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UVEITIS CAUSED BY TREATMENT FOR MALIGNANT MELANOMA: A CASE SERIES

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Background/Purpose: To report the largest case series to date of uveitis occurring in association with immunomodulatory therapy for malignant melanoma.

Methods: A retrospective multicenter case review. Twenty-two patients with uveitis occurring in association with either immunotherapy or targeted immune therapy for malignant melanoma were identified.

Results: Of 22 patients, 11 had anterior uveitis in isolation. The remainder showed a variety of clinical features including panuveitis, ocular hypotony, papillitis, cystoid macular edema, and melanoma-associated retinopathy. Most patients responded well to treatment.

Conclusion: We report the largest case series to date of patients with uveitis secondary to drug treatment for malignant melanoma. These cases are likely to increase in number in the future as newer immunomodulatory therapies for cancers are developed and the indications for these drugs increase. A dilemma arises when patients respond well to these drugs but develop vision-threatening side effects.

RETINAL CASES & BRIEF REPORTS 15:718–723, 2021

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In recent years, immunomodulatory drugs have become increasingly important in the treatment of metastatic cancer. The treatment of metastatic malignant melanoma in particular has changed remarkably with the advent of these newer treatments.[1]

Checkpoint inhibitors enhance the effect of the immune system against tumor cells by inhibiting pathways that suppress the immune response. These suppressive pathways act as natural "checkpoints" on the immune system, but some tumor cells are able to take advantage of these systems to avoid immune attack.

Two such pathways are the PD1 (programmed cell death 1) and CTLA-4 (cytotoxic T-lymphocyte antigen 4) pathways. When tumor cells activate these surface receptors on lymphocytes, the immune response against the tumor cell is suppressed. Specific immunotherapy drugs that target the PD1 or CTLA-4 pathway assist the immune system to detect and destroy tumor cells.[1,2]

Other targeted immune therapies help to prevent melanoma growth and spread. Sixty percent of melanomas express mutations in the regulatory enzyme BRAF. Mutations in the *BRAF* gene allow for unregulated proliferation and angiogenesis of

tumor cells. Enzymes downstream of *BRAF* include mitogen-activated protein kinases (MEKs). Pharmacological inhibition of BRAF and/or MEK provides another target against melanoma, and these drugs may be used in combination as treatment for metastatic disease.[1,2]

Modulation of the immune response can potentially lead to unwanted effects. An association between these drugs and systemic autoimmunity was noted in clinical trials. Uveitis was also reported, but cases were generally mild.[3,4] Because these drugs were approved, a number of reports have described patients with significant ocular inflammation. The series presented here is the largest to date, detailing a range of uveitis presentations occurring in patients treated with these drugs.

Methods

This was a multicenter, retrospective study of Australian patients with melanoma who presented to ophthalmologists with uveitis in association with checkpoint inhibitors and/or targeted immune therapy. Twenty-one patients had cutaneous melanoma and one patient had a choroidal primary melanoma. None of the patients had a previous history of uveitis. All of the patients had a negative review of systems. Patients number 1 to 4 did have a laboratory work-up to rule out other causes of uveitis, whereas for the remainder of the patients, a laboratory work-up was not deemed necessary as the uveitis was presumed to be drug-induced, based on the clear temporal relationship to starting the drug. Owing to the large number of heterogenous patients, the complex treatment regimens, and the influence of multiple systemic factors, we were not able to collect any meaningful rechallenge data.

Results

Twenty-two cases were identified. Nine patients were women. The age range was 30 to 80 years. Eleven cases presented with uncomplicated anterior uveitis (Table 1). In 20 cases, the uveitis involved both eyes; in one case, it was unilateral, and one patient had undergone an enucleation of the fellow eye previously. The onset of uveitis occurred 2 weeks to 18 months after starting immunomodulatory therapy. A total of six agents were implicated in the development of uveitis. A further two patients may have additionally received two other agents that were being assessed in placebo-controlled clinical trials. In this series, the drugs most commonly associated with uveitis were dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor). Eleven patients received these drugs, which were invariably given together. These two drugs were the only ones implicated in the development of uveitis in seven cases. In four of these cases, the uveitis was controlled with topical steroids only. Overall, 13 of our series received either a BRAF inhibitor or MEK inhibitor, and in nine cases, these were the only drugs associated with the uveitis. In seven of these nine cases, the inflammation was treated with topical steroids only. Eight cases had chronic or recurrent uveitis requiring ongoing treatment. Fourteen cases had only a single episode of uveitis, which remained quiescent at the end of the steroid treatment course (Table 1).

Of the checkpoint inhibitors, ipilimumab (anti–CTLA-4) was given in eight cases, nivolumab (anti-PD1) was given in six cases, and pembrolizumab (anti-PD1) was given in five cases. In many cases, these drugs were given in combination. Of those patients who received checkpoint inhibitors only (without BRAF or MEK inhibitors), six of nine required topical steroid only to treat their disease. Three patients received treatment with both checkpoint inhibitors and BRAF/MEK inhibitors, of whom one had inflammation that could be controlled with topical steroid only.

We describe two cases in greater detail, which are of particular interest.

Case 1

An 80-year-old woman underwent enucleation of the right eye for choroidal melanoma. Ten years later, she was diagnosed with liver and bony metastases and commenced treatment with pembrolizumab, with an excellent response in terms of her metastases. After 2 months, she developed blurred vision in her remaining eye (acuity reduced to 6/18) with moderate anterior chamber and vitreous inflammation and optic disk hyperemia. The intraocular pressure was 4 mmHg. She commenced topical steroid drops, but the inflammation rapidly worsened with vision of count fingers and worsening hypotony with choroidal effusions (Figure 1). Pembrolizumab treatment was withheld,

None of the authors has any financial/conflicting interests to disclose.

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Table 1. Summary Table Showing Patients With Uveitis Occurring Secondary to Treatment for Melanoma

Case	Sex	Age	Systemic Melanoma Rx Before Development of Uveitis	Time from Melanoma Therapy to Uveitis Symptom	Type of Uveitis	Eye(s) Affected	Uveitis Treatment	Uveitis Progression
1	Female	80	Pembrolizumab	2 months	Panuveitis, hypotony, and choroidal effusions	OS	Steroids (topical, oral, periocular, and intravitreal) and vitrectomy	Chronic/recurrent
2	Male	30	Ipilimumab and nivolumab	5 months	AAU, IU, CME, disk edema, periphlebitis, and MAR	OU	Steroids (topical, oral, and IV), mycophenolate, and infliximab	Chronic/recurrent
3	Female	69	Ipilimumab, pembrolizumab, dabrafenib, and trametinib	4 months	AAU and IU	OU	Steroids (topical and oral)	Chronic/recurrent
4	Female	55	Dabrafenib, trametinib, ipilimumab, and pembrolizumab	10 months	AAU and CME	OU	Steroids (topical, oral, and intravitreal)	Chronic/recurrent
5	Female	53	Dabrafenib and trametinib	18 months	AAU and IU	OU	Topical steroids	Single episode
6	Male	70	Nivolumab	1 month	AAU	OU	Topical steroids	Chronic/recurrent
7	Male	56	Ipilimumab	1 month	AAU	OU	Steroids (topical and oral)	Single episode
8	Male	64	Dabrafenib and trametinib	3 months	AAU	OU	Topical steroids	Single episode
9	Male	72	Vemurafenib (BRAF inhibitor), ± cobimetinib (MEK inhibitor) *clinical trial*	3 months	AAU and papillitis	OU	Topical steroids	Single episode
10	Female	64	Vemurafenib	18 months	AAU and CME	OU	Topical steroids	Chronic/recurrent
11	Male	80	Dabrafenib and trametinib	6 weeks	AAU	OU	Topical steroids	Single episode
12	Female	43	Dabrafenib and trametinib	10 months	AAU and CME	OS	Topical steroids	Single episode
13	Female	47	Dabrafenib and trametinib	4 months	AAU and IU	OU	Topical steroids	Single episode
14	Male	69	Ipilimumab and pembrolizumab	N/A	AAU	OU	Topical steroids	Single episode
15	Male	70	Pembrolizumab, dabrafenib, and trametinib	9 months	AAU	OU	Topical steroids	Single episode
16	Female	43	Dabrafenib and trametinib	3 weeks	Panuveitis and later chronic AAU	OU	Steroids (oral and topical)	Chronic/recurrent
17	Male	62	Ipilimumab and nivolumab	3 weeks	AAU	OU	Topical steroids	Single episode
18	Male	64	Dabrafenib, trametinib ± spartalizumab (anti-PD1) *clinical trial*	10 weeks	AAU	OU	Topical steroids (oral steroids also given for systemic disease)	Single episode
19	Male	62	Nivolumab	6 weeks	AAU	OU	Topical steroids	Single episode
20	Male	44	Ipilimumab and nivolumab	4 weeks	AAU	OU	Topical steroids	Single episode
21	Female	59	Ipilimumab and nivolumab	2 weeks	AAU	OU	Topical steroids	Single episode
22	Male	44	Dabrafenib and trametinib	8 months	AAU and CME	OU	Steroids (topical, oral, right periocular, and left intravitreal)	Chronic/recurrent

AAU, acute anterior uveitis; IU, intermediate uveitis; CME, cystoid macular edema; MAR, melanoma-associated retinopathy; OU, oculus uterque = both eyes; OS, oculus sinister = left eye.

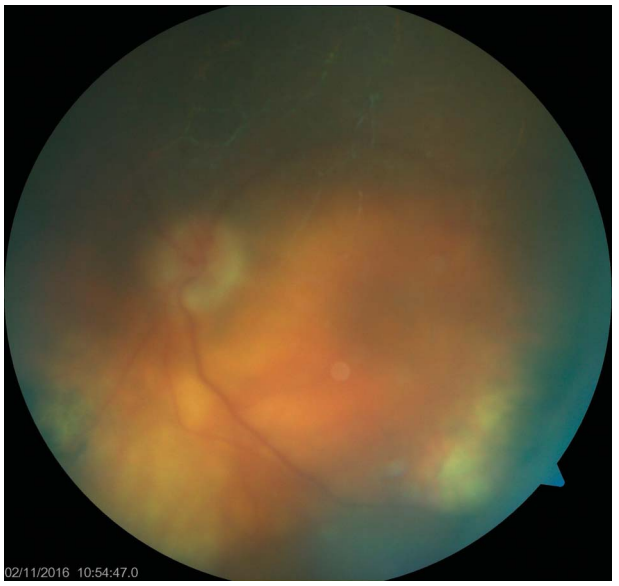


Fig. 1. The left eye of Case 1 showing vitreous haze. There are underlying choroidal effusions.

and she received two orbital floor injections of triamcinolone (40 mg/1 mL) 3 weeks apart, with an initial partial improvement but subsequent deterioration. There was a poor response to intravitreal triamcinolone (4 mg in 0.1 mL) with only partial response of the inflammation and ongoing hypotony with effusions. High-dose (1 mg/kg) oral steroids were not tolerated. A vitrectomy with silicone oil was performed to treat the effusions/hypotony. The visual acuity failed to improve beyond count fingers, and the pembrolizumab was withheld indefinitely.

Case 2

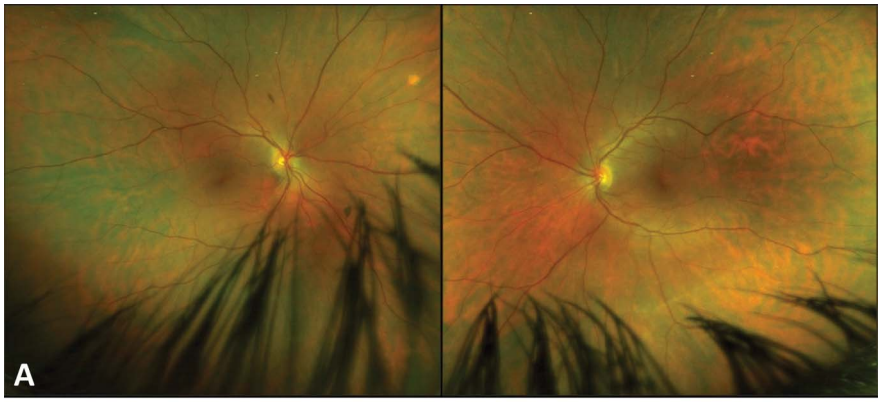
A 30-year-old white man was diagnosed with metastatic melanoma to the liver, brain, and lungs. He was commenced on ipilimumab and nivolumab with a near complete response and undetectable metastases. After three courses of treatment, he developed autoimmune hepatitis, and the treatment was discontinued. Nivolumab monotherapy was then recommenced. Five months after the start of the treatment, he developed photopsias, floaters, and nyctalopia. Visual acuity was 6/6 in each eye, despite bilateral anterior and intermediate uveitis, cystoid macular edema, disk edema, and retinal periphlebitis. He was initially treated with topical steroids, followed by the addition of oral prednisolone initially 100 mg daily, which was then tapered to 50 mg daily. After 6 weeks of this treatment regimen, there was little clinical response, and he developed a steroid response with raised intraocular pressure.

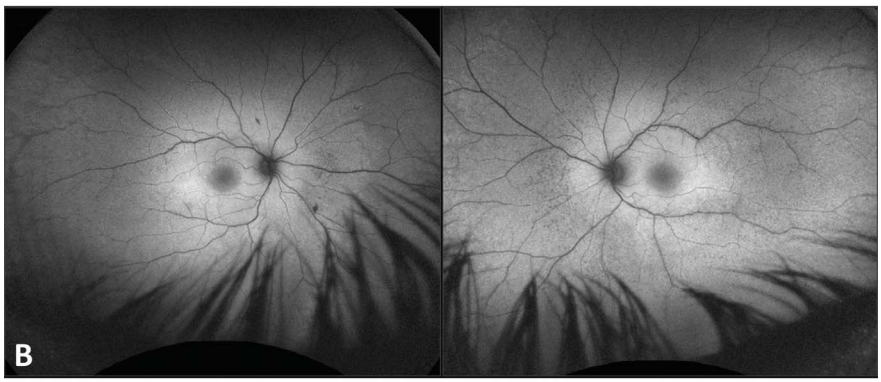
Wide-field fundus autofluorescence showed an enlarged foveal area of hypoautofluorescence with an area of generalized hyperautofluorescence extending beyond the vascular arcades in each eye (Figure 2). Electrophysiology showed bilateral reduction of the pattern electroretinogram and markedly reduced rod and cone responses on full-field electroretinogram with reduction of the B wave for all testing conditions and a significant electronegative B wave. On and off bipolar recordings showed loss of the ON bipolar pathway but preservation, although reduced, of the OFF bipolar pathway (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/ICB/A80, Figure 2, Supplemental Digital Content 2, http://links.lww.com/ICB/A81, and Figure 3, Supplemental Digital Content 3, http://links.lww.com/ICB/A82). The electrophysiology was consistent with a melanoma-associated retinopathy. The clinical picture otherwise was consistent with previously reported checkpoint inhibitor-associated panuveitis.

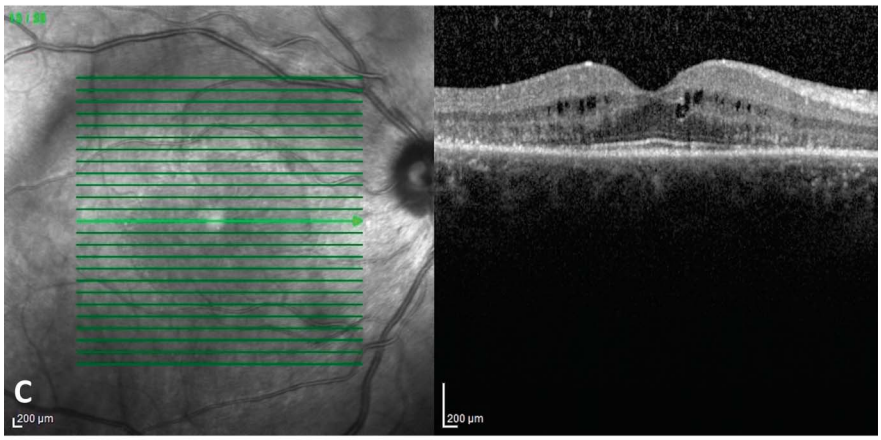
The patient was treated with 3 days of IV methylprednisone and tapering oral corticosteroid thereafter. Mycophenolate was commenced, but the response was insufficient to allow prednisolone taper below 20 mg daily. Infliximab infusions were commenced. Repeat electrophysiology at 3 months of follow-up showed no further progression of the electrophysiological changes, and Snellen visual acuity remained 6/6 bilaterally.

Discussion

These cases illustrate the spectrum of uveitis presentations that can occur secondary to immunomodulatory therapies for malignant melanoma, and this series is the largest to date. The uveitis was uncomplicated anterior uveitis in 11 cases. In 14 cases, the inflammation could be controlled with topical steroids only. This suggests that most drug-induced uveitis is likely to be mild, as suggested by the findings from clinical trials.[3,4] In some cases, the uveitis was much more severe: In Case 1, the patient developed a severe panuveitis with subsequent permanent visual loss. Panuveitis has been described, but in previous cases, there was a response to treatment. In some reports, the inflammation was associated with the development of uveal effusions.[5] In other cases, "sarcoid-like" granulomatous ophthalmic inflammation has been described.[6] There is one other report of chronic hypotony occurring in association with pembrolizumab-induced uveitis, and this patient also lost vision in one eye as a result. Otherwise, reports of permanent vision loss from drug-induced uveitis are rare.[7]







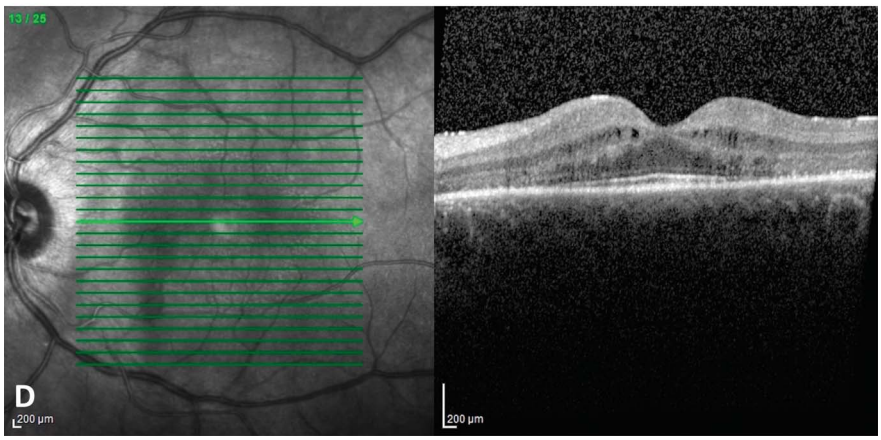


Fig. 2. Color images, fundus autofluorescence, optical coherence tomography, and electrophysiology for Case 2. **A.** Color fundus photographs of both eyes (**B**) autofluorescence of both eyes (**C**) optical coherence tomography of the right eye, and (**D**) optical coherence tomography of the left eye, both showing cystoid macular changes.

Case 2 showed aspects of both checkpoint immunotherapy–induced uveitis and melanoma-associated retinopathy. We suspect that this patient may have had low-grade melanoma-associated retinopathy before starting immunotherapy, which was significantly exacerbated by the immune-modulating drugs. The electronegative electroretinogram shows one of the largest reductions in B wave that we have seen in this condition (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/ICB/A80, Figure 2, Supplemental Digital Content 2, http://links.lww.com/ICB/A81, and Figure 3, Supplemental Digital Content 3, http://links.lww.com/ICB/A82). Despite cessation of his immunotherapy, this patient has had ongoing immune uveitis. Immunosuppressive therapy including infliximab has halted any further progressive vision loss, which has also been shown in repeat electrophysiology.

As discussed, in many of our cases, the presentation of uveitis was mild. Eleven patients had anterior uveitis, which was treated with topical steroids only. In eight cases, the uveitis was predominantly anterior but with additional features including intermediate uveitis, cystoid macular edema, or papillitis. Reported complications of drug-induced anterior uveitis include posterior synechiae, cystoid macular edema, retinal vasculitis,[8] papillitis, or neuroretinitis.[9] Of the more severe cases in this series, seven patients required oral steroid treatment, three required intravitreal steroids, two received periocular steroid, and one received IV steroid.

It is likely that the underlying mechanism of the uveitis in immunotherapy-induced intraocular inflammation is unintended breakdown in tolerance to "self" antigens that results from the targeted modulation of the immune system to better attack the cancer cells. A large number of our patients have regular but intermittent courses of immunotherapy or change agents because of comorbidities and trial protocols. The decisions regarding treatment cessation or rechallenging are "contaminated" by systemic factors, and we were unable to analyze this in a way that generated useful additional information. As further immune-based treatments for advanced cancers are developed, ophthalmologists are likely to see an increasing number of cases of uveitis as reported in the present case series, which is sufficiently large to demonstrate the variety of types and severity of uveitis that can occur. Oncologists should be aware of the potentially vision-threatening adverse effects of these drugs and have a low threshold for referral to their ophthalmic colleagues. A collaborative approach is essential to appropriately manage the complex medical needs of this group of patients.

Key words: checkpoint, immunotherapy, melanoma, uveitis.

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