

# Prevalence of ocular hypertension and glaucoma in patients with chronic ocular graft-versus-host disease

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## Abstract

**Purpose** To evaluate the prevalence of ocular hypertension (OHT) and glaucoma in patients with chronic ocular graft-versus-host disease (GVHD).

**Methods** We performed a retrospective chart review of 218 patients diagnosed with chronic ocular GVHD. Ocular hypertension was defined as intraocular pressure (IOP)  $\geq 24$  mmHg in either eye without any glaucomatous optic disc changes. Glaucoma suspect was defined as optic disc changes with a cup-to-disc ratio  $\geq 0.7$  in either eye or asymmetry of  $\geq 0.3$  between the two eyes. Glaucoma was defined by glaucomatous optic disc changes plus glaucomatous visual field defects in two consecutive reliable visual field tests. The number of cases of ocular hypertension, glaucoma, and glaucoma suspects was evaluated.

**Results** Thirty-three patients (15 %) were diagnosed with OHT, eight patients (3.6 %) with suspicion of glaucoma, and one patient (0.4 %) with glaucoma. OHT occurred within 6 months of developing ocular GVHD in 60 % of the cases and within the first year in 76 %. High IOP normalized in 67 % of patients when the dosage of topical or systemic corticosteroids was lowered, and 27 % of patients required anti-glaucoma therapy.

**Conclusions** Ocular hypertension is a common complication in patients with ocular GVHD, with a prevalence of 15 %. The rise in intraocular pressure is often transient and resolves with

management of corticosteroids in most cases. However, clinicians should be aware that nearly one-third of the patients with OHT might require anti-glaucoma treatment. The prevalences of glaucoma and suspicion of glaucoma were not higher than in the general population.

**Keywords** Graft-versus-host disease · Ocular hypertension · Ocular surface disease · Glaucoma

## Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is extensively used as a treatment for various malignant and non-malignant hematological disorders [1, 2]. Graft-versus-host disease (GVHD) is caused by an inflammatory response that occurs when donor-derived immune cells recognize and attack the recipient's tissues [3]. GVHD is a multi-organ disorder affecting various organs including skin, liver, mouth, gastrointestinal tract, and eyes, and is a major cause of morbidity after bone marrow transplantation [4]. Ocular GVHD most commonly presents with symptoms of chronic dry eye or ocular surface disease, and is reported in 40–60 % of patients undergoing allogeneic HSCT [5–9].

Ocular hypertension (OHT) and glaucoma have been described as complications during the clinical course of various ocular surface inflammatory diseases such as ocular cicatricial pemphigoid, Stevens–Johnson syndrome, atopic keratoconjunctivitis, and vernal keratoconjunctivitis [10–13]. The use of steroids, the presence of inflammation, and scarring are some of the suggested mechanisms that lead to increased intraocular pressure (IOP) in patients with ocular surface disease [10, 12, 14, 15]. Systemic corticosteroids are a standard treatment in many patients with systemic GVHD, and

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patients with ocular GVHD usually receive topical corticosteroids. Limited information is available regarding OHT and glaucoma in patients with chronic ocular graft-versus-host disease. The purpose of this study is to evaluate the prevalence of ocular hypertension, suspicion of glaucoma, and glaucoma in a cohort of patients with chronic ocular graft-versus-host disease.

## Methods

We reviewed the medical records of 241 patients with a diagnosis of chronic ocular GVHD after allogeneic HSCT and who were part of an oncology protocol according to the records at the Cornea Service, Massachusetts Eye and Ear Infirmary (MEEI), between May 2007 and December 2012. We excluded patients with incomplete records, previous history of elevated intraocular pressure, or alterations in the optic disc or visual fields tests. The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki. The diagnosis of chronic ocular GVHD was based on history of allogeneic HSCT, the presence of systemic graft-versus-host disease in organs other than the eyes, new onset (post HSCT) of dry eye symptoms, frequent use of eye drops, and at least two of the following: presence of corneal fluorescein staining, tear break-up time  $\leq 10$  s, and Schirmer I test score  $\leq 10$  mm in either eye [16]. The principal diagnosis of all patients included in the current study was GVHD-related dry eye. The time of diagnosis of ocular GVHD was defined by the date of the patient's first post-HSCT report of ocular symptoms in their medical records, provided that ocular GVHD was later confirmed at the MEEI Cornea Clinic.

For the purpose of this study, we defined 'ocular hypertension' as IOP  $\geq 24$  mmHg in either eye on at least one examination at our clinic, without evidence of glaucomatous optic disc changes [17–20]. IOP measurements were performed with a pneumatonometer (Model 30, Reichert Technologies; Depew, NY, USA). Inconsistent readings were, by protocol, systematically confirmed by Goldmann applanation tonometry. 'Suspicion of glaucoma' was defined as optic disc changes with cup-to-disc ratio  $\geq 0.7$  in either eye or asymmetry of  $\geq 0.3$  between the two eyes [21–24]. 'Glaucoma' was defined as the presence of glaucomatous optic disc changes along with corresponding glaucomatous visual field defects in at least two consecutive reliable visual field tests. Visual fields were considered to be glaucomatous if a reliable visual field test showed a cluster of  $\geq 3$  points on the pattern deviation plot with a sensitivity below 5 % [11, 25, 26]. Temporary elevation of IOP after intraocular surgery or laser procedures (e.g., YAG capsulotomy) was not considered as

OHT. Descriptive statistics are presented as the mean  $\pm$  standard deviation (SD), median, and range for continuous variables, and as percentages for categorical variables.

## Results

The final analysis included 218 patients, 124 males and 94 females with a mean age of  $52 \pm 12$  years (range, 21–75 years), with a mean follow-up of  $565 \pm 540$  days (demographic findings are shown in Table 1). We excluded 23 patients with incomplete records regarding date of HSCT or onset of dry eye symptoms, intraocular pressure and optic disc examination ( $n = 13$ ), patients with a history of glaucoma prior to bone marrow transplant (4), patients with visual field defects due to intracranial pathology (2), and other causes of elevated IOP, such as autoimmune uveitis and infectious chorioretinitis (4). Thirty-three patients (15 %) presented with ocular hypertension, eight patients (3.6 %) were diagnosed as glaucoma suspects, and one patient (0.4 %) with glaucoma. Ocular hypertension was diagnosed at a median of 127 days (mean  $320 \pm 408$ ) after the diagnosis of ocular GVHD. The first episode of elevated IOP occurred within 6 months of developing ocular GVHD in 60 % of the cases and within the first year in 76 %.

From the 33 patients who developed OHT, six patients (18 %) were treated with anti-glaucoma medications and 27 patients (82 %) were managed conservatively (reduction in corticosteroid therapy). Intraocular pressure returned to normal levels after one episode of high IOP in 18 patients (67 %) managed conservatively after a median of 62 days (mean  $66 \pm 31$ ), with no further IOP elevations or optic disc glaucomatous changes reported in these patients during a median follow-up of 311 days (mean  $495 \pm 472$ ). Seven patients

**Table 1** Demographics in the studied population

Characteristics	$n = 218$
Age, years (mean $\pm$ SD)	51 $\pm$ 12 years
Gender (%)	
Male	124 (57)
Female	94 (43)
Race (%)	
Caucasian	169 (78)
African	4 (2)
Others	6 (3)
Unknown	39 (17)
Family history of glaucoma (%)	
Negative	124 (57)
Positive	23 (10)
Unknown	71 (33)

SD standard deviation

(26 %) who were managed conservatively developed a second episode of OHT at a median of 55 days (mean  $135 \pm 143$ ) after the first episode. In four patients (57 %) who presented a second episode of OHT, the IOP returned to normal levels without treatment after a median of 50 days (mean  $63 \pm 53$ ) from the second episode, and three patients (43 %) required anti-glaucoma medication. Overall, ocular hypertension resolved in 67 % ( $n=22$ ) of patients managed conservatively, 27 % ( $n=9$ ) were treated with anti-glaucoma medications, and 6 % ( $n=2$ ) did not have a follow-up visit due to hospitalization or death due to complications of systemic GVHD.

Among the 33 patients who developed ocular hypertension, 88 % had a history of treatment with systemic (oral) corticosteroids, 58 % with topical corticosteroids. Only 3 % had no history of treatment with corticosteroids. Among glaucoma suspects, 87 % received treatment with systemic corticosteroids, 13 % with topical corticosteroids, and 13 % with neither topical nor systemic steroid therapy. The one patient who developed glaucoma had been treated only with oral corticosteroids (Table 2).

In general, patients treated with anti-glaucoma medications either had high IOP of  $\geq 30$  mmHg, persistent high IOP  $\geq 24$  mmHg for three or more visits, or IOP  $\geq 24$  mmHg with persistent inflammation that limited tapering of topical or systemic corticosteroids due to active systemic or ocular GVHD. Intraocular pressure control was achieved with topical anti-glaucoma medications in seven patients, and two patients required laser trabeculoplasty. The patient who developed glaucoma responded initially to topical anti-glaucoma therapy but later developed vitreous hemorrhage due to concurrent diabetic retinopathy and uncontrolled OHT, and required glaucoma tube-shunt surgery. Details of anti-glaucoma treatments used in this cohort are described in Table 3.

## Discussion

This study demonstrates a high prevalence of ocular hypertension in patients with ocular graft-versus-host disease. More than 75 % of the patients with ocular hypertension experienced the first episode of high IOP

within a year from the ocular GVHD diagnosis. While most of the ocular hypertension episodes were transient and responded to reduction of topical or systemic corticosteroids, nearly one-third of the patients required anti-glaucoma treatment.

The prevalence of ocular hypertension in the general population ranges between 2.7 and 3.8 % [21, 27–29]. OHT increases with age, from 1.7 to 2.7 % in the age group of 40 to 49 years, 2.7–4.6 % in the 50 to 59 years range, to 4.1–7.5 % in people older than 80 years [21, 28, 29]. In the studied cohort with chronic ocular GVHD, ocular hypertension was present in 15 % of the patients (median age of 54 years), which is significantly higher than that reported in the general population for the same age range [21, 27–29]. Glaucoma was present in 0.4 % of the patients, similar to reports in the general population (0.4–5 %) [21, 29–33]. Similarly, the prevalence of glaucoma suspects in the present study (4 %) was not significantly different than that in the general population (5.6 %) [21].

Elevated intraocular pressure in the context of ocular surface disease has been suggested to be secondary to a combination of factors that include ocular surface inflammation, conjunctival scarring, changes in episcleral venous pressure, and use of topical and systemic corticosteroids [10–12]. The corneal epithelium is the most critical barrier of the eye against intraocular penetration of topical drugs; therefore, a compromised epithelial function due to ocular surface disease likely allows increased absorption of topical corticosteroids, making these patients particularly prone to develop OHT [34, 35]. One study found a prevalence of steroid-induced glaucoma in 0.9 % after hematopoietic stem cell transplantation [36]. In the present study, 97 % of the patients who developed OHT had previously been treated with corticosteroids, and among these, two-thirds resolved without additional therapy after reduction of corticosteroid dosing. Since corticosteroid-induced ocular hypertension is usually temporary and responds to discontinuation of the drug [14, 37], our findings suggest that the IOP rise in patients with ocular GVHD is caused, mainly, by the effect of corticosteroids used to

**Table 2** Corticosteroid administration route in the patients with ocular hypertension, glaucoma, and glaucoma suspects

Corticosteroids	Ocular hypertension $n=33$ (%) <sup>*</sup>	Glaucoma suspects $n=8$ (%) <sup>*</sup>	Glaucoma $n=1$ (%)
Systemic (oral) corticosteroids	29 (88)	7 (87)	1 (100)
Topical corticosteroids	19 (58)	1 (13)	0
Both systemic + topical corticosteroids	16 (48)	1 (13)	0
No corticosteroids	1 (3)	1 (13)	0

<sup>\*</sup>Percentages may not add up to 100 % because categories are not mutually exclusive

**Table 3** Anti-glaucoma therapy in the patients who developed ocular hypertension and glaucoma

Disease	Treatment	No. of patients (%)
Ocular hypertension ( <i>n</i> = 33)	Topical anti-glaucoma eye drops	7 (21 %)
	Topical anti-glaucoma eye drops + selective laser trabeculoplasty	2 (6 %)
Glaucoma ( <i>n</i> = 1)	Topical anti-glaucoma eye drops + glaucoma valve surgery	1 (100 %)

treat systemic or ocular GVHD. Moreover, if we exclude the 22 patients who responded to a reduction of systemic or topical corticosteroid administration from the overall population with ocular hypertension, the percentage of OHT in the studied population (5 %) would be comparable to that in the general population [21, 27–29]. Interestingly, 40 % of the patients with OHT and the one patient who developed glaucoma had been treated only with systemic corticosteroids before the rise in IOP was detected. Although, in general, topical corticosteroids are more likely to cause OHT, studies have shown that systemic corticosteroids can increase IOP, especially with high doses or chronic use [38–41]. Topical corticosteroids regularly used in the treatment of ocular GVHD-related dry eye are milder corticosteroids with less potential to cause OHT than more potent topical corticosteroids [42]. This can explain why a considerable group of patients in the studied cohort who had only received systemic corticosteroids presented with OHT. This is particularly important since approximately half of the patients undergoing allogeneic hematopoietic stem cell transplantation will develop systemic GVHD, and most of them, will eventually require treatment with long-term systemic corticosteroids [6, 43, 44]. Still, most of these patients are likely to visit the ophthalmologist only in the presence of ocular symptoms and, since rise in IOP is generally asymptomatic, the condition may remain unnoticed in the absence of regular checkups. The possibility of silent ocular hypertension, glaucoma, or irreversible vision loss emphasizes the importance of periodic monitoring in patients undergoing HSCT, especially those under treatment with systemic corticosteroids.

Treatment of glaucoma in the context of chronic ocular GVHD disease is challenging due to the well-known toxicity of topical anti-glaucoma medications to the ocular surface, which can aggravate the underlying ocular surface disease [45, 46]. In this study, ocular hypertension resolved in 67 % of the patients after lowering the dose of topical or systemic corticosteroids. Interestingly, one report showed that improvement in the ocular surface condition enhanced IOP control in patients with glaucoma and concurrent ocular surface disease [15]. The decision to treat ocular hypertension

with anti-glaucoma medications should weigh the risks of sustained OHT against their toxicity on the ocular surface. In this regard, preservative-free anti-glaucoma compounds have significant advantages over preserved ones, and should be the first option in cases where conservative management is considered insufficient [47, 48].

The main limitations of this study relate to its retrospective design. Records of personal and family history of glaucoma, past use and dosage of corticosteroids, or specific time of ocular symptoms onset (after HSCT) were not available in all cases, as well as details regarding the particular reasons for the decision to start anti-glaucoma medications or follow a conservative management. Our retrospective analysis is limited by unavailability of corneal pachymetry values, to rather confirm corneal thickness is within normal range. However, none of the patients in the included cohort presented central corneal scars, neovascularization, thinning, or conjunctivalization that could, potentially, have altered IOP measurements. We were not able to compare the specific types of corticosteroids used by patients who developed OHT and by those who did not. Additionally, in general, the majority of patients with chronic GVHD receive corticosteroids in different forms, dosages, routes of administration, and frequency, and these patterns of treatment change constantly depending on their clinical response. Further controlled prospective studies are required to further evaluate the specific risk factors associated with ocular hypertension in patients with graft-versus-host disease.

In summary, this study shows that ocular hypertension in patients with ocular graft-versus-host disease is highly prevalent, while glaucomatous optic neuropathy is uncommon. In 75 % of the patients with ocular hypertension, the rise in intraocular pressure occurs within a year after the development of ocular GVHD, but this increase is transitory and responds to reduction in the dose of corticosteroids in a large proportion of cases. However, nearly one-third of the patients with ocular hypertension may require anti-glaucoma treatment. The establishment of a protocol that assesses intraocular pressure in patients undergoing HSCT, and particularly in those who develop systemic GVHD, should be part of any complete bone marrow transplantation program.

### Compliance with Ethical Standards

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**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** For this type of study formal consent is not required.

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