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## Ophthalmic Immune-Related Adverse Events of Immunotherapy: A Single-Site Case Series

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Immune checkpoint inhibitors including antibodies against programmed-cell death protein-1 (PD-1) and cytotoxic T-lymphocyte—associated-antigen 4 have been shown to improve survival in patients with advanced cutaneous melanoma.<sup>1</sup> The combination of ipilimumab (Yervoy, Bristol-Myers Squibb, New York, NY), a monoclonal antibody to cytotoxic T-lymphocyte—associated-antigen 4, and nivolumab (Opdivo, Bristol-Myers Squibb), an anti—PD-1, was approved by the US Food and Drug Administration in 2015 for the treatment of metastatic cutaneous melanoma.<sup>2</sup> The indications for these agents have expanded since then to include a broader range of malignancies. Immune-related adverse events (irAEs) involving eyes and periocular structures from these agents have been reported, but trends and incidence rates have been difficult to ascertain because of rarity.

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No animal subjects were used in this study.

A retrospective chart review was performed of 1474 patients treated with nivolumab with or without ipilimumab from January 2010 to August 2018 at Yale Smilow Cancer Center. All patients were treated with immunotherapy as first line for metastasis. Of the 1474 patients, 15 (1.0%) developed an ophthalmic irAE. Twelve patients were treated for metastatic cutaneous melanoma, 2 patients were treated for metastatic uveal melanoma, and 1 patient was treated for metastatic non—small-cell lung carcinoma. The mean age at the time of ocular symptoms onset was 60.6 years (range, 43—79 years; standard deviation, 10.7), and 9 (60%) were women. The mean number of infusions administered before the onset of ocular symptoms was 3.6 (range, 1—10 cycles; standard deviation, 2.9), and follow-up time was 25 months (range, 1—85 months). All but 1 patient experienced bilateral ophthalmic irAEs. Ophthalmic toxicities included ocular myasthenia gravis, corneal punctate epithelial erosions,<sup>3</sup> subconjunctival hemorrhage, corneal perforation,<sup>3</sup> uveitis, hypotony maculopathy, cystoid macular edema, serous retinal detachment, choroiditis, Vogt-Koyanagi-Harada—like syndrome,<sup>4</sup> optic neuritis, and melanoma-associated retinopathy (MAR). Table 1 provides a summary of these cases. Two notable cases are discussed.

### **Case 14: Melanoma-Associated Retinopathy.**

A 79-year-old woman with metastatic cutaneous melanoma developed bilateral floaters and photopsia after 1 cycle of ipilimumab and nivolumab. A posterior vitreous detachment was noted on ophthalmic examination. Immunotherapy was continued for 3 cycles, after which she developed nyctalopia, transaminitis, rash, and hypopituitarism. Immunotherapy was discontinued, and high-dose intravenous steroids were administered. Full-field electroretinogram revealed attenuated b-wave and preserved dark-adapted negative a-wave, indicative of poor bipolar cell function and intact photoreceptor function. The presence of anti-retinal antibodies was confirmed on an autoimmune retinopathy panel. She was diagnosed with MAR on the basis of these findings, and intravenous immunoglobulins were administered. At 10 months since symptom onset, her visual acuity was 20/20 in both eyes but without improvement in dark adaptation, and her metastatic disease had complete response to treatment. This is the first case of MAR induced by nivolumab and ipilimumab. The co-occurrence of multiorgan irAE (transaminitis and hypophysitis) suggests that MAR was also triggered by immunotherapy.

### **Case 15: Optic Disc Edema.**

A 61-year-old woman underwent 4 cycles of ipilimumab/nivolumab combination therapy followed by a single cycle of nivolumab monotherapy when she developed blurry vision in the left eye. Her visual acuity was 20/20 in the right eye and 20/100 in the left eye with relative afferent pupillary defect in the left eye. She had bilateral optic nerve swelling and marked depression of visual fields. Cerebrospinal fluid studies revealed normal opening pressure and absence of malignant cells. Immunotherapy was discontinued, and the patient received systemic corticosteroids followed by intravenous immunoglobulin therapy and infliximab. Her disease progressed, and she died 18 months later. She is the first described in the literature with nivolumab-associated optic neuritis.

## Discussion.

Although antibodies against cytotoxic T-lymphocyte—associated-antigen 4 and PD-1 are thought to cause adverse events through generalized activation of the host's immune system and decrease in self-tolerance (the same mechanism by which these therapies work against malignancies), the specific mechanism of inducing adverse events is not known. The rate of systemic irAE in the setting of immunotherapy with ipilimumab and nivolumab is as high as 96%;<sup>1</sup> however, the incidence of ophthalmic irAE is low. Our series of 15 patients with ophthalmic irAEs from a total of 1474 patients treated with nivolumab with or without ipilimumab (incidence rate of 1.0%) underscores the rare occurrence. Only cases 3 and 10 had nivolumab monotherapy, whereas others had combination therapy. Because of the small number of patients in the cohort, there was no distinguishable pattern between the monotherapy group and the combination treatment group.

The range of ocular manifestations from these agents is remarkable. Although dry eye and conjunctivitis may be considered relatively trivial, case 4 stresses the potential for spontaneous corneal perforation resulting from severe ocular surface disease. Uveitis can be as mild as anterior chamber cells and mildly decreased vision, but as demonstrated by cases 8 and 9 choroidal effusion refractory to local and systemic corticosteroid can leave the patient with permanent vision loss. Because of such heterogeneity of outcomes, one cannot make generalized therapeutic recommendation or prognostication of visual outcomes for ophthalmic irAEs. Although these ocular surface, intraocular, and periocular events can have other causes, for example, MAR as a paraneoplastic sequelae of cutaneous melanoma, the simultaneous incidence of ophthalmic events with extraocular irAE of immunotherapy suggests that an ophthalmic event is associated with immunotherapy.

Several prior reports have extrapolated the incidence of irAEs to tumor response and concluded that irAEs are markers of therapy efficacy.<sup>5</sup> In the present series, 8 of 15 patients had progression of primary malignancy (cases 1, 4, 5, 7, 8, 11, 13, and 15), and 2 of them died during the follow-up period (cases 11 and 15). These outcomes suggest that ophthalmic irAEs may not be markers of systemic response to therapy in contrast to what has been proposed by other authors.<sup>5</sup> Larger cohorts are needed to correlate systemic prognosis with ocular adverse events.

In conclusion, ophthalmic irAEs associated with nivolumab with or without ipilimumab are rare but can vary from benign to sight-threatening. Visual outcomes and systemic response to inciting immunotherapy are difficult to predict. Ophthalmologists and oncologists knowledgeable in the management of adverse events of immunotherapy should work in concert to manage the ocular manifestations when using these powerful agents.

## References

1. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377:1345–1356. [PubMed: 28889792]
2. Hazarika M, Chuk MK, Theoret MR, et al. U.S. FDA approval summary: nivolumab for treatment of unresectable or metastatic melanoma following progression on ipilimumab. *Clin Cancer Res*. 2017;23:3484–3488. [PubMed: 28087644]

3. Nguyen AT, Elia M, Materin MA, et al. Cyclosporine for dry eye associated with nivolumab: a case progressing to corneal perforation. *Cornea*. 2016;35:399–401. [PubMed: 26771550]
4. Wong RK, Lee JK, Huang JJ. Bilateral drug (ipilimumab)-induced vitritis, choroiditis, and serous retinal detachments suggestive of Vogt-Koyanagi-Harada syndrome. *Retin Cases Brief Rep*. 2012;6:423–426. [PubMed: 25389947]
5. Maire C, Vercambre-Darras S, Devos P, et al. Metastatic melanoma: spontaneous occurrence of auto antibodies is a good prognosis factor in a prospective cohort. *J Eur Acad Dermatol Venereol*. 2013;27:92–96. [PubMed: 22145691]

**Table 1.** Characteristics, Findings, and Outcome of Patients Who Developed Ocular Immune-Related Adverse Event after Nivolumab with or without Ipilimumab

Case	M/ F	Primary Cancer	Age at Ocular Symptom, yrs	Immunotherapy	No. of Immunotherapy Cycles at the Onset of Ocular Symptoms	VA at Presentation		Ocular Finding	Treatment	Concurrent Systemic IrAE	Cessation Immunotherapy	Systemic Outcome	Ocular Outcome	Duration of Follow- up Since Ocular Event (mos)
						OD	OS							
1	F	Uveal melanoma	62	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	1	20/20	20/400	Myasthenia gravis - blepharoptosis and diplopia	Systemic corticosteroids, IVIG	Lipase elevation Transaminitis	Yes	POD	20/20, 20/400 Improving diplopia and ptosis	7
2	M	Non-small cell lung carcinoma	51	Nivolumab 240 mg + ipilimumab 102 mg	1	20/20	20/20	Conjunctival papillary reaction andSCH OU	Neomycin/ polymyxin B/ dexamethasone eye drops	Lipase elevation Transaminitis	Yes	PR	20/20, 20/20 Complete resolution	3
3 <sup>3</sup>	F	Cutaneousmelanoma	45	Nivolumab 3 mg/kg	2	20/25	20/20	Severe dry eyes OU	Topical cyclosporine	New joint pain in hands, elbows, knees, feet	No	CR	20/20 OU Complete resolution	27
4 <sup>3</sup>	M	Cutaneousmelanoma	58	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg x 2 then nivolumab monotherapy x 6	8	20/400	20/50	AtraumaticcornealperforationOD	Corneal glue, bandage contact lens, artificial tears, topical cyclosporine 0.05% eye drops	Colitis, lipase elevation	Yes	POD	20/25 OU Complete resolution with residual corneal scarring	54
5	F	Uvealmelanoma	71	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg x 2	2	20/40	20/400	Keratic precipitates and anterior uveitis OU	Topical prednisolone acetate 1% then topical difluprednate 0.05%,systemic corticosteroid	Rash, colitis,panhypopituitarism	No	POD	20/60, 20/400 Complete resolution of anterior chamber cells	25
6	M	Cutaneousmelanoma	74	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg x 2	2	20/25	20/30	Keratic precipitates, peripheral anterior synechiae, and anterior uveitis OU	Topical prednisolone acetate 1%, topical atropine, systemic corticosteroid	Diarrhea	No	PR	20/25, 20/30 Resolution of cells	1
7	F	Cutaneousmelanoma	53	Nivolumabmonotherapy x 9 then nivolumab 1 mg/kg plus ipilimumab 3 mg/kg x 1	10	20/25	20/20	Anterior uveitis and vitritisOU	Systemic and topical corticosteroid	Lipase elevation, hypo- pituitarism	Yes	POD	20/20, 20/20 Chronic uveitis requiring topical therapy	26
8	M	Cutaneous melanoma	67	Nivolumab 1 mg/kg plus ipilimumab 3mg/kg x 3	3	20/40	20/40	Anterior uveitis, 360° posterior synechiae OU	Topical prednisolone acetate 1%, sub- tenon corticosteroid,systemic corticosteroid	Nephritis	Yes	POD	20/150, 20/40 Choroidal effusion and hypotony maculopathy	2
9	M	Cutaneousmelanoma	69	Nivolumab 1 mg/kg plus ipilimumab 3mg/kg x 4	4	20/40	20/150	Anterior uveitis and choroidal effusion OU	Systemic and topical corticosteroid	Rash, myalgia, fatigue	Yes	PR	20/50, 20/150 Persistent choroidal effusion	1
10	F	Cutaneousmelanoma	68	Nivolumab 1 mg/kg monotherapy x 2 then nivolumab 3 mg/kgmonotherapy x 5	7	20/30	20/40	CME OU	Systemic corticosteroid for pneumonitis (not for ocular event)	Pneumonitis	Yes for pneumonitis	S	Unknown	12
11	F	Cutaneous melanoma	54	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	1	20/70	20/70	Subfoveal fluid OU	Systemic corticosteroid	Colitis, pneumonitis, transaminitis	Yes	POD, deceased	20/25 OU Complete resolution	29

Case	M/ F	Primary Cancer	Age at Ocular Symptom, yrs	Immunotherapy	No. of Cycles at the Onset of Ocular Symptoms	VA at Presentation		Ocular Finding	Treatment	Concurrent Systemic irAE	Cessation Immunotherapy	Systemic Outcome	Ocular Outcome	Duration of Follow- up Since Ocular Event (mos)
						OD	OS							
12	M	Cutaneous melanoma	52	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	6	20/25	20/40	Serous RD OU	Systemic and sub-tenon corticosteroid	Transaminitis	Yes	CR	CF, 20/400 Chronic serous RD OU	79
13 <sup>a</sup>	F	Cutaneous melanoma	43	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	1	20/30	20/100	VKH-like syndrome OU	Systemic corticosteroid	Diffuse vitiligo	Yes	POD	20/20 OU Complete resolution of VKH	85
14	F	Cutaneous melanoma	79	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	1	20/20	20/25	MAR OU	Systemic corticosteroid, IVIG	Transaminitis, rash, hypophysitis	Yes	CR	20/20 OU Ongoing MAR on IVIG	10
15	F	Cutaneous melanoma	61	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg x 4 then nivolumab monotherapy x 1	5	20/20	20/100	Optic disc swelling OU	Systemic corticosteroid, infliximab	Colitis, pleural effusion	Yes	POD, deceased	20/70, CF Bilateral optic neuropathy with pallor	15

CF = counting fingers; CME = cystoid macular edema; CR = complete response; irAEs = immune-related adverse events; IVIG = intravenous immunoglobulin; MAR = melanoma-associated retinopathy; OD = left eye; OS = right eye; OU = both eyes; POD = progression of disease; PR = partial response; RD = retinal detachment; S = stable; SCH = subconjunctival hemorrhage; VA = visual acuity; VKH = Vogt-Koyanagi-Harada.