



## Refractive Ocular Hypotony Associated with Immune Check Point Inhibitors

Ankur Sudhir Gupta<sup>1</sup>, Nicholas Dolan<sup>2</sup> and James Kasenchak<sup>1\*</sup>

<sup>1</sup>Geisinger Eye Institute, Danville, PA, USA

<sup>2</sup>Marshall University Medical School, Huntington, WV, USA

\*Corresponding Author: James Kasenchak, Geisinger Eye Institute, Danville, PA, USA.

Received: April 20, 2022

Published: May 18, 2022

© All rights are reserved by James Kasenchak, et al.

### Abstract

We present a case of severe hypotony complicated by cystoid macular edema, optic neuritis and panuveitis secondary to immune check point inhibitors. This is a unique case due to the severity of the complications from the check point inhibitors and the fact that it was refractory to treatment. It will serve as a guide for oncologist and ophthalmologists to recognize the importance of early diagnosis and treatment of the ocular complications of these increasingly commonly prescribed medications.

**Keywords:** Checkpoint Inhibitor; Hypotony; Panuveitis; Cancer; Choroidal Folds

### Abbreviations

PD-1: Programmed Cell Death-1; CTLA-4: Cytotoxic T-Lymphocyte antigen-4; VA: Visual Acuity; IOP: Intraocular Pressure; AC: Anterior Chamber; OCT: Optical Coherence Tomography; VKH: Vogt-Koyanagi-Harada; UBM: Biomicroscopy

### Introduction

Nivolumab and ipilimumab are monoclonal antibodies that can be used as monotherapy or in combination therapy when treating a variety of cancers. Nivolumab targets G4 Programmed Cell Death-1 (PD-1) immune checkpoint inhibitor, and ipilimumab targets cytotoxic T-Lymphocyte antigen-4 (CTLA-4) [1]. The PD-1 ligand pathway, as well as CTLA-4 pathway, play major roles in several cancer pathologies [2]. Due to the systemic administration and the immune activating mechanisms of these drugs, they increase the risk of systemic autoimmune reactions. Thus, there is a wide side effect profile that includes ocular and orbital involvement such as bilateral uveitis, hypotony maculopathy, cataracts, cystoid macular edema, serous retinal detachment, choroiditis, VKH-like-syndrome, and optic neuritis [3]. In this report, we describe a case

of bilateral hypotony retinopathy secondary to a smoldering panuveitis, following combination therapy of nivolumab and ipilimumab for clear cell renal carcinoma.

### Case Report

A 68-year-old man with a history of clear cell renal carcinoma that was placed on nivolumab for 12 treatment cycles and ipilimumab for 4 treatment cycles. His only other chronic medical condition was type 2 diabetes mellitus, diet controlled. The patient was seen two months after starting treatment with ipilimumab and nivolumab with complaints of blurry vision and seeing black dots. Visual acuity (VA) was 20/400 bilaterally. Intraocular pressure (IOP) was 7 mmHg and 8 mmHg in the right and left eye respectively. On the slit lamp exam, bilateral, dense keratic precipitates were observed, 2+ cells in the anterior chamber (AC), posterior synechiae of the iris, and 1+ nuclear sclerosis of the lens. At this visit, the patient was diagnosed with bilateral anterior uveitis and placed on topical prednisolone 1% every 2 hours as well as cyclopentolate 2% twice a day. Initial lab infectious and inflammatory workup included a Lyme panel, RPR, FTA-ABS, ACE, ESR, and QuantiFERON TB Gold Plus (values shown in Table 1), significant only

for a mild elevation in ESR. The patient came for a follow up visit 4 days later and was told to continue his steroid regimen.

RPR Screen	Non Reactive
FTA-ABS	Non Reactive
Angiotensin-1-Converting Enzyme	Value = 36 (normal limits = 9-67)
Erythrocyte Sedimentation Rate	Value = 21 (normal limits = 0-15)
Quantiferon TB Gold Plus	Negative
Lyme IgG/IgM Antibodies	Negative

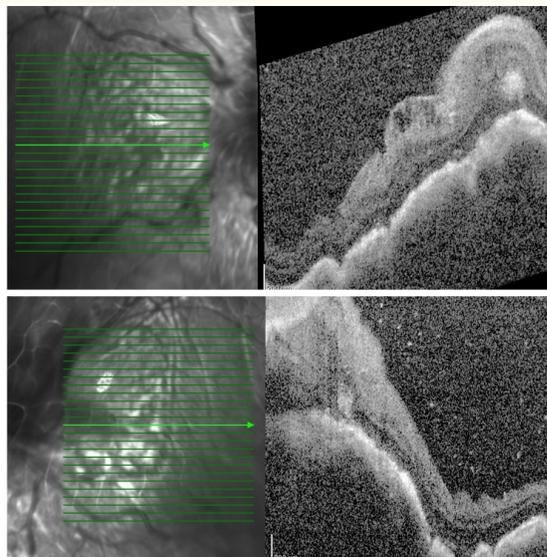
**Table 1:** Lab Results.

At follow up appointments 1 and 2 weeks later, there were similar findings on slit lamp exam with progressive improvement in the AC inflammation. The VA improved to 20/150 bilaterally while IOP dropped to 4mmHg in both eyes. Subtle vitritis was now evident on exam. The hypotony was attributed to ciliary body shut down. Patient was told to taper topical prednisolone from twice a day to once a day and referred to ophthalmology for cataract evaluation.

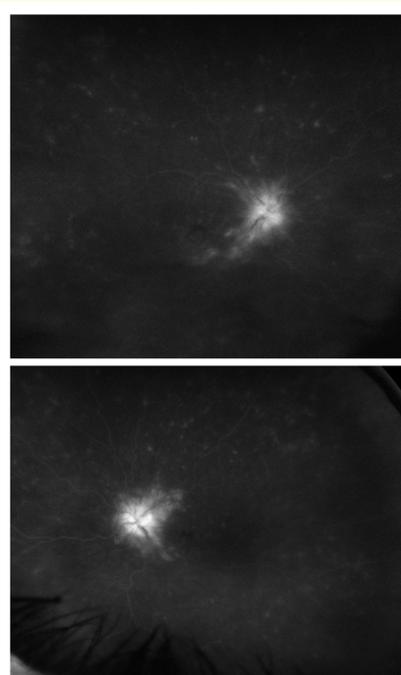
On his exam with ophthalmology there was bilateral blepharitis of the eyelids, trace injection of the conjunctiva, posterior synechiae of the iris, 2+ posterior subcapsular cataract in the lens, and vitreous syneresis. Fundoscopic exam showed a poor view of the macula, vessels, and periphery. The patient was scheduled and underwent a successful cataract surgery with implantation of intraocular lenses. The patient’s visual acuity was 20/150 OD and 20/200 OS and was still hypotonus.

After cataract surgery he was sent for a retina consult. The results of optical coherence tomography (OCT) are shown in figure 1 and revealed severe choroidal folds along optic nerve swelling. The fluorescein angiography in figure 2 revealed extensive vasculitis and vascular leakage along with disc hyperfluorescence and petaloid leakage in the macula.

At this point the patient was diagnosed with panuveitis, hypotony maculopathy, cystoid macular edema, serous retinal detachment, choroiditis, Vogt-Koyanagi-Harada (VKH) disease like syndrome, and optic neuritis at this time. At this appointment, it was felt that nivolumab was the inciting agent. He was started on difluprednate 0.05% and atropine 1% at this appointment and after discussion with oncology he finished his last cycle of nivolumab.

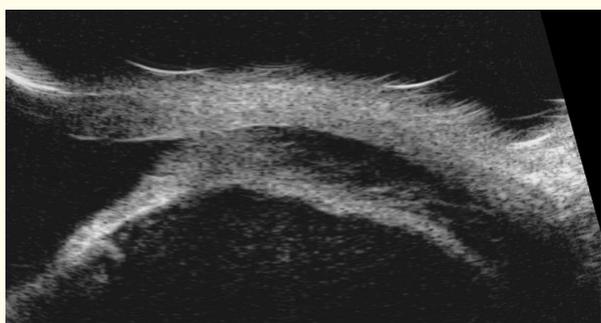


**Figure 1:** Top image shows the OCT results of the right eye with severe choroidal folds and CME. The bottom image shows the same findings in the left eye.



**Figure 2:** Fluorescein angiogram late phase shows diffuse leakage from the optic disc and subtle vasculitis with pinpoint hyperfluorescence in the periphery.

On follow-up there was minimal improvement on exam and imaging, so he was given bilateral 1 mL subtenons Kenalog (40 mg/mL) injections, continued atropine, and the difluprednate was stopped. Unfortunately, there was minimal improvement in vision or exam findings. The patient was only able to count fingers from 3 feet on visual acuity assessment. Patient was started on oral prednisolone (60 mg), continued atropine and restarted on difluprednate. Again, with minimal improvement. At this point ultrasound biomicroscopy (UBM) was performed and revealed extensive membranes with ciliary body atrophy (Figure 3). He remains with poor vision and no significant improvement of the hypotony.



**Figure 3:** UBM scan of the right eye showing extensive membranes with ciliary body atrophy. The left eye had similar findings.

## Discussion

Immune checkpoint inhibitors are an important advancement that have helped reduce mortality in a variety of cancers, however, it is crucial to recognize the side effect profile related to these drugs. Ipilimumab has been noted to cause a variety of ocular and orbital findings, including conjunctivitis, episcleritis, uveitis, iritis, blepharitis, orbital inflammation, and VKH syndrome [4-9]. Although rare, uveitis is the most common documented ocular side effect and has been noted in less than 1% of patients. We present a unique case because our patient presented with almost all associated ocular adverse reactions related to these drugs.

Hypotony maculopathy can be described as low intraocular pressures that result in vision loss due to papilledema with or without the presence of choroid or retina folding. The patient initially had bilateral panuveitis, which has been documented as a precipitating event that can lead to hypotony [10]. However, such

severe hypotony is usually not observed making this case particularly interesting. Ipilimumab and nivolumab's roles in the development of hypotony are likely due to the immunological effects leading to pro-inflammatory states even in immune privileged tissues.

Our hypothesis to explain the pathology is that persistent uveitis led to inflammation and eventually destruction of the ciliary body. Acute inflammation of the ciliary body may cause aqueous hyposecretion and low IOP. This reduction in IOP is reversible with control of intraocular inflammation. In contrast, chronic inflammation may lead to ciliary body damage and atrophy of the ciliary processes, resulting in permanent hypotony. Hypotony may result in hypotony maculopathy, vision loss, and/or phthisis. Chronic hypotony can be treated with long-term local steroid administration in some cases. Surgery is indicated if there is ciliary body traction from a cyclitic membrane that can be released and if the ciliary processes are preserved. If ciliary processes are atrophic, vitrectomy with intraocular silicone oil or viscoelastic may help maintain ocular anatomy and increase IOP. In some of these cases, vision improvement after surgery can be significant; these gains may, however, be transient [11]. Another described mechanism that can lead to such severe hypotony is the formation of a cyclitic membrane over the ciliary body that completely blocked aqueous fluid production [12]. A decrease from either the outflow or the production in the ciliary bodies leads to decreased intraocular pressures, which in turn diminishes the forces holding the outer layers of the eye together and makes the eye susceptible to retinal folding (as observed in our patient). However, anterior-segment OCT images were not successful in imaging such a membrane or any ciliary processes. Subsequent efforts were made to visualize ciliary body structures with a UBM. Due to the fact that our patient had such severely low pressures, it is likely a combined effect of these described mechanisms that lead to this pathology.

Identification of initial signs and prompt treatment is crucial to save the patient's vision and prevent further damage. The common presenting signs of uveitis include redness, sensitivity to light, visual changes, tearing, and pain in the anterior eye [12]. In addition to stopping the offending agent (i.e. nivolumab and ipilimumab), the patient should be started on topical corticosteroids. If the patient is found to have hypotony maculopathy, treatment includes: Addressing the underlying cause of the compromised aqueous circulation aggressively.

Immune checkpoint inhibitors are becoming more and more popular in the treatment of different cancers. Due to the increased usage, physicians need to be able to identify and refer patients for immediate treatment because of the vision-threatening side effects these drugs present. Also, whenever starting patients on these drugs, patients should be encouraged to seek immediate treatment if any orbital or ocular symptoms occur.

### Acknowledgements

None.

### Conflict of Interest

The authors report no financial interest or any other conflict of Interest.

### Bibliography

1. Kooshkaki O., et al. "Combination of Ipilimumab and Nivolumab in Cancers: From Clinical Practice to Ongoing Clinical Trials". *International Journal of Molecular Sciences* 21.12 (2020): 4427.
2. Buchbinder EI and Desai A. "CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition". *American Journal of Clinical Oncology* 39.1 (2016): 98-106.
3. Zhou L and Wei X. "Ocular Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors in Lung Cancer". *Frontiers in Immunology* 12 (2021): 701951.
4. Papavasileiou E., et al. "Ipilimumab-induced Ocular and Orbital Inflammation--A Case Series and Review of the Literature". *Ocular Immunology and Inflammation* 24.2 (2016): 140-146.
5. Nallapaneni NN., et al. "Ipilimumab-induced hypophysitis and uveitis in a patient with metastatic melanoma and a history of ipilimumab-induced skin rash". *Journal of the National Comprehensive Cancer Network* 12.8 (2014): 1077-1081.
6. Baughman DM., et al. "Bilateral Uveitis and Keratitis Following Nivolumab Treatment for Metastatic Melanoma". *Medical Case Reports (Wilmington)* 3.2 (2017): 8.
7. Obata S., et al. "Vogt-Koyanagi-Harada Disease-Like Uveitis during Nivolumab (Anti-PD-1 Antibody) Treatment for Metastatic Cutaneous Malignant Melanoma". *Case Report on Ophthalmology* 10.1 (2019): 67-74.
8. Attia P., et al. "Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4". *Journal of Clinical Oncology* 23.25 (2005): 6043-6053.
9. Tsui E and Gonzales JA. "Retinal Vasculitis Associated with Ipilimumab". *Ocular Immunology and Inflammation* 28.6 (2020): 868-870.
10. Thomas M., et al. "Hypotony Maculopathy: Clinical Presentation and Therapeutic Methods". *Ophthalmology Therapy* 4.2 (2015): 79-88.
11. Tran VT., et al. "Appraisal and management of ocular hypotony and glaucoma associated with uveitis". *International Ophthalmology Clinics* 40.2 (2000): 175-203.
12. Agrawal RV., et al. "Current approach in diagnosis and management of anterior uveitis". *Indian Journal of Ophthalmology* 58.1 (2010): 11-19.