Case Report

Hypotony and Anterior Uveitis following Dual Therapy with Nivolumab and Ipilimumab for Metastatic Melanoma: A Case Report

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Abstract

Purpose: To describe a rare case of hypotony and anterior uveitis following dual therapy with nivolumab and ipilimumab for metastatic melanoma.

Methods: Case report.

Results: Here, we present the case of a 64-year-old man taking nivolumab and ipilimumab dual therapy for BRAF+ (v-raf murine sarcoma viral oncogene homolog B1) metastatic melanoma. After treatment for 3 months, he presented to the ophthalmology clinic with bilateral intraocular pressures of 1 mmHg, bilateral keratic precipitates, cataracts, posterior synechiae, and anterior chamber inflammation. He improved with topical medications and the cessation of immunotherapy.

Conclusions: Immunotherapies are a novel class of chemotherapy that has increased in prevalence for the treatment of numerous malignancies. There are many rare complications from these medications that are sparsely reported. Knowledge of ocular hypotony as a potential consequence of nivolumab and ipilimumab is important, particularly as it may arise months after treatment initiation and necessitate immunotherapy cessation.

Keywords: Hypotony, Ipilimumab, Melanoma, Nivolumab, Uveitis

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Introduction

The widespread adoption of immune checkpoint inhibitors has revolutionized cancer treatment over the past decade. The first immune checkpoint inhibitor to be authorized was ipilimumab for the treatment of malignant melanoma.[1,2] Soon after the approval of ipilimumab, numerous immune checkpoint inhibitors were subsequently developed and authorized including pembrolizumab, nivolumab, atezolizumab, and durvalumab.[2] Typically, the gold standard for the treatment of melanoma is surgical excision; however, in advanced cases of unresectable or stage IV metastatic melanoma, systemic therapy or radiation therapy is used.[1] In the context of melanoma, dual therapy with nivolumab and ipilimumab became common after a landmark trial found improved 5-year survival.[3] Despite dual therapy with nivolumab and ipilimumab becoming a standard treatment option, certain toxicities associated with these medications are not well described in the literature. More specifically, rare ophthalmologic complications, most often uveitis, may arise following immune checkpoint inhibitor treatment.[4,5] In certain cases, the severity of ophthalmological complications can necessitate the cessation of dual therapy. Here, we describe

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the case of a 64-year-old man being treated with nivolumab and ipilimumab dual therapy for 2 months, developing ophthalmological symptoms a month later, and presenting with bilateral hypotony and anterior uveitis.

Case Report

A 64-year-old man was referred with a 1-month history of decreased visual acuity and a 2-week history of photosensitivity in July 2022. His past medical history was significant for stage IV metastatic BRAF+ (v-raf murine sarcoma viral oncogene homolog B1) melanoma, hypothyroidism, pancreatic failure, and type II diabetes mellitus being treated with metformin and insulin. He had begun treatment for metastatic BRAF+ melanoma with nivolumab and ipilimumab dual therapy from March 2022 to June 2022, when he was transitioned to nivolumab maintenance therapy. On examination, his best-corrected visual acuity was 20/50+2 in the right eye and 20/40−1 in the left eye. His intraocular pressures were 1 mmHg bilaterally. Anterior segment examination revealed a clear cornea with diffuse stellate keratic precipitates. The anterior chamber had 3+ cells and 3+ flare consistent with anterior uveitis. There were segmental posterior synechiae in both eyes. The anterior chamber angle was open. Both lenses demonstrated 2–3+ nuclear and early posterior subcapsular cataractous changes. Examination of the posterior segment revealed a quite vitreous with a normal retina and optic nerve. Treatment with dexamethasone and cyclopentolate was promptly initiated. At 1-week follow-up, slit-lamp examination showed similar findings with improved anterior chamber inflammation, and his intraocular pressures had risen to 2 mmHg bilaterally. At 2-week follow-up, his best-corrected visual acuity had improved to 20/30−2 bilaterally and his intraocular pressures were 9 mmHg in the right eye and 8 mmHg in the left eye. At his initial presentation and throughout the follow-up, no retinal or vitreous pathology was observed. There was no evidence of any visually significant hypotonous side effects including hypotony maculopathy or significant choroidal effusions. Figure 1 shows the patient's optical coherence tomography and fundus imaging at the time of initial presentation in July 2022 which demonstrated a lack of hypotonous changes.

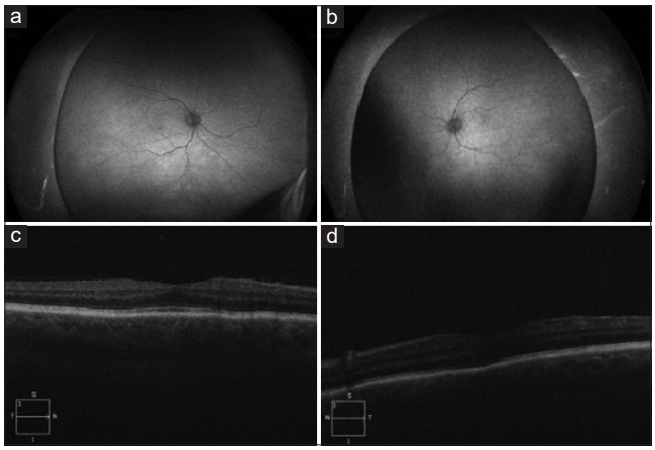

Figure 1: The patient's (a) right eye (OD) ultra-widefield fundus image, (b) left eye (OS) ultra-widefield fundus image, (c) OD optical coherence tomography (OCT), (d) OS OCT showing no hypotony maculopathy and no choroidal effusions

After discussion between the patient and their oncologist, the patient's nivolumab and ipilimumab dual therapy was terminated midway through July 2022 secondary to his ocular complications. He was subsequently started on the second-line treatment of dabrafenib and trametinib. Five weeks after the cessation of nivolumab and ipilimumab and continued treatment with topical dexamethasone and cyclopentolate in both eyes, his intraocular pressures were stable at 9 mmHg in his right eye and 8 mmHg in his left eye. His intraocular pressures have remained stable over the following year, and he remains on topical steroid and cycloplegic treatment. Patient consent was obtained.

Discussion

We present a case of bilateral uveitis and hypotony in a 64-year-old man following treatment with nivolumab and ipilimumab dual therapy for stage IV melanoma. Ophthalmological complications of immune checkpoint inhibitor therapies are rare and sparsely documented, with uveitis being the most common toxicity.[4,5] In particular, hypotony is an important complication to consider during nivolumab and ipilimumab dual therapy, due to the high risk of developing vision-compromising pathologies such as corneal decompensation, accelerated cataract formation, choroidal or suprachoroidal hemorrhage, and maculopathy. To the best of our knowledge, there are only two previously published reports of hypotony associated with nivolumab and ipilimumab dual therapy, although in these cases, they were used for the treatment of stage IV renal cell carcinoma.[6,7]

The literature suggests that immune checkpoint inhibitor-associated hypotony is likely a result of ciliary body inflammation or, more uncommonly, ciliary body atrophy secondary to anterior uveitis.[6-9] Interestingly, it appears that the onset of hypotony is variable in relation to the timing treatment initiation. Lee *et al*. reported the case of a patient developing symptoms within 1 week of initiating dual therapy, whereas our case and Gupta *et al*.'s patient were seen 2 months after initiating dual therapy.[6,7] There has also been one case reported of nivolumab-only treatment associated with hypotony.[9] Notably, there have been a handful of reports of hypotony associated with pembrolizumab, also a PD-1 inhibitor similar to nivolumab.[8,10-13] Interestingly, with a suspected 1-month history of hypotony, our patient did not show any retinal pathology. It is likely that his hypotony worsened more acutely after he developed uveitis. Importantly, hypotony is an established consequence of anterior uveitis secondary to ciliary body dysfunction, and this may play a contributing role in the pathogenesis of hypotony as a complication of immunotherapy. Given the potentially severe consequences

of untreated hypotony and uveitis, our case raises awareness regarding the importance of prompt ophthalmological referral in the setting of patients undergoing immunotherapy with ocular complaints such as changes to visual acuity, pain, and photosensitivity.

Uveitis, posterior synechiae, and progressed cataract development are more common findings.[6,7,9-11] Our case is consistent with the literature, with the patient having developed bilateral segmental posterior synechiae and significant nuclear sclerotic cataracts with early posterior subcapsular cataractous changes, otherwise unlikely findings in a 64-year-old male. Possibly, the acute development of cataracts may be accelerated by uveitis and corticosteroid treatment.[6] Notably, our case demonstrates symptom improvement with topical corticosteroid and cycloplegia treatment. Symptoms also improved with the discontinuation of nivolumab and ipilimumab.

In conclusion, we describe a patient with bilateral uveitis and hypotony following dual therapy with nivolumab and ipilimumab for stage IV melanoma. As the treatment armamentarium for advanced melanoma continues to broaden and the prevalence of immune checkpoint inhibitors increases, understanding these rare, vision-threatening, ophthalmological toxicities becomes increasingly crucial. Notably, in many cases of advanced melanoma where the prognosis is poor, ensuring stable visual capabilities is vital in maintaining patient quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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