Cyclosporine for dry eye associated with anti-PD-1 therapy

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Additional data and information can be provided by emailing the corresponding author

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ABSTRACT

**Purpose:** To present a clinical case of severe dry eye associated with Nivolumab that progressed to corneal perforation

**Background:** Nivolumab is an PD-1 (programmed cell death protein 1) antagonist that exerts its anti-tumor effect by upregulating host T cell immunity.

**Case Presentation:** A 58-year old man with metastatic melanoma was referred for management of severe bilateral dry eyes after undergoing his 6th cycle of Nivolumab. The right eye progressed to corneal perforation which was acutely treated with corneal gluing. Nivolumab therapy was subsequently discontinued due to this adverse event. When the patient exhibited evidence of recurrent metastases, Nivolumab was restarted. The patient’s ocular surface was able to sustain continued therapy with Nivolumab with an intensive approach that included topical cyclosporine.

**Conclusions:** PD-1 antagonists can cause or worsen dry eye disease to the point of corneal perforation Given that its’ anti-tumor effect is immune mediated, therapies targeting ocular surface inflammation can be effective for stabilizing dry eye disease in patients who are treated with anti-PD-1 agents.
**History**

A 58 year-old man with metastatic melanoma from a primary nasal sinus tumor was referred to ophthalmology for bilateral eye irritation. Around this time, he was undergoing his 6th cycle of Nivolumab (3 mg/kg) for treatment of metastatic melanoma. His metastatic lesions had been regressing favorably in response to Nivolumab, an immunomodulatory agent that upregulates host immunity. The patient was assessed to have dry eye syndrome for which he was started on preservative-free artificial tears and lubricating ointment at bedtime. For the next 2 weeks, he continued to experience persistent burning in both eyes and was then referred to a cornea specialist.

**Examination**

On presentation to the Cornea service, his corrected visual acuity was 20/30 in the right eye and 20/25 on the left. His examination was notable for a low tear meniscus and diffusely distributed punctate epithelial erosions in both eyes. A basic secretion test (Schirmer’s with anesthesia) was performed which yielded values less than 4.0 mm from each eye.

**Treatment and Clinical Course**

The patient was recommended to intensify the frequency of lubricant tear use to at least 6-8 times daily. Additionally, he received bilateral lower eyelid punctum plugs and was started on topical cyclosporine (0.05%) twice daily in both eyes. However, due to overseas travel, the patient reported difficulty adhering to this medication regimen. Two weeks later, he returned to the office with a perforated right eye cornea. Examination of the right eye was notable then for a 1.8 mm by 1.4 mm paracentral epithelial defect within which there was variable corneal thinning and a small focus of Seidel-positive leakage. The chamber was shallow but without iris plugging to the perforation site. This was acutely managed with corneal glue and a bandage contact lens. The left eye had a small epithelial defect without associated stromal thinning.
Further treatment with Nivolumab was held in light of this adverse event. In the weeks that followed, the right eye was stabilized with adherence to a regimen that included preservative-free artificial tears, daily topical loteprednol (0.5%), topical cyclosporine, autologous serum tears, oral doxycycline and Vitamin C. The left eye had exhibited areas of slight stromal thinning (80-90% normal stromal thickness) but it was similarly stabilized with lubricating tears (artificial and serum), topical cyclosporine, and a bandage contact lens. One month after the right eye cornea was glued, the full-thickness defect had healed but there remained a stromal scar with marked corneal thinning (Figure 1).

One year after Nivolumab was discontinued, abdominal imaging revealed a pancreatic head mass that was biopsy-positive for melanoma. After additional imaging revealed further sites of probable metastases, a decision was reached to restart Nivolumab. In a recent clinic visit, the patient has cleared all sites of metastases with several additional treatment cycles. His ocular surface has been maintained bilaterally with scleral lenses, topical cyclosporine, frequent surface lubrication and cautery of both upper and lower lid puncta.

Discussion

The programmed cell death protein 1 (PD-1) is a membrane receptor that is involved in downregulating host immunity.\textsuperscript{1-3} Activation of this pathway promotes the apoptosis of antigen-specific T cells, which serves to promote host tolerance for self-antigens. Nivolumab is an antibody capable of disrupting this pathway; in doing so, it exerts anti-tumor activity by upregulating host T cell immunity. Expectedly, many of the adverse effects associated with Nivolumab are immune-mediated.\textsuperscript{1,4} While there is not much written about the ocular side effects of this drug class, we hypothesized that the upregulation of T cell activity could be the cause of worsening dry eye disease.\textsuperscript{4}

If this were true, it follows that a therapeutic strategy targeting T cells may be of benefit. The utility of controlling ocular surface inflammation for the treatment of dry eye has been demonstrated by prior studies investigating the use of topical cyclosporine for this end.\textsuperscript{5} Cyclosporine functions as a
calcineurin inhibitor and in doing so it downregulates the transcription of interleukin-2. The downstream effect of this inhibition is a reduction in T cell activation. Dry eye patients treated with cyclosporine have been shown to have reduced levels of proinflammatory cytokines on the ocular surface,\(^6\) which is presumably responsible for the improvement in symptoms,\(^7\) surface staining\(^7\) and conjunctival goblet cell density.\(^8\) Because cyclosporine exerts its effect by inhibiting the activation of relatively naïve T cells, its peak effect is delayed given the presence of mature T lymphocytes that are already activated. For this reason, bridging patients with a mild topical corticosteroid can be helpful.

The patient’s poor compliance with the initial medication regimen may have contributed to the progression towards perforation. Medication adherence, though, was improved after the right eye required corneal gluing. However, this adverse event led to the withdrawal of Nivolumab therapy, which had been highly effective at resolving the patient’s metastatic disease. When follow-up imaging showed recurrent metastases, treatment with Nivolumab was econsidered. Ocular surface stability was a prerequisite for receiving continued anti-PD-1 therapy. This was achieved with an intensive approach that includes topical cyclosporine, which provides local inhibition of T cell activity on the ocular surface.

**Conclusion**

Topical cyclosporine may be useful for treating dry eyes associated with immunomodulatory agents like Nivolumab, which markedly upregulate T cell activation. In caring for patients with ocular side effects associated with cancer treatment, the delivery of proper ophthalmic care is critical.
References


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Jessica Chow, MD
Disclosures

• None
CC: bilateral eye irritation

HPI: 58 year-old man with a history of metastatic melanoma from a primary nasal sinus tumor is referred for bilateral burning eyes. He was undergoing his 6th cycle of Nivolumab therapy (an antibody to the programmed cell death protein 1 or PD-1).

No pre-existing history of dry eye disease before cancer treatment.
PMHx/POHx:

• 2010 - Primary nasal sinus tumor – s/p total ethmoidectomy, wide bilateral sphenoidectomy with adjuvant radiation, biopsy-positive for melanoma
• 2012 - Liver biopsy confirmed metastatic melanoma
• 2013 – Admitted for high-dose interleukin-2 (IL-2) therapy
• 2013 – Progression despite IL-2 therapy, started on Nivolumab
• 2013 – By Cycle #5, liver/kidney lesions regressed

Medications:

• See above
• Venlafaxine
• Compazine
• Pantoprazole
• Viagra
**Allergies:** NKDA

**FMHx:** non-contributory

**SocHx:** no significant alcohol consumption, no tobacco smoke

**ROS**
+diarrhea, +intermittent abdominal cramping

Pertinent items have been mentioned and are otherwise negative or non-contributory
The patient was evaluated to have dry eyes and was started on polyvinyl alcohol-povidone, preservative-free (Refresh, PF) 4 times daily to both eyes and Refresh PM ointment at bedtime.

The patient had persistent burning symptoms in both eyes and was subsequently referred to the Cornea service.
<table>
<thead>
<tr>
<th></th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Acuity (distance, with correction)</td>
<td>20/30</td>
<td>20/25</td>
</tr>
<tr>
<td>Pupils</td>
<td>No relative afferent pupillary defect</td>
<td>No relative afferent pupillary defect</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>14 mm Hg</td>
<td>14 mm Hg</td>
</tr>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
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<td>----------------------</td>
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</tr>
<tr>
<td>Motility</td>
<td>Full</td>
<td>Full</td>
</tr>
<tr>
<td>External</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lids/lashes</td>
<td>Well-positioned, no Meibomian gland dysfunction</td>
<td>Well-positioned, no Meibomian gland dysfunction</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Trace bulbar injection</td>
<td>Trace bulbar injection</td>
</tr>
<tr>
<td>Cornea</td>
<td>Moderate fluorescein staining, diffusely distributed</td>
<td>Moderate fluorescein staining, diffusely distributed</td>
</tr>
</tbody>
</table>
*Facsimile of patient’s surface staining
<table>
<thead>
<tr>
<th></th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens</td>
<td>1+ NS</td>
<td>1+ NS</td>
</tr>
<tr>
<td>Vitreous</td>
<td>Clear, no vitritis</td>
<td>Clear, no vitritis</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>C/D 0.3</td>
<td>C/D 0.3</td>
</tr>
<tr>
<td>Macula</td>
<td>No serous detachment</td>
<td>No serous detachment</td>
</tr>
<tr>
<td>Vessels</td>
<td>No vasculitis</td>
<td>No vasculitis</td>
</tr>
<tr>
<td>Periphery</td>
<td>No retinitis</td>
<td>No retinitis</td>
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</tbody>
</table>
Increase preservative-free artificial tears to 6-8 times daily and continue lubricating ointment at bedtime.

The patient received bilateral lower lid punctal plugs and was started on topical *cyclosporine* (0.05%) twice daily to both eyes.
The patient had difficulty adhering to this regimen due to international travel and returned to the United States 2 weeks later with a perforated right eye cornea.
Differential diagnosis

- Dry eye exacerbated by Nivolumab therapy
- Radiation keratopathy
- Multifactorial
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Lids/lashes</td>
<td>Well-positioned, no Meibomian gland dysfunction, +lower lid punctum plug</td>
<td>Well-positioned, no Meibomian gland dysfunction, +lower lid punctum plug</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Trace bulbar injection</td>
<td>Trace bulbar injection</td>
</tr>
<tr>
<td>Cornea</td>
<td>1.8mm x1.4mm epi defect, variable stromal thinning, small focus of Seidel-positive leakage</td>
<td>Small &lt;1.0mm epi defect without stromal thinning</td>
</tr>
<tr>
<td>Anterior chamber</td>
<td>Shallow peripherally, no iris plugging to wound</td>
<td>Normal</td>
</tr>
</tbody>
</table>
The right eye was acutely treated with corneal glue and a bandage contact lens.

His ocular surface regimen was intensified to include: **Oral doxycycline, Vitamin C**

<table>
<thead>
<tr>
<th>RIGHT EYE</th>
<th>LEFT EYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical loteprednol 0.5% daily</td>
<td>Topical cyclosporine 2x/day</td>
</tr>
<tr>
<td>Topical cyclosporine 2x/day</td>
<td>Autologous serum tears 4-6x/day</td>
</tr>
<tr>
<td>Autologous serum tears 4-6x/day</td>
<td>Preservative-free artificial tears 6-8x/day</td>
</tr>
<tr>
<td>Preservative-free artificial tears 6-8x/day</td>
<td>Lubricating ointment at bedtime</td>
</tr>
<tr>
<td>Lubricating ointment at bedtime</td>
<td></td>
</tr>
</tbody>
</table>
1 month later:
Nivolumab was discontinued due to this adverse event.

One year later, melanoma metastases were detected on repeat abdominal imaging.

The patient was restarted on Nivolumab.
In a recent visit, he has completed with 20\textsuperscript{th} cycle of \textbf{Nivolumab} and has achieved resolution of all metastatic lesions.

He is able to continue receiving this highly effective cancer treatment with an ocular surface stabilized by an intensive approach (previous regimen and has since had bilateral upper and lower lid punctal cautery).
Discussion

• The **programmed cell death protein 1 (PD-1)** is a membrane receptor that activates the **programmed cell death** of T lymphocytes
  • Promotes tolerance to self-antigens
  • Protects against autoimmunity

• **Nivolumab** is an antibody against PD-1, which inhibits the pathway thereby upregulating host immunity

• We hypothesize that this upregulation of T cells is responsible for the ocular side effects associated with anti-PD-1 therapy

• Dry eye was a reported side effect in 2 out of 207 patients in a Phase I Study with Nivolumab
• Other ocular side effects include anterior uveitis
• We previously reported 2 cases of dry eye associated with Nivolumab adequately treated with topical cyclosporine to be able to continue cancer treatment
  • One patient after completing Nivolumab therapy was able to be weaned off of topical cyclosporine

The case presented may have had a much more dramatic course given a multitude of possible contributing etiologies:

- History of radiation
- Use of punctal occlusion but nonadherence with medication regimen (cyclosporine to counteract inflammation)
• Cyclosporine is a calcineurin inhibitor. It inhibits the transcription of interleukin-2, which in turn downregulates the activation of naïve T cells

• Its peak effect may be delayed due to the presence of mature T cells already active on the ocular surface

• Patients can be bridged with a mild topical corticosteroid such as loteprednol


Conclusions

• Topical cyclosporine can be a useful agent for treating dry eye in patients receiving anti-PD-1 therapy

• In the setting of cancer treatment, proper ophthalmic care is critical