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Case report

Bilateral uveitis associated with nivolumab therapy for metastatic non-small cell lung cancer

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ABSTRACT

Purpose: To report a case of bilateral uveitis secondary to intravenous nivolumab therapy in a patient with stage IV non-small cell lung cancer.

Observations: A 53-year-old male with stage IV non-small cell lung cancer presented with gradual onset of blurry vision in the left eye for nine days after completion of the first cycle of intravenous nivolumab chemotherapy. At initial presentation, best-corrected visual acuity was 20/25 in the right eye and 20/30 in the left eye. Slit lamp biomicroscopy examination of the left eye showed temporal injection of the conjunctiva and sclera, granulomatous keratic precipitates, and vitreous cells in the posterior segment. Imaging studies, including fundus photography, fluorescein angiography, fundus autofluorescence, optical coherence tomography, iridocyanine green angiography, and B scan ultrasonography, demonstrated acute inflammation in the posterior segment of the right eye and anterior, intermediate and posterior segments of the left eye. Nivolumab was discontinued and the patient received a course of corticosteroids resulting in resolution of visual complaints. The patient subsequently developed elevated and sustained intraocular pressures and decreased visual acuity in the left eye secondary to treatment complications. The patient was then lost to follow-up.

Conclusions and Importance: To our best knowledge, this is a rare case of bilateral uveitis secondary to intravenous nivolumab use and the sixteenth reported case of nivolumab-induced uveitis. Physicians should be aware of possible ocular complications associated with the use of nivolumab and provide prompt treatment when necessary.

1. Introduction

Nivolumab (Opdivo; Bristol-Myers Squibb, Princeton, NJ) is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma, advanced renal cell carcinoma, classic relapsed Hodgkin lymphoma, and metastatic or chemotherapy-resistant non-small cell lung cancer (NSCLC). Adverse effects, including fatigue, pruritus, rash, anorexia, diarrhea, vitilgo, hypothyroidism, pneumonitis, dry eyes and corneal perforation, have been noted with the use of nivolumab.[1–3] Recently, there have been ten reported cases of anterior uveitis, one reported case of intermediate/posterior uveitis and four reported cases of panuveitis associated with nivolumab use.[7,12–17,24–29] We report a case of nivolumab-associated bilateral uveitis in a 53-year-old male with NSCLC with metastasis to the adrenal glands and meninges.

2. Case report

A 53-year-old male with stage IV NSCLC involving the adrenal glands and meninges presented with gradual onset of blurred vision in the left eye (OS) over nine days. The patient had recently completed his first cycle of intravenous nivolumab (2 doses at 3mg/kg) nineteen days prior to the onset of visual symptoms. Prior to this therapy, the patient had received two cycles of carboplatin/taxol and four cycles of carboplatin/pemetrexed. There was no prior ocular history.

At initial presentation, best corrected visual acuity (BCVA) was 20/25 in the right eye (OD) and 20/30 OS. Intraocular pressures measured by TonoPen were 17 mmHg OD and 18 mmHg OS. Pupils were round

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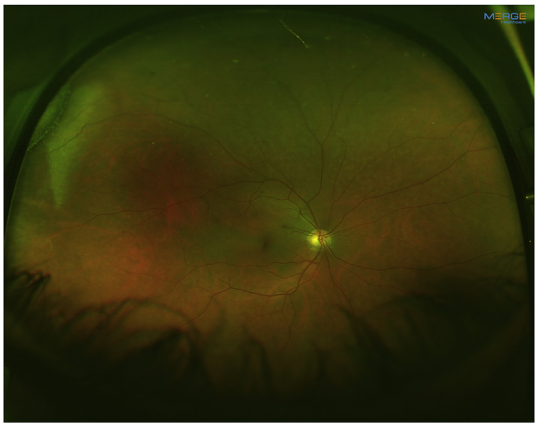

Fig. 1. Retinal pigment epithelium mottling OD – This widefield fundus photo of the right eye shows trace temporal mottling secondary to nivolumab use.

and equally reactive to light. Extraocular fields by confrontation were full in both eyes (OU). Extraocular motility evaluation showed full ductions OU.

Anterior segment evaluation with slit lamp biomicroscopy was unremarkable OD. The OS was remarkable for episcleral injection, fine pigmented keratic precipitates, 2+ cell and 1+ flare in the anterior chamber, and 2+ white, vitreous cells. Anterior cell and flare and vitreous cell were graded via the SUN criteria.

Fundus examination with indirect ophthalmoscopy was performed OU which demonstrated bilateral temporal mottling of the retinal pigment epithelium (Figs. 1 and 2). OS was also remarkable for vitreous haze (Fig. 2). Fluorescein angiography showed late leakage and staining of the optic disc in both eyes. Optical coherence tomography demonstrated choroidal thickening in both eyes, as well as vitreous cells in the left eye (Figs. 3 and 4). B-scan ultrasonography demonstrated moderately dense vitreous opacities, posterior vitreous detachment, and moderately dense sub-hyaloid opacities OS (Fig. 5). There was no evidence of metastatic cancer in either eye.

Nivolumab was discontinued and prednisone (1 mg/kg) was initiated. Nine days after change in management, the BCVA had improved to 20/20 OU with decrease in the mottling of the retinal pigment epithelium OU and inflammatory cells OS. The improvement in signs and symptoms associated with discontinuation of therapy suggested a diagnosis of nivolumab-induced bilateral uveitis.

At a subsequent follow-up visit, the patient was noted to have worsening cell and flare in the anterior chamber and vitreous cell in the posterior cavity of the left eye. Intraocular pressures were noted to be as high as 50 mm Hg OS by TonoPen. Corticosteroid therapy had been previously discontinued. Concern was raised for uveitis glaucoma versus endogenous endophthalmitis and the patient underwent

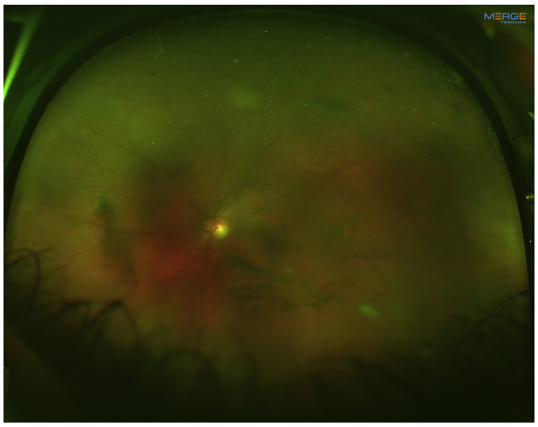

Fig. 2. Retinal pigment epithelium mottling and vitreous haze OS – This widefield fundus photo of the left eye shows temporal mottling, vitreous haze and overlying vitreous opacities secondary to nivolumab use.

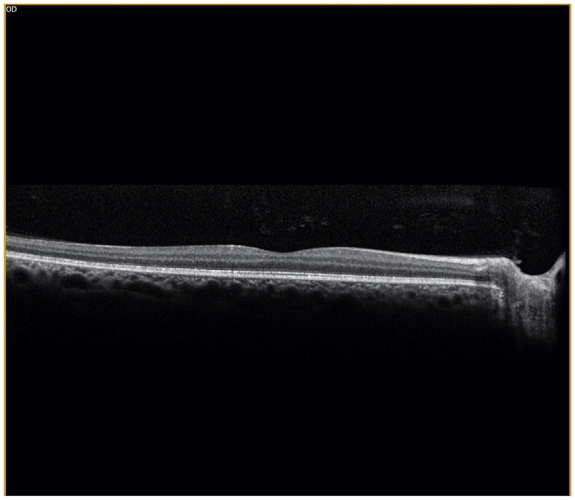

Fig. 3. Choroidal thickening OD – This optical coherence tomography (OCT) photo of the right eye shows choroidal thickening secondary to nivolumab use.

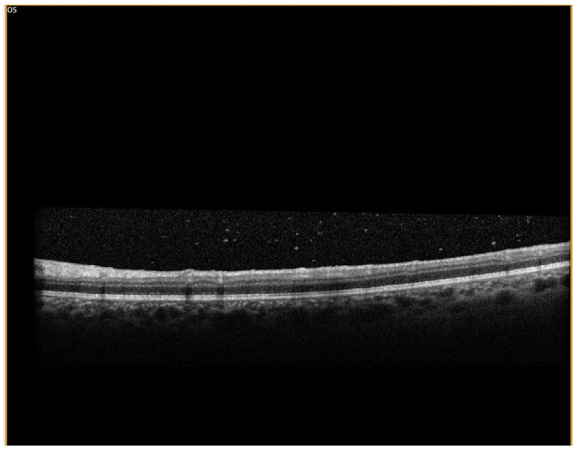

Fig. 4. Choroidal thickening and vitreous cell OS – This optical coherence tomography (OCT) photo of the left eye shows choroidal thickening and vitreous cells secondary to nivolumab use.

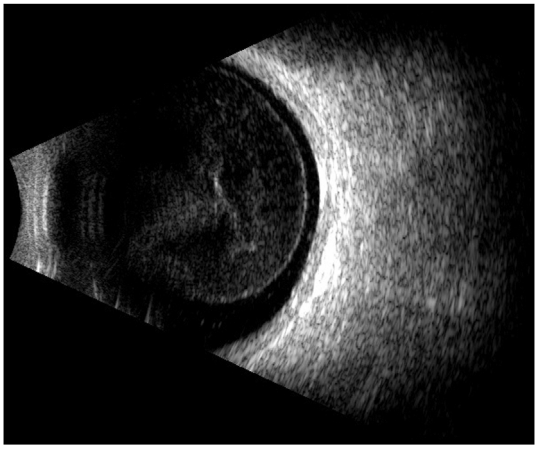

Fig. 5. Vitreous and sub-hyaloid opacities OS – This ultrasound image shows the dense vitreous opacities and sub-hyaloid opacities of the left eye secondary to nivolumab use.

diagnostic vitrectomy and lensectomy. Gram stain and organism cultures were negative. Biopsy results were only positive for inflammatory cells. At the patient's most recent follow-up, intraocular pressure of the left eye remained elevated and the patient visual's acuity had decreased to hand motion. Vision loss was attributed to sustained, elevated intraocular pressures. No alternative cancer treatments had been started. Patient was lost to ophthalmologic follow-up after this visit.

3. Discussion

Nivolumab is a fully human immunoglobulin G4 PD-1 immune checkpoint inhibitor antibody used in the treatment of advanced NSCLC. By blocking the PD-1 signaling pathway, nivolumab can restore a patient's T-cell mediated anti-tumor immunity.[1] Nivolumab exerts its effects by upregulating T cell activity. There has been inflammatory meditated adverse effects reported such as pneumonitis, hepatitis and nephritis associated with nivolumab.[1–4]

Blockage of the PD-1 pathway causes immune cells to shift to a proinflammatory Th1/Th17 state, leading to increased production of interferon g, interleukin-2, tumor necrosis factor a, interleukin-6 and interleukin-17 and a decreased production of interleukin-5 and interleukin-13.[5] This proinflammatory state is of particular interest, as elevated Th17 levels have been previously associated with active scleritis and active uveitis in the eye.[6,7]

Monoclonal antibodies with mechanisms of action similar to nivolumab have presented with comparable immune-related adverse events. Uveitis was reported in 0.4% and 1.1% of patients who were treated biweekly and tri-weekly with pembrolizumab, an anti-PD-1 monoclonal antibody.[8] 1.3% of the adverse events associated with ipilimumab, a monoclonal antibody that upregulates T-cell mediated immunity by targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), involved the eye.[9] In particular, there have been multiple cases of corticosteroid-responsive orbital inflammation, uveitis, and peripheral ulcerative keratitis associated to ipilimumab.[10]

Naranjo et al. previously described a set of criteria that could be used to determine causation between medication and an adverse drug effect. Using this algorithm, we can categorize the association between the use of nivolumab and the development of uveitis in our patient as either definite, probable, possible or doubtful[19.23,24]. Given the patient's clinical presentation, recent nivolumab use and prompt clinical response to corticosteroid therapy, it is possible that the bilateral uveitis seen in this patient was trigged by the administration of nivolumab.[11,23] The exact mechanism of this drug-induced uveitis is still largely unknown; however, both inflammatory and toxic reactions have been suggested as possible triggers.[19–22] It is possible that administration of nivolumab may have led to a proliferation of T-cells with cross-reactivity to uveal antigens, thereby triggering an immune response.[30]

Our report of a nivolumab-induced uveitis would be consistent with previously published literature. Velasco et al. reported a case of autoimmune uveitis and Jaccoud's arthropathy secondary to treatment with nivolumab (at cycle 28 of 10 ml/kg given once every three weeks) in a patient with metastatic clear cell renal cell carcinoma.[7] Richardson et al. reported a case of bilateral uveitis associated with nivolumab use in a patient with metastatic scalp melanoma that responded adequately with topical, oral and intravitreal glucocorticoids.[12] In particular, multiple case reports document incidences of bilateral anterior uveitis in patients receiving nivolumab therapy.[13–17] Interestingly, our patient presented with a bilateral uveitis with a predilection for the posterior cavity of the eye.

This case report underscores the importance of understanding both the pathophysiology of panuveitis and the drug mechanism of action of nivolumab. A timely corticosteroid regimen (1mg/kg) has been shown to improve clinical outcomes and reduce the risk of vision loss or blindness in patients with uveitis.[18] Given the acuity in which this patient developed panuveitis secondary to one cycle of nivolumab, prompt treatment was essential. It is possible that corticosteroid therapy was discontinued too abruptly in the patient's clinic course, leading to progression of the uveitis, obstruction of the aqueous outflow pathways and eventual visual complications. Although it was not assessed in this case, it is possible that T-cell target pharmacotherapy, such as azathioprine or cyclosporine, may be effective in treating ocular manifestations of nivolumab toxicity.

4. Conclusion

To our best knowledge, this is a rare case of bilateral uveitis secondary to intravenous nivolumab use and the sixteenth reported case of nivolumab-induced uveitis. Nivolumab is known to upregulate T-cell activity and may shift the immune cells in the eye into a pro-inflammatory state. Physicians should be aware of possible ocular inflammatory complications associated with the use of nivolumab and provide prompt treatment when necessary.

5. Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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