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# Nivolumab-Induced Ulcerative Keratitis—A Case Report

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**Purpose:** To describe a case of nivolumab-induced ulcerative keratitis rapidly recovering on topical steroid treatment and to determine changes in cytokine levels in the tear fluid caused by nivolumab.

**Methods:** We report a 34-year-old man receiving nivolumab for metastasized melanoma with severe dry eye symptoms and a persistent corneal epithelial defect. Levels of cytokine and matrix metalloproteinase in tear fluid were measured by multiplex immunoassays.

**Results:** The corneal epithelial defect failed to recover for antiviral and lubrication therapy but resolved within 48 hours after topical steroid therapy was initiated. No recurrence of corneal ulceration was observed with intermittent topical steroid therapy during the remaining period of nivolumab treatment. No Sjögren disease-related autoantibodies were detected in the patient's serum. The levels of inflammatory cytokines and matrix metalloproteinases in the tear fluid were markedly elevated after nivolumab treatment.

**Conclusions:** Our observations suggest that nivolumab treatment induces a local autoimmune ocular surface disorder resulting in corneal ulceration that promptly resolves using steroid eye drops. The integrity of the corneal epithelial layer can be sustained using intermittent topical steroid therapy in patients receiving nivolumab.

**Key Words:** corneal ulceration, ocular surface, nivolumab, immune checkpoint inhibitors

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Immune-checkpoint inhibitors are a relatively new group of immunomodulatory agents applied in the first or second line of tumor therapy with a rapidly broadening spectrum of indications including melanoma malignum, nonsmall-cell lung cancer, renal cell carcinoma, Hodgkin disease, and breast cancer.<sup>1</sup> The most widely studied inhibitor is nivolumab, a monoclonal antibody blocking the programmed death-1 (PD-1) receptor. It was the first drug in this group to get FDA approval in 2015, followed by 5 other inhibitors.<sup>1,2</sup> These drugs activate

T-cells enabling a stronger immune attack on tumor cells. However, this attack is not specifically targeted and might cause, therefore, a wide range of autoimmune adverse reactions including skin rash, colitis, pneumonitis, myositis, myocarditis, and thyroid gland insufficiency. Ocular side effects include anterior uveitis, conjunctivitis, immune retinopathy, endotheliitis, corneal allograft reaction with graft rejection, and moderate to severe dry eye disease.<sup>3–5</sup> Nivolumab treatment has been linked to severe dry eye symptoms leading to corneal ulceration in as few as 3 patients so far. Dry eye symptoms developed typically after the first couple of cycles of nivolumab treatment. Corneal perforation was observed in 1 of the 3 cases, and conjunctival coverage was necessary to avoid perforation in another case. Topical steroid or cyclosporine led to the rapid healing or stabilization of the corneal surface in all of these cases.<sup>4,5</sup> The aim of this study was to describe a new case of nivolumab-induced corneal ulceration and to provide deeper insight in the role of inflammatory cytokines and matrix metalloproteinases (MMPs) in the tear fluid.

## CASE REPORT

A 34-year-old man received nivolumab treatment for metastasized skin melanoma. The patient initially received 7 nivolumab infusions on a biweekly basis followed by infusions every 4 weeks. The patient developed dry eye symptoms regularly around the third or fourth day after each infusion. After the 10th treatment cycle, the patient was referred to the ophthalmology department with severe dry eye symptoms. Best corrected visual acuity of the patient was 20/20 in the right eye and 20/125 in the left eye. Slitlamp examination revealed a small corneal epithelial defect and injection of the bulbar conjunctiva in his left eye and punctate corneal erosions with mild conjunctival injection in his right eye. Tear production and tear film stability were reduced: Schirmer tear production test was 6 mm both sides and the tear breakup time was 2 seconds in both eyes. Corneal sensitivity was normal in both eyes. For suspected herpes simplex keratitis, acyclovir ophthalmic ointment was initiated 3 times daily along with oral acyclovir 3 times 800 mg daily. Artificial tear drops were prescribed for lubrication. After 3 months of such treatment, the corneal epithelial defect still measured 4 mm (Fig. 1A). Subsequently, antiviral treatment was stopped, and the patient was administered with unpreserved dexamethasone eye drops 4 times daily. The corneal epithelial defect healed within 2 days thereafter (Figs. 1B–D). Best corrected visual acuity returned to 20/25 in the left eye. Routine laboratory investigations failed to detect any autoantibodies indicative of Sjögren syndrome (anti-ribonucleoprotein, -Sm, -Ro-52, -Ro-60, -SSB/La, -Scl-70, -centromere protein-B, -Jo1). Erythrocyte sedimentation rate (5 mm/h) and C-reactive protein (1 mg/mL) were within normal limits. Punctal plugs were inserted, and topical intermittent steroid therapy was synchronized with the nivolumab therapy ensuring corneal integrity for the entire duration of the nivolumab treatment. The right eye was successfully treated with lubrication therapy during the entire treatment period. Tear samples

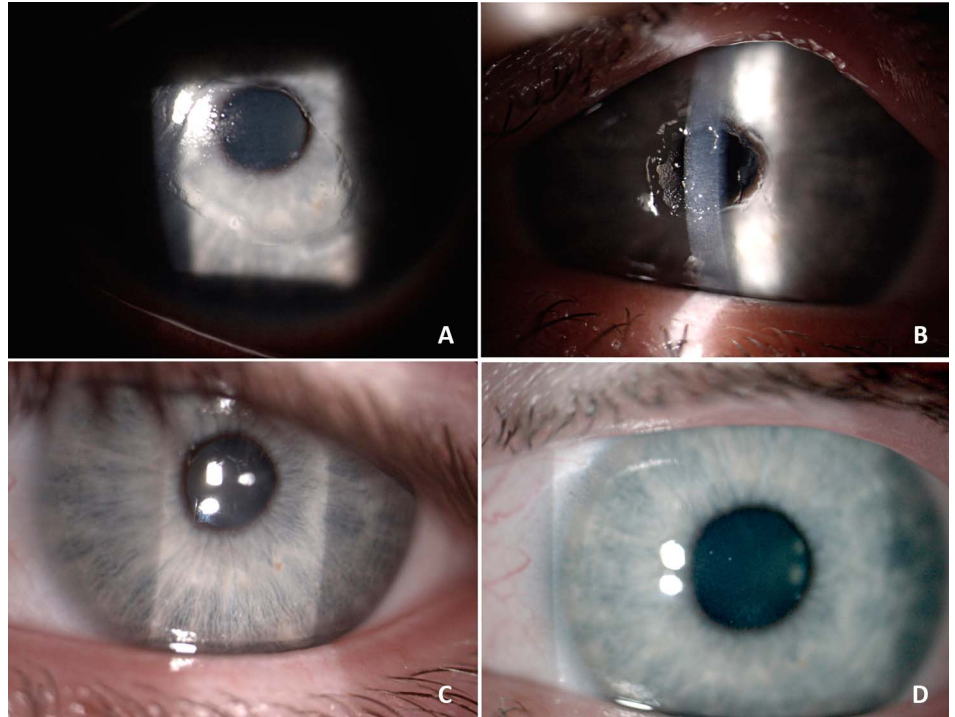
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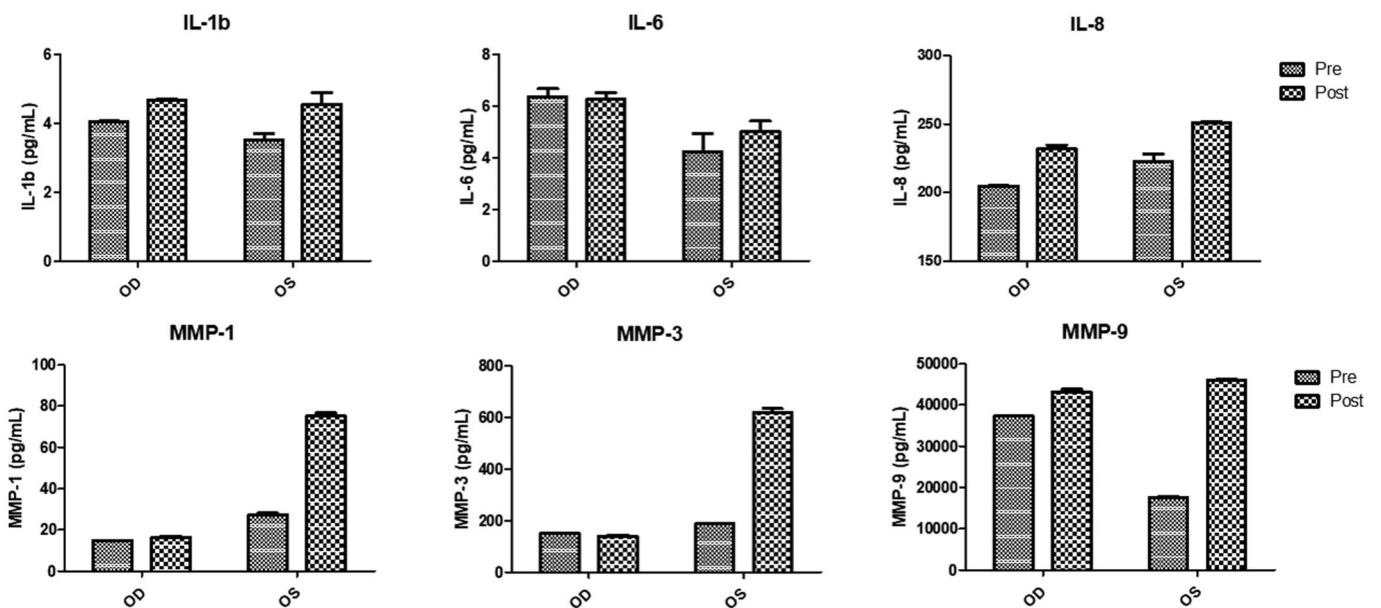
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**FIGURE 1.** Corneal photographs of the affected left eye of the patient. A, A 4-mm corneal epithelial defect before topical steroid treatment. B, One day after the initiation of the treatment, the epithelial defect was substantially smaller. C, No epithelial defect was seen on the second day of treatment. D, On day 4, the corneal epithelial layer is completely restored, only a tiny central sub-epithelial haze was left over. (The full color version of this figure is available at [www.corneajrnl.com](http://www.corneajrnl.com).)

from both eyes were collected right before and 7 days after the 16th treatment cycle with nivolumab. Schirmer tear strips (TEAR strips; Contacare Ophthalmics and Diagnostics, Gujarat, India) were inserted without topical anesthesia for 5 minutes. Care was taken to avoid contamination of the strip by using sterile gloves for insertion and sterile tweezers for removal. The tear migration length was recorded immediately after sampling, and samples were stored frozen. Tear proteins were extracted from the strip in 150  $\mu$ L PBS + 25  $\times$  complete

protease inhibitor cocktail (Roche, Basel, Switzerland). Levels of cytokines (interferon [IFN]- $\gamma$ , interleukin [IL]-1 $\beta$ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and tumor necrosis factor [TNF]- $\alpha$ ) and MMPs (MMP-1, MMP-3, and MMP-9) in the tear fluid were measured using the Proinflammatory Panel 1 10-plex assay and the MMP 3-Plex assay (Meso Scale Discovery, Rockville, MD), respectively. Signals for IL-1 $\beta$ , IL-6, and IL-8 could be detected in all tear samples (Fig. 2). The other 7 tested cytokines (IFN- $\gamma$ , IL-10, IL-12 p70, IL-13, IL-2, IL-4,



**FIGURE 2.** Levels of cytokines and MMPs in the tear samples before (pre) and 7 days after (post) nivolumab treatment. Interleukins show a mild to moderate elevation after nivolumab treatment in both eyes; however, MMPs are markedly elevated in the left eye on nivolumab treatment.

and TNF- $\alpha$ ) were undetectable or below the limit of detection. In the affected eye, levels of IL-1 $\beta$  ( $3.52 \pm 0.20$  pg/mL), IL-6 ( $4.25 \pm 0.68$  pg/mL), and IL-8 ( $222.80 \pm 5.32$  pg/mL) before treatment in the tear fluid were moderately elevated after nivolumab treatment ( $4.55 \pm 0.34$  pg/mL,  $5.01 \pm 0.41$  pg/mL, and  $251.35 \pm 0.25$  pg/mL, respectively). Signals for the 3 tested MMPs (MMP-1, MMP-3, and MMP-9) could be detected in all tear samples (Fig. 2). Levels of MMP-1 ( $27.27 \pm 0.83$  pg/mL), MMP-3 ( $187.47 \pm 1.87$  pg/mL), and MMP-9 ( $17,545.80 \pm 369.83$  pg/mL) in the tear fluid of the affected eye before treatment were approximately 3-fold lower than those after nivolumab treatment ( $75.32 \pm 1.37$  pg/mL,  $620.14 \pm 13.86$  pg/mL, and  $46,046.18 \pm 284.36$  pg/mL, respectively).

## DISCUSSION

Nivolumab-induced corneal ulceration is a recently described disease entity reported in only 3 cases thus far.<sup>4,5</sup> It starts with severe dry eye symptoms after a couple of nivolumab treatment cycles. The disease might progress to corneal ulceration and initially resemble a herpes simplex keratitis. This might lead to a diagnostic error and inadequate treatment of the corneal ulcer. After unsuccessful antiviral treatment, topical steroid and lubrication therapy restored corneal integrity within a very short time, quickly relieving the symptoms. The same disease course was observed in the previously reported cases as well. Nivolumab is known to cause many systemic autoimmune side effects. The possibility of nivolumab-induced Sjögren syndrome was straightforward but could not be confirmed by the detection of Sjögren-specific autoantibodies. An initial near-normal Schirmer test and normal values thereafter also indicated that nivolumab-induced ulcerative keratitis is primarily not caused by a decreased tear production. IL-1 and MMPs are known to play an important role in corneal tissue degradation in various pathological processes including dry eye disease, corneal melting, peripheral ulcerative keratitis, and recurrent corneal erosions.<sup>6–10</sup> ILs and MMPs in the tear fluid showed an elevation in both eyes but more pronounced in the left eye with the corneal ulcer, indicating that ILs and MMPs play an important role in nivolumab-induced corneal ulceration as well. The source of MMPs in this particular process is not yet clear. They might be produced by keratocytes or by T-cells invading the corneal stroma as seen in other autoimmunity-mediated corneal diseases.<sup>8–10</sup> The exact pathophysiological mechanism of nivolumab-induced keratitis is still

unknown. Activation of T-cells causing local or systemic autoimmunity plays presumably a pivotal role. This process might not only affect the lacrimal gland leading to decreased tear production but, more importantly, also cause an autoimmunity-mediated inflammation of the ocular surface leading to corneal epithelial defects and ulceration.

With the broadening spectrum of indications and growing number of patients receiving immune checkpoint inhibitors, ophthalmologists are expected to encounter an increasing number of ocular side effects. Therefore, it is of paramount importance to recognize immune checkpoint inhibitor-induced keratitis and corneal ulceration and immediately start topical steroid therapy. With a promptly started and appropriate therapy, corneal ulceration/perforation can be avoided and the essential immune checkpoint inhibitor therapy be continued.

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