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ORIGINAL ARTICLE

Recurrent grade 4 panuveitis with serous retinal detachment related to nivolumab treatment in a patient with metastatic renal cell carcinoma

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Abstract

Blockade of programmed cell death-1 (PD-1) has become one of the most promising immunotherapies for many human cancers. However, immune-related adverse events can be produced by anti-PD-1 therapy. Uveitis is a rare but potentially devastating side effect of anti-PD-1 therapy. Delay in diagnosis or improper treatment may eventually lead to irreversible blindness. Therefore, it is important for the oncologist and the ophthalmologist to recognize and manage this adverse event properly in patients receiving anti-PD-1 therapy in a timely manner. Here we present a grade 4 panuveitis with bilateral serous retinal detachment following treatment with nivolumab for metastatic renal cell carcinoma. Oral prednisone, topical steroid eye drops, periorbital injection of steroid and finally intravitreal injection of steroid implant were administered in our patient. We observed that intravitreal injection of dexamethasone implant, but not the periorbital injection of steroid or the steroid eye drops, was effective to control the posterior uveitis and serous retinal detachment. Oral prednisone was also effective, but it might affect the efficacy of anti-PD-1 therapy and promote tumor growth. We also summarize 15 cases of uveitis reported to date related to nivolumab or pembrolizumab therapy in the present study. The symptoms, signs, potential underlying mechanisms and treatment options regarding this adverse event are discussed.

Keywords Uveitis · Anti-PD-1 · Retinal detachment · Dexamethasone implant

Abbreviations

AC	Anterior chamber
BCVA	Best-corrected visual acuity
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
EAU	Experimental autoimmune uveitis
FDA	Food and Drug Administration
FFA	Fluorescent fundus angiography
irAEs	Immune-related adverse events
NSCLC	Non-small cell lung cancer
OCT	Optical coherence tomography
PD-1	Programmed cell death-1
PD-L1/L2	Programmed cell death ligand 1/ligand 2
VA	Visual acuity

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Introduction

Immune checkpoints are inhibitory regulators of the host immune responses. They mediate self-tolerance and prevent autoimmune damage by downregulating T-cell proliferation and activation. Being exploited by the tumor cells, the immunosuppressive checkpoints were found to play a crucial role in tumor immune evasion. Blockade of checkpoint pathways, resulting in restoration of antitumor immune responses, has led to the development of new immunotherapies for many human cancers.

Programmed death 1 (PD-1), a member of the CD28 family, is one of the most widely studied immune checkpoints. As a key negative immunoregulator, PD-1 is essential in peripheral tolerance [1]. While PD-1 is inducibly

expressed on activated T cells, its ligands PD-ligand 1 (PD-L1) and PD-ligand 2 (PD-L2) are widely expressed in various tissues [2]. Importantly, in 2002, Dong et al. reported that PD-L1 was highly expressed on various tumor cells [3]. Subsequent laboratory and clinical findings indicated that high PD-L1 expression was associated strongly with accelerated tumor growth and poorer prognosis [3–5]. The above evidence implicated the PD-1/PD-L pathway in mediating tumor immune evasion. Further experimental results revealed that highly expressed PD-L1 on tumor cells may contribute to immune evasion by actively inducing tumor-specific T cell apoptosis [3]. Blockade of the PD-1/PD-L signaling using monoclonal antibodies against PD-1 exhibited robust antitumor potential [6]. The success of PD-1 inhibition in treating cancers were translated recently from the bench side to clinic. Starting in 2014, anti-PD-1 agents nivolumab (Opdivo), pembrolizumab (Keytruda), and anti-PD-L1 agent atezolizumab have been approved by the US Food and Drug Administration (FDA) one after another for treating advanced human cancers and have become the most promising cancer immunotherapies [7–9].

Immune checkpoint inhibition therapy may elicit immune-related adverse events (irAEs) involving many organs such as skin, liver, gut, endocrine tissues and eye [10]. Immune-related ocular toxicities (uveitis, dry eyes, conjunctivitis, orbital inflammation, etc.), which are less common but potentially sight-threatening, have exhibited a higher incidence among cancer patients on checkpoint inhibitors when compared with control treatments [10, 11]. In cancer patients treated with anti-PD-1 agents, ocular side effects related to PD-1 blockade have been increasingly reported, among which uveitis is one of the most frequently discussed. Uveitis refers to inflammation of the uvea, a highly vascularized layer that lies between the retina and the sclera. It is an ophthalmic emergency requiring prompt treatment, since it affects not only the uveal tract, but also other vital eye tissues including the lens, retina, optic nerve and the vitreous. The symptoms, mechanisms and treatment options of uveitis related to anti-PD-1 therapy have yet to be comprehensively assessed. Here we present a case of recurrent panuveitis with serous retinal detachment in a patient with metastatic renal cell carcinoma treated with nivolumab. It was classified as grade 4 [best-corrected visual acuity (BCVA) of 20/200 or worse] ocular irAE according to the common terminology criteria for adverse events (CTCAE) version 4.0 [12]. In addition, uveitis cases related to anti-PD-1 therapy reported in the literature were also summarized. Currently available data regarding ocular toxicities of atezolizumab (anti-PD-L1) treatment is limited, therefore, is not included. The symptoms, time of occurrence, treatment of uveitis as well as the antitumor efficacy of PD-1 inhibitors were discussed.

A 64-year-old female was referred to our clinic with redness and floaters in the right eye. She was diagnosed with non-small cell lung cancer (NSCLC) and underwent pulmonary resection (left lower lobectomy) in 2009. Two years later, bone and lymph node metastases were found, gefitinib (Iressa) was given. In 2016, the patient was diagnosed with renal cell carcinoma and surgical resection was applied. Four months after nephrectomy, pulmonary and liver metastases from renal cell carcinoma were detected. Treatment with sunitinib (Sutent) was started with poor response. Subsequently, nivolumab (140 mg, iv) was initiated as a second-line treatment once every 2 weeks. One month later, a significant decrease in pulmonary and liver metastases was observed on follow-up CT. After six cycles of nivolumab treatment, the patient started to suffer from redness and floaters in the right eye.

On ophthalmologic examination, her BCVA was 20/40 in the right eye (OD) and 20/32 in the left eye (OS). Slit-lamp examination revealed keratoprecipitates, positive Tyndall effect, anterior chamber (AC) cells in both eyes. No hypopyon was found in the AC. Vitreous floaters were observed in the right eye. Dilated fundus examination was unremarkable. Ultrasound examination detected minimal echogenicity in the vitreous. Serologic investigation revealed negative for syphilis, rheumatoid factor, and tuberculosis. The complete blood count (CBC) results were normal except for a low hemoglobin count. The erythrocyte sedimentation rate (ESR) was increased. Treatment with topical prednisolone acetate (1%) q2h was initiated in the right eye. One week later, the AC inflammation resolved significantly. Nivolumab therapy was continued at this point.

One month later, however, the patient returned to our clinic with further visual loss in both eyes. On examination, her vision was 20/125 in the right eye and 20/63 in the left eye. Bilateral posterior synechiae was present (Fig. 1). One week later, her vision dramatically dropped to 20/500 in the right eye and 20/400 in the left eye. Bilateral retinal detachment involving the posterior pole and the inferior retina was demonstrated by ultrasound scan (Fig. 2). Optical coherence tomography (OCT) further confirmed serous retinal detachment involving the fovea in both eyes (Fig. 3a, b). Fundus photography showed blurred disc margins bilaterally which suggested the presence of optic disc edema in both eyes (Fig. 4a, b). Significant bilateral thickening of the peripapillary retinal nerve fiber layer was revealed by OCT (Fig. 4c, d). In addition, fluorescein fundus angiography (FFA) demonstrated leakage of dye at the edematous disc during the late phase of angiography (Fig. 4e–h). According to the CTCAE classification, a diagnosis of grade 4 uveitis with serous retinal detachment related to nivolumab treatment was made. After discussion with the oncologist, nivolumab therapy was discontinued. Treatment with pulsed intravenous methylprednisolone 500 mg/day was

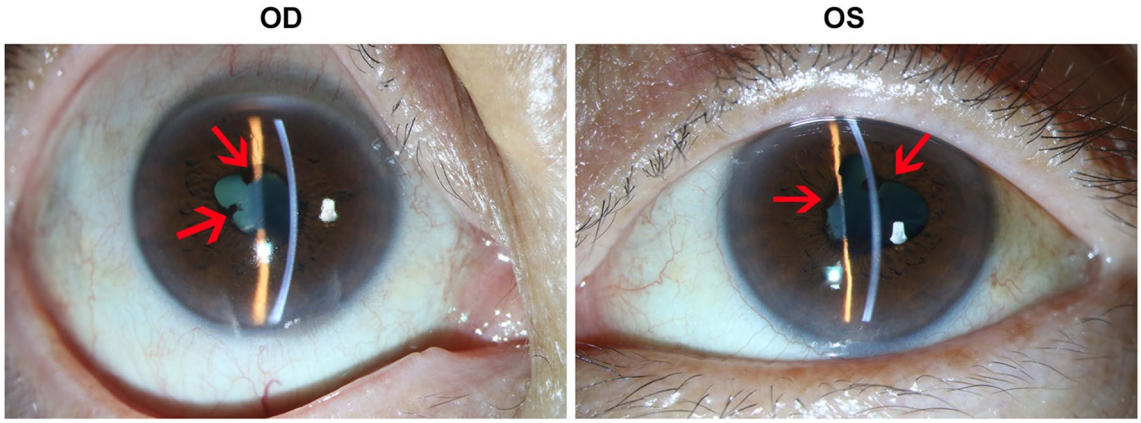

Fig. 1 Bilateral slit lamp images showing posterior synechiae (red arrows)

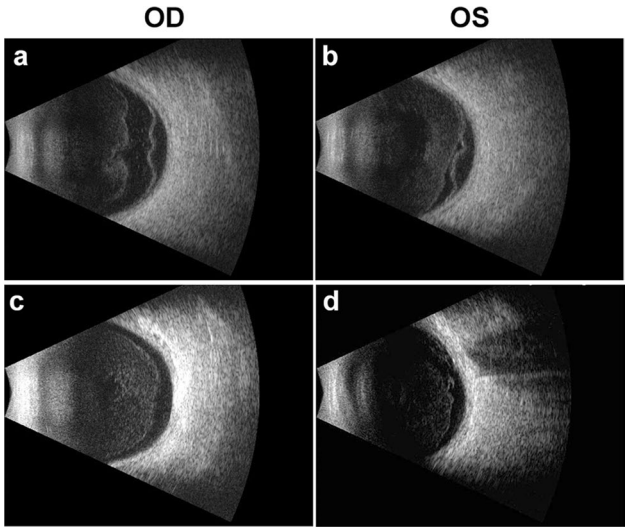

Fig. 2 Ultrasound examination during and after treatment. **a, b** Bilateral ultrasound images showing retinal detachment and posterior vitreous detachment in both eyes during treatment. **c, d** Images showing retinal reattachment after treatment in both eyes

immediately started. Five days later, her visual acuity (VA) improved to 20/40 in both eyes. Intravenous methylprednisolone was stopped, oral prednisone (30 mg/day) was subsequently given to the patient and the dose was tapered to 5 mg/day over 2 months. With the treatment, retinal detachment improved significantly in both eyes (Figs. 2c, d, 3c, d). Her VA was 20/60 OD, 20/80 OS on the follow-up exams. However, increased liver metastases were found on follow-up CT exam during the treatment of uveitis. Therefore, nivolumab therapy (140 mg/2 weeks) was resumed 6 weeks after discontinuation. Unfortunately, recurrence of uveitis occurred 2 weeks after reinitiation of nivolumab. Inflammatory cells were present in the AC. Subretinal fluid and chorioretinal folds were present in the right eye predominantly (Fig. 3e, f). Furthermore, marked disc edema was found in the left eye (Fig. 4i). Fundus image of the right eye was not available due to the presence of posterior synechiae and cataract. Topical prednisolone acetate (1%) q2h was given in conjunction with periorbital injection of methylprednisolone (40 mg). After treatment, the anterior inflammation resolved, however, posterior inflammation and the subretinal fluid both increased (Fig. 3g, h). Bilateral intravitreal injections of dexamethasone implant (Ozurdex) were then given. The subretinal fluid eventually resolved (Fig. 3i, j). On the last follow-up exam, the patient's final VA was 20/70 OD, 20/35 OS. The posterior inflammation was well controlled with intravitreal Ozurdex implant (Fig. 4j). The side effects of nivolumab were closely monitored by the oncologist and no other signs of immune-related adverse events were detected in this patient.

Discussion

Uveitis is a rare but potentially devastating side effect of anti-PD-1 therapy. In the last 2 years, with the widespread use of PD-1 inhibitors in cancer patients, an increasing number of cases of uveitis have been reported as an ocular side effect. Most cases are mild or monophasic anterior uveitis. In the present work, we present a case of recurrent grade 4 panuveitis with serous retinal detachment in a patient treated with nivolumab. Various treatment responses of nivolumab related uveitis are reported. More importantly, we demonstrat for the first time that intravitreal injection of dexamethasone implant, other than periorbital injection of steroid, is effective for persisting and recurring posterior inflammation and serous retinal detachment induced by anti-PD-1 agents.

The relationship between PD-1 and immune regulation within the ocular microenvironment has been studied extensively. It is known that eye is an immune-privileged site, wherein an excessive immune response is suppressed by local and systemic mechanisms [13]. Ocular immune

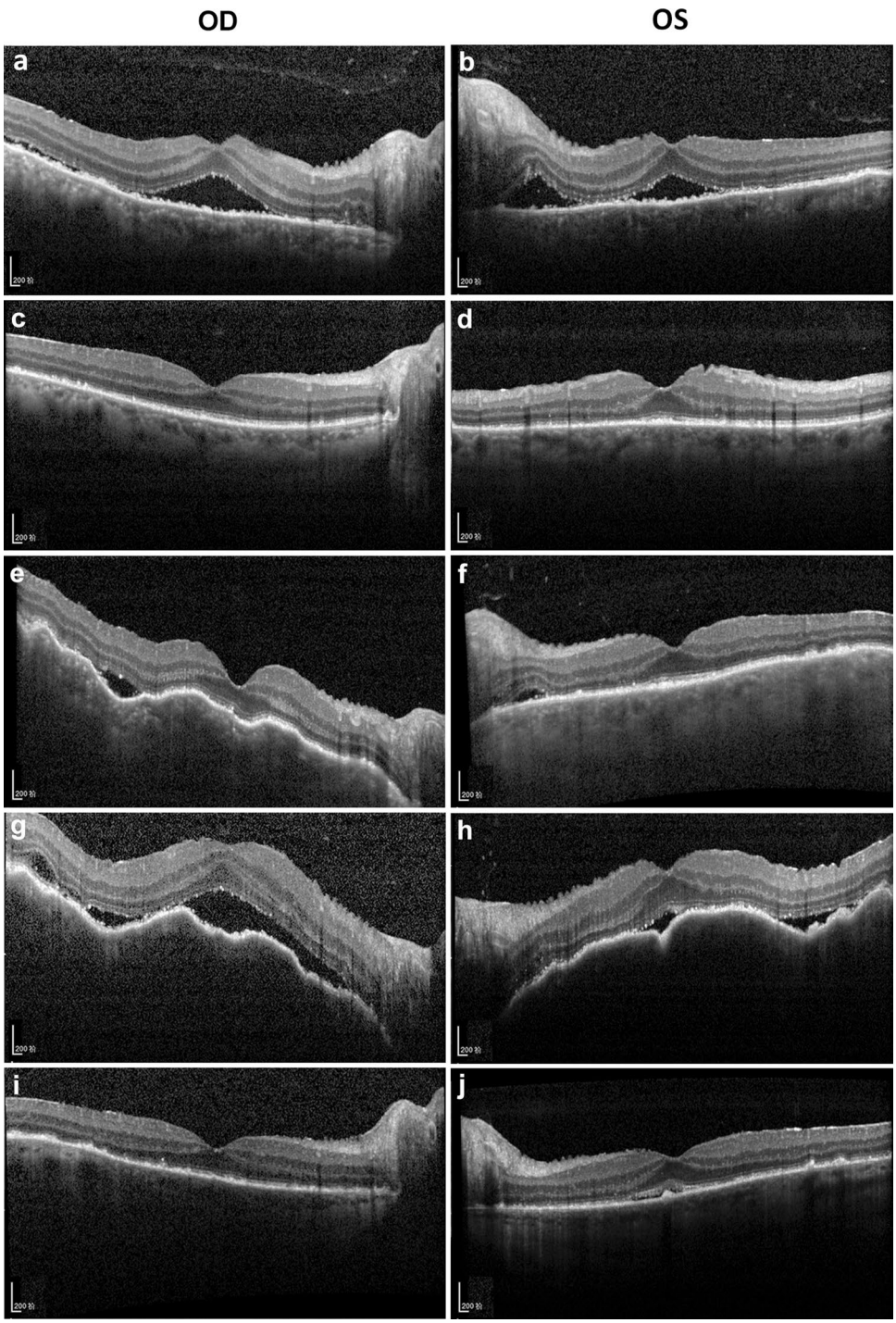

Fig. 3 Bilateral optical coherence tomography (OCT). **a, b** OCT images showing serous retinal detachment in both eyes during treatment. **c, d** Images showing resolution of serous retinal detachment in both eyes after treatment. **e, f** Images showing subretinal fluid as well as chorioretinal folds in the right eye (OD) and subretinal fluid in the left eye (OS) after reinitiation of anti-PD-1 therapy. **g, h** Images showing increased serous retinal detachment and chorioretinal folds in the right eye (OD) and increased subretinal fluid as well as chorioretinal folds in the left eye (OS) after treatment with topical prednisolone acetate combined with periorbital methylprednisolone injection. **i, j** Images showing retinal reattachment and resolution of the chorioretinal folds in both eyes after treatment with intravitreal dexamethasone implant

privilege is considered an important evolutionary adaptation to protect the ocular structure and function from destructive immune responses. Multiple mechanisms have been presumed to contribute to ocular immune privilege including the blood–ocular barriers, a lack of lymphatic drainage, the presence of immunosuppressive factors within the eye and the regulation of systemic immune responses [14]. More recently, studies have revealed a crucial role for PD-1/PD-L1 pathway in establishing ocular immune privilege [15]. PD-L1, which is constitutively expressed in the eye, may mediate ocular immune privilege by inducing apoptosis of T cells and conversion of Treg cells [16, 17]. In a mouse model of corneal allotransplantation, inhibition of PD-1 or PD-L1 led to the collapse of immune privilege in the eye and accelerated corneal allograft rejection [16]. Furthermore, PD-1/PD-L1 pathway has been shown to be responsible for

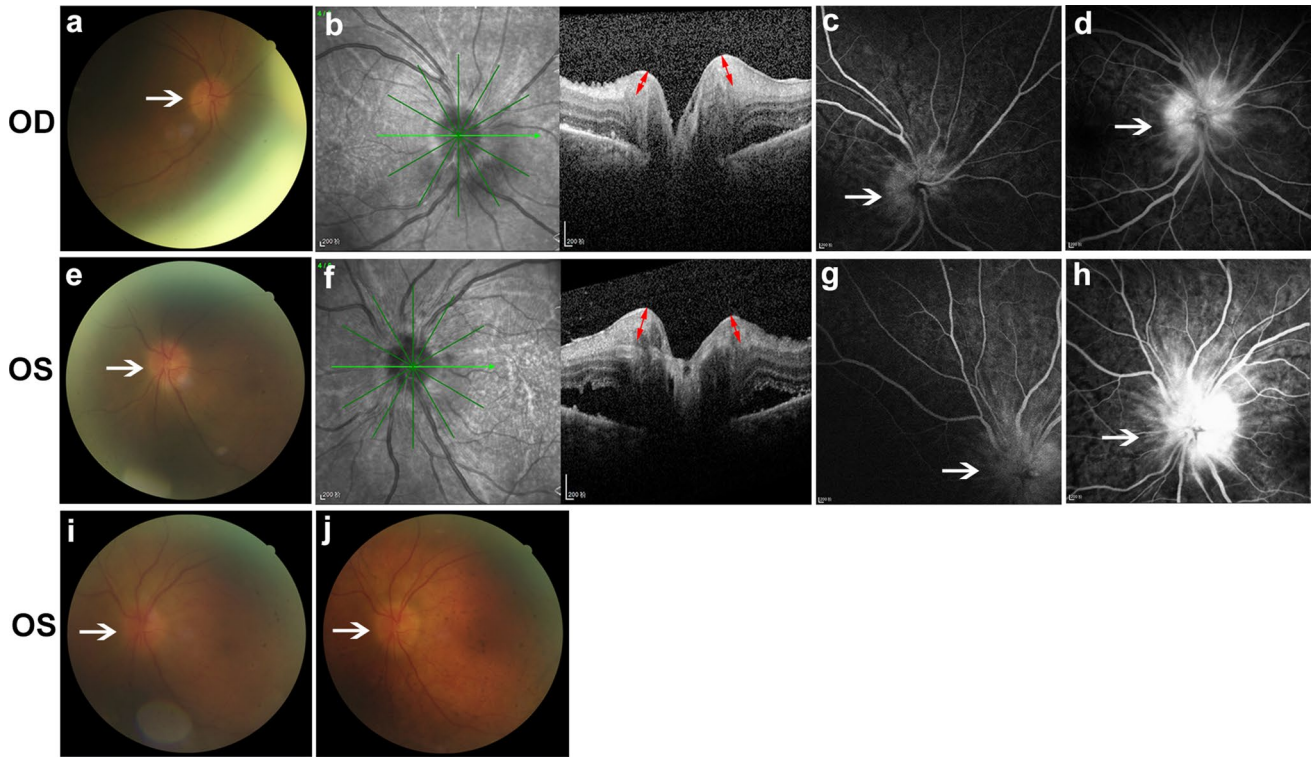

Fig. 4 Images showing bilateral optic disc swelling and leakage. **a, b** Fundus photographs showing blurred disc margins bilaterally (white arrows). **c, d** Images showing significant peripapillary retinal nerve fiber layer thickening bilaterally (red double arrows). **e**–**h** Fluorescein fundus angiography (FFA) reveals **e, f** early hypofluorescence (white arrows) and **g, h** late hyperfluorescence (white arrows) in the optic disc area. **i, j** Fundus photographs showing **i** blurred disc margin in the left eye (OS) after reinitiation of anti-PD-1 therapy and **j** resolution of optic disc edema after treatment with intravitreal dexamethasone implant

the suppression of disease progression and recurrence in a model of experimental autoimmune uveitis (EAU) [18]. The above evidence cumulatively indicated that PD-1/PD-L pathway may play an essential role in the maintaining of ocular immune privilege and suppression of autoimmune diseases. In patients receiving anti-PD-1 treatment, the compromise of the immune privilege status of the eye caused by systemic PD-1/PD-L1 inhibition may explain the occurrence of autoimmune ocular inflammatory diseases such as uveitis.

We reviewed 15 cases of uveitis (including our case) reported to date related to nivolumab or pembrolizumab therapy in cancer patients [19–31] (Table 1). The time of uveitis onset after the first nivolumab/pembrolizumab infusion ranged widely from 12 days to 14 months (median time: 9 weeks). The typical initial presenting complaint was bilateral blurred vision or redness. Among the 15 cases, uveitis was bilateral in 13 cases despite 1 patient who underwent unilateral enucleation due to choroidal melanoma and another case wherein the laterality was not described. In nine cases (60%), inflammation was confined to the anterior segment. Seven cases (47%) were diagnosed with CTCAE grade 2 uveitis. Grade 3 uveitis (posterior/pan-uveitis) was reported in five cases (33%). Three cases (20%) were categorized as CTCAE grade 4. Macular edema and serous retinal detachment/subretinal fluid were observed in six (40%) and four cases (27%), respectively. Recurrence of uveitis following reinitiation of anti-PD-1 therapy was reported in two cases treated with pembrolizumab, but none with nivolumab in the previous literature.

In addition to anti-PD-1 therapy, uveitis has been reported in other immune checkpoint therapies, such as treatment with cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors (ipilimumab and tremelimumab). CTLA-4 is another immune checkpoint which negatively regulates immune responses through mechanisms distinct from PD-1. While PD-1 pathway inhibits T cell response primarily in peripheral tissues (e.g., the tumor site), CTLA-4 regulates T-cell activation in lymph nodes [32]. This may partially explain the higher overall rate of irAEs induced by CTLA-4 blockade when compared with PD-1/PD-L1 blockade [33–35]. Currently, there is a lack of data comparing the incidence, pattern, and the time of occurrence of immune-related uveitis induced by CTLA-4 and PD-1/PD-L1 inhibitors. Notably, in a phase I study of ipilimumab and nivolumab combination therapy in melanoma patients, the incidence of uveitis was found to be higher than previously reported

Table 1 Summary of cases of uveitis related to anti-PD-1 therapy (nivolumab and pembrolizumab)

Authors and year	Age (year), sex	Tumor type	Antitumor efficacy of anti-PD-1 mAbs	Timing of uveitis onset	Diagnosis	CTCAE grade	Initial VA	Management of uveitis	Visual outcome	Cessation of anti-PD-1mAbs	Recurrence of uveitis after resume of anti-PD-1 mAbs	Follow-up
(a) Nivolumab-related cases												
Our case	64, F	NSCLC Metastatic renal cell carcinoma	Significant tumor response	11 weeks (6 infusions)	Bilateral panuveitis	4	20/500 OD, 20/400 OS	(i) Topical and oral steroids (ii) Intravenous and periorbital injection of methylprednisolone (iii) Intravitreal dexamethasone implant	Final VA: 20/70 OD, 20/35 OS	Yes	Yes	7 months
Theillac et al. 2017 [19]	55, F	Metastatic melanoma	No tumor progression until steroid treatment	4 weeks (3 infusions)	Bilateral anterior uveitis	2	20/20 OD, 20/40 OS	(i) Topical dexamethasone eye drops (ii) Oral prednisone	Final VA: 20/20 OU	Yes	No	1 month
Baughman et al. 2017 [20]	92, F	Metastatic melanoma	Regression of known tumor, increase of new metastatic lesions with steroid treatment	~4–6 weeks (3 infusions)	Bilateral anterior uveitis	4	20/250 OD, 20/200 OS	(i) Topical prednisolone (ii) Cyclopentolate dilating drops	Final VA: 20/50 OU	No	N/A	3 months
Matsuo et al. 2017 [21]	60, F	Metastatic melanoma	Reduction of metastatic lesions	6 weeks (2 infusions)	Bilateral VKH-like posterior uveitis	3	20/13 OU	(i) Betamethasone eye drops (ii) Oral prednisolone	Complete remission	No	N/A	9 months

Table 1 (continued)

Authors and year	Age (year), sex	Tumor type	Antitumor efficacy of anti-PD-1 mAbs	Timing of uveitis onset	Diagnosis	CTCAE grade	Initial VA	Management of uveitis	Visual outcome	Cessation of anti-PD-1mAbs	Recurrence of uveitis after resume of anti-PD-1 mAbs	Follow-up
Richardson et al. 2017 [22]	74, F	Scalp melanoma	Complete regression of the tumor lesions	5 months	Bilateral panuveitis	3	20/100 OD, 20/40 OS	(i) Topical and prednisolone (ii) Intravitreal triamcinolone	Final VA: 20/40 OU	Yes	N/R	8 months
Kanno et al. 2017 [23]	54, F	Metastatic melanoma	Tumor response detected	9 weeks (4 infusions)	Bilateral anterior uveitis	2	24/20 OU	(i) Betamethasone eye drops (ii) Oral prednisone	Uveitis resolved	No	N/A	4.5 months
Arai et al. 2017 [24]	55, M	Metastatic melanoma	Metastatic tumors remained static	2 weeks (1 fusion)	Bilateral anterior uveitis	2	Blurry vision	(i) Topical steroid drops (ii) Topical mydriatic drops	Uveitis controlled	No	N/A	11 months
Karlin et al. 2016 [25]	66, F	Metastatic NSCLC	Tumor response detected	18 weeks (10 fusions)	Bilateral anterior uveitis	2	20/100 OD, 20/200 OS (VA limited by PSC cataracts)	(i) Topical prednisolone drops (ii) Cyclopentolate drops	Final VA: 20/40 OD, 20/200 OS	No	N/A	3 weeks
de Velasco et al. 2016 [26]	60, M	Metastatic clear cell renal cell carcinoma	Complete tumor response	14 months (28 infusions)	Anterior uveitis (laterality N/R)	2	N/R	(i) Intraocular steroid treatment	Uveitis resolved	Yes	N/R	2 years
(b) Pembrolizumab-related cases												
Aaberg et al. 2017 [27]	54, F	Metastatic unilateral uveal melanoma	No tumor progression	9 weeks (4 infusions)	Posterior uveitis	3	20/20 OS (right eye enucleated)	(i) Intraocular dexamethasone implant	Uveitis resolved after 4 months, recurred 7 months later	No	N/A	15 months

Table 1 (continued)

Authors and year	Age (year), sex	Tumor type	Antitumor efficacy of anti-PD-1 mAbs	Timing of uveitis onset	Diagnosis	CTCAE grade	Initial VA	Management of uveitis	Visual outcome	Cessation of anti-PD-1mAbs	Recurrence of uveitis after resume of anti-PD-1 mAbs	Follow-up
Basilious et al. 2016 [28]	63, F	Metastatic melanoma	N/R	N/R	Bilateral anterior uveitis	4	20/30 OD, 20/25 OS	(i) Topical and oral steroids (ii) Cataract surgery OU (iii) Intravitreal triamcinolone	Final VA: 20/30 OD, 20/200 OS	Yes	N/R	13 months
Hanna et al. 2016 [27]	78, F	Metastatic scalp melanoma	Significant tumor response	12 days (1 infusion)	Bilateral panuveitis	3	Blurred vision	(i) Oral prednisone (ii) Sub-Tenton's triamcinolone injections (iii) High-dose intravenous methylprednisolone	Uveitis resolved	Yes	N/R	4 weeks
Diem et al. 2016 [29]	60, –	Metastatic melanoma	Partial tumor response	3 months (after an elective unilateral cataract surgery)	Bilateral panuveitis	3	Reduced VA	(i) Topical steroids and antibiotics (ii) Systemic steroids	Uveitis resolved VA improved	Yes	Yes	6 months
Diem et al. 2016 [30]	75, M	Metastatic melanoma	Complete regression	Pre-existing asymptomatic uveitis, three relapses during nivolumab treatment	Bilateral anterior uveitis	2	N/R	(i) Topical prednisolone drops (ii) Scopolamine drops	Uveitis resolved	No	N/A	32 weeks
Abu Samra et al. 2016 [31]	82, M	Metastatic melanoma	N/R	2 months (3 infusions)	Bilateral anterior uveitis	2	N/R	(i) Topical steroid	Uveitis resolved	Yes	Yes	–

F female, *M* male, *CTCAE* common terminology criteria for adverse events, *VA* visual acuity, *mAbs* monoclonal antibodies, *NSCLC* non-small cell lung cancer, *OD* right eye, *OS* left eye, *OU* both eyes, *N/R* not reported, *N/A* not applicable, *PSC* posterior subcapsular, – not available

monotherapy (6% vs < 1%) [36, 37]. Meanwhile, dual blockade of PD-1 and CTLA-4 produced an enhanced antitumor efficacy when compared with ipilimumab or nivolumab as a single agent. Therefore, uveitis may serve as a marker of response to immune checkpoint blockade therapy in addition to being considered as a drug-related toxicity. Among the 15 reviewed cases, tumor activity upon presentation of uveitis was described in 7 cases in which either complete or partial antitumor response was detected (Table 1). In a case of metastatic melanoma reported by Hanna et al., the patient was initially treated with ipilimumab during which no significant drug-related toxicities were presented, however, tumor progression was found 3 months later. After switching to pembrolizumab treatment, the patient soon developed symptoms including blurred vision (uveitis), acute onset of ataxia, and hearing loss. Simultaneously, robust regression of metastatic tumor was detected [29]. Moreover, in our case, nivolumab treatment successfully induced regression of the metastatic tumor when the symptoms of uveitis occurred. While the above evidence supported the assumption about uveitis being a potential marker for disease response, it made the management of the immune-related uveitis challenging. In regards of possible compromise of the antitumor activities of the immune checkpoint inhibitory agents, the application of corticosteroids requires careful consideration.

Mild uveitis (anterior/grade 2) induced by PD-1 blockade can be controlled with topical corticosteroids. In severe cases or pan/posterior-uveitis, systemic steroids might be considered. The immunosuppressive effect of systemic steroids should be taken into consideration in patients undergoing immune checkpoint inhibitor treatment. Long-term use of systemic steroid should be avoided. In our case, the patient was initially treated with topical prednisolone acetate (1%). However, one month later, the inflammation progressed to the posterior segment with VA rapidly dropped to 20/500 OD, 20/400 OS. Pulsed intravenous methylprednisolone (IVMP) was then administered, followed by oral prednisone. The patient's VA and retinal detachment improved dramatically with systemic steroid therapy. Considering the immunosuppressive effect of steroid, a rapid tapering of oral corticosteroids combined with periocular steroid injection was arranged after her condition was well controlled.

Moreover, discontinuation of the immune checkpoint therapy might be required to effectively control the irAEs. In a study of dual blockade of PD-1 and CTLA-4 in melanoma patients, drug cessation caused by all types of irAEs affected up to 45% patients [38]. Among the 15 reviewed cases (Table 1), the decision to cease anti-PD-1 treatment after induction of uveitis was made in 8 cases. In practice, whether to discontinue the anti-PD-1 agents requires thorough discussion between the oncologist, the ophthalmologist and the patient. When the ocular inflammation is mild or only involves the anterior segment, discontinuation of the anti-PD-1/PD-L1 agents may not be required. In our case, the ocular inflammation was severe and fallen into the category of grade 4 ocular side effects. Nivolumab was stopped by the oncologist and systemic steroid was administrated. Unfortunately, increased liver metastases were found 6 weeks after discontinuation of nivolumab. The increased metastases might be associated with discontinuation of nivolumab or/and administration of systemic immunosuppressant.

Recurrence of uveitis occurred 6 weeks after reinitiation of anti-PD-1 therapy in our case, although it was not reported in the previous literature. It is important to be aware of the recurrence of side effect after the reinitiation of anti-PD-1 therapy. Dose titration of anti-PD-1 agents for individual patient might be needed. It is important to find the balance of malignancy control and minimization of side effects during anti-PD-1 therapy. The management of the recurrence of uveitis was also challenging. In our case, we hesitated to give high-dose systemic steroid in view of the increased liver metastases, instead, we decided to administrate local injections. The posterior uveitis and serous retinal detachment were well controlled with intravitreal injection of Ozurdex, but not with periorbital injection of steroid. This therapeutic option was not reported in the previously reported nivolumab-related uveitis cases.

Uveitis is one of the major causes of blindness worldwide. Although uveitis is a relatively uncommon side effect, prompt recognition of the manifestations and appropriate management are critical in patients receiving PD-1 inhibitors. Improper treatment of uveitis may cause permanent ocular damage and irreversible visual loss, which may affect the quality of life and treatment compliance in cancer patients. With the increasing use of anti-PD-1 therapy in cancer treatment, it is important for the oncologist and the ophthalmologist to understand this ocular complication thoroughly. Most importantly, cooperation between them is required for the development of appropriate therapy for individual patients in a timely manner.

Author contributions All authors, WW, W-CL and LC, take responsibility for the integrity of the data. All authors made substantial contributions to data interpretation, discussion, manuscript preparation, review, revision and final approval.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from the patient for publication of this case report.

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