



Bilateral corneal perforation in Ipilimumab/Nivolumab - associated peripheral ulcerative keratitis

Julia Aschauer^{*}, Ruth Donner, Jan Lammer, Gerald Schmidinger

Department of Ophthalmology and Optometry, Medical University of Vienna, Waehringer Guertel 18-20, 1090, Vienna, Austria

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ABSTRACT

Purpose: To present a case of immune checkpoint inhibitor-induced bilateral peripheral ulcerative keratitis that progressed to corneal perforation requiring keratoplasty in both eyes.

Observations: We describe the course of a 60-year-old man treated with a combination of Ipilimumab and Nivolumab for metastatic melanoma who presented with foreign body sensation and epiphora in both eyes. Bilateral immune-related peripheral ulcerative keratitis was refractory to topical anti-inflammatory therapy, necessitating repetitive, but unsuccessful cyanoacrylate gluing procedure followed by bilateral lamellar mini-keratoplasty.

Conclusions and importance: Combined immune checkpoint inhibition revokes the corneal immune privilege and can lead to auto-immune keratitis with recalcitrant progression to ulceration and perforation.

1. Introduction

Immune checkpoint inhibitors were introduced with the goal to up-regulate the adaptive immune response through T-cell mediated cytotoxicity in order to reverse immune evasion by cancer cells. Two of the most important of these potent anti-tumor agents are specific antibodies that target cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1).

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a monoclonal antibody against CTLA-4, whereas Nivolumab (Opdivo, Bristol-Myers Squibb) is a monoclonal antibody binding to PD-1, both of which are used as a mono- and combination therapy for metastatic melanoma.

Based on the mechanism of action of immune checkpoint inhibitors, T-cell activation may be overwhelming with subsequently induced toxic auto-immune effects that have been described in various organ systems and are now known as “immune-related adverse events” (irAEs).¹

According to recent literature reviews, dry eye disease (1–24%) and uveitis (1%) are the most common among a wide range of ophthalmic and orbital complications.^{2,3} Here we present a case of bilateral peripheral ulcerative keratitis and inexorable progression to corneal perforation in both eyes with combined Ipilimumab and Nivolumab use.

2. Case report

A 60-year old man first presented to our clinic complaining of foreign body sensation and epiphora. Beside arterial hypertension, his medical history was positive for metastatic melanoma of the right sole of foot, which had been diagnosed a year before. He had been treated with radical excision of the lesion as well as lymphadenectomy at the time of diagnosis, followed by combined Nivolumab and Ipilimumab immunotherapy.

At first presentation, the patient achieved a best-corrected visual acuity of 20/40 in both eyes. Slit-lamp anterior segment exam showed peripheral corneal thinning and scarring from the inferior cornea encroaching on the visual axis with superficial and deep corneal neovascularization in both eyes. The findings were compatible with a healed corneal ulceration. At the time of first presentation the epithelium was intact in both eyes. No infiltration or lipid exudation was noted. Fluorescein staining showed only inferiorly-focused punctal epithelial erosions consistent with Oxford grade II, and a tear film break-up time of 6 seconds suggesting keratoconjunctivitis sicca. Topography showed bilateral irregular astigmatism. Incipient cataract formation was noted in both eyes, which may explain the reduced visual acuity of 20/40. There were no additional pathologic alterations of the anterior and vitreous chambers, as well as the posterior segment. Eyelid position was regular, without lagophthalmos. As the patient had been under close

^{*} Corresponding author. Department of Ophthalmology and Optometry, Medical University Vienna, Waehringer Guertel 18-20, 1090, Vienna, Austria.

E-mail address: Julia.aschauer@meduniwien.ac.at (J. Aschauer).

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monitoring of the treating oncologists and rheumatic diseases had been ruled out with laboratory investigations (including antineutrophil cytoplasmic antibodies (c-ANCA, p-ANCA) titers, antinuclear antibodies, rheumatoid factor, angiotensin-converting enzyme, and complement factor levels such as C3, C4 and CH50), corneal ulceration was deemed an immune-related adverse event associated with Ipilimumab and Nivolumab therapy. Thus, anti-inflammatory treatment was commenced being prednisolone acetate eye drops (1%) four times daily as well as intense unpreserved hourly lubrication and oral tetracycline (doxycycline 100 mg twice daily). Due to the perfect anti-tumor response, Nivolumab and Ipilimumab were continued at the same dose by the oncologist.

Four months later, the patient presented with right eye pain, increased tearing and photophobia. The exam showed injection with a round pinpoint, paracentral corneal perforation at the inferior pupillary margin concealed by iris tissue tamponade on the right eye. The anterior chamber was fully maintained and the Seidel test was negative for aqueous humor leakage. The epithelium was intact. There were no changes in signs and symptoms since the last follow-up in the left eye. It was decided to place a therapeutic contact lens in both eyes. Prednisolone acetate was increased to 6x and topical cyclosporine (0,4%) was started three times daily with additional antibiotic shielding using ofloxacin (ofloxacin-sine 3mg/ml). However, one month later, the Seidel test was positive. The corneal defect was sealed at the slit lamp using a drop of cyanoacrylate glue (Dermabond, Ethicon) with subsequent therapeutic contact lens placement.

Two months later, the cyanoacrylate glue on the right eye was displaced and a new perforation site was identified on the left eye (Fig. 1), both corneas showing Seidel positive test results. The eyes were still moderately inflamed with the patient still reporting pain and photophobia. Cyanoacrylate gluing was repeated at the slit lamp for both eyes with additional anterior chamber air injection for an ab-interno sealing effect with renewal of the therapeutic contact lenses. At this time point, the oncologist reported a further systemic immune-related adverse event being arthritis. The patient therefore received oral prednisolone (1mg/kg/day) with gradual tapering over weeks for severe joint pain. Overall, tumor response was extraordinarily satisfying and immune checkpoint inhibitor treatment interruption declined by both, the treating oncologist as well as the patient.

A month later, still being treated with a low dose of oral cortisone (5 mg – end of tapering), beside high dose topical anti-inflammatory therapy, there was no improvement of the corneal complication in both eyes, with active corneal neovascularization and non-healing perforation. The patient thus underwent lamellar mini-keratoplasty in both eyes. Post-operative treatment was kept unpreserved using dexamethasone-dihydrogenphosphate (0.1%) six times daily, ofloxacin four times daily, topical cyclosporine (0.4%) three times daily and intense lubrication in both eyes. The patient was stable with low-grade inflammation and superficial neovascularization in both eyes one month after surgery (Fig. 2). Nivolumab and Ipilimumab were stopped 4 months after keratoplasty due to non-progression disease, and the patient remained stable until the last follow-up appointment six months

after surgery. Table 1 summarizes the time course of the disease and the interventions performed throughout follow-up.

3. Discussion and conclusions

This case report puts emphasis on the potential severity, persistence and treatment resistance of ocular immune-related adverse events observed with the use of immune checkpoint inhibitors for progressed systemic malignancies.

The patient developed ulceration with perforation of the peripheral cornea in both eyes, which was treatment-resistant to high-dose un-specific (cortisone) and specific (T-cell inhibitory) anti-inflammatory therapy. He underwent minimally-invasive therapeutic interventions including repetitive cyanoacrylate gluing at the slit-lamp with the goal of delaying therapeutic keratoplasty and surgical trauma, as an exacerbation of immune-related complications by any kind of (iatrogenic) trauma is well-known. However, at last, only corneal sectoral lamellar keratoplasty led to a long-term stabilization of corneal findings during ongoing Ipilimumab/Nivolumab treatment, while striking tumor response including metastatic regression was observed. At this time, the patient received oral steroid therapy, which assumably blunted the negative effects of iatrogenic (surgical) trauma, and it cannot be ruled out that earlier consideration of oral steroid treatment could have prevented corneal perforation in the first place.

This specific case presents a patient with symptoms of pain, epiphora and photophobia, and signs of apparent inflammation (vasculitis of the adjacent conjunctiva). These features are commonly observed with peripheral ulcerative keratitis. Although the exact patho-mechanism of the peripheral ulcerative keratitis remains unclear, it has been hypothesized that abnormal T-cell responses initiate antibody production and immune complex deposition in the corneal stroma, with subsequent up-regulated chemotaxis of inflammatory cells and destruction of the peripheral cornea.⁴ “Paracentral corneal melt” or “keratolysis” is similar and yet distinct from peripheral ulcerative keratitis. Differentiation between these entities is often difficult, but the former one is commonly described as a “quiet eye” in patients with rheumatoid arthritis, with almost complete lack of concomitant conjunctival inflammation.⁵

CTLA-4 inhibitors (e.g. Ipilimumab) are reportedly associated with a higher frequency of irAEs as well as more severe reactions compared with PD-1 inhibitors.^{6,7} Moreover, as compared with a monotherapy, the incidence of irAEs is particularly high in the setting of an intra-class combination therapy, where more than 90% of patients may be affected.⁸ The specific manifestations of ocular and orbital side effects of Ipilimumab/Nivolumab treatment can thereby range from severe dry eye disease over uveitis and (epi)-scleritis, to Graves’ ophthalmopathy, orbital myositis, and even choroidal neovascularization development.^{9–11} In regards to the cornea and the anterior segment of the eye, anterior uveitis and keratoconjunctivitis sicca are the most common complications.¹² As for such anterior segment complications, there are small case series and case reports on Ipilimumab or Nivolumab therapy: One Ipilimumab case series included one patient who developed peripheral ulcerative keratitis as described here, which though resolved on

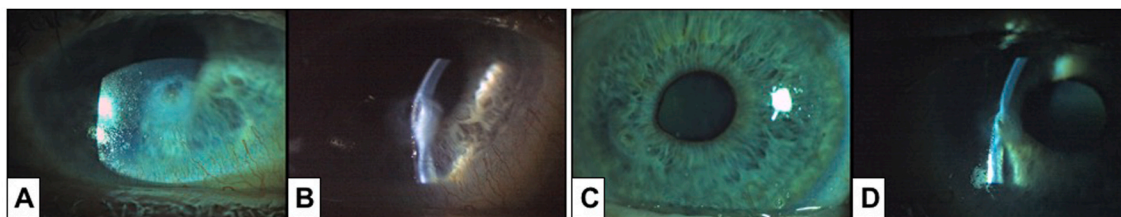


Fig. 1. Bilateral corneal perforation. A: Diffuse illumination of the right eye shows inferior peripheral corneal ulceration with stromal thinning and superficial neovascularization as well as a small round perforation site. B: Slit view of the perforation site of the right eye where previous gluing was performed. C: Diffuse illumination of the left eye shows stromal thinning inferiorly with superficial neovascularization and the perforation site with partial iris tamponade. D: Slit view of the left eye perforation site with iris tamponade.

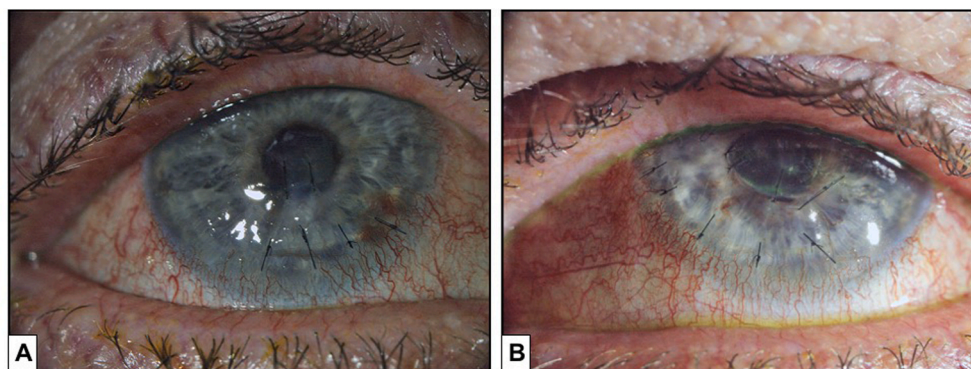


Fig. 2. Post-operative findings after lamellar keratoplasty A and B: One month after sectoral lamellar keratoplasty in the inferior cornea with sparing of the visual axis in the right (A) and left (B) eye shows stable low-grade inflammation, superficial neovascularization and clear lamellar transplants.

Table 1
Summary of disease course and interventions during follow-up.

Time point (months)	Oncology findings & interventions	Ocular findings	Ocular interventions
0	Dx of melanoma - Start of Nivolumab & Ipilimumab treatment		
12		Peripheral corneal thinning, scarring, neovascularization, dry eye	Topical steroids, lubrication, systemic doxycycline
16		Right iris-tamponade corneal perforation, Seidel -	Bandage contact lens, topical steroids, topical cyclosporine, topical antibiotics
17		Right corneal perforation, Seidel +	Cyanoacrylate gluing right eye
19	Dx of painful arthritis - Start of oral prednisone	Bilateral corneal perforation, Seidel +	Cyanoacrylate gluing both eyes
20	Systemic prednisone tapered	Bilateral corneal perforation, Seidel +	Bilateral lamellar mini keratoplasty
21	Systemic prednisone stopped	Stable post keratoplasty	Topical steroids, topical cyclosporine, topical antibiotics
24	Stop of Nivolumab & Ipilimumab treatment	Stable post keratoplasty	Topical steroids, topical cyclosporine
26		Stable post keratoplasty	Topical steroids, topical cyclosporine

topical corticosteroids.¹³ However, all of the seven patients in this series had to discontinue Ipilimumab therapy during follow up, either due to unbearable systemic irAEs or due to tumor progression.¹³ Concerning Nivolumab associated, cornea-related irAEs, there are three case reports describing different scenarios of unilateral corneal ulceration that responded well to topical anti-inflammatory medication,^{14–16} as well as one case report of chronic corneal graft rejection which failed to appear responsive to topical, subconjunctival as well as intravenous cortisone.¹⁷

In this presented case, the patient received oral prednisone for arthritis associated pain – a systemic manifestation and adverse effect of the immunomodulating agents. Systemic steroids and/or immunosuppressants are usually started in patients with peripheral ulcerative keratitis for treatment of the underlying systemic condition, i.e. rheumatoid arthritis, and not primarily for the ocular morbidity. In specific, the oral steroids hereby serve as a bridging therapy until

immunosuppressant therapy achieves effective control of the disease, which usually takes 4–6 weeks.⁴

In summary, recognizing the potential for a diverse spectrum of ophthalmic immune-related adverse effects in checkpoint inhibitory therapy is crucial in order to ensure prompt medical attention in the context of an inter-disciplinary approach to manage these patients. They need to be instructed to present to their treating physician at every onset of new ocular symptoms, and ophthalmology specialist referral should be included in future oncologic follow-up guidelines. Because along with the optimal treatment of the primary malignant pathology, containment of its adverse events by timely detection, assessment, and treatment of symptoms remains substantial for patient motivation and ultimate therapeutic success.

Patient consent

Consent to publish the case report was obtained from the patient.

Author statement

Julia Aschauer: Investigation, Conceptualization, Writing - Original Draft, Ruth Donner: Writing - Review & Editing, Jan Lammer: Writing - Review & Editing, Gerald Schmidinger: Resources, Writing - Review & Editing.

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