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Severe corneal manifestations of graft-versus-host disease: Experience of a tertiary referral center

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ABSTRACT

Purpose: Graft-versus-host disease (GVHD) is a common complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). GVHD may affect several organs, including ocular manifestations, ranging from dry eye syndrome to sight-threatening corneal ulceration or perforation. Limited information is available about characteristics and treatments of ocular GVHD and its relation to general prognosis.
Methods: We retrospectively analyzed data from 140 patients from a tertiary ophthalmological center and confronted it with systemic data from a national bone marrow transplantation database.
Results: Most patients were treated with artificial tears, vitamin A ointment, topical anti-inflammatory agents (mostly cyclosporin and steroid drops), autologous serum eye drops, scleral lenses and punctal silicone plugs. We identified a high proportion of severe ocular manifestations, such as corneal ulceration or perforation (33 patients, 23.6 %), occurring with a median of 39 months (interquartile range (IQR): 16–96) after transplantation. Overall survival did not differ in patients with severe to non-severe ocular GVHD (5-year mortality of 8 % without and 13 % with severe ocular involvement, $p = 0.53$ for survival curves comparisons). Multivariate analysis revealed that male patients and HLA mismatch allo-HSCT were independently associated with an increased risk of severe ocular manifestations. Moreover, a high proportion of complications occurred after non-steroidal anti-inflammatory drug (NSAID) treatments.
Conclusions: Patients with GVHD should therefore undergo close ophthalmological monitoring and they should not, in any case, be treated with local ocular NSAIDs, due to the severity of potential complications.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment for certain hematological diseases. Graft-versus-host disease (GVHD) is one of the main complications of allo-HSCT. It is a multi-systemic immune-mediated disease, with various clinical presentations, resulting from a reaction between the donor's immunocompetent cells and the host's tissues. Acute GVHD (aGVHD) mainly occurs within 100 days post-allo-HSCT, with an incidence of 30–50 %, while chronic GVHD (cGVHD) usually occurs after 100 days, with an incidence of 30–60 % [1–4]. There is a continuum between aGVHD and cGVHD, but cGVHD can appear *de novo* [5].

Physiopathology of aGVHD relies mainly on donor T cells' interaction with host or donor antigen-presenting cells, activation and expansion of T-helper (Th) and T-cytotoxic (Tc) cells, as well as inflammatory mediator release [6,7]. The physiopathology of cGVHD is complex, and involves several cell types, including donor T lymphocytes, chronic inflammation and fibrosis [8].

aGVHD mainly affects skin, the digestive tract and liver. cGVHD may affect all organs, including skin, liver, gastro-intestinal tract, lungs and musculoskeletal system [1,8]. Mucocutaneous involvement is the most common manifestation of GVHD, and ocular manifestation can be found in 60 % of GVHD patients [9].

Ocular surface involvement varies from dry eye syndrome to sight-threatening corneal ulceration or perforation [10]. Other manifestations of ocular GVHD (oGVHD) are hyperemia and even

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pseudomembranous conjunctivitis for acute GVHD. Chronic GVHD includes eye dryness (with various levels of corneal fluorescein staining, decreased tear break-up-time, and/or decreased Schirmer's tear secretion), filamentary keratopathy, corneal ulcer and corneal perforation [11]. Ocular GVHD severity may be assessed with the National Institutes of Health (NIH) consensus eye scoring of chronic GVHD from 0 (no symptoms) to 3 (severe dry eye symptoms, significantly affecting activities of daily living or being unable to work because of ocular symptoms or loss of vision due to keratoconjunctivitis sicca) [12,13].

In mild dry eye syndrome manifestations, patients are not always referred to an ophthalmologist for a clinical assessment and patients are treated with artificial tears. For moderate to severe forms, anti-inflammatory agents can be administered, such as topical steroids, topical cyclosporine (from 0.05 % to 2 %), topical tacrolimus and autologous serum eye drop (ASED) [14]. Topical azithromycin is also used for its anti-inflammatory properties [14,15]. To increase tear volume, oGVHD treatment may include obstruction of canalicular puncta with silicone plugs or punctal cauterization, when recurrent plug extrusion occurs [16,17]. In cases of persistent ulceration, or in some cases of corneal perforation, the amniotic membrane can be sutured to the ocular surface (overlay graft) or directly sutured on the melted corneal stroma (inlay graft) [18]. Tarsorrhaphy may be used in cases of corneal exposure, sometimes in association with a bandage contact lens or amniotic membrane. As a last resort, tectonic keratoplasty may be needed for rare advanced corneal perforation [19].

Few studies have focused on the severe ocular complications of GVHD in relation to systemic features. The purpose of this study is to report characteristics and treatments of oGVHD patients in our tertiary center, and to relate severe oGVHD cases to overall survival and GVHD in other organs.

2. Materials and methods

2.1. Study design

This is a monocentric retrospective study. All the patients were followed in the Rothschild Foundation Hospital (Paris, France). The patients were identified in the electronic medical records of the hospital by means of a database search for the keywords "graft-versus-host" and "GVH". All the records were manually checked for the consultation motive and only the patients with an actual ocular GVHD diagnosis were included, according to 2014 NIH consensus criteria definition: new onset of dry, "gritty", or painful eyes, cicatricial conjunctivitis, keratoconjunctivitis sicca and confluent areas of punctate keratopathy after HSCT [12]. Exclusion criteria were as follows: medical history of dry eye syndrome before HSCT, ocular conditions that affect the ocular surface, including infection, allergic conjunctivitis, contact lens wear, glaucoma, or ophthalmic surgery. We analyzed all the medical records of the patients and gathered data on sex, age and visual acuity at each visit, medical examination, topical and systemic treatment. NIH eye scoring of chronic GVHD was calculated using medical record information for all the patients at the time of the study.

The Rothschild Foundation Hospital is a tertiary ophthalmologic center, therefore all patients were followed in another hospital for the management of their hematological disorder. Most patients were followed at the Saint-Louis Hospital (Paris, France). Their medical records were checked manually. For other patients, we collected data from the ProMISe database from the European Society for Blood and Marrow Transplantation. We obtained hematological and allo-HSCT data to complete our analysis, as well as data on GVHD and mortality.

Retrospective chart-review approval was obtained from the hospital's Institutional Review Board. The study adhered to the tenets of the Declaration of Helsinki.

2.2. Statistical analysis

Statistical analyses were performed using Stata (version 17, StataCorp). Continuous variables were expressed as mean ± standard deviation (SD) and compared using a student's t-test. Categorical data were expressed as proportions and were compared using Fisher's Exact Test or Chi2, depending on the number of patients. Logistic regressions were used for univariate analysis. Multivariate logistic regressions were adjusted on age, sex and HLA mismatch. GraphPad Prism 10.0.2 (GraphPad Software) was used for data analysis and graphic representation of Kaplan-Meier curves.

3. Results

A total of 145 patients have been referred to our tertiary center for ocular GVHD assessment. After matching with the national database, only 140 patients were analyzed (Fig. 1). Among them, 71 patients (50.7 %) were male, (Table 1). The median age of the patients was 52 years. The most frequent indication for allo-HSCT was acute myeloid leukemia (56 patients, 40 %). Most patients received reduced intensity conditioning (85 patients, 60.7 %) and the graft source was from peripheral blood in 103 patients (73.6 %). Most donors were HLA-matched related or unrelated donors (n = 124, 88.6 %). The median time between transplant and ophthalmology consultation was 36.5 months (min.-max. 1–382), reflecting a clear majority of chronic oGVHD, with only 1 patient with an interval under 3 months (0.71 %). Median follow-up in ophthalmology was 8.5 months (min.-max. 0–147).

Ocular manifestations are reported in Table 2. Most of our patients presented eye dryness symptoms (127 patients, 90.7 %) and punctate keratitis (112 patients, 80.0 %). Conjunctival fibrosis was present in 32 patients (22.9 %). Severe corneal complications were noted in 33 patients, with corneal ulceration (23.6 %) complicated for 7 patients with corneal perforations (5 %). A total of 95.7 % of our patients had a maximum score of 2 or 3, according to the cGVHD NIH eye scoring system (Table 3, 37.1 % score 2, and 58.6 % score 3). Among all patients, 109 had acute non-ocular GVHD (77.9 %, mostly grade I-II 60.0 %) and 127 had chronic non-ocular GVHD (90.7 %, with 47.9 % severe cGVHD). Only 4 patients had neither acute nor chronic non-ocular GVHD (2.9 %).

Concerning treatments, 134 patients (95.7 %) were treated with artificial tears (Table 4) and 87 (62.1 %) with vitamin A ointment. Topical anti-inflammatory agents were used with most patients, mainly cyclosporin drops (from 0.05 % to 2 %, 71 patients, 50.7 %), steroid drops (32 patients, 22.9 %) and tacrolimus drops (3 patients, 2.1 %). Autologous serum eye drops were used by 41 patients (29.3 %). Forty-six patients (32.9 %) had contact lenses, mostly scleral lenses (41 patients, 29.3 %), while the 5 other patients had soft lenses, or were not specified. Fifty-six patients (40.0 %) received punctal silicone plugs. Sixteen

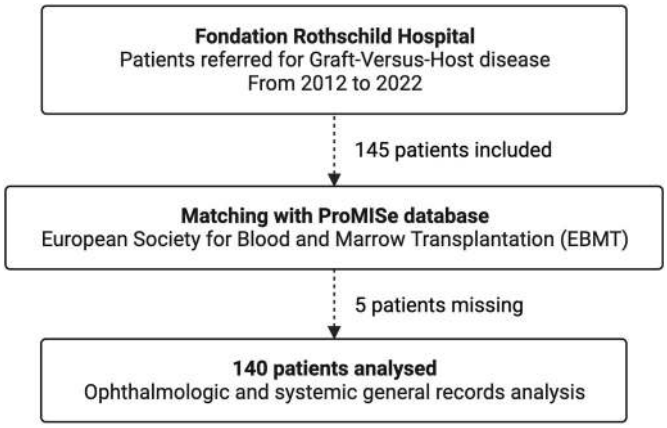

Fig. 1. Flowchart of the study.

Table 1
Demographics, hematological and transplant characteristics.

Characteristics	Total
Patients	140
Sex, Male, N (%)	71 (50.7 %)
Age, year, median (min., max.)	52 (10–76)
Ophthalmological follow-up, months, median (min., max.)	8.5 (0–147)
Interval between HSCT and first ophthalmologic referral, months, median (min., max.)	36.5 (1–382)
Hematological disease, N (%)	
- Acute myeloid leukemia	56 (40.0 %)
- Others	18 (12.9 %)
- Multiple myeloma	12 (8.6 %)
- Non-Hodgkin lymphoma	12 (8.6 %)
- Acute lymphoid leukemia	11 (7.9 %)
- Myelodysplastic syndrome	7 (5.0 %)
- Myeloproliferative syndrome	7 (5.0 %)
- Chronic myeloid leukemia	7 (5.0 %)
- Chronic lymphoid leukemia	4 (2.9 %)
- Hodgkin lymphoma	4 (2.9 %)
- Aplastic anemia	2 (1.4 %)
Conditioning regimens	
- Reduced intensity conditioning	85 (60.7 %)
- Myelo-ablative conditioning	55 (39.3 %)
Donors	
- Matched related or unrelated donors	124 (88.6 %)
- Mismatched related or unrelated donors	16 (11.4 %)
Graft source	
- Peripheral blood stem cells	103 (73.6 %)
- Bone marrow	37 (26.4 %)

Table 2
Ocular manifestations.

Ocular manifestations	N (%)
Eye dryness/Sicca	127 (90.7 %)
Punctate keratitis	112 (80.0 %)
Blepharitis	66 (47.1 %)
Conjunctival fibrosis	32 (22.9 %)
Filamentary keratopathy	43 (30.7 %)
Corneal ulceration	33 (23.6 %)
Neovascularization	12 (8.6 %)
Corneal perforation	7 (5.0 %)
Bacterial infection	6 (4.3 %)
Herpes infection	3 (2.1 %)

Table 3
GVHD characteristics.

GVHD characteristics	Total
Diagnosis of non-ocular acute GVHD during follow-up, N (%)	109 (77.9 %)
- Grade I-II, N (%)	84 (60.0 %)
- Grade III-IV, N (%)	25 (17.9 %)
- Interval between HSCT and aGVHD, months, median (IQR)	0.97 (0.59–1.57)
Diagnosis of non-ocular chronic GVHD during follow-up	127 (90.7 %)
- Mild, N (%)	24 (17.1 %)
- Moderate, N (%)	35 (25.0 %)
- Severe, N (%)	67 (47.9 %)
- Interval between HSCT and cGVHD, months, median (IQR)	6.72 (4.95–11.44)
Maximum National Institute Health eye scoring of GVHD	
- Score 0, N (%)	4 (2.9 %)
- Score 1, N (%)	2 (1.4 %)
- Score 2, N (%)	52 (37.1 %)
- Score 3, N (%)	82 (58.6 %)

GVHD: Graft-versus-Host disease; aGVHD: Acute GVHD; cGVHD: Chronic GVHD; IQR: Interquartile range.

patients (11.4 %) underwent corneal amniotic membrane surgery for the management of persistent epithelial defect inlay and overly grafts when stromal melt was present, followed by 2 tectonic keratoplasty 1.4 % due to corneal perforation. One patient underwent evisceration (0.7 %),

Table 4
Ocular treatments.

Ocular treatments	N (%)
Tear Substitution and Retention Therapies	
- Artificial tears	134 (95.7 %)
- Punctal plug	56 (40.0 %)
Anti-inflammatory agents	
- Topical cyclosporin	71 (50.7 %)
- Topical steroids	32 (22.9 %)
- Topical azithromycin	31 (22.1 %)
- Oral doxycycline	28 (20.0 %)
- Topical tacrolimus	3 (2.1 %)
Therapeutic lens	
- Scleral	41 (29.3 %)
- Soft	3 (2.1 %)
Trophic and pro-healing therapies	
- Vitamin A ointment	87 (62.1 %)
- Autologous serum eye drops	41 (29.3 %)
- Amniotic membrane	16 (11.4 %)
Tectonic grafts: keratoplasty	2 (1.4 %)
Evisceration	1 (0.7 %)

carried out for a corneal perforation complicated by endophthalmitis, that did not respond to antibiotics. Seven patients (5.0 %) had cataract surgery during follow-up.

As most of our patients had a score of 2 or 3 with the NIH eye score, we wanted to further study the most severe patients. Therefore, we focused on patients with corneal ulceration or perforation (Table 5). In this sub-group of 33 patients (23.6 % of the total), oGVHD complications emerged, with a median of 39 months (min.-max.:1–330, IQR 16–96) after transplantation. Among this subgroup, 7 patients were hospitalized (21.2 %) in the ophthalmology department for a median of 6.5 days (95 % confidence interval 2.6–15.7), 15 patients had at least 1 surgery, including corneal amniotic graft, keratoplasty or evisceration (45.5 %), with a median of 2 per patient. Healing time (defined as complete epithelialization with fluorescein test) was less than 7 days for 5 patients (15.2 %), between 7 and 14 days for 8 patients (24.2 %), and more than 14 for 8 patients (24.2 %). Among these 33 patients, 5 (15.2 %) received topical non-steroidal anti-inflammatory drugs (NSAIDs, topical indomethacin, or flurbiprofen) before the complication, whereas no patients in the group without severe corneal involvement were treated with NSAIDs ($p < 0.001$). Three patients were treated with NSAIDs, 3 drops a day after cataract surgery as standard protocol, in ignorance of the diagnosis of systemic GVHD or the NSAID precautions (and there was no ocular involvement at that time). First patient was a 63-year-old male and was treated with indomethacin 3 drops/day after cataract surgery. It was stopped due to severe superficial punctate keratitis at day 8 and complicated with a corneal ulceration at day 15. He presented a corneal perforation in same eye 3 months after the surgery treated with amniotic membrane graft. Second patient was a 68-year-old female treated with indomethacin 3 drops/day after cataract surgery, stopped at day 6 due

Table 5
Characteristics of patients with corneal ulceration or perforation.

Patients with corneal ulceration or perforation (n = 33)	Total
Months after transplantation, median (min.-max.)	39 (1–330)
Hospitalized patients, N (%)	7 (21.2 %)
Hospitalization duration, days, median	6.5
Recurrence, N (%)	2 (6.1 %)
Patients with surgery	15 (45.5 %)
Number of surgeries among surgery patients, median	2
Healing duration, N (%)	
- Less than 7 days	5 (15.2 %)
- Between 7 and 14 days	8 (24.2 %)
- More than 14 days	8 (24.2 %)
- Lost to follow-up	12 (36.4 %)
Risk factors	
- Topical non-steroidal anti-inflammatory	5 (15.2 %)
- Cataract surgery less than 3 months before	3 (9.1 %)

to large corneal ulceration treated with amniotic membrane graft with good result. Third patient was a 69-year-old male treated with indomethacin 3 drops/day after cataract surgery. He presented a corneal ulceration after surgery observed by an ophthalmologist in another center. The patient was seen in our center only 1 month after surgery and the ulceration was re-epithelializing after indomethacin discontinuation. Fourth patient, a 68-year-old female, was treated within 3 weeks of indomethacin, with 3 drops/day in another center after a YAG capsulotomy and presented corneal ulceration 1 month after the capsulotomy. The deep ulceration was treated with 2 consecutive amniotic membrane grafts. The fifth patient, a 43-year-old male, had a past history of ulceration related to oGVHD followed in our center, but was treated with local NSAID treatment in addition to local dexamethasone for an indeterminate period by his family practitioner. Despite immediate cessation and a 2-amniotic membrane graft, the cornea perforated, and the patient underwent tectonic keratoplasty. In comparison, 4 patients underwent cataract surgery during follow-up without NSAIDs and we did not observe any corneal complications.

To better understand the evolution toward severe oGVHD, we analyzed possible risk factors for corneal ulceration or perforation (Table 6). The male patient had an odds ratio (OR) of 2.36 in univariate analysis (p = 0.039). All the other factors listed in Table 7 were not significantly associated, such as acute or chronic GVHD, whether affecting skin, mucosa, liver or gastro-intestinal tract. In multivariate analysis (Table 8), sex (OR 2.78, p = 0.019) and HLA mismatch allo-HSCT had an OR of 3.69 versus HLA matched related or unrelated allo-HSCT (p = 0.025).

We compared the overall survival of patients with corneal ulceration and those without. Kaplan-Meier curves were not significantly different (Fig. 2, p = 0.53), with a 5-year mortality of 8 % without and 13 % with severe ocular involvement. Hematological median follow-up time from transplantation was 99 months (min.-max.: 8–446).

4. Discussion

Ocular GVHD is frequently associated with other organ involvement in patients with allo-HSCT. In this study, we reported the management of severe oGVHD and investigated the relationship between these patients and GVHD affecting other organs. We are therefore reporting a large series of patients with oGVHD followed in a reference center for ophthalmology. Our findings revealed that patients with severe corneal manifestations were not associated with severe GVHD of other organs and we did not observe a difference in overall survival. An important result was that a significative amount of severe corneal complication was due to inadequate NSAID use with GVHD patients.

In our study about patients with ocular GVHD, 77.9 % of them presented acute non-ocular GVHD and 90.7 % non-ocular cGVHD. Most of our patients presented severe manifestations of oGVHD, with mostly NIH score of 2 and 3. Liao et al. observed a median onset of GVHD 8 months after HSCT, with more severe cases involving delayed diagnosis, including corneal complications [20]. However, the median time between transplant and ophthalmology consultation in our study was 36.5 months and only 1 patient presented symptoms less than 3 months after transplantation. The main reason is that our hospital is a referral center, and patients with mild manifestations were followed and treated only by the hematologist or a general ophthalmologist. In most cases, oGVHD diagnosis was already done and patients were mostly referred to our center for severe manifestations or complications. Therefore, we observed severe corneal complications in 23.6 % of our patients, with either corneal ulceration or perforation.

oGVHD is a complex disease, affecting multiple ocular structures. Firstly, inflammation and fibrosis affect the lacrimal gland of oGVHD patients with organ destruction by activated T cells [21]. This leads to decreased tear production and tear instability. Among this, conjunctiva and cornea are also affected. In cornea, recruitment of donor CD4 and CD8 T cells has been observed [7]. This includes notably an increased expression of matrix metalloproteinase 9 (MMP-9), which has been associated with superficial punctuate keratis, delayed corneal healing and perforation [22–24]. However progression to corneal perforation is not a common complication of GVHD. The reported cumulative incidence of corneal perforation ranges from 0.8 to 4.9 % in the literature

Table 6
Predictive factors for severe corneal manifestations, univariate analysis.

Characteristics	OR	CI	p-value
Sex, male versus female	**2.36**	**1.04–5.36**	**0.039**
Age, over 50 years	1.33	0.61–2.93	0.476
Transplantation conditioning, RIC versus MAC	0.99	0.45–2.21	0.988
Graft source, peripheral blood graft vs. bone marrow	1.06	0.44–2.55	0.900
HLA mismatched versus matched donors	2.93	0.99–8.62	0.051
Induction treatment with thymoglobulin (ATG)	1.10	0.50–2.42	0.819

RIC: Reduced intensity conditioning; MAC: Myelo-ablative conditioning; ATG: Anti-thymocyte globulin.

Table 7
Associated manifestations of graft-versus-host disease with severe corneal manifestations, univariate analysis.

Characteristics	OR	CI	p value
Acute GVHD	0.46	0.19–1.19	0.081
- Grade III-IV vs. no aGVHD	1.07	0.36–3.21	0.899
- Skin acute GVHD	1.03	0.63–1.68	0.902
- Liver acute GVHD	0.53	0.14–1.93	0.336
- Lower gastro-intestinal acute GVHD	1.61	0.58–4.62	0.380
- Upper gastro-intestinal acute GVHD	0.61	0.17–2.26	0.463
Chronic GVHD	0.66	0.19–2.32	0.523
- Skin chronic GVHD	0.91	0.41–2.01	0.819
- Mucosal chronic GVHD	0.51	0.22–1.17	0.113
- Mucosal chronic GVHD excluding oGVHD	1.12	0.51–2.47	0.773
- Liver chronic GVHD	0.88	0.37–2.10	0.771
- Pulmonary chronic GVHD	0.69	0.27–1.76	0.439
- Muscle/articular chronic GVHD	2.57	0.55–12.15	0.232

OR: Odds Ratio; GVHD: Graft-versus-Host disease; oGVHD: Ocular GVHD.

Table 8
Predictive factors for corneal manifestations, multivariate analysis.

Characteristics	OR	CI	p value
Sex, male versus female	**2.78**	**1.18–6.57**	**0.019**
Age, over 50 years	1.46	0.64–3.31	0.366
HLA mismatched versus matched donors	**3.69**	**1.18–11.54**	**0.025**

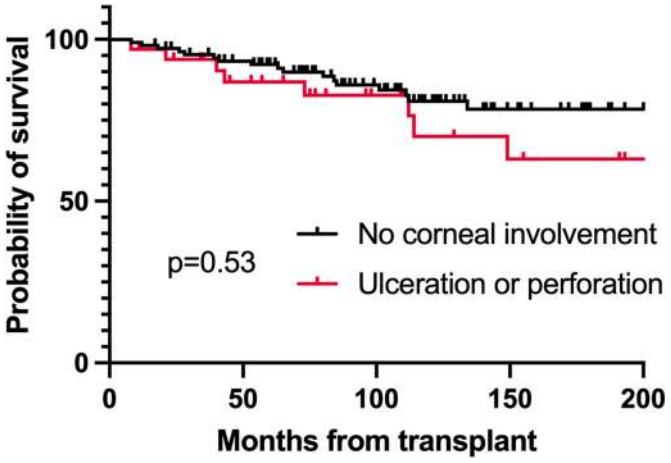

Fig. 2. Kaplan-Meier curves of overall survival comparison between patients with corneal ulceration or perforation and those without.

and is reported in Table 9 [25–28]. In our study, we found an incidence of corneal perforation of 5 % and an incidence of corneal ulceration of 23.6 %. Our cohort is therefore representative of more severe oGVHD. In another series of 14 corneal perforations, ocular GVHD was diagnosed on average 9.5 months after allo-HSCT and corneal perforation 37 months after [29]. Most of these patients were on steroid treatments (topical, systemic, or both).

Concerning risk factors for corneal ulceration or perforation, males and patients with HLA mismatched allo-HSCT were at increased risk of severe ocular manifestations. Jeppesen et al. found that cutaneous cGVHD was a risk for oGVHD, as well as extensive non-ocular GVHD, oral cavity and nail manifestations, and that oGVHD was associated with increased overall and non-relapse mortality [30]. We did not find any significant associated organ involvement with severe ocular disease. In our study, NSAIDs (indomethacin or flurbiprofen) use was an important risk factor for severe ocular complications (15.2 % of severe cases). NSAIDs have already been associated with severe corneal complications, including ulceration and corneal melting, especially in patients with rheumatic arthritis or Sjögren's syndrome [31,32]. NSAID-associated corneal melting seems to be associated with elevated MMP expression [33].

In patients with ocular GVHD and severe corneal involvement, the tear film environment is characterized by an elevated presence of inflammatory cytokines that drive a persistent inflammatory state. Concurrently, a reduction in epidermal growth factor (EGF) levels undermines the epithelial healing process, and this pro-inflammatory milieu contributes to the induction of matrix metalloproteinases (MMPs), which weaken the corneal surface through tight junctions and extracellular matrix degradation [34]. In addition, the neurotrophic component related to NSAID use diminish corneal sensitivity, potentially hindering normal epithelial maintenance and increasing the likelihood of persistent epithelial defects and associated direct epithelial-stromal interactions. These altered interactions could further promote MMP induction and thus perpetuate corneal damage and impaired healing.

Another study by Iwamoto et al. suggested that NSAIDs delay corneal healing by reducing production of 12-hydroxyheptadecatrienoic acid, a ligand for leukotriene B4 receptor 2 [35]. Therefore, ulceration and perforation occurring in oGVHD patients are the result of a complex multifactorial process, where NSAIDs seem to delay corneal healing in patients with otherwise decreased tear quality and quantity, associated with corneal chronic inflammation. All our patients were already treated for oGVHD and the mortality rate of patients with corneal or perforation mortality was no different from other patients in our study. However, as most of our patients had severe form of oGVHD, other studies are needed to compare non-severe oGVHD and severe oGVHD association with overall outcome.

Most of our patients are treated with artificial tears, but the majority of them needed either topical steroids, cyclosporin or autologous serum drops as well (69.1 %), as in Lin et al. [26]. But our patients were more often treated with punctal plugs (40.0 %) and lenses (32.9 %). Amniotic membrane transplantation was used in 11.4 % of our patients for its immunomodulatory function, as well as decrease in fibrosis [36]. This is consistent with amniotic membrane use in various immune-related ocular surface disease or neurotrophic keratitis [37,38].

Strengths of our study is firstly the use of electronical database search to collect all GVHD patients followed in our center to present a complete analysis of therapeutic management of oGVHD in our center. Moreover, we worked closely with the hematologists to analyze non-ophthalmological factors and transplantation details, helped with the data from the ProMISe database from the European Society for Blood and Marrow Transplantation. The limitations of our study are firstly its retrospective nature, wich may result in a lack of data for some patients. Secondly, we may have lacked power to demonstrate a difference in overall survival of patients with corneal ulceration and those without or to highlight risk factors. Finally, as we already said, most of our patients had severe form of oGVHD. Therefore, we believe that for future studies, more patients are required with more diverse severity and with a prospective design.

Table 9
Literature of corneal manifestations of ocular graft versus host disease.

Study	oGVHD	Corneal ulceration	Corneal perforation
Stevenson et al., 2013	243	4 (1.6 %)	2 (0.8 %)
Lin et al., 2015	61	N/A	3 (4.9 %)
Sinha et al., 2021	405	N/A	15 (3.7 %)
Aldebasi et al., 2022	28	2 (7.4 %)	0 (0 %)

N/A: Not applicable, no data reported in the studies.

As a conclusion, corneal ulceration and perforation are severe complications of ocular GVHD, requiring specialist ophthalmological care. We found that male and patients treated with HLA-mismatched allo-HSCT were at increased risk of complications and therefore should undergo increased ophthalmological monitoring, particularly after ophthalmological surgery, and in any case should not be treated with local ocular NSAIDs, regarding the severity of the potential complications.

CRediT authorship contribution statement

A. Bourdin: Writing – original draft, Software, Methodology, Formal analysis, Data curation. **V. Gournay:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **S. Doan:** Writing – review & editing, Resources. **P.H. Prata:** Writing – review & editing, Data curation. **E. Kaphan:** Writing – review & editing. **D. Michonneau:** Writing – review & editing, Validation. **G. Socié:** Writing – review & editing, Validation. **R. Peffault de Latour:** Writing – review & editing, Supervision, Methodology, Conceptualization. **E.E. Gabison:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Conceptualization.

Disclosure

None of the authors have conflicts to disclose.

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