and abundant scarring in both eyes



**Fig. 4** A 65-year-old African American patient status post bone marrow transplant and a diagnosis of cGVHD complains of severe discomfort, dryness and decreased vision. **a** an absent tear meniscus is noted. **b** areas of subepithelial haze in the interpalpebral cornea and mucus filaments are noted on the right cornea. **c** Staining of the superior limbal area suggestive of superior limbal keratitis is noted

most widely used regimen includes a combination of either cyclosporine or tacrolimus with a brief course of methotrexate [12, 22]. For higher risk groups (such as mismatched donors, older patients) more intensive immunosuppression is often required [2, 4, 22].

#### Treatment of established GVHD

Although many therapeutic options have been used in the management of ocular GVHD, adequate treatment remains a challenge. The management is guided by a multidisciplinary approach, including adjustment of immunosuppression and aggressive supportive care. The treatment approach should include multiple strategies (topical and oral medications, surgery, environmental control, and systemic immunosuppression). Communication with the transplantation team is crucial in the optimal management of GVHD patients. Symptomatic mild cGVHD may often be treated with local therapies alone (e.g., artificial tears, topical steroid, serum drops). However, in patients with cGVHD that involves three or more organs or severe damage in any single organ, systemic immunosuppressive therapy may be considered.

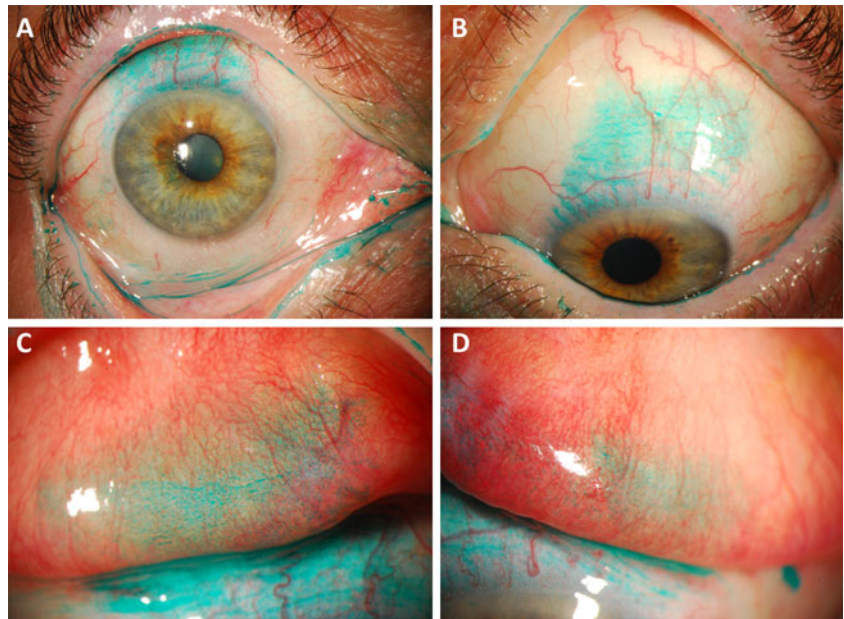
Use of steroids (with or without a calcineurin inhibitor) is the standard of care, but findings of a randomized trial of more than 300 patients with cGVHD observed no difference between cyclosporine plus prednisone versus prednisone alone [29].

#### Treatment of ocular GVHD

Patients with ocular symptoms need close ocular supportive care focused on improving ocular surface moisture and decreasing ocular surface inflammation.



**Fig. 5** A 61-year-old white female patient status post bone marrow transplant and a history of cGVHD complains of severe decreased vision, discomfort and dryness. **a** and **b** slit lamp photos show prominent lissamine green staining in the upper limbal region of both eye. **c** and **d** everted upper lids show punctate staining of the tarsal conjunctiva and prominent subconjunctival scarring



### Topical lubricants

The traditional treatment for dry eye symptoms consists of topical lubricants [26]. Many brands are available and there is a large individual variability in symptoms relief efficiency and tolerance. No data is available on the efficacy of specific artificial tears medications in ocular GVHD. Although artificial tears and lubricants are needed to lubricate the ocular surface, ocular cGVHD is a complex problem of the ocular surface with multiple dysfunctional tear components.

### Topical corticosteroids

Corticosteroids remain essential for controlling active chronic graft-versus-host disease. Systemic steroids represent the mainstay in the treatment of acute (exacerbations of) cGVHD but not enough data are available on the efficacy of topical steroids in ocular GVHD. In a small study of seven patients with conjunctival GVHD, resolution or improvement of the conjunctival signs was achieved using topical corticosteroids but the signs of keratoconjunctivitis sicca remained unchanged [30]. Patients receiving topical corticosteroids should be monitored for adverse effects. In presence of corneal epithelial defects, stromal thinning, or infiltrates, topical corticosteroids are contraindicated.

### Topical cyclosporine A

Cyclosporine A is a cyclic polypeptide produced by the fungus *Tolypocladium inflatum* Gams. Cyclosporine 0.05 % ophthalmic emulsion (Restasis; Allergan, Inc., Irvine, CA) has been FDA-approved for treatment of dry eye disease since 2003 [31]. Cyclosporine A emulsion has shown to decrease the

number of activated T cells in the ocular surface, increases the goblet cell density of the conjunctiva, decreases epithelial cell apoptosis and reduce proinflammatory cytokines [32]. Treatment with CsA, 0.05 % or 0.1 %, gave significantly greater improvement than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values) in patients with moderate to severe dry eye not related to GVHD [33]. In a small study of eight cGVHD patients treated with cyclosporine 0.05 %, ophthalmic suspension twice a day for at least 3 months. Researchers noted mean Schirmer scores increases, tear breakup time improvement and subjective symptoms improvement [34]. In another study of only 16 patients (32 eyes) with GVHD, dry eye symptoms improved in 62.5 % of patients and corneal fluorescein staining improved in all eyes after a mean follow-up of 90 days [35]. Baptista Malta reported a retrospective study with 105 patients, of whom 43 patients developed cGVHD. All patients were initially started on topical cyclosporine before the HSCT. They conclude that cyclosporine is helpful in decreasing the incidence and severity of dry eyes in patients who are under topical cyclosporine before the HSCT [36].

Although beneficial effect of topical cyclosporine on ocular GVHD has been documented in several studies comprised of small number of cases, there is at present, no large randomized study that clearly suggests its usefulness as a consequence of the rare incidence of ocular GVHD.

### Tacrolimus

FK506 (tacrolimus) is a macrolide antibiotic extracted from the soil fungus *Streptomyces tsukubaensis* and its mechanisms of action and pharmacokinetics are similar to CsA [37], although

the immunosuppressive potency of tacrolimus *in vitro* is 50–200 times greater. Although the beneficial effect of systemic tacrolimus on ocular GVHD has been observed [14, 37], topical administration might form a better treatment option because of the adverse effects associated with its long-term systemic administration. Except for two case reports in which ocular GVHD was successfully treated, not enough data is available on the use of topical tacrolimus [38, 39].

#### Autologous serum eye drops

Fox et al. described serum drops as a tear substitute free of preservatives in 1984 [40]. Autologous serum contains vitamin A, epidermal growth factor, fibronectin, transforming growth factor beta, which all are needed for a healthy ocular surface epithelium [41]. The efficacy and safety of autologous serum drops were investigated in a small study of 14 patients with ocular GVHD and severe cGVHD not responsive to conventional artificial tears therapy. After 4 weeks of treatment, significant improvement was observed in dryness symptoms and fluorescein scores, and also in rose bengal staining and tear break-up time [42]. The improvement was noted in all patients at the 4-week follow-up [42]. The risk of contamination and subsequent infection forms a possible complication of autologous serum drops.

#### Contact scleral lenses

In patients with cGVHD affecting the ocular surface, two different types of lenses can be used, the bandage soft lens and the scleral rigid lens. The fluid-ventilated, gas-permeable scleral lens has been effective in mitigating symptoms and resurfacing corneal erosions in the treatment of moderate and severe ocular surface disorders of multiple etiologies. The fluid-filled reservoir shields the cornea from blink trauma, noxious environmental stimuli, and inflammatory mediators in the tears. The body-temperature saline reservoir also prevents corneal cooling and nerve firing that occurs during the inter-blink intervals [43].

One of the scleral lenses used (Boston Scleral Lens Prosthetic Device) was approved for the management of corneal disorders by the Food and Drug Administration in 1994. Takahide published a retrospective review on nine patients fitted for refractory ocular surface disease secondary to cGVHD [44]. Contact lens fitting was prompted by debilitating ocular discomfort, visual impairment, or keratopathy. Some of the patients evaluated were using artificial tears, cyclosporine eye drops, punctal plugs, autologous serum tears, and moisture chamber eye wear. All patients reported improvement of ocular symptoms, reduced use of topical lubricants after fitting and improvement in the ocular surface disease index [44].

The same group published results of 33 consecutive patients with severe dry eye from cGVHD, unresponsive

to conventional therapy. Ninety-four percent of patients reported improvement in photophobia in the worse eye. Ninety seven percent of patients reported improvement in life quality with no complications noted during the follow-up period [45].

Schornack reported the successful use of the Jupiter scleral contact lens (Medlens Innovations, Front Royal, VA or Essilor Contact Lens, Inc., Dallas, TX) in the management of ten eyes of five patients with cGVHD. All patients had improvement in symptoms and some improved visual acuity. Jupiter lenses are commercially available in the US, and may therefore be more accessible and affordable to patients who could potentially benefit from this treatment [46].

Although scleral lenses are maybe the most important tool in the armamentarium, their use is not widespread. Published data suggests that scleral rigid gas permeable lenses are an important therapeutic option for patients with recalcitrant ocular surface compromise and debilitating symptoms. In our experience, high cost, inadequate fitting, poor tolerance by some patients, and discomfort with blinking in presence of severe meibomian gland disease and keratinization are some of the drawbacks. To our knowledge, no comparative prospective study has evaluated these two different types of available scleral lenses.

### Prognosis of GVHD

#### Systemic GVHD

Cahn and colleagues recently reported on a multicenter study comparing the IBMTR (International Bone Marrow Transplant Registry) and the Glucksberg scales. In general, patients with grade C (IBMTR) [47] or grade III (Glucksberg) [48] acute GVHD have about a 30 % probability of long-term survival. Those with grade D/grade IV acute GVHD, have under 5 % long-term survival. Patients without GVHD or with grade A-B/grade I-II acute GVHD have above 80 % probability of long-term survival [49].

#### Ocular GVHD

Few reports have studied the long-term prognosis in patients affected with ocular cGVHD. Sales et al., in a case series of 49 patients, report that in the long-term, many patients with cGVHD may experience improved dry eye symptoms as a result of effective treatment. Although only nine patients completed this 3-year prospective case series, stable visual acuity, tear production, and lissamine green staining and a statistically insignificant improvement in dry eye symptoms was reported [50].



Another retrospective cohort study reported that of 56 patients with cGVHD, 39 % developed symptoms of photophobia, irritation and foreign body sensation [51]. Over time, patients required fewer topical medications to control their symptoms; only 5 % of patients required more than two medications for dry eye disease management at the end of follow-up [51].

In contrast, Ogawa et al.'s series of 53 patients suggested that the symptoms of dry eye, including ocular fatigue, foreign body sensation, pain, blurring, photophobia, and epiphora, were almost universally worse among 22 participants at 30 months after HSCT in comparison to before HSCT [16].

## Conclusions

As the number of stem-cell transplants performed worldwide increases, it is important that ophthalmologists taking care of these patients are able to understand the basics of HSCT, as well as to recognize and treat the ophthalmic manifestations and complications of GVHD. Early recognition and treatment of ocular GVHD may be important to halt the progress of this sight threatening disease. A multidisciplinary approach is needed. An individualized assessment of each patient and the combined use of the different medications and devices available is needed to help these patients deal with a chronic, and in some cases, very difficult to treat debilitating disease.

## Methods of literature search

A PubMed literature search was conducted for manuscripts related to GVHD and ocular GVHD. Key words included GVHD, acute GVHD, chronic GVHD, ocular GVHD, scleral contact lenses, serum drops and cyclosporine.

**Conflicts of interest** None.

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