



Immune checkpoint inhibitor associated ocular hypertension (from presumed trabeculitis)

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ABSTRACT

Purpose: Immune checkpoint inhibitors (ICIs) are associated with a range of immune-related adverse ophthalmic events. To date, there are scant reports of ocular hypertension coupled with ICI-associated uveitis. However, in instances of ocular hypertension in the context of only mild uveitic reaction and absence of synechiae, trabeculitis is considered. This series describes our observations of presumed trabeculitis in the setting of ICI therapy and investigates the clinical findings, treatment and outcome of these patients.

Observations: Two eyes of 2 patients (both male aged 65 and 43) developed a mild anterior uveitis and elevated intraocular pressure (IOP) with open angles and no evidence of peripheral anterior synechiae in association with ICI treatment for their malignancy; and were considered to have presumed unilateral trabeculitis. The patients underwent 10 cycles (6.53 months) and 2 cycles (3.33 months) respectively of ICI therapy before developing ophthalmic symptoms. Neither patient was on systemic or topical steroid treatment at time of diagnosis and there was no suspicion of a viral etiology for the inflammation. Following management, the anterior uveitis resolved and IOP rapidly returned to normal in both eyes: ICI therapy was discontinued in both patients (and uneventfully re-challenged at a lower dose in one patient) and both eyes were treated with a combination of topical and/or oral glaucoma medications and topical steroids.

Conclusions and Importance: Uveitic ocular hypertension has been described with ICI. However, another immune-related mechanism for ocular hypertension with unique clinical characteristics, includes trabeculitis. We describe two cases of trabeculitis in the setting of ICI-therapy. The intraocular inflammation and elevated intraocular pressure which characterizes trabeculitis often responds rapidly to conservative treatment. In both patients checkpoint inhibitor therapy was discontinued and, in one patient, was re-challenged at a lower dose without recurrence. Immunotherapy is now more widely used for cancer treatment and its potential ocular manifestations should be shared with the ophthalmic community.

1. Introduction

Immune Checkpoint Inhibitors (ICI) are an anti-cancer therapy that are now widely used to treat advanced cancers. There are three main classes of checkpoint inhibitors, which act by potentiating the immune system to attack cancer cells. The classes include cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), programmed cell death (PD-1) and programmed cell death protein 1 (PD-L1) inhibitors. They have been approved by the FDA to treat various types of cancers such as melanoma,

non-small-cell lung cancer, renal-cell carcinoma, urothelial carcinoma and Hodgkin's lymphoma.¹ By unleashing the immune system to attack cancer cells, ICIs can also cause an inflammatory reaction in healthy cells, thereby resulting in immune-related adverse events. The incidence of ocular immune-related adverse events occurs in about 1% of patients and can involve various parts of the eye such as: ocular surface, uveal tract, retina, extraocular muscles, cranial nerves and optic nerve.²⁻⁴

ICI-induced inflammation to the uveal tract (anterior, posterior and/or panuveitis) is well documented,⁵⁻³⁵ but none has been reported about

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ICI-induced trabeculitis. This study presents two cases of trabeculitis in the setting of ICI therapy and we explore the clinical findings, treatment and outcome of each.

1.1. Findings

Case 1: A 65 year-old male was undergoing treatment with pembrolizumab for metastatic conjunctival melanoma of the right eye, when he developed a presumed unilateral trabeculitis in the left eye 6.53 months (10 cycles) after initiation of immunotherapy. Table 1 outlines patient medical history, ocular symptoms at presentation and ICI treatment regimen. He had no ocular symptoms and the trabeculitis was found incidentally on routine follow-up where he presented with a unilateral non-granulomatous anterior uveitis (graded according to the classifications outlined by the Standardization of Uveitis Nomenclature (SUN) Working Group³⁶) without corneal edema and intraocular pressure (IOP) of 52 mmHg, as measured with Goldmann applanation tonometry in the left eye. There were no cells visible in the anterior vitreous and gonioscopy confirmed that angles were open to ciliary body 360° with no evidence of peripheral anterior synechiae or abnormal pigment distribution. The irises were equal in pigmentation, without iris atrophy or iris nodules. Inflammation of the posterior segment was deemed unlikely based on exam and imaging with fundus photography, autofluorescence and optical coherence tomography. Table 2 outlines pertinent ocular history, clinical features of the ophthalmic findings at presentation and follow-up, as well as visual outcomes. Of note, this patient had a history of steroid response in the past, for which he was taking timolol-dorzolamide ophthalmic solution and brinzolamide ophthalmic solution twice a day in both eyes. He was not being treated with any systemic or topical steroids at the time of the presentation of the trabeculitis. He was treated with topical prednisolone acetate ophthalmic suspension and oral acetazolamide, and the immunotherapy was discontinued. At the time he was re-evaluated (7 days after onset), the anterior uveitis resolved, IOP returned to normal (13 mmHg) and vision returned to 20/20. Optic nerves remained healthy on fundus examination up until his last recorded follow-up.

Case 2: A 43 year-old male was undergoing treatment with ipilimumab/nivolumab combination therapy followed by nivolumab monotherapy for metastatic cutaneous melanoma when he developed a presumed unilateral trabeculitis in the right eye 3.33 months (2 cycles) after initiation of immunotherapy. Table 1 outlines patient medical history, ocular symptoms at presentation and ICI treatment regimen. He reported symptoms of redness and headache when he presented with a bilateral non-granulomatous anterior uveitis (graded according to the classifications outlined by the Standardization of Uveitis Nomenclature (SUN) Working Group³⁶) without corneal edema and IOPs of 33 mmHg in the right eye and 16 mmHg in the left eye, as measured with Goldmann applanation tonometry. There were no cells visible in the anterior vitreous and gonioscopy confirmed that angles were open to ciliary body 360° with no evidence of peripheral anterior synechiae or abnormal pigment distribution. The irises were equal in pigmentation, without iris

atrophy or iris nodules. Inflammation of the posterior segment was deemed unlikely based on exam and imaging with fundus photography, autofluorescence and optical coherence tomography. Table 2 outlines pertinent ocular history, clinical features of the ophthalmic findings at presentation and follow-up, as well as visual outcomes. This patient was not using any systemic or topical steroids at the time of the presentation of the trabeculitis. He was treated with topical prednisolone acetate ophthalmic suspension and timolol-brimonidine ophthalmic solution and the immunotherapy was discontinued. At the time he was re-evaluated (10 days after onset), the mild anterior uveitis resolved, IOP returned to normal (19 mmHg) and vision remained stable at 20/20. Immunotherapy was later re-challenged at a lower dose and there has been no recurrence of ocular hypertension, and no change in optic nerve appearance with fundus imaging, to-date.

2. Discussion

Elevated IOP in the context of acute anterior uveitis can be due to a variety of mechanisms including: obstruction/dysfunction of the trabecular meshwork (TM) due to inflammatory cells/debris, synechial angle closure, increased resistance to outflow from the use of topical or periocular steroids, or trabeculitis.³⁷ Trabeculitis is an inflammation of the trabecular meshwork and is more commonly seen with a viral-associated uveitis. Physical swelling of the trabeculum is thought to decrease its porosity, resulting in elevated IOP.³⁸ Typically, trabeculitis will present with a minimal to modest anterior chamber reaction along with elevated IOP which responds rapidly to topical steroids. Elevated IOP caused by physical obstruction of the TM with inflammatory cells or secondary angle closure is typically associated with a more severe inflammatory reaction and can be more challenging to control. Chronic cases often require glaucoma surgery to achieve long-term IOP control.

We present a case series of 2 eyes in 2 patients who developed presumed unilateral trabeculitis in the context of ICI therapy for their malignancies, an entity in which little has been reported on in the past. In both eyes, the intraocular pressure was markedly elevated with mild concomitant anterior uveitis. Following treatment with topical and/or oral glaucoma medications and topical steroids, the IOP rapidly returned to normal and inflammatory reaction resolved. No patient was on topical or systemic steroids at presentation of ocular symptoms, which helps to rule out a steroid-induced pressure elevation. It should be noted that patient 1 did have a history of steroid response years prior and at the time of presentation was not on any steroids but was on IOP-lowering medications. Despite this regimen, he developed a trabeculitis and required steroid treatment to treat the intraocular pressure. Given that the irises were equal in pigmentation without iris atrophy, and posterior segment examination including fundus autofluorescence and optical coherence tomography did not reveal intraocular inflammation, a viral etiology was deemed unlikely, although confirmatory bloodwork was not performed in these patients. The authors agree that the absence of confirmatory bloodwork or PCR analysis of the anterior chamber does

Table 1
Patient profile, presenting ocular symptoms, medical treatment and follow-up.

Patient	Age (yrs)	Gender	Drug at time of dx	Primary Cancer Diagnosis	No. of CPI cycles prior to ophthalmic dx	Time on drug till symp (mos)	Ocular symptoms	CPI D/C?	Alive	CPI re-started after resolution of trabeculitis?	Time to most recent follow-up (mos)
1	65	M	Pembrolizumab 2 mg/kg, q3 weeks	conjunctival melanoma	10	6.53	none	Y	Y	N	19.27
2	43	M	Ipilimumab 3mg/kg + nivolumab 1mg/kg (once), followed by nivolumab 480mg (once)	cutaneous melanoma	2	3.33	redness and headache	Y	Y	Y Nivolumab 240mg q2w	5.70

Yrs = years, dx = diagnosis, No. = number, CPI = Checkpoint Inhibitor, symp = symptoms, mos = months.

Table 2
Pertinent ocular history, clinical findings at initial visit and follow-up and visual outcomes.

Pt	Laterality of trabeculitis	Anterior chamber of affected eye(s) at dx	IOP of affected eye(s) at dx (mmHg)	VA of affected eye(s) at dx	Ophthalmic Treatment	Time to resolution of trabeculitis (days)	Anterior chamber of affected eye(s) after treatment	IOP of affected eye(s) at most recent follow-up (mmHg)	VA of affected eye(s) at most recent follow-up	Other intraocular inflammation (Y/N)	Prior h/o elevated IOP? (mmHg)
1	Left	gr 2+ cells and diffuse KPs OS	52	20/30 + 1	Prednisolone acetate 1% q2h and Acetazolamide sequels PO (in addition to current regimen)	7	deep and quiet	13	20/20-1	N	Y OD Tmax:27 OS Tmax: 26 (h/o steroid response, tx with Timolol-dorzolamide and brinzolamide BID OU)
2	Right	gr 1+ cells/flare and diffuse KPs OU	33/16	20/20	Prednisolone acetate 1% QID and Timolol-brimonidine BID	10	deep and quiet both eyes	19/19	20/20	N	N

Pt = patient, dx = diagnosis, IOP = intraocular pressure, VA = visual acuity, h/o = history of, OD = right eye, OS = left eye, OU = both eyes, KPs = keratic precipitates, q2h = every 2 hours, PO = oral, QID = four times a day, BID = two times a day, Tmax = highest recorded intraocular pressure, tx = treated.

make it difficult to definitively rule out viral etiology. However, rapidly resolving ocular hypertension that has not returned to date (without the use of antiviral therapy) and in the absence of other clinical signs of intraocular viral involvement points to perhaps an overlooked cause of trabeculitis such as immune-checkpoint inhibitor associated ocular hypertension.

Though this is a series of only two cases, several important points were observed. First, the timing of trabeculitis had a variable range (after 2 or 10 cycles), and may be related to the ICI regimen. Combination ICI is believed to cause more severe and immediate adverse effects compared to monotherapy.¹ Consistent with this notion, patient 2 was treated with combination anti-CTLA-4 therapy (ipilimumab) and anti-PD-1 therapy (nivolumab) and developed symptoms within the shortest duration (after 2 ICI cycles). Whereas patient 1 was treated with PD-1 monotherapy and developed trabeculitis after 10 cycles, indicating that long-term monitoring for potential adverse effects in these patients is of utmost importance. Similar trends have been reported in patients with optic neuritis secondary to ICI therapy.³⁹ Second, the elevated IOP/inflammation resolves with ICI cessation, topical steroids and anti-glaucoma medications. Patient 1 remains stable and has not had a flare or recurrence in 19.27 months. In addition, re-challenging on a de-escalated potentially life-preserving drug regimen is possible, and not always associated with recurrent trabeculitis. Upon discontinuation of ICI treatment and resolution of trabeculitis, patient 2 was tapered off all topical drops and re-started on anti-PD1 monotherapy (nivolumab) at a lower dose, and ocular symptoms have remained stable to date (5.70 months), without the need for re-initiating topical treatment.

Abnormalities in intraocular pressure, in the context of immune checkpoint inhibition, have been previously reported. A comprehensive literature review from 2016 to 2020 revealed many reported cases of uveitis associated with ICI therapy,⁵⁻³⁵ though the majority of these cases reported hypotony, normal IOP or gave no mention of IOP. Only 2 cases^{34,35} reported elevated IOP or glaucoma in association with ICI therapy and neither were thought to be due to trabeculitis. Douglas et al.³⁴ reported a single patient with a history of sarcoidosis (without systemic steroid treatment) on ICI therapy who developed acute glaucoma and was treated with ocular steroids. There were no details pertaining to the IOP or the presence of intraocular inflammation and the author admits that it was unclear whether the glaucoma was a true immune-related adverse event. Fierz et al.,³⁵ reported a 43-year-old man with metastatic cutaneous melanoma treated with ipilimumab who

developed profound bilateral intraocular inflammation (anterior and intermediate uveitis, papillitis and choroiditis) and elevated IOPs (35 and 43 mmHg) after 2 cycles of ICI therapy. The inflammation and elevated IOP resolved with glaucoma drops, topical and oral steroids and ipilimumab cessation. This published case demonstrates that elevated IOP with checkpoint inhibition can occur in the context of extensive intraocular inflammation, which is not restricted to the anterior segment alone.

Although there are no cases reporting ICI-associated trabeculitis in the literature, there is evidence that supports the potential association between the two. It is known that the trabecular meshwork is comprised of connective tissue beams and sheets of lamellae⁴⁰ and there are reports in the literature which link the development of connective tissue disease (Sjogren's) with the use of ICIs.⁴¹ Therefore it follows that if ICI can be associated with connective tissue inflammation in other parts of the body; it can also affect the TM in a similar way, causing edema of the trabecular beams and elevated IOP.

3. Conclusions

In summary, this case series highlights a few important observations: 1. The occurrence of presumed trabeculitis in the setting of ICI therapy can occur early in the treatment course but also as late as 10 drug cycles (particularly in patients on monotherapy), and 2. The presumed trabeculitis responds rapidly to appropriate management and uneventful re-challenge of ICI (at a lower dose) is possible without trabeculitis recurrence. Both patients in this cohort had normal IOP and resolved anterior uveitis after drug cessation, topical steroids and systemic/topical glaucoma medications. Confirmatory bloodwork and/or PCR testing would be of added value to definitively rule out viral etiology for similar cases. Given the increasing use of ICI as first line treatment for many malignancies, it is useful for glaucoma specialists and comprehensive ophthalmologists to be aware of this unique disease entity.

Patient consent

Oral consent to publish the case report was 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

JP: *Consultant for:* Allergan, Glaukos, CorneaGen, Aerie, Santen, New World Medical.

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