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Review Article

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Immune Checkpoint Inhibitor (ICI) Induced Corneal Graft Rejection

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ABSTRACT

Purpose: To demonstrate a case of corneal graft rejection in a patient on immune checkpoint inhibitor (ICI) Cemiplimab, a PD-1 inhibitor, for metastatic cutaneous squamous cell carcinoma (CSCC).

Case: A 64-year-old male presented with sudden deterioration in left vision at the end of January 2024, just 4-5 days after commencing on Cemiplimab for his inoperable SCC of the scalp. He previously underwent a left penetrating keratoplasty (PK) for corneal decompensation and scarring secondary to severe herpes zoster ophthalmicus (HZO).

Ophthalmological examination revealed: left best-corrected visual acuity (BCVA) to count fingers (CF) only, intra-ocular pressure (IOP) of 11 mmHg, anterior segment demonstrated diffusely oedematous cornea with hyperaemic limbus, descemet membrane folds and keratic precipitates. The corneal graft sutures remained intact. A corneal topography and pachymetry assessment demonstrated central corneal thickness (CCT) measurement of 764 um.

Based on the above findings, a left corneal graft rejection was suspected. The patient was treated vigorously with hourly topical dexamethasone, in addition to systemic oral prednisone. Despite close follow-up and vigorous treatment, there was progression of corneal graft rejection with minimal preservation of his left vision.

Discussion: Cemiplimab is a PD-1 inhibitor on T-cells. This reactivation of the immune system, while beneficial in targeting tumours, can also precipitate immune-mediated damage to healthy tissues, including allografts such as corneal transplants.

This case highlights the need for vigilant ophthalmological monitoring in patients undergoing ICI therapy, particularly those with a history of corneal transplantation. Baseline ophthalmological screening should be performed prior to initiating cemiplimab or any other ICI, followed by regular follow-up to detect early signs of graft rejection.

Abbreviations

The following abbreviations are used in this manuscript:

ICI	:	immune checkpoint inhibitor
CSCC	:	Cutaneous squamous cell carcinoma
SCC	:	Squamous cell carcinoma
PK	:	Penetrating Keratoplasty
HZO	:	Herpes zoster ophthalmicus
BCVA	:	Best corrected visual acuity
CF	:	Count fingers
IOP	:	Intraocular pressure
CCT	:	Central corneal thickness
SOTRs	:	Solid organ transplant recipients
HSV1	:	Herpes simplex virus type 1
IRAEs	:	Immune-related adverse events

Keywords: Corneal Graft, PD-1 inhibitor, Cemiplimab

Introduction

Solid organ transplant recipients (SOTRs) face a significantly increased risk of developing cutaneous squamous cell carcinoma (CSCC), attributed to long-term immunosuppressive therapy,

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which impairs immune surveillance [1]. While most CSCC cases in SOTRs can be managed surgically, some progress to loco-regional recurrence or metastasis, necessitating systemic therapy.

Immune checkpoint inhibitors (ICIs), particularly PD-1 inhibitors like cemiplimab, have revolutionized the treatment of advanced CSCC. By blocking the PD-1 receptor on T-cells, Cemiplimab enhances the immune system's ability to target and destroy cancer cells, leading to durable responses in immunocompetent patients [2]. However, in SOTRs, this immune reactivation can inadvertently trigger graft rejection, making the use of PD-1 inhibitors complex and requiring careful monitoring [3].

Ocular toxicities, including corneal graft rejection, are a concern with ICIs. This adverse effect likely arises from the disruption of ocular immune privilege—a protective state maintained by PD-1 signaling. Inhibition of PD-1 by cemiplimab can break this immune privilege, leading to an immune-mediated attack on the corneal graft [4].

A 64-year-old male presenting with sudden left vision deterioration, four cycles post Cemiplimab; a PD-1 inhibitor, for metastatic cutaneous squamous cell carcinoma (CSCC). He has a complex medical history, including corneal transplants for corneal decompensation and scarring secondary to herpes zoster ophthalmicus (HZO) on background of dual renal transplant rejection, and immune-mediated thrombocytopenia. Ophthalmic examination revealed left corneal graft rejection. This was managed with vigorous topical corticosteroids and prophylactic systemic anti-viral therapy. Additionally, the patient was concurrently on systemic steroids and immunomodulators for other pre-existing conditions as above. Cepilimab treatment was continued with close ophthalmological follow-up. Despite close ophthalmological follow-up and vigorous treatment, there was progression of corneal graft rejection with minimal preservation of his left vision. However, the right-sided corneal graft remained intact with no evidence of rejection and complete preservation of his vision.

This case represents the first documented instance of cemiplimab-induced corneal graft rejection and the third associated with immune checkpoint inhibitors (ICIs). This case underscores the importance of continuous monitoring and regular ophthalmological follow-up due to the potential for progression of rejection and hence loss of vision, particularly if ICI therapy is continued. Given the risk of subclinical graft rejection, baseline ophthalmological screening is recommended for all corneal graft recipients before initiating ICI therapy.

Case Presentation

A 64-year-old male presented with sudden deterioration in vision at the end of January 2024, just 4-5 days after commencing on Cemiplimab for his inoperable squamous cell carcinoma of the scalp, and six months after previously successful corneal transplant surgery in this eye.

The patient's medical history is notable for end-stage renal failure secondary to medullary cystic kidney disease, leading to two unsuccessful renal transplants. He is currently on hemodialysis and maintains immunosuppressive therapy with mycophenolate and prednisone. He has chronic thrombocytopenia secondary to immune thrombocytopenia (ITP), managed with romiplostim and mycophenolate. Additionally, he has metastatic cutaneous squamous cell carcinoma (CSCC).

His medical history also includes bilateral penetrating keratoplasty surgeries for corneal decompensation and scarring secondary to severe herpes virus infections. Penetrating keratoplasty (PK) is a form of corneal transplant that replaces the entire cornea including all layers with a healthy donor cornea. Several years ago, he underwent a right PK for herpes simplex virus (HSV1) keratitis. In June 2023, he underwent left PK for corneal decompensation and scarring secondary to severe herpes zoster ophthalmicus (HZO). The corneal grafts are at potential risk of rejection due to ongoing immunosuppressive therapy. Therefore, he was given topical dexamethasone 0.1% eye drops four times daily, regular use of preservative free lubricating drops, and prophylactic antivirals in the form of oral valaciclovir 500mg twice daily.

During this follow up visit in February 2024, the patient complained of progressive reduction in vision in the left eye, foreign body sensation, redness, pain and light sensitivity [5,6]. Ophthalmic examination revealed significant reduction in his left best-corrected visual acuity to counting fingers only, compared to his baseline post-corneal graft vision of 6/24 (His right visual acuity remained stable at 6/6). His left intra-ocular pressure remained stable at 11 mmHg. Anterior segment examination of the left eye demonstrated signs of endothelial corneal graft rejection, including a hyperemic limbus with a diffusely edematous cornea and Descemet's membrane folds. The corneal graft sutures remained intact. There was a streak of keratic precipitates inferiorly at the graft-host junction, gradually extending superiorly. Additionally, there was an anterior chamber reaction, although it was difficult to appreciate cells in the anterior chamber given significant corneal edema. There was no view to the posterior segment.

A corneal topography and pachymetry assessment demonstrated central corneal thickness measurement of 764 um. The thinnest area of cornea measured 742um, with peripheral cornea thickness maximum measurement at 1050 um.

Based on the above clinical findings and investigation results, a left corneal graft rejection was suspected.

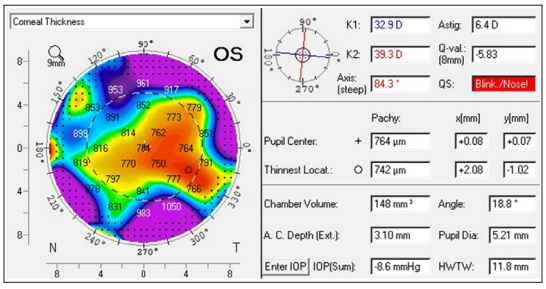

Figure 1: This is a figure is illustrating the pachymetry findings demonstrating high corneal thickness, with central corneal thickness of 764um

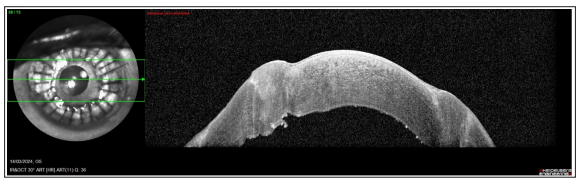

Figure 2: This is a figure is a cross-sectional view of the cornea demonstrating a thick and oedematous cornea secondary to graft rejection

Treatment

Given that a corneal graft rejection was suspected, and in the context of immune-suppression, this necessitated a prompt and vigorous treatment plan. Topical steroids are the primary treatment of acute graft rejection and as post-operative prophylactic therapy for high-risk transplant recipients. For this patient, the topical dexamethasone 0.1% eye drops were increased to every waking hour, in addition to commencing systemic oral prednisone 30mg daily, while continuing the oral valaciclovir 500mg twice daily [7]. He was also on immune suppresors including mycophenolate and tacrolimus for his other pre-existing conditions. He was subsequently closely monitored by ophthalmologists through weekly reviews with very slow tapering/weaning of his topical corticosteroid eye drops according to the American Society of Clinical Oncology guidelines for management of immune-related ocular adverse events in patients treated with immune checkpoint inhibitor therapy, with slight modifications depending on the patient's clinical findings.

On his most recent ophthalmological assessment, the patient's left vision was improved to 6/150 and the topical dexamethasone 0.1% eye drops was weaned to four times daily. The contralateral eye demonstrated no evidence of corneal graft rejection, and visual acuity was stable at 6/6.

Discussion

The advent of immune checkpoint inhibitors (ICIs) such as cemiplimab, a PD-1 inhibitor, has revolutionized the treatment of various malignancies by harnessing the immune system's capabilities to combat cancer [8]. However, the immune-enhancing properties of these agents are accompanied by a spectrum of immune-related adverse events (irAEs), which can affect multiple organ systems, including the eyes. Cemiplimab, like other PD-1 inhibitors, exerts its effect by blocking the PD-1 receptor on T-cells, thereby preventing the downregulation of the immune response that cancer cells typically exploit to evade immune surveillance. This reactivation of the immune system, while beneficial in targeting tumors, can also precipitate immune-mediated damage to healthy tissues, including allografts such as corneal transplants [1].

Corneal graft rejection following the initiation of immunotherapy therapy are of single case reports but serious manifestation of irAEs. The rejection is typically characterized by the appearance of keratic precipitates (KPs), subepithelial infiltrates, and, in some cases, corneal edema—all indicative of an immune-mediated inflammatory response against the corneal graft. In this case, the patient developed these signs of graft rejection very rapidly after starting cemiplimab, despite being on a regimen of immunosuppressive medications such as mycophenolate and prednisone. This suggests that the immune activation triggered by cemiplimab may overwhelm the immunosuppressive measures in place, leading to graft rejection.

The pathophysiology underlying this adverse effect is likely related to the disruption of ocular immune privilege, a phenomenon where the eye is typically shielded from systemic immune responses to prevent inflammation that could impair vision. PD-1 plays a crucial role in maintaining this immune privilege by modulating the activity of T-cells within the ocular environment [2,3]. The inhibition of PD-1 by cemiplimab can therefore lead to a breakdown of this protective mechanism, resulting in an immune attack on the transplanted corneal tissue [9].

At a molecular level, the PD-1/PD-L1 axis plays an essential role in maintaining peripheral tolerance and ocular immune privilege. Corneal endothelial and epithelial cells constitutively express PD-L1, which contributes to suppression of effector T-cell activation and promotes immune deviation through mechanisms such as anterior chamber–associated immune deviation (ACAID). Disruption of this pathway through PD-1 blockade removes inhibitory signalling required to restrain T-cell receptor (TCR) activation, resulting in heightened T-cell proliferation, reduced apoptosis, and increased effector cytokine production, including interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α) [2,7,10].

The reversal of T-cell exhaustion is a key therapeutic mechanism of PD-1 inhibitors but can inadvertently promote alloimmune responses in graft recipients. IFN-γ released by reactivated Th1 cells upregulates major histocompatibility complex (MHC) expression on corneal endothelial cells and enhances chemokine production, particularly CXCL9 and CXCL10, promoting recruitment of CXCR3+ effector T cells to the graft site [3,11]. PD-1 blockade may also reduce regulatory T-cell (Treg) suppressive function while skewing differentiation toward Th1 and Th17 phenotypes; Th17-associated IL-17 signalling is increasingly recognised as a contributor to corneal allograft failure and steroid-resistant rejection [12].

Although our patient was receiving systemic immunosuppressive therapy (mycophenolate, prednisone, tacrolimus), PD-1 blockade acts downstream of calcineurin and IL-2 inhibition, amplifying T-cell activation despite pharmacologic suppression. PD-1 inhibition enhances T-cell metabolic fitness, increases mitochondrial biogenesis, and restores effector molecule production, including granzyme B and perforin, enabling robust alloimmune cytotoxicity even in immunosuppressed individuals [13]. These mechanisms may explain the rapid onset of graft rejection observed in this case, occurring within days of cemiplimab initiation.

The interplay between local corneal immune privilege and systemic immune activation highlights the vulnerability of corneal grafts to PD-1 pathway interference. Corneal endothelial cells are non-regenerative, and immune-mediated endothelial loss leads to irreversible graft oedema, underscoring the importance of early detection. Biomarkers such as aqueous humour IFN-γ, IL-17, CXCL9, and CXCL10, in addition to early clinical signs such as

keratic precipitates or subtle endothelial dysfunction, may indicate subclinical rejection and warrant early intervention [11,12].

Given the increasing use of PD-1 inhibitors for metastatic CSCC and other malignancies, a mechanistic understanding of how these agents disrupt ocular immune homeostasis is critical. A more detailed understanding of PD-1-mediated immune modulation supports baseline ophthalmic assessment, close interval monitoring during treatment cycles, and aggressive topical corticosteroid therapy at the first sign of inflammation. Future work examining cytokine profiles, immune-cell phenotyping, and PD-L1 expression dynamics in corneal grafts may improve risk stratification and enable personalised monitoring strategies for transplant recipients receiving immunotherapy.

As of writing, there are only two other reported cases of corneal graft rejection associated with ICI therapy, making our case the third in the literature. The first case involved a woman with unresectable squamous cell lung cancer who experienced corneal graft rejection after her ninth cycle of nivolumab, another PD-1 inhibitor. Despite aggressive systemic and local corticosteroid therapy, the graft could not be salvaged, resulting in total corneal opacification. The second case described an 85-year-old woman with bilateral corneal grafts who developed simultaneous rejection in both eyes three months after starting pembrolizumab for metastatic urothelial carcinoma [5]. Notably, this rejection occurred despite the patient's adherence to a regimen of once-daily fluoroethylene, a topical corticosteroid typically used to suppress the alloimmune response [5]. The patient was asymptomatic, and the rejection was only discovered during a routine clinical exam [5]. Although the initial rejection was managed effectively with intensive topical dexamethasone, the rejection recurred eight weeks after tapering the therapy, ultimately leading to the discontinuation of pembrolizumab to prevent the risk of bilateral blindness [5].

This case highlights the need for vigilant ophthalmological monitoring in patients undergoing ICI therapy, particularly those with a history of corneal transplantation in a patient with advanced CSCC. Baseline ophthalmological screening should be performed prior to initiating cemiplimab or any other ICI, followed by regular follow-up to detect early signs of graft rejection. Prompt intervention with corticosteroid therapy, as seen in this patient, can be effective in managing corneal graft rejection, although the risk of recurrence remains high, especially if ICI therapy is continued.

Given the growing use of ICIs in oncology, clinicians must be aware of the potential for such ocular irAEs and the importance of a multidisciplinary approach in managing these patients. Collaboration between oncologists and ophthalmologists is essential to balance the therapeutic benefits of cemiplimab with the need to preserve graft integrity and overall ocular health.

Conclusion

In conclusion, our report highlights what is presumed to be the first incidence of corneal graft rejection directly associated with cemiplimab. While the potential complications related to ocular immune privilege are significant, the role of cemiplimab in the management of CSCC cannot be understated. As a PD-1 inhibitor, cemiplimab has proven to be a crucial therapeutic agent in the treatment of CSCC, particularly for cases that are locally advanced or metastatic and not amenable to surgery. This emphasizes the necessity of balancing the substantial benefits of cemiplimab in controlling aggressive cancer growth with the need for vigilant monitoring and proactive management of its irAEs. Ongoing research and development of comprehensive guidelines for monitoring and managing these adverse events are essential to maximize the therapeutic potential of cemiplimab while minimizing its risks.

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Institutional Review Board Statement

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Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines.

Data Availability Statement

The original contributions presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author(s).

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Data collection, S.B. and D.A.; Data analysis, S.B. and D.A.; Interpretation, S.B., D.A., M.H., A.W.T.; drafting, and editing of article, S.B., D.A.; critical revision, M.H., A.W.T.; supervision and final approval of version, M.H., A.W.T. All authors have read and agreed to the published version of the manuscript.

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