Review Article

Update on ocular graft-versus-host disease

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Ocular graft-versus-host disease (oGVHD) occurs as a complication following hematopoietic stem cell transplantation and is associated with significant ocular morbidity resulting in a marked reduction in the quality of life. With no current consensus on treatment protocols, management becomes challenging as recurrent oGVHD often refractory to conventional treatment. Most authors now diagnose and grade the disease based on criteria provided by the National Institutes of Health Consensus Conference (NIH CC) or the International Chronic oGVHD (ICCGVHD) consensus group. This article will provide an insight into the diagnostic criteria of oGVHD, its classification, and clinical severity grading scales. The inflammatory process in oGVHD can involve the entire ocular surface including the eyelids, meibomian gland, corneal, conjunctiva, and lacrimal system. The varied clinical presentations and treatment strategies employed to manage them have been discussed in the present study. The recent advances in ocular surface imaging in oGVHD patients such as the use of meibography and in vivo confocal microscopy may help in early diagnosis and prognostication of the disease. Researching tear proteomics and identification of novel potential tear biomarkers in oGVHD patients is an exciting field as they may help in objectively diagnosing the disease and monitoring the response to treatment.

Graft-versus-host disease (GVHD) often limits the success of allogeneic hematopoietic stem cell transplantation (allo-HSCT) due to its morbidity and mortality in the posttreatment period. Ocular GVHD (oGVHD), the most common long-term complication, has a varying spectrum of disease severity, mediated by immune dysregulation and tissue inflammation with single or multisystem involvement resulting in tissue fibrosis and organ dysfunction.[1] Characteristic diagnostic features involving skin, mouth, gastrointestinal (GI) tract, lung, fascia and genitalia, eyes, nails, scalp, or hair have been observed.[2]

Clinical manifestations of systemic acute GVHD (aGVHD) mostly involve skin, GI tract, and liver. Acute oGVHD is a relatively rare manifestation of aGVHD with an incidence of about 7.2% among post-allo-HSCT patients.[3,4] Chronic GVHD (cGVHD) is a complex immune-mediated disorder that can target multiple organs, usually manifesting in the first year after HSCT, and may occur in up to 30–70% of the patients undergoing HSCT.[5] The incidence of chronic oGVHD has been reported to be about 40–60%[6,7] with lower incidences of only one-third being affected as noted by some recent Asian studies.[8–10] Up to 60–90% of the patients with chronic GVHD may show oGVHD manifestations.[11–13]

Risk factors for oGVHD include male recipients of female donors,[14] skin,[7,13,14] oral mucosa,[7,13] liver,[15] or GI tract involvement during acute or chronic stages of GVHD and lung involvement in cGVHD.[10] Preexisting diabetes,[10] recipients of transplants from Ebstein-Barr Virus (EBV) positive donors, Asian and other ethnicities compared to Caucasian ethnicity were more likely to develop oGVHD.[15] It has been found that the incidence of severe dry eyes in cGVHD is higher in recipients of peripheral blood stem cell transplantation (PBSCT) or bone marrow transplantation (BMT) in comparison to those receiving cord blood transplantation (CBT).[16] This review is a comprehensive overview of the current understanding of the oGVHD. A PubMed search was conducted using the keywords: GVHD, transplant, HSCT, BMT, PBSCT, dry eye disease (DED), dry eye. Featured articles from the year 1983 till May 2020 were included.

Current Perspectives on oGVHD Diagnostic Criteria Definition and Grading

Historically, post-allo-HSCT GVHD classification was deliberated as aGVHD when onset was within the first 100 days of HSCT or cGVHD when it occurred thereafter.[1] To standardize the tools on reporting cGVHD, the 2005 National Institutes of Health (NIH) Consensus Development

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Projects on Criteria for Clinical Trials in Chronic GVHD issued guidelines for standardized diagnostic criteria, severity scoring, interpretation of histopathology reports, development and validation of biomarkers, response criteria, designing clinical trials, ancillary therapy, and supportive care. The NIH Consensus Conference (NIH CC) classified GVHD based on differences in organ involvement rather than the period of symptoms manifestation whereas in aGVHD manifestation seen after the first 100 days, persisting from a prior episode and occurring as a recurrence or of late-onset were also included. The broad category of cGVHD included classic GVHD and overlap syndrome. Overlap syndrome was characterized by the occurrence of aGVHD and cGVHD symptoms together.[17–19] As per the NIH criteria, diagnosis of cGVHD requires at least one diagnostic manifestation of GVHD or a distinctive GVHD manifestation supported by biopsy, laboratory tests, or radiology in the same or another organ.[19] The revised 2014 NIH criteria changed little in terms of 2005 diagnostic criteria but addressed certain areas of controversy such as overlap syndrome, distinguishing active GVHD features from irreversible "fixed" deficits, and also revised the diagnostic criteria for certain organs including the eye. Some authors have recommended that the diagnosis of oGVHD alone should be enough to confirm cGVHD.[6,20] Risk factors for cGHVD include human leukocyte antigen (HLA) mismatch or an unrelated donor, older patient or donor age, female donor for a male recipient, donor lymphocyte infusion, mobilized peripheral blood cell graft, and previous aGVHD.[21]

Definition of oGVHD diagnostic criteria

The two widely acknowledged diagnostic criteria for oGVHD are as follows:

NIH CC 2014 criteria: The diagnostic criteria were based on Schirmer's test and slit-lamp examination [Table 1].[2]

The International Chronic oGVHD (ICCGVHD) consensus group diagnostic criteria are based on scores derived from the Ocular Surface Disease Index (OSDI), Schirmer's test without anesthesia, corneal fluorescein staining (CFS), conjunctival injection, and presence of systemic GVHD. The diagnostic categories included no oGVHD, probable oGVHD, and definite oGVHD [Table 2].[20]

While a comparative study of the newer NIH 2014 criteria and ICCGVHD criteria found moderate agreement between the two, ICCGVHD criteria were noted to be better at differentiating oGVHD patients from non-oGVHD DED, due to its more stringent criteria which also considers the status of systemic GVHD.[22] It is interesting to note that the study reporting the validation of ICCGVHD criteria for oGVHD, in comparison to Best Clinical Practices (BCPs), found that BCPs tended to over-diagnose the milder cases of oGVHD, while there was a better agreement between the two in higher severity of disease (BCP was defined as oGVHD evaluation by a highly trained single expert in ophthalmology with extensive [>20 years] clinical experience in evaluating oGVHD patients, based on comprehensive clinical examination).[23]

Other diagnostic criteria, which have been used in studies on GVHD, include the following:

The Japanese Dry Eye Society criteria for diagnosing dry eye, modified in 2016, requires only the presence of an unstable tear film (tear film breakup time [TFBUT <5 s]) and subjective symptoms (in contrast to the 2006 criteria which had required positive results in ≥2 of the following categories: subjective symptoms, abnormalities of tears, and epithelial damage for diagnosis of dry eye).[24] All published data from Japan on oGVHD have employed the 2006 criteria and the 2016 version is yet to be used in published literature describing oGVHD patients.[25]

An extension of the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) criteria originally meant for conventional DED has been recently advocated for diagnosing oGVHD in patients undergoing allo-HSCT[26] according to which any new positivity or worsening of the existing disease after allo-HSCT may be considered to be sufficient for diagnosing oGVHD. Diagnosis required ocular surface discomfort symptoms with OSDI score ≥13 along with any one of the following; TFBUT <10 s; tear osmolarity >308 mOsm/L in either eye (or an inter-eye difference >8 mOsm/L); ocular surface staining (>5 corneal spots, >9 conjunctival spots or lid wiper epitheliopathy of ≥2 mm in length and/or ≥25% sagittal width).[27]

Prospective comparison of the degree of agreement between three oGVHD diagnostic criteria (NIH criteria, ICCGVHD criteria, and TFOS DEWS ll criteria) applied before and after allo-HSCT, noted that oGVHD diagnosis was higher when the pre-allo-HSCT evaluation was not included as compared to inclusion of pre-allo-HSCT evaluation. TFOS DEWS-ll criteria was found to provide a higher proportion of diagnosis as oGVHD possibly due to the incorporation of TBUT in diagnostic criteria, which made patients with the hyper-evaporative disease and Meibomian gland (MG) abnormalities inclusive even in presence of normal Schirmer's

Table 1: Ocular GVHD diagnostic criteria and grading scale according to the NIH criteria (2014)				
Diagnostic Criteria	Schirmer test ≤5 mm/5 min or Schirmer test 6-10 mm/5 min due to other causes and KCS by slit-lamp examination (Preferably with confirmation of normal Schirmer test values at an established baseline)			
Severity Grade	**Score 0**	**Score 1**	**Score 2**	**Score 3**
Symptoms	KCS confirmed by an ophthalmologist in the absence of symptoms, the requirement of eye drops or ADL	Mild	Moderate	Severe
The requirement of lubricant eye drops		≤3 times/day	>3 times/day or punctal plug	Special eyewear required to relieve pain
ADL impairment		Not affected	Partially affected without new vision impairment due to KCS	Significantly affected or unable to work or loss of vision due to KCS

KCS: keratoconjunctivitis sicca, ADL: activities of daily living

Table 2: Ocular GVHD diagnostic criteria and grading scale according to the International Consensus Criteria on chronic ocular graft-versus-host disease (ICCGVHD)

Diagnosis	None (points)	Probable ocular GVHD (points)	Definite ocular GVHD (points)	
Systemic GVHD (−)	0-5	6-7	≥8	
Systemic GVHD (+)	0-3	4-5	≥6	
Severity scale	Schirmer test (mm)	CFS (points)	OSDI (points)	Conjunctival injection
0	>15	0 (No staining)	<13	None
1	11-15	<2 (Minimal Staining)	13-22	Mild/Moderate
2	6-10	2-3 (Mild-moderate staining)	23-32	Severe
3	≤5	>4 (Severe staining)	≥33	-
oGVHD disease severity	None	Mild-Moderate	Severe	
The total score is obtained by adding the severity score for Schirmer test + CFS + OSDI + conjunctival injection	0-4	5-8	9-11	

CFS-corneal fluorescein staining, OSDI-ocular surface disease index. Adapted with permission from Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI, *et al*. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: proposed diagnostic criteria for chronic GVHD (Part I). Sci Rep 2013; 3:3419

test. The influence of a pre-allo-HSCT evaluation on diagnostic performance seems to be much more for NIH and ICCGVHD criteria emphasizing that majority of pre-allo-HSCT DED cases were due to tear film instability.[26] Pre-allo-HSCT evaluation for DED is now widely recommended to help differentiate between preexisting dry eye and the new-onset DED diagnosed as oGVHD post-allo-HSCT.

Severity grading

Various grading schemes devised for scoring the severity of ocular involvement in cGVHD include Jab's grading for conjunctival involvement in aGVHD[4] and Robinson's grading for conjunctival involvement in cGVHD.[28] [Tables 3 and 4] The most commonly used are the NIH and ICCGVHD scoring systems. The other grading criteria described include the German/Austrian/Swiss (GAS) Consensus Conference[29,30] and Japanese Dry eye score.[25]

The NIH scoring system ranges from score 0 for asymptomatic keratoconjunctivitis sicca (KCS) diagnosed on slit lamp by an ophthalmologist up to Score 3. A notable modification in the 2014 consensus was the removal of Schirmer's test values from NIH 2005 severity scoring criteria as it was found to have a high false-positive or false-negative rate in various studies with poor correlation to change in symptoms [Table 1].[2,31]

A more detailed scoring system by the ICCGVHD elaborated severity score of 0 to 3 each is assigned to OSDI, Schirmer, and CFS while conjunctival hyperemia (based on slit-lamp photographs) is scored from 0 to 2 [Table 2].[20]

German/Austrian/Swiss Consensus Conference on Clinical Practice in cGVHD (GAS CC) proposed a comprehensive grading and staging criteria for oGVHD including the involvement of different ocular tissues, inflammatory activities, the presence of complications, and functional impairment. The extent of ocular surface involvement including the eye and MGs, severity of inflammation, and complications such as corneal perforation, secondary glaucoma, and deterioration of visual acuity are documented.[29,30]

The ICCGVHD criteria emphasize more on comprehensive coverage of objective findings by incorporating the OSDI which is a more specific patient symptom metric as compared to the subjective assessment of symptoms or the frequency of instillation of eye drops in the NIH criteria. However, oGVHD patients presenting exclusively with lid or MG involvement may be missed by the ICCGVHD criteria. GAS CC is an even more comprehensive approach in grading the disease by additionally including the involvement of lids, MGs, or lacrimal glands and the presence of complications due to oGVHD. Unlike the NIH CC, both GAS CC and ICCGVHD criteria included parameters, reflective of the severity of ocular surface inflammation activity.[20,30]

Clinical Features

Clinical symptoms

Eye pain and lacrimation are the main complaints in acute oGVHD.[32] The clinical symptoms of chronic oGVHD usually resemble those seen in DED or (KCS syndrome. The distinctive manifestations of chronic oGVHD as per the NIH consensus criteria comprise new onset of dry, "gritty," or painful eyes.[2] Other symptoms may include irritation, watering, photophobia, redness, and blurring.[33]

Clinical signs

Acute oGVHD [Fig. 1], commonly presents as pseudomembranous or hemorrhagic conjunctivitis.[32,34] A less severe form with conjunctival injection or chemosis may also be seen.[4] Corneal signs include epithelial sloughing,[4,35] corneal epithelial keratitis, or filamentary keratitis which may be secondary to the conjunctival cicatrization due to the disease.[36] Some patients may present with lagophthalmos.[37] Ocular involvement in aGVHD is considered an extremely poor prognostic sign associated with higher GVHD-related mortality.[32] The clinical grading system for conjunctival involvement in acute ocular GVHD is given in Table 3.[4]

Chronic oGVHD primarily is a result of inflammatory and fibrotic changes in the ocular surface comprising of the cornea, conjunctiva, lacrimal glands, MGs, and eyelids. It should

be noted that other factors such as conditioning regimens, irradiative therapy, and immunosuppression might also impact the clinical manifestations in addition to the GVHD disease process itself.

Corneal signs due to the KCS syndrome include punctate keratitis, epithelial erosions, and epithelial defects which may progressively worsen to keratinization, stromal thinning, melt, and perforation [Fig. 2a]. Recurrent corneal perforation, sometimes bilaterally, is not uncommon with calcareous degeneration or lipid keratopathy being seen rarely. The progression from the stage of epithelial ulceration to perforation tends to be rapid and is often refractory to standard medical or surgical treatment modalities.[38-41] Progressive ocular surface inflammation leads to corneal neovascularization, conjunctivalization, and less commonly limbal stem cell deficiency, which will adversely affect visual acuity.[41-44] Decreased corneal sensation tends to predispose the development of neurotrophic ulceration.[45]

Conjunctival involvement is a distinctive aspect of chronic oGVHD, seen in about half of the chronic oGVHD, and is a marker for severe systemic involvement of GVHD.[4,46] Less severe cases manifest as conjunctival hyperemia or chronic conjunctivitis involving both palpebral and bulbar conjunctiva. Other less common features include cicatricial conjunctivitis with obliteration of fornices, cicatricial entropion, symblepharon, ankyloblepharon, and lagophthalmos, which could progress to conjunctival keratinization and punctal occlusion.[4,46,47] Conjunctival subepithelial fibrosis seen as fine white lines under intact conjunctival epithelium is indicative of a past insult.[48] The grading scale for cicatricial conjunctivitis in chronic oGVHD is given in Table 4.[49] Pseudomembranous and serosanguineous conjunctivitis are less frequently seen forms of conjunctival involvement which though more characteristic of acute oGVHD, have been seen in chronic oGVHD too.[4] Subtarsal fibrosis in upper tarsus noted in 40% chronic oGVHD cases along with the worsening of ocular surface epitheliopathy in these patients was suggested to be of diagnostic value in oGVHD.[50] Decreased conjunctival goblet cell density and increased squamous cell metaplasia and surface keratinization of the ocular surface has also been noted.[45] Superior limbal keratoconjunctivitis (SLK) like inflammation has been reported as a manifestation of oGVHD, which can worsen to LSCD and corneal pannus formation. This has been attributed to soft tissue microtrauma from increased frictional forces compounded by tear mucin deficiency due to goblet cell loss.[51]

Meibomian glands (MG) are severely affected by rapid and aggressive destruction over time in chronic oGVHD[52] resulting in unstable tear film aggravating the DED. T-cell-mediated damage to the MG epithelial cells is primarily responsible for the gland dysfunction with hyperkeratinization of duct epithelium and sub-epithelial-stromal fibrosis contributing to obstructive Meibomian Gland Dysfunction (MGD) in chronic GVHD.[53] The prevalence of MGD ranges from about 47.8–68.4% in oGVHD.[54,55] The MG loss and damage in oGVHD are often more severe than those seen in other DED such as Sjogren's syndrome.[56] Early detection and aggressive management can perhaps help in minimizing damage in oGVHD as few studies have shown some reversibility of MG damage in the initial stages.[52,57,58] Meibography revealed a loss of about 80% MG function in oGVHD patients

Table 3: Clinical staging for acute conjunctival GVHD

Stage	Description
1	Conjunctival hyperemia
2	Conjunctival hyperemia with a chemotic response or serosanguinous exudates
3	Pseudomembranous conjunctivitis
4	Pseudomembranous conjunctivitis plus corneal epithelial sloughing

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Table 4: Clinical staging for chronic conjunctival GVHD

Stage	Description
1	Hyperemia of bulbar or palpebral conjunctiva in at least one eyelid
2	Fibrovascular changes of the palpebral conjunctiva along the superior border of the upper eyelid, or the lower border of the tarsal plate of the lower eyelid, with or without conjunctival epithelial sloughing, involving 25% of the total surface area in at least one eyelid.
3	Fibrovascular changes of the palpebral conjunctiva along the superior border of the upper eyelid, or the lower border of the tarsal plate of the lower eyelid, involving 25-75% of the total surface area in at least one eyelid
4	Changes as in grade 3 involving >75% of the total surface area with or without cicatricial entropion in at least one eyelid

evaluated over 1 year with over 25% being refractory to treatment.[52] Lid margin irregularity, vascular engorgement, plugging of MG, and displacement of mucocutaneous junction due to duct outlet obstruction are also seen.[52,59] *In vivo* confocal microscopy (IVCM) imaging has documented morphological changes like inflammatory cell infiltration, gland atrophy, and fibrosis.[59] Morphological changes in MG seem to have a multifactorial etiology inflammatory damage of glands due to the GVHD alone. Besides damage before allo-HSCT,[58,60] conjunctival inflammation related to GVHD, mechanical compression due to subconjunctival fibrosis, effects of condition regimen with radiation therapy or chemotherapy also seem to be responsible factors. MG gland infiltration by tumor cells or immunosuppression damaging cell viability[52,58,61] were held to be responsible reasons for poor correlation of MG loss to the severity of oGVHD or subconjunctival fibrosis.[48,52,58] However, MG loss does seem to be more with increasing severity of oGVHD.[55] As pretransplant upper lid, MG atrophy has been implicated to be a predictive factor for the likelihood of oGVHD,[58] close monitoring of the MG status by infrared meibography or pre- and post-allo-HSCT IVCM can help in early detection of the posttransplant ocular inflammatory process.[52,58] Prevalence of posterior blepharitis associated with MGD has been reported in 47–63% of chronic GVHD patients, with a significant correlation with the severity of KCS symptoms.[54,62]

Lacrimal gland involvement is responsible for the tear aqueous deficiency in oGVHD with the resultant DED or KCS being the most characteristic feature in up to 69 to 77%
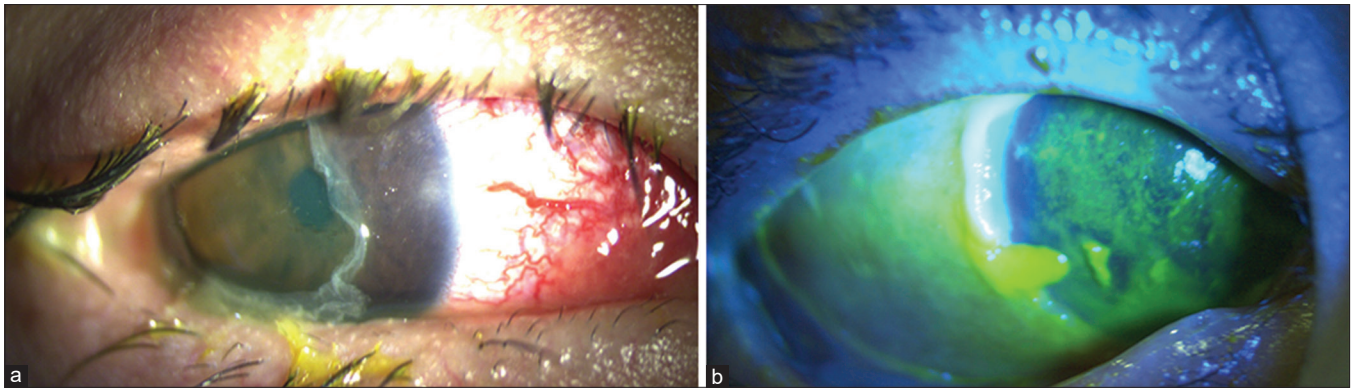
Figure 1: a and b: Clinical photograph of a case of acute ocular GVHD showing conjunctival and corneal epithelial involvement with hyperemia, acute pseudomembranous conjunctivitis, and corneal epithelial sloughing (a); fluorescein staining showing extensive ocular surface involvement with significant inflammation (b)
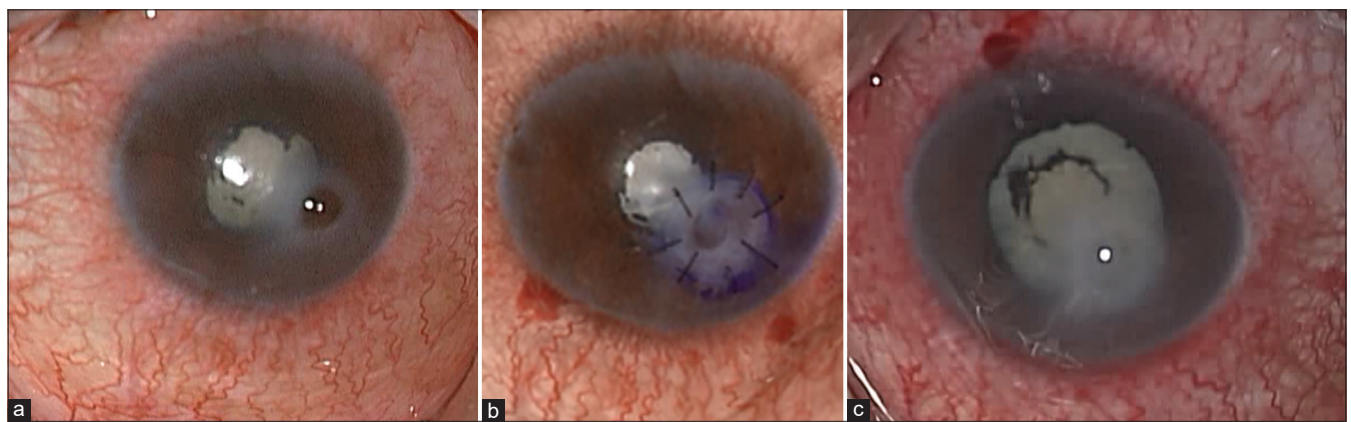

Figure 2: Clinical picture of a case of chronic ocular GVHD with corneal melt with perforation (a); tectonic patch graft performed for corneal melt (b); an intraoperative picture of the same eye at the time of cataract surgery (c)
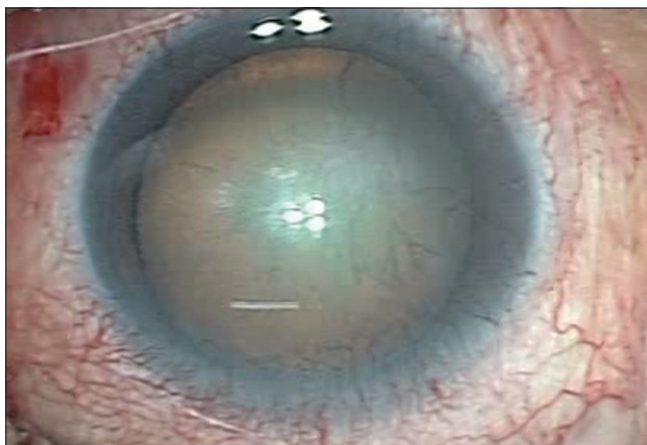

Figure 3: Clinical picture of a case of chronic ocular GVHD showing keratoconjunctivitis sicca with LSCD, corneal vascularization, and mild corneal epithelial haze with cataract

of oGVHD cases.[63] Fibrosis and inflammation caused by stromal fibroblasts with T-cell infiltration centers around the periductal area of the lacrimal gland lead to the destruction of the tubuloalveolar secretory units.[64,65] Epithelial-mesenchymal transition of the host cells may be triggered by the migration of inflammatory cells and large amounts of cytokines produced

or radiation therapy before the HSCT. About 50% of these infiltrating stromal fibroblasts are thought to be of donor origin which along with T-cells and recipient-derived fibroblasts contribute to the pathogenesis of GVHD.[53,66,67] Bilateral nasolacrimal duct obstruction (NLDO) leading to dacryocystitis has been reported in oGVHD.[68,69] NLDO induced by epithelial and subepithelial inflammation and punctal occlusion – both inflammatory and spontaneous have also been observed.[70,71]

Eyelids abnormities (lagophthalmos, trichiasis, poliosis, entropion, and less commonly, ectropion) occur due to chronic tarsal conjunctival inflammation, atrophic eyelid alterations, keratinization, and cicatricial changes.[72] True cicatricial ectropion due to mechanical shortening of the anterior lamella caused by cutaneous involvement of GVHD has also been reported.[73] Increased eyelid laxity in oGVHD, resulting from higher elastolytic enzyme (like MMP-9) activity mediated by the chronic inflammatory process both due to GVHD and systemic malignancy, compounds the ocular discomfort symptoms and ocular surface signs.[74] Eyelid skin may exhibit scleroderma-like skin lesions, pigmentary discolorations, vitiligo, and dermatitis.[36]

The other less commonly seen signs which may be seen in chronic oGVHD include cataract, episcleritis, scleritis, posterior scleritis, anterior uveitis, vitritis, and serous choroidal detachment.[29] Myeloablative chemotherapy instead of total

body irradiation as a conditioning regimen is associated with a lower rate of cataract formation and posterior segment complications.[22]

Newer Diagnostic Modalities

Though several new diagnostic methods have been added to the armamentarium of DED diagnostics,[75] the ones about the evaluation of oGVHD in recent literature will be discussed here. There is no single adequate test for oGVHD diagnosis with a combination of clinical parameters and investigational modalities being recommended.

Meibography

Meibography is a technique of *in vivo* observation of MGs[48,56-58,61,76,77]. Meibography in oGVHD shows complete or partial MG loss/atrophy, structural alteration such as distortion, or dilation of ducts.[52,56,58] Occasional finding of slender MG either pre- and early-post-HSCT has been attributed to long-term immunosuppression causing sebaceous hyperplasia which results in obstruction MGD and can be reversed in some cases.[57] As MG loss seen prior to the allo-HSCT can progress rapidly following oGVHD onset, noninvasive meibography for routine evaluation of hematological malignancies patients before and at regular follow-up posttransplant has been recommended.[58] Early detection of MGD is helpful in oGVHD prediction allowing the treating physician initiation of appropriate therapy before the onset of significant damage.[52,58]

Various subjective[76,78,79] and objective methods[77,78,80,81] for grading meibography images have been described. A cutoff value of 40% of MG area calculated using image analysis software has been adopted for diagnosing MGD in oGVHD patients.[55] Consensus on the correlation of MG area loss on meibography to oGVHD severity is not conclusive with some in agreement[55,56] and few others[48,58] not concurring. The same also applies to the correlation between ocular surface clinical parameters and MG loss on meibography.[52,55,58] Hence, besides local inflammation there seems to exist a multifactorial etiology for MGD in oGVHD.

Tear interferometry

Non-contact tear interferometry visualizes the interferometric pattern of the lipid layer of the tear film and measures its thickness, thereby providing a functional MG assessment.[77] There is a paucity of studies evaluating the lipid layer in oGVHD. A higher grade of severity of lipid layer interferometric pattern changes have been seen in oGVHD patients on DR-1s tear film lipid layer interferometry (Kowa, Tokyo, Japan) assessment[59,82] with greater instability of the lipid layer in oGVHD patients as compared to Sjogren's syndrome.[83] While different tear interferometric patterns have been described to correlate with different DED subtypes of DED, inadequate tear volume makes it difficult to observe a typical interference pattern in severe aqueous deficient (AD) Sjögren's syndrome, oGVHD, or Stevens-Johnson syndrome.[84] oGVHD with afflictions of the lacrimal gland and MG manifests a combined AD-evaporative DED and shows a reduced lipid layer thickness (LLT) in tear interferometry in comparison to non-oGVHD and healthy eyes.[85]

In vivo confocal microscopy

IVCM changes in oGVHD include decreased corneal epithelial cell density,[86] epithelial dendritic cell (DC), conjunctival epithelial immune cell (EIC),[87,88] increased goblet immune cell (GIC),[88] anterior stromal cell density, anterior stromal extracellular matrix (ASEM) accumulation (reflective of engraftment of donor fibroblasts or altered fibroblast cell populations in the host cornea),[89] reduced sub-basal nerve number and density, altered branching, reflectivity and increased tortuosity,[87–89] and altered conjunctival epithelia and stromal immune cell density.[87] IVCM changes seem to correlate well with disease severity scores (Japanese Dry Eye score, ICCGVHD).[88] While the comparison of corneal and conjunctival IVCM changes between oGVHD patients and healthy controls or post-HSCT patients without oGVHD revealed significant changes in the former,[86,88,89] these changes were of comparable severity in oGVHD and non-oGVHD DED of comparable severity. This suggests that IVCM changes are reflective of a local inflammatory phenomenon seen in oGVHD DED rather than due to systemic GVHD.[87] IVCM can, therefore, be a useful tool to study the cellular structural changes in DED with and without GVHD.[86] IVCM study of MG morphology in post-allo-HSCT revealed atrophic glands with increased surrounding fibrosis with inflammatory cellular infiltration in oGVHD compared to numerous compact glandular acini units evident in post-HSCT non-oGVHD patients.[59]

Tear film osmolarity

Tear film osmolarity is a global indicator of DED irrespective of the subtype or etiology and is considered its best single predictor[90] with a cutoff value of >310 mOsm/L for diagnosing oGVHD (98.4% sensitivity and 60.7% specificity).[91] A cutoff value of 312 mOsm/L has been recommended for differentiating definite oGVHD (as per ICCGVHD criteria) from non oGVHD (sensitivity of 91% and specificity of 82%).[92] There is a significantly raised tear osmolarity in oGVHD with a good correlation with the severity of clinical parameters (Schirmer's, TBUT, OSDI) and staining scores[57,90–92] and increasing disease severity.[91,92] Though its diagnostic efficacy in oGVHD is good, it is noted to be lower than that of Schirmer's and TBUT, with clinical dry eye tests showing a higher correlation coefficient for chronic oGVHD probability compared to tear osmolarity.[91,92] Currently, tear osmolarity in isolation is not recommended to diagnose oGVHD but is a useful supplement to clinical dry eye tests used in oGVHD diagnosis in post-allo-HSCT, given its ease of performance by non-ophthalmologist and with lower interobserver.[22,91,92]

A novel digital imaging analysis technique for quantification and morphological characterization of corneal fluorescein staining which may help distinguish DED due to Sjogren's and oGVHD has been recently proposed by Pelligrini *et al*.[93] Shimizu *et al*. evaluated corneal higher-order aberrations (HOAs) using Zernike analysis in anterior segment optical coherence tomography (CASIA system, SS-1000, Tomey, Japan) and found higher corneal HOAs in chronic ocular GVHD eyes than the non-GVHD and normal eyes, which correlated with visual acuity and severity scores.[94]

Role of Tear Biomarkers, Inflammatory Mediators, and Protein in Diagnostics

The immune reaction in GVHD comprises of donor T-cells trigger of host antigen-presenting cells (APCs), which activate the donor effector T-cells to mediate the target tissue damage. The precise role of the various subtypes of T-cells, cytokines,

and B-cells is not clear.[95] Though CD4+ and CD8+ T-cells are the predominant infiltrates in ocular surface tissues in chronic oGVHD,[96] it is difficult to classify it as pure T-Helper cell-1, T-Helper cell-2, or T-Helper cell-17-mediated disease. Studies evaluating tear cytokines in oGVHD found raised intercellular adhesion molecule-1 (ICAM-1),[97] interleukin-1 receptor antagonist (IL-1Ra),[98] IL-2,[99] IL-1 β,[97] IL-6,[9,97,99,100] IL-8,[9,85,97,98] IL-10,[9,98,99] IL -2AP70,[9] IL-17A,[9,99] interferon gamma (IFN- γ),[9,99,100] tumor necrosis factor- α (TNF-α),[99] matrix metallopeptidase 9 (MMP-9),[9,101] and vascular endothelial growth factor (VEGF).[9] Among these IL-10, IL-6, and TNF-α, IL-8, ICAM-1, IL-12AP70, VEGF, IFN- γ, and MMP-9 were found to have a fair correlation with the clinical ocular surface evaluation tests.[9,97,99,100] While these biomarkers were not raised, tear MMP 7 and MMP 9 were noted to be elevated non-oGVHD eyes post-allo-HSCT.[9] Certain tear cytokines have been proposed as possible biomarkers for chronic oGVHD (ICAM-1, IL-8, IL-1 β, IL-10, IL-17, IL-6, CXCL-10, TNF-α, MMP-9, and VEGF).[9,97–99] Comparative study of cytokines in oGVHD with non-oGVHD DED observed raised levels of ICAM-1, IL-1β, IL-6, and IL-8 and reduced levels of IL-7 and EGF.[97] Lower levels of IL-7, EGF, and IP-10 in oGVHD patients suggest a disease protective role for these mediators.[97,98] While cGVHD was conventionally thought to be T-helper cell2-mediated, recent evidence points towards the role of T-helper17 cells as key effector cells in cGVHD which is supported by raised tear levels of IL-6, IL-17 A, IL-1β, and TNF-α in oGVHD patients.[99,102] IL-17A and IL-6 may also have a role in triggering proliferation and alterations of the germinal B-cell, which are now believed to influence cGVHD pathogenesis.[103]

Recent reports of increased conjunctival neutrophil infiltration[104] and tear inflammatory mediators[101] produced by them (neutrophil elastase, MMP-9, MMP-8, and myeloperoxidase [MPO]) highlights the role of neutrophils in oGVHD immunopathogenesis with these neutrophils releasing nuclear chromatin complexes as extracellular DNA (eDNA) webs that are termed neutrophil extracellular traps (NETs).[105] oGVHD is associated with excessive accumulation of NETs which are recognized to be contributory to pathologic changes (corneal epitheliopathy, conjunctival fibrosis, ocular surface inflammation, and MGD) seen.[85]

Neutrophil secreted biomarkers (eDNA, neutrophil gelatinase-associated lipocalin [NGAL], Oncostatin M [OSM], and tumor necrosis factor F superfamily member14 [TNFSF14]) could be useful in differentiating DED due to oGVHD from other etiologies. Besides, raised levels of neutrophil elastase, myeloperoxidase, IL-8, TNF-α, and brain-derived neurotrophic factor (BDNF) were obtained in ocular washings of oGVHD.[85]

Tear total tear protein levels are reduced in oGVHD.[9] An extensive tear proteomic profiling identified 79 proteins to be differentially expressed in oGVHD as compared to non-oGVHD.[102] Structural proteins, nucleic acid binders, and oxidoreductase enzymes were seen to be prominently upregulated proteins while enzyme modulators, hydrolases, carrier proteins, receptor binding proteins, and defense and immunity-related proteins were down-regulated. Histone proteins, which are known to have pro-inflammatory proteins, were the most highly unregulated and may be associated with the increased NET formation in these eyes while Lipocalin-1, which has numerous protective effects, was the

Table 5: Treatment strategies in ocular GVHD

Treatment Type	Treatment Modality	Strategy/Goal
Pharmacological Therapy	Preservative-free artificial tears Lubricating viscous ointment	Ocular surface lubrication
	Mucolytic eye drops: acetylcysteine (5-10%) Oral muscarinic agonists (pilocarpine, cevimeline)	Tear preservation
	Topical erythromycin ointment Systemic tetracycline antibiotics (doxycycline, minocycline) and macrolide antibiotics (azithromycin)	Prevention of tear evaporation
	Topical corticosteroid drops Topical immunosuppressants (Cyclosporine, tacrolimus) Topical IL-1 receptor antagonist (Anakinra)	Reduction of inflammation
	Autologous serum eyedrops Umbilical cord or allogenic serum eye drops	Epithelial support
	Recombinant DNAse eye drops Immunoglobulin eye drops Heparin eye drops	Newer agents being evaluated for their activity against NETs
Environmental and Dietary modifications	Eyelid care and warm compresses; Humidified environment, humidifiers; Nutritional supplements (fish oil, flaxseed oil)	Tear preservation, Prevention of tear evaporation, Reduction of inflammation
Eyewear and Contact Lens	Occlusive eyewear, moisture goggles Bandage contact lens, rigid gas-permeable and scleral contact lens (PROSE)	Epithelial support
Surgical Intervention	Punctal occlusion (silicone plugs, thermal cauterization)	Tear preservation
	Superficial debridement (filamentary keratitis, pseudomembranes)	Epithelial support
	Partial tarsorrhaphy	Prevention of tear evaporation
	Amniotic membrane transplantation	Epithelial support, Reduction of inflammation
	Mucous membrane grafts Ocular surface and fornix reconstruction; Limbal stem cell transplantation	Ocular surface reconstruction epithelial support
	Cataract surgery Keratoplasty - penetrating/lamellar (therapeutic, tectonic, optical) Keratoprosthesis	Visual Rehabilitation

most downregulated protein. Other protective proteins such as Lysozyme-C and Lactotransferrin were also downregulated.[106]

Treatment

A multidisciplinary approach and coordination with the HSCT team are imperative in the management of oGVHD. In recent times, with greater emphasis on organ-specific treatment, increasing systemic immunosuppression is no longer considered an optimal treatment approach for organ-specific GVHD. The three-pronged treatment approach, as adopted in another ocular surface immune-mediated inflammatory disease, comprises lubrication and tear preservation, prevention and control of tear evaporation, and most importantly, reducing ocular surface inflammation [Table 5].[107]

Medical management

Lubrication and tear preservation

In both acute and chronic oGVHD with severe aqueous deficiency dry eye, topical lubrication with non-preserved phosphate-free artificial tears is the first-line treatment. Frequent use of tear substitutes throughout the day supplemented with viscous ointment before bedtime helps not only in preserving the ocular surface but also in diluting tears inflammatory mediators. Topical mucolytics (acetylcysteine [5–10%]) is beneficial in DED with filamentary keratitis. Though oral secretagogues, such as pilocarpine or cevimeline (selective muscarinic agonists), may be beneficial in stimulating aqueous tear flow in chronic oGVHD induced sicca symptoms, their use is limited by adverse drug reactions and toxicity. Dual treatment with topical secretagogues rebamipide and diquafosol have been used in oGVHD patients with beneficial effects.[108]

Tear preservation with punctal occlusion, either with silicone plugs (reversible) or thermal cauterization (usually irreversible) may be performed. The number of puncta to be occluded is guided by disease severity and Schirmer's test. However, the threshold for silicone plugs punctal occlusion should be low, especially in chronic oGVHD, where lacrimal gland dysfunction is irreversible. Spontaneous plug loss is a common complication, probably due to punctal subepithelial fibrosis.[71] Thermal cautery may be considered in severe cases with recurrent plug extrusion. Any associated blepharitis and MGD should be treated accordingly and achieving a maximal reduction in the lid and ocular surface inflammation is mandatory before punctal occlusion.

Prevention of tear evaporation

Tear film instability and evaporative dry eye due to MGD should be treated on usual lines with warm compresses, lid scrubs, and maintenance of lid hygiene. Topical erythromycin ointment and systemic tetracycline antibiotics, mainly doxycycline and minocycline, and macrolide antibiotics, azithromycin, help to reduce inflammation of the MGs, and subsequently meibum secretion and tear film quality. Further, nutritional supplements such as fish oil (omega-3 fatty acids) and flaxseed oil (2000 mg/d) may be helpful owing to their anti-inflammatory properties.

The use of moist chamber goggles to increase the periocular humidity has been employed to alleviate discomfort in DED patients, though the effects may be transient.[109,110]

Reducing ocular surface inflammation

Topical steroids are used in both acute and chronic oGVHD, although their role in the former remains controversial. While some studies did not find a role for topical steroid therapy in altering the disease course of pseudomembranous conjunctivitis,[4,111] Kim *et al.* suggested that the use of aggressive topical steroid therapy along with pseudomembrane removal may help improve epithelial healing and reduce cicatricial changes in these patients.[112] In chronic oGVHD, they are helpful in patients presenting with cicatricial changes.[28] Topical steroids are contraindicated in patients with corneal epithelial defects, stromal thinning, or infection. Adverse effects of long-term steroid use (glaucoma, cataracts, corneal thinning, and secondary infectious keratitis) are common comorbidities in these eyes. Hence, the use of topical immunosuppressants, (cyclosporine [CsA] eye drops, and tacrolimus ointment) has been advocated.

Topical CsA eye drops have been used with some success in patients with chronic oGVHD and KCS refractory to conventional lubrication and steroid drops. An increase in goblet cell density and epithelial cell turnover in the conjunctiva along with improvement in symptoms, corneal fluorescein staining, and basal tear secretion has been noted. Tacrolimus is similar to CsA but with greater immunosuppressive potency, and its systemic use has also shown to be beneficial in ocular GVHD.[113]

Topical IL-1 receptor antagonist (IL-1Ra) or Anakinra 2.5% (FDA approved immunomodulatory drug for rheumatoid arthritis treatment), has shown some promise in a double-masked randomized control trial with improvement in symptoms and reduction in corneal epitheliopathy after 12 weeks of instillation in oGVHD.[114] Topical Tranilast acts by inhibiting the production and/or release of ocular inflammatory mediators and cytokines and in collagen synthesis as well as TGF-β induced matrix production and is effective in treating mild dry eye associated with cGVHD.[115]

Sub-anticoagulant dose heparin (100 IU/mL) by diminishing the effects of NETs has been shown to have a therapeutic effect in oGVHD.[85] Deoxyribonuclease I (DNase), a major extracellular endonuclease, selectively targets extracellular DNA, and thus degrades NET. Early clinical trials have demonstrated the therapeutic potential of topical recombinant human deoxyribonuclease I (0.1% DNase), pulmozyme (Genentech) in patients with oGVHD DED without severe adverse effects.[116] Intravenous immunoglobulin (IVIG) through its immunomodulatory activity may reduce autoimmune-mediated inflammation in DED.[117] Topical IVIG drops application for oGVHD DED which is currently being investigated in Phase1/ll clinical trials.

Biological tear substitutes

Appropriate management of corneal epithelial erosions, corneal ulcers, and perforations are required to maintain the health and integrity of the corneal surface. Biological tear substitutes such as autologous serum act like preservative-free tears being rich in nutrients such as epithelial and nerve growth factors, cytokines, vitamin A, fibronectin, and transforming growth factor-A. It acts by providing lubrication and improving corneal sensitivity, thereby contributing to enhanced integrity.[118] However, their use is not recommended in presence of active

inflammation, systemic infections, extremes of age (infant or elderly), or overall poor health such as malnutrition. Umbilical cord serum eye drops or allogeneic serum eye drops have been tried as alternatives but are limited by the risk of transmission of serious blood-borne diseases.[119] Topical therapy with autologous platelet lysate drops rich in platelet-derived growth factors (PDGF), known to improve wound healing and corneal re-epithelization, is a safe and effective option for oGVHD patients refractory to conventional therapy.[120,121]

Contact lenses have also been used to provide ocular surface protection in oGVHD, as in other ocular surface disorders. Soft silicone hydrogel bandage contact lenses and rigid gas-permeable scleral lenses such as Prosthetic Replacement of Ocular Surface Ecosystem (PROSE) have been tried.[122] However, they should be used with caution, especially in the acute setting, keeping in mind the increased risk of infection and ischemia.

Surgical management

Surgical intervention is mostly reserved as the last resort and may be necessary for severe cases. Superficial epithelial debridement and removal of filaments are helpful in cases of filamentary keratitis. Amniotic membrane transplantation may be required in cases of persistent epithelial defects, superior limbic keratoconjunctivitis, and symblepharon formation.[123,124] ProKera (Bio-Tissue, Inc., Doral, FL), an FDA (U.S. food and Drug Administration) approved device, is a polymethylmethacrylate ring akin to a symblepharon ring that functions as a carrier for cryopreserved amniotic membrane. Its use has been described in acute oGVHD to restore ocular surface integrity and prevent more severe complications.[125] Severe cases of DED may even warrant a temporary tarsorrhaphy[126] to decrease ocular surface exposure. Mucous membrane grafts and skin grafts may be required for the management of cicatricial lid disease. Allogenic limbal stem cell transplantation from the same hematopoietic stem cell donor,[41,43,44,127] lamellar keratoplasty,[128] tectonic patch grafts [Fig. 2b], and penetrating keratoplasty[126] are performed in a limited capacity and only as a final effort, given a poor prognosis for graft survival because of severe preexisting ocular surface inflammation. Ocular surface stem cell transplantation using conjunctival and limbal allografts obtained from the patient's HSCT donor has been reported to be a promising treatment modality associated with good long-term survival of the graft.[41,43,44] Keratoprosthesis may also be considered in severe cases for visual rehabilitation with bilateral blindness; osteo-odonto keratoprosthesis has been successfully performed in a few cases.[129]

Cataract surgery in ocular GVHD

A cataract occurs commonly in patients of oGVHD, and is multifactorial in origin, resulting from a combination of toxicity from chemotherapeutic agents, total body irradiation (TBI) for the pretransplant conditioning process, and prolonged high-dose systemic and topical steroids [Fig. 2c]. In addition to keratopathy secondary to DES (dry eye syndrome), cataract is the most common cause of vision loss in oGVHD. Posterior subcapsular cataract (PSC) is the most frequently encountered and is present in most cases. Nuclear sclerosis is also present in many cases, but is relatively more common in older patients, suggesting the involutional cataract component [Fig. 3]. The reduction of glare acuity in the presence of a reasonably good Snellen's visual acuity is common.[130,131]

As cataract surgery can induce or exacerbate a preexisting DES, it is important to aggressively treat the DES and optimize the ocular surface before performing cataract surgery in oGVHD. Frequent lubrication, topical anti-inflammatory, and immunosuppressive therapy, use of punctal plugs as needed and prior treatment of any lid and adnexal pathology are important. Another preoperative challenge is obtaining accurate biometry readings and intraocular lens power calculation. Both optical biometry and topography evaluation should be performed. It is recommended to obtain multiple readings; in case of discrepancy, it is best to defer the surgery, optimize the ocular surface, and re-evaluate after a few weeks.[132]

Although the literature on cataract surgery in GVHD is limited, micro-incision cataract surgery (MICS) with phacoemulsification is beneficial in reducing ocular surface complications as compared to extracapsular cataract extraction.[133,134] Biplanar or triplanar clear corneal incisions, anterior limbal incision, or scleral tunnel incisions may be considered. Clear corneal incisions are suitable for cases with the optimized ocular surface while in severe cases, refractory to the best treatment, it will be best to consider scleral incisions for cataract surgery. The majority of the postoperative complications are due to DES (punctate keratopathy, filamentary keratitis, recurrent corneal epithelial defects), which may worsen to stromal melt and perforation in severe cases. Topical nonsteroidal anti-inflammatory drugs should be used with caution, particularly in cases of severe oGVHD, as they may increase the risk of corneal melt and ulceration. Increased IOP in the early postoperative period, worsening of preexisting glaucoma, significant visual axis opacification (VAO), and cystoid macular edema also occur commonly. About 18–44% of VAO have been reported to require yttrium aluminum garnet (YAG) capsulotomy.[133,134] Close observation and follow-up in the postoperative period and patient counseling regarding the continuation of preoperative lubricants and anti-inflammatory therapy in addition to antibiotics and steroids is of utmost importance.

Conclusion

oGVHD is a complex disease, which often shows a recurrent course and may be refractory to conventional DE therapy. It could involve the whole ocular surface, necessitating a multipronged approach of treatment. DED significantly affects the ocular surface, necessitating a multipronged approach of treatment. oGVHD may manifest as part of multisystem involvement or de-novo, in patients with no signs of systemic GVHD. It is imperative that every patient before allogeneic HSCT, be referred to a cornea specialist, to evaluate the baseline parameters for the pre-HSCT diagnosis of DED. It is also desirable to maintain a regular follow-up of these patients for early diagnosis of changes that occur on the ocular surface post HSCT. Newer diagnostic modalities have helped in diagnosing the disease earlier and also monitor its response to treatment. More recently introduced treatment agents such as topical platelet lysate and Heparin drops have shown promise, but further studies are required to establish their efficacy.

Conflicts of interest

There are no conflicts of interest.

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