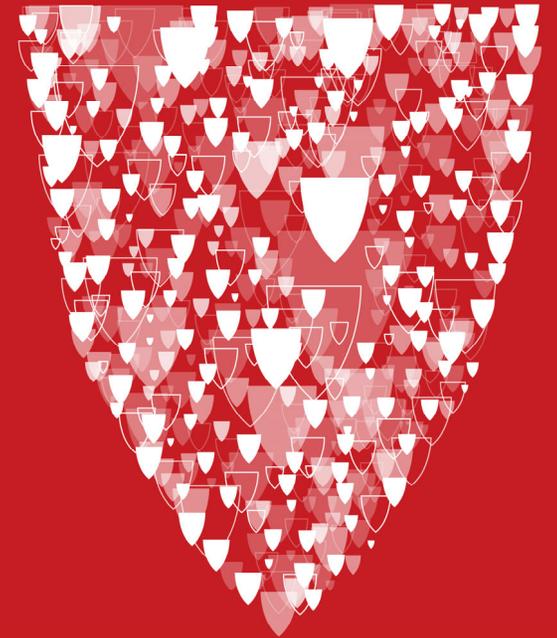


Systemic Immunotherapy and the Eye: A Retrospective Look at Ocular Toxicities

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Case Presentation

- **A 78-year-old man presented with a one-week history of bilateral blurred vision and ocular irritation.**
- He had a history of keratoconus and underwent PK in the right eye 30 years earlier and DALK in the left eye 16 years earlier.
- Ocular history also included CEIOL OU, strabismus surgery OS for esotropia, moderate-stage POAG OD, and glaucoma suspect OS.
- Ocular medications included prednisolone acetate 1% once daily OU, brimonidine BID OD, dorzolamide-timolol BID OD, and latanoprost QHS OU.
- The patient was diagnosed with urothelial carcinoma 10 months earlier and progressed to metastatic disease despite treatment with Bacillus Calmette–Guérin (BCG) therapy. He began treatment with pembrolizumab and enfortumab vedotin two and a half months prior to presentation and had completed four treatment cycles.

Initial Examination and Treatment

- **Baseline BCVA (prior to initiation of cancer treatment):** 20/30 OD and 20/25 OS.
- **On presentation:** BCVA declined to 20/40 OD and 20/60 OS. IOP 12 mmHg OU.
- **Slit-lamp examination:** Bilateral mucoid discharge and mild diffuse conjunctival injection. New 360-degree corneal neovascularization was noted in the right eye, extending approximately 1 mm beyond the graft-host junction, along with corneal edema and stromal haze.
- **Treatment:** He was treated empirically with prednisolone acetate 1% QID OD and topical moxifloxacin QID OU.

Clinical Course

- **Day 3:** Eye discharge resolved, moxifloxacin discontinued. Prednisolone increased to q1hr OD.
- **Day 7:** Corneal edema resolved. Improvement in stromal haze and corneal neovascularization. Prednisolone gradually tapered.
- **Week 3:** No longer had any signs of graft rejection. Prednisolone maintained at BID OD.
- **Month 3:** The patient self-discontinued prednisolone drops. Developed neovascularization inferiorly at the graft-host junction, a small (<0.5 mm) hyphema, and corneal edema in the right eye. Prednisolone increased to 6x daily OD and then gradually tapered to qday.
- **Month 5:** Graft rejection completely resolved.
- **Month 6:** BCVA 20/25 OD and 20/30 OS without any signs of transplant rejection.

*** Pembrolizumab was continued throughout the patient's course.*

Research Questions

1. Are there other patients in the hospital system who experienced corneal transplant rejection after starting an immune checkpoint inhibitor?
2. What other ocular immune related adverse events are associated with immunotherapy treatment?
3. What are the demographics surrounding these adverse events and how soon after immunotherapy initiation do these events appear?
4. What impact do these adverse events have on visual acuity – both acutely and long-term?

Immune Checkpoint Inhibitors

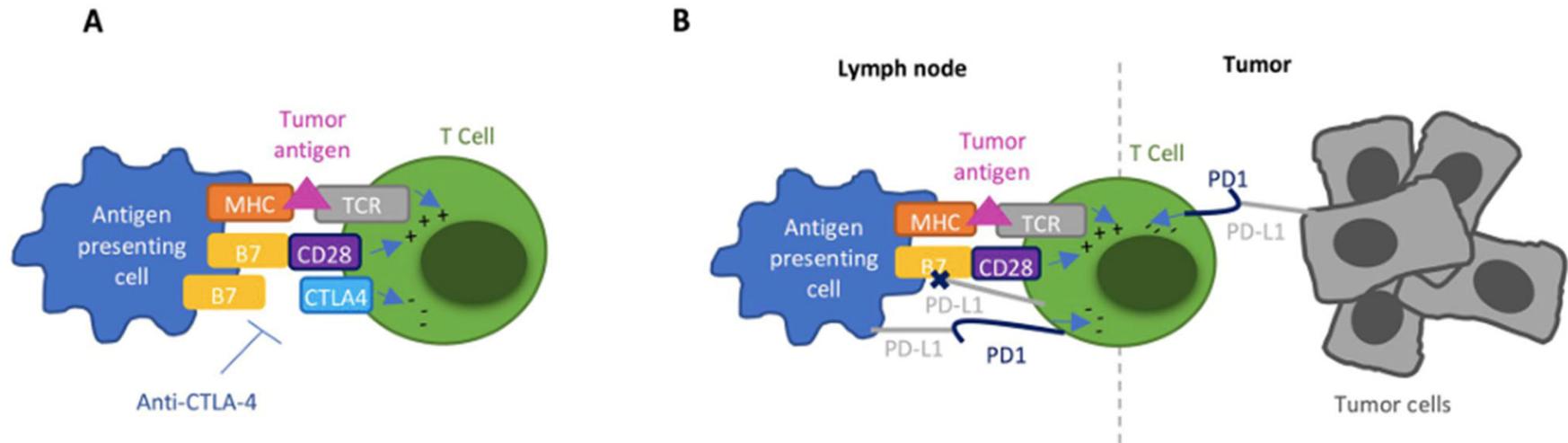


Fig. 1 Mechanism of action. **A** Tumor antigen presentation by the major histocompatibility complex (MHC) receptor and B7/CD28 costimulatory signal are both necessary for CD8 T-cell activation. CTLA-4 downregulates T-cell immune function. Anti-CTLA-4 antibodies inhibit this downregulation and stimulate the immune system. **B** Interaction between PD1 and PD-L1 takes place in the lymph node and in the tumor microenvironment. PD1 downregulates T-cell function as well. Through PD-L1 binding PD1, tumors can escape immunosurveillance. Anti-PD-1 or -PD-L1 antibodies prohibit this and will restore the anti-tumor response

Martens, et al. J Ophthalmic Inflamm Infect. 2023 Feb 22;13(1):5.

Methods

- Retrospective study
- Collaboration between ophthalmology and oncology departments
- Patients treated with an immune checkpoint inhibitor between 2017-2025 at University Hospitals Seidman Cancer Center
- Included patients who developed an ocular immune-related adverse events (irAEs)

Question 1: Are there other patients in the hospital system that experienced corneal transplant rejection after starting an immune checkpoint inhibitor?

- 10 patients with prior corneal transplant and then treated with immune checkpoint inhibitor
 - **2 patients with graft rejections**
 - **PK rejection** – after 4 cycles of pembrolizumab despite prednisolone 1x daily
 - **DMEK rejection** – 7 cycles of pembrolizumab, then underwent DMEK, then rejection after 2 more cycles in the setting of self-discontinuation of prednisolone drops
 - 3 patients with stable grafts
 - 5 patients with unclear rejection status
 - Either lost to follow up, transitioned to hospice, or deceased

Question 2: What other ocular immune related adverse events are associated with immunotherapy treatment?

	<i>Frequency (%)</i>
Uveitis	7 (36.8%)
Anterior uveitis	4
Anterior and intermediate uveitis	2
Panuveitis	1
Cornea & ocular surface	6 (31.6%)
Corneal transplant rejection	2
Dry eye	2
Persistent epithelial defect/keratolysis	1
Drug-induced conjunctivitis	1
Orbit and ocular adnexa	3 (15.8%)
Orbital myositis	1
Canalicular and punctal stenosis	1
Periocular dermatitis	1
Neuro-ophthalmologic	1 (5.3%)
Binocular diplopia secondary to autoimmune thyroiditis	1
Retina	2 (10.5%)
Retinal pigment epithelium (RPE) changes	1
Cystoid macular edema	1
Total events	19

Question 3: What are the demographics surrounding these adverse events and how soon after immunotherapy initiation do these events appear?

Age	55.2±18.4 years
Sex	64.7% female
Race	
White	76.5%
Black	17.6%
Unspecified	5.9%
Cancer stage	3.3±0.7
Cancer types	
Melanoma	7
Lung adenocarcinoma	3
Hodgkin's lymphoma	2
Cervical cancer	1
Urothelial cancer	1
Uterine cancer	1
Breast adenocarcinoma	1
Tonsillar squamous cell	1
Number of treatment cycles before ocular irAEs developed	4.1±3.4
Immune checkpoint inhibitor	
Pembrolizumab	10
Nivolumab	2
Durvalumab	1
Ipilimumab + nivolumab	3
Pembrolizumab + nivolumab	1

Question 4: What impact do these adverse events have on visual acuity – both acutely and long-term?

- BCVA decreased significantly during the irAE, declining from 0.06 ± 0.11 LogMAR (Snellen 20/23) to 0.22 ± 0.30 LogMAR (Snellen 20/35) ($p = 0.004$).
- Most patients experienced a favorable response to treatment of their ocular irAE with no significant difference observed between baseline and post-treatment BCVA ($p = 0.17$).

Discussion

- Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but may pose a risk for immune-mediated complications.
- Ocular immune-related adverse events (irAEs) are rare but can lead to significant changes in vision.
- Most cases of ocular irAEs were uveitis-related and responded well to topical corticosteroids.
- Several rare irAEs were identified such as corneal transplant rejection, orbital myositis, and retinal pigment epithelium changes.
- Early recognition of ocular irAEs and ophthalmology referral are essential so that treatment can be initiated to prevent long-term ocular morbidity.

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