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Corneal melt in a patient with graft-versus-host disease following allogeneic stem cell transplantation

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Abstract
Ocular complications are most prevalent after HSCT and relate to chronic graft-versus-host disease (GVHD), with the development of dry eye disease, destruction of the ocular surface, or corneal melt. The given case study is of a 35-year-old male patient who had acute myeloid leukemia after HSCT in February 2021. The development of serious bilateral dry eye was noted, as chronic GVHD was diagnosed 8 months after the procedure. The initial management technique consisted of preservative-free lubricants, autologous serum eye drop, punctal plugs, and topical steroid, and the patient had the best results over a period of more than one year. In January 2023, the patient complained about soreness in the left eye and blurred vision again. Following further examination, the diagnosis was that the superior limbal keratitis had developed, which is complicated by the corneal thinning and ulceration. Anterior segment optical coherence tomography (OCT) revealed the corneal thickness of 233 microns, equivalent to 50 percent stromal thinning and hence the culmination of corneal melt diagnosis. It was managed with a combination of two treatment modalities; the first management involved systemic corticosteroid therapy (e.g., oral prednisolone 30mg daily, which was tapered gradually to 5mg/week), and the second a topical Lotemax therapy with Loteprednol Etabonate. Corneal melt is more prevalent in patients with chronic ocular GVHD, and thus the importance of early diagnosis and prompt immunosuppressive treatment program cannot be overstated to prevent vision loss.

Keywords: Loteprednol etabonate, eye pain, lubricant eye drops, corneal ulcer, dry eye syndrome, prednisolone

Introduction
Chronic graft-versus-host disease (cGVHD) that occurs in approximately 45.3% of patients within one year after allogenic Hematopoietic Stem Cell Transplantation (HSCT) is one of the most serious complications that occurs after allogenic Hematopoietic Stem Cell Transplantation (HSCT) and not only results in high mortality rate but also greatly affects the quality of life [1, 2]. It's characterized by fibrosis and chronic inflammation from both B and T cells, which affects several organs at once, including skin, oral mucosa, lungs, and liver. GVHD-enabled fibrosis is a critical morbidity factor resulting in organ failures and life-threatening instances [3-5]. In the context of critical GVHD-led complications, ocular challenges are prominent, with 40% to 60% patients presenting with severe eye-related issues, where Dry Eye Disease (DED) has emerged as a typical symptom of chronic ocular GVHD [6-8].

Ocular GVHD manifests in response to chronic inflammatory mechanisms triggered by cytokines, which severely affect lacrimal glands, meibomian glands, conjunctiva, eyelids, and cornea. This results in tear film instability and hyperosmolarity, which are reflective of severe ocular surface chronic inflammation [9, 10]. This persistent inflammation has been reported to overexpress MMP-9 (matrix metalloproteinases) within the conjunctival tissues in patients presenting with severe ocular GVHD. These finding underscores their critical role Corneal melt is characterized by rapid thinning of corneal stroma culminating in full-thickness corneal perforation and ultimately developing severe vision loss or blindness, making it a very critical ophthalmic emergency [13]. in the degradation of stromal collagen matrix [11].

This compromises corneal epithelial integrity; in case of an epithelial defect, underlying stroma becomes more prone to either enzymatic degradation or inflammatory pathways, resulting in stromal thinning, ulceration, or corneal melt [9, 12].

The risk of developing corneal melt is exacerbated in patients with ocular GVHD due to multifaceted complications such as severe dryness, chronic inflammation, and potential neurotrophic deficiency [14, 15]. Management of cornel melting is often a challenging process. Case studies suggest a dual approach to address these challenges. Chronic inflammation is initially treated via immunosuppressive therapeutic agents (systemic and topical), which causes corneal melt to stop altogether. To enhance the outcomes of treatment, patients are introduced to intense local therapy, which, in addition to shielding the ocular surface, accelerates the healing process [16].

These findings lead to their synergistic significance in the prevention of vision-threatening complications and the decrease in surgical intervention requirements.

In this case study, the management of a patient with corneal melt induced by post-HSCT chronic ocular GVHD was successfully managed. It highlights the significance of early diagnosis, using AS-OCT to measure the thickness of the cornea to effectively diagnose and follow up the progression and the effectiveness of a multi-step treatment regimen in restricting the disease progression without severely affecting the vision of patients.

Case Presentation

Patient Information and Medical History

The patient (35-year-old male) in Apollo Hospital, Delhi, was diagnosed with acute myeloid leukemia in August 2020. He had successfully undergone an allogeneic hematopoietic stem cell transplantation (HSCT) on February 28, 2021, and did not report any complications.

Initial Ocular GVHD Presentation and Management

The patient began experiencing critically advanced ocular symptoms in line with chronic GVHD after eight months post-HSTC in November 2021. Symptoms reported by patients included severe dryness, grittiness, foreign body sensation, and episodic burning pain, which are all characteristics of bilateral ocular symptoms.

Ophthalmological evaluation confirmed severe dry eye disease secondary to chronic ocular graft-versus-host disease (GVHD), which also manifested in the oral mucosa. Clinical examination revealed conjunctival injection, reduced tear film, and diffuse punctate epithelial erosions on corneal fluorescein staining. Schirmer's test scores were markedly reduced (<5 mm in both eyes at 5 minutes). The patient was presented with a multi-modal treatment regimen for ocular GVHD, which provided adequate symptomatic control and maintained ocular surface stability over a year with close follow-up, as summarized in Table 1.

Table 1: Initial Management of Chronic Ocular GVHD (November 2021)

Therapeutic Intervention	Details	Purpose
Lubrication	Preservative-free artificial tears (Thealoz Duo gel) hourly	To stabilize the tear film and protect the ocular surface
Anti-Inflammatory	Topical corticosteroid (Loteprednol etabonate 0.5%) twice daily in cycles	To control ocular surface inflammation
Punctal Occlusion	Punctal plugs were inserted in all four puncta	To conserve natural and artificial tears
Autologous Serum	Autologous serum eye drops (20%) four times daily	To provide epitheliotropic growth factors

Presentation of Corneal Melt

In January 2023, the patient presented again with a three-week history of acute worsening of left eye pain, accompanied by photophobia and significantly reduced visual acuity. On examination, his best-corrected visual acuity was significantly decreased in the left eye and recorded at 6/60. Slit-lamp examination showed a superior paracentral area of limbal keratitis, adjacent epithelial defect, and underlying stromal thinning with a translucent base, indicative of active corneal melt (Figure 1).

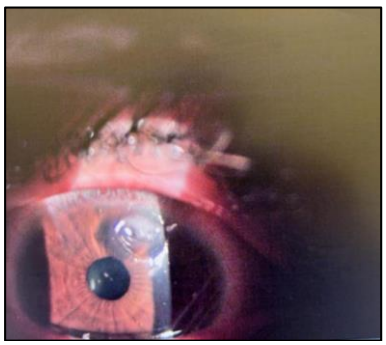

Fig 1: Active Corneal Melt at Presentation

To establish the extent of corneal melt, Anterior segment optical coherence tomography (AS-OCT) was performed immediately, which quantitatively revealed corneal thinning with a maximum of 233 microns at the thinnest dimension. This was an indication of a 50 per cent loss of stromal mass compared to the normal corneal environment.

Management, Clinical Course, and Outcome

Active ocular GVHD and progressive corneal melt were identified. The patient was placed under vigorous medical treatment:

- Systemic Immunosuppression: Prednisolone 30 mg (0.5 mg/kg/day) in one dose, which is to be reduced at 5 mg/week.
- Topical Immunomodulation: Loteprednol etabonate 0.5% (G. Lotemax) was used up to 4 times daily.
- Optimum Ocular Surface Nourishment: Intensive application of the existing protocol of preservative-free lubricants, autologous serum tears, and punctal plugs was observed.

A significant decrease in ocular pain and photophobia was noted in the post-treatment period after a span of 1 week during the twice-weekly follow-up (Figure 2).

Fig 2: Early Response to Aggressive Immunosuppressive Therapy

The removal of the epithelial defects and restoration of the ocular surface stability were guaranteed with the help of slit-lamp examination, which proves that the wound healing process is unproblematic. The systemic therapeutic regimen was halted six weeks after there was no reporting of thinning. Over the months, the ocular surface returned to a quiet state, the stromal thinning remained stable and vascularized, and the patient's visual function in the left eye improved (Figures 3 and 4). No surgical intervention is required.

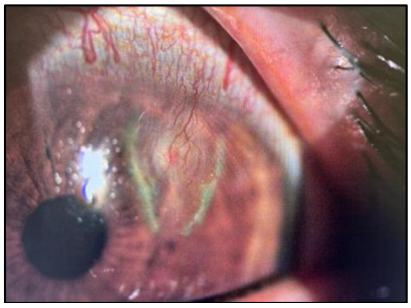

Fig 3: Stabilization after one month of Treatment

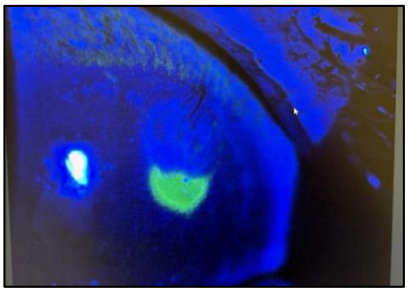

Fig 4: Residual staining after one month of Treatment

Discussion

This case study exemplifies the successful resolution of one of the severe ophthalmic complications of chronic GVHD, highlighting the critical nature of robust monitoring and aggressive therapeutic intervention, particularly where high-risk patients are concerned. Corneal melt has emerged as a critical vision-threatening complication of ocular GVHD; its pathogenesis encompasses a severely dysregulated ocular surface, often highlighted by tear deficiency, chronic immune-mediated inflammation, epithelial defect, and stromal disintegration [17]. In ocular GVHD, a consistent epithelial defect allows inflammatory cells to invade into the stroma, which leads to a series of inflammatory events involving the release of cytokines such as TNF-α and MMPs like MMP-2 and MMP-9. This enzymatic release initiated corneal melt with enzyme-driven degradation of collagen, ultimately resulting in thinning of stroma [18, 19].

Ocular GVHD is a multifaceted disease to treat due to the systemic autoimmune nature of its pathophysiology, and one needs to treat it as a multidimensional disease. Aggressive lubrication with preservative-free lubricants, punctal occlusion to retain tears, and, to minimize evaporative DED, meibomian gland dysfunction is initially treated with maximal supportive topical therapy. Despite this treatment, studies demonstrate their limitation in resolving chronic inflammation thoroughly, which is a critical factor in promoting corneal melt and epithelial breakdowns [20, 21]. This failure underscores the role of systemic immunosuppression. Initiation of systemic corticosteroids was one of the most important treatment choices that was applied in this case study. They are regarded as the first-line immunosuppressive therapy in the situations of GVHD-induced ocular complications, as was the case in this study; high dosage oral prednisolone was administered because it was able to inhibit immune-mediated destruction and at the same time promote the healing of the corneal surface by reducing the infiltration of inflammatory cells and enzyme degradation, inhibits the further degradation of stroma [17]. The management plan proved to be effective in the prevention of corneal melt and the elimination of surgical intervention to effectively respond to the underlying causatives of inflammation, meaning that a person must be sensitive to the presence of the condition and have the capability of effectively managing it.

The management strategy that was used by the clinicians in this case to cure severe ocular surface complications is widely supported by literature, especially when considering GVHD. Research states that topical steroids are of limited effectiveness, and indeed have a resolution of lymphocyte-mediated inflammation to some degree; their regular usage may also result in side effects or have a small to no effect on progressive disease. This supports the standard of systemic immunosuppression treatment, i.e., the administration of corticosteroids, as the main treatment tool to counter the intricate autoimmune etiology of GVHD, which relates to the corneal melt and other vision-threatening diseases [22, 23]. On the same note, the choice of employing OCT to measure corneal thickness was effective not only to analyze the intensity of the corneal melt but also to show the effectiveness of therapeutic intervention. This is one of the abilities of OCT that are being proclaimed in the literature in the management and progression of advanced disease. Corneal thinning visualization with OCT support is justified by the studies on severe ocular patients with GVHD and, consequently, its efficacy in mapping the stage of disease severity and its treatment [24, 25].

There are some learning lessons in this study. It must be appreciated that frequent and reasonably frequent monitoring and ophthalmic follow-up at the conclusion of HSTC is essential due to the possibility of chronic ocular GVDA formation, despite its stable nature over an extended period. Another manifestation of a medical emergency in this case study that must be addressed as soon as reported is corneal melt, and systemic immunosuppression is necessary. This is necessary as it minimizes the possibility of surgical correction of such complications. Additionally, this case study encourages ophthalmologists and transplant hematologists to make interdisciplinary attempts to cautiously treat patients who are brought up with acute ocular issues following HSTC.

Conclusion

The case report acknowledges the possibility of the treatment of one of the biggest challenges for chronic

GVHD patients, namely, vision-risking corneal melt, correctly. This is evidence that follow-up and long-term monitoring are necessary in post-HSCT patients and how to minimize the development of complicated progressive ocular symptoms, such as dry eye or stromal thinning. The importance of quantification of the corneal melt degree by OCT in ocular GVHD diagnosis and treatment is described in this work, and demonstrates its poor performance as such. The case study was of special interest because the case received early corticosteroid systemic immunosuppressive therapy to eliminate the cytokine-driven inflammatory etiology. A strong topical supportive care was also utilized to strengthen it. Resolving corneal melt after such a management plan is in favor of the success of the management to not only prevent the disease but also minimize the need for any surgical process and loss of sight. These findings suggest that the management of ocular GVHD complications needs to be on a multidimensional process of management and interdisciplinary cooperation of professionals in both directions in order to minimize the risk of complications and promote the visual capabilities of the concerned patient.

Acknowledgments
The authors declare no conflict of interest.

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