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A case of panuveitis and retinal vasculitis associated with pembrolizumab therapy for metastatic lung cancer

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ABSTRACT

Purpose: To report a case of panuveitis and retinal vasculitis associated with pembrolizumab therapy for metastatic lung cancer.

Observations: A 71-year-old man, who was diagnosed with metastatic lung cancer (squamous cell carcinoma), presented with blurry vision 2 weeks after the initiation of pembrolizumab monotherapy. His best-corrected visual acuity (BCVA) was 20/20 OU, and slitlamp examination revealed fine keratic precipitates, anterior chamber cells (1+) and flare (1+) in both eyes. Dilated fundus examination showed no remarkable finding in the right eye and vitreous haze (2+), perivascular exudates, and vessel sheathing in the left eye. Fluorescence angiography demonstrated dye leakage from the optic disc and both retinal arteries and veins extending from the posterior to the peripheral retina in both eyes. The patient was diagnosed with panuveitis and retinal vasculitis as Grade 3 immune-related adverse event (irAE). Pembrolizumab was discontinued and oral prednisone 70mg/day was given for 1 week. The dose was reduced to 30mg/day for the next 3 weeks and was then stopped. One month after the treatment, intraocular inflammation became quiescent. With a good response to the treatment of irAE, pembrolizumab was restarted. Recurrence of ocular inflammation occurred over the next 1.5 years, but all of which were successfully treated with sub-Tenon's injection of triamcinolone acetonide (STTA). The patient maintained BCVA of 30/20 OU at the latest visit.

Conclusions and importance: We showed a case of retinal vasculitis occurred as an irAE of pembrolizumab for metastatic lung cancer. Retinal vasculitis was well managed with transient pembrolizumab discontinuation and oral corticosteroid therapy, and pembrolizumab was restarted with the aid of STTA. As ocular irAEs might be controlled by local corticosteroid therapy, the decision to continue immune checkpoint inhibitor therapy should be made on a case-by-case basis.

1. Introduction

Since the first immune checkpoint inhibitor (ipilimumab) which targets cytotoxic T-lymphocyte antigen 4 (CTLA-4) was approved by the US Food and Drug Administration (FDA) in 2011 for treatment of metastatic melanoma, immune checkpoint inhibitor therapy has drastically changed the paradigm of cancer treatment. Currently approved immune checkpoint inhibitors by FDA target CTLA-4, programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1), and cancer immunotherapy using checkpoint inhibitors has considerably improved outcomes across many malignant tumors by activating immune reaction against cancer cells. However, as immune checkpoint proteins also suppress self-targeting immune response, immune checkpoint blockade can cause immune-related adverse events (irAEs).[1]

The skin, gastrointestinal tract, and endocrine organs are frequently affected by immune checkpoint inhibitors, and the incidence rate of systemic irAEs was reported to be as high as 96% in the patients with advanced melanoma treated with nivolumab plus ipilimumab combination therapy.[2] Although the reported frequency of ocular irAEs among patients treated with immune checkpoint inhibitors is not so high,[3–5] some patients may experience a severe ocular irAE and lost their vision unless adequately treated. Herein, we present a rare case of panuveitis

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and retinal vasculitis associated with pembrolizumab (PD-1 inhibitor) therapy for metastatic lung cancer.

2. Case report

A 71-year-old man diagnosed as having right upper lobe squamous cell carcinoma (cT4N1M1b, StagelVB) presented with blurry vision. He was started on pembrolizumab monotherapy 2 weeks prior, and skin rashes developed on his fingers and neck 9 days after pembrolizumab administration. He had a 46.5-pack-year history of smoking and had a medical history for chronic obstructive pulmonary disease. His ocular and family histories were unremarkable, and he had no known food and drug allergies. On initial examination, 18 days after the initiation of pembrolizumab, his best-corrected visual acuity (BCVA) was 20/20 OU. The intraocular pressure was 16 mmHg OD and 14 mmHg OS. Slitlamp examination revealed fine keratic precipitates, anterior chamber cells (1+) and flare (1+), and nuclear sclerotic cataract (2+) in both eyes. Dilated fundus examination showed no remarkable finding in the right eye and vitreous haze (2+), perivascular exudates, and vessel sheathing in the left eye. Optical coherence tomography (OCT) B-scan images of the macula appeared almost normal in the right eye and visualized multiple scattered hyperreflective spots in the neural retina in the left eye (Fig. 1). Fluorescence angiography (FA) demonstrated dye leakage from the optic disc and both retinal arteries and veins extending from the posterior to the peripheral retina in both eyes. Indocyanine green angiography (ICGA) showed multifocal dye staining in retinal arteries on late-phase image (Fig. 2). Systemic work-up to explore the cause of uveitis failed. Blood examinations showed elevated white blood cell count (10100/μL), ALP (344U/L), BUN (24.7 mg/dL), decreased albumin (3.9 g/dL), and negative for tuberculosis (negative T-SPOT), syphilis, toxoplasmosis, and fungal infection. Chest computed tomography neither showed bilateral hilar lymphadenopathy nor parenchymal lung changes.

After the consultation with the pulmonologist in charge, pembrolizumab was thought to be a putative cause of bilateral non-granulomatous panuveitis in this case. As panuveitis is classified as Grade 3 irAE according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0,[6,7] pembrolizumab administration was discontinued and oral prednisone 70mg/day (1 mg/kg/day) was given for 1 week. The dose of prednisone was reduced to 30mg/day (0.43mg/kg/day) for the next 3 weeks and was then stopped. On biomicroscopic findings after corticosteroid therapy, the right eye developed multiple blot hemorrhages, soft exudates, and vessel sheathing. On the other hand, the inflammation in the left eye was alleviated: the vitreous haze resolved, and perivascular exudates and vessel sheathing became less evident. Multiple scattered hyperreflective spots disappeared on OCT and angiographic findings were also improved. Only mild dye leakage from the optic disc and retinal vessels was left on FA, and faint staining in retinal arteries was recognized on ICGA (Fig. 3). Following a good response to the treatment of irAE, pembrolizumab administration was restarted after prophylactic sub-Tenon's injection of triamcinolone acetonide (STTA) (20mg/0.5ml) to both eyes. Recurrence of ocular inflammation occurred once in the right eye and twice in the left eye over the next 1.5 years. The recurrences were successfully treated with STTA, and the patient's BCVA was 30/20 OU at the latest visit (Fig. 4).

3. Discussion

Uveitis is one of the most common ocular irAEs, and there are several case reports of anterior, posterior, and panuveitis associated with pembrolizumab therapy.[8] However, to the best of our knowledge, only 2 cases of pembrolizumab-associated retinal vasculitis have been reported, both of which occurred during treatment of metastatic melanoma.[9,10] With our case, we convey that retinal vasculitis can occur as pembrolizumab irAE in patients with metastatic lung cancer.

FA and ICGA showed the features of retinal vasculitis: being non-occlusive, involving the entire retina, and affecting both arteries and veins. Multiple scattered hyperreflective spots observed on OCT might reflect focal ischemia secondary to retinal vasculitis as seen in paracentral acute middle maculopathy[11] or cellular infiltration resulting from inflammation[12] as the findings disappeared after treatment. Potential etiology based on arteriole- or venule-predominance of retinal vasculitis was classified by Rosenbaum JT and associates.[13] In the classification, diseases which can cause both retinal arteritis and phlebitis are relapsing polychondritis, granulomatosis with polyangiitis (GPA), Crohn's disease/ulcerative colitis, frosted branch angiitis, and tuberculosis. Our case did not fulfill the diagnostic criteria for any of these diseases, but the immune responses occurred in these disorders could help understand the pathogenesis of retinal vasculitis in our case. Regarding the mechanism by which retinal vasculitis occurred in this case, we can only hypothesize that some retinal vascular components or surrounding retinal tissues were recognized as self-antigens by immune cells in the condition that T cell mediated immune response was augmented by immune checkpoint inhibitor.

The irAE was managed effectively according to CTCAE v5.0:

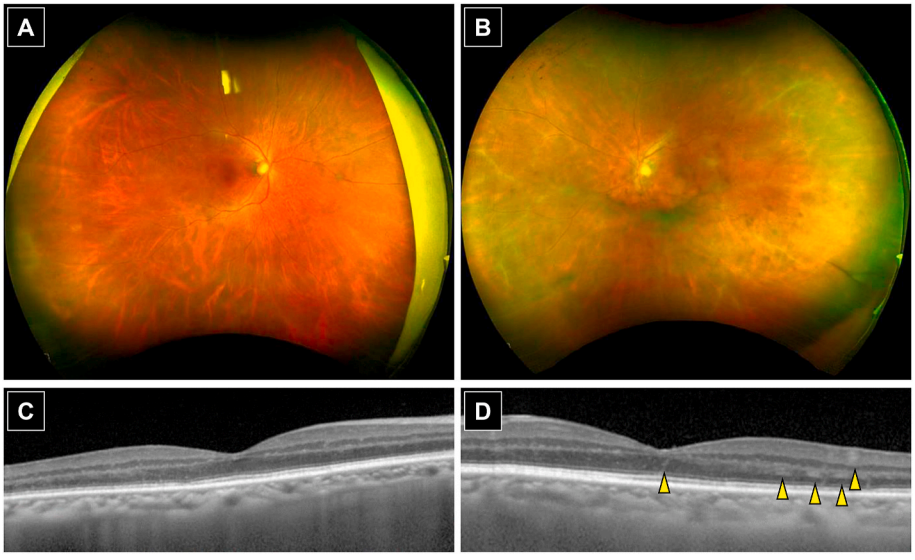

Fig. 1. Color fundus photography and spectral domain optical coherence tomography (SD-OCT) at presentation. Color fundus photography shows no abnormalities in the right eye (A) and vitreous haze, perivascular exudates, and vessel sheathing in the left eye (B). SD-OCT demonstrates no remarkable changes in the right eye (C) and multiple scattered hyperreflective spots in the neural retina in the left eye (arrowheads) (D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

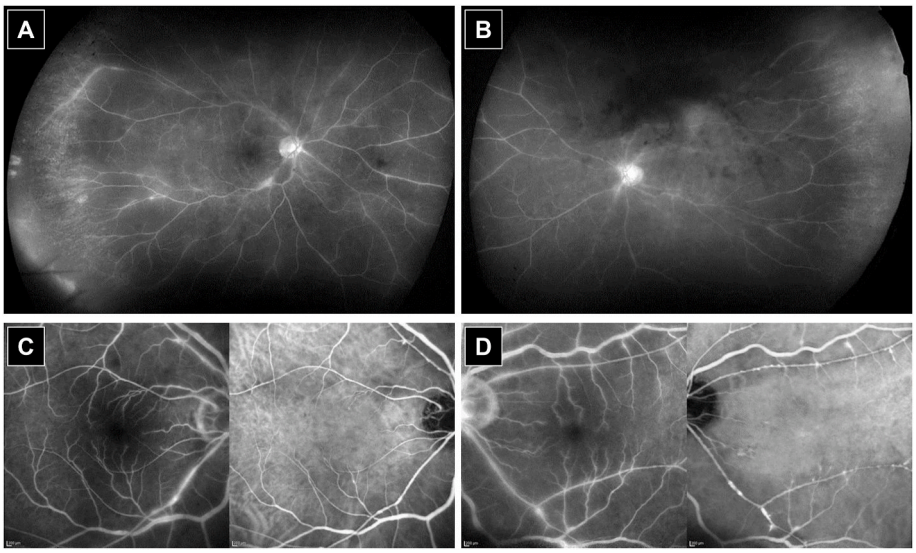

Fig. 2. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) at presentation. FA reveals dye leakage from the optic disc and both retinal arteries and veins extending from the posterior to the peripheral retina in both eyes (A, B, and the left panels of C and D). ICGA showed multifocal dye staining in retinal arteries on late-phase image (the right panels of C and D).

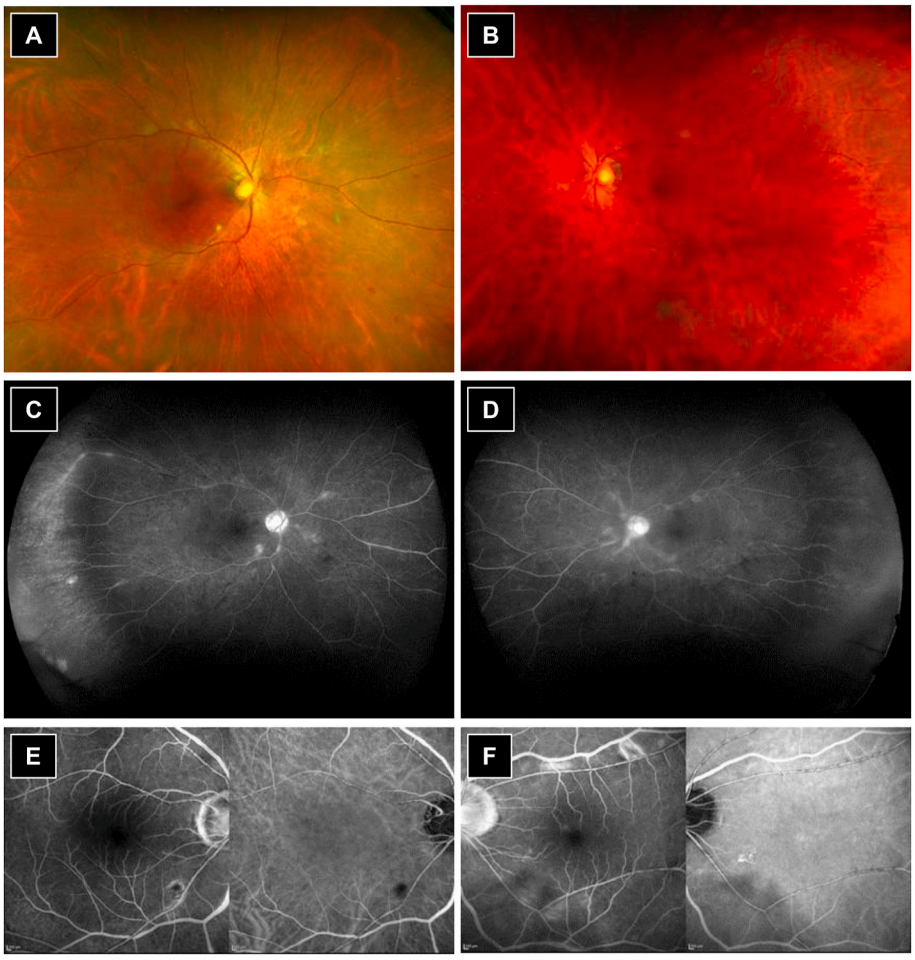

Fig. 3. Color fundus photography, fluorescein angiography (FA), and indocyanine green angiography (ICGA) 1 month after pembrolizumab discontinuation and oral corticosteroid therapy. Color fundus photography shows multiple blot hemorrhages, soft exudates, and vessel sheathing in the right eye (A) and faint vitreous haze, mild perivascular exudates, and vessel sheathing in the left eye (B). FA exhibits only mild dye leakage from the optic disc and retinal vessels in both eyes (C, D, and the left panels of E and F), and ICGA demonstrates faint dye staining in retinal arteries (the right panels of E and F). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

pembrolizumab was discontinued and corticosteroid was administrated. We are unable to explain the reason for the transient deterioration of retinal findings in the right eye, but intraocular inflammation gradually subsided in both eyes. Although the guideline says "immune checkpoint inhibitors therapy should be permanently discontinued for Grade 3–4 irAE",[7] we obtained the patient's consent and restarted pembrolizumab therapy for the treatment of metastatic lung cancer. Recurrences of ocular inflammation occurred as expected, but timely periocular

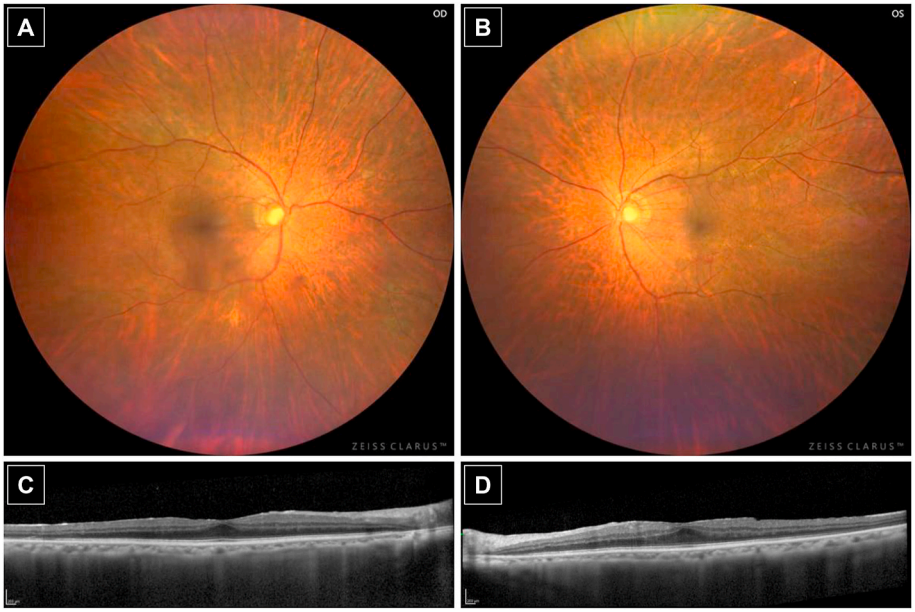

Fig. 4. Color fundus photography and spectral domain optical coherence tomography (SD-OCT) 18 months after initial presentation. Color fundus photography demonstrates several soft exudates in both eyes (A, B), a small vitreous opacity in the right eye (A), and mild vessel sheathing in the left eye (B). No distinct abnormality is displayed on SD-OCT images in both eyes (C, D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

corticosteroid injection ameliorated the inflammation, and the patient maintained a good vision. Manusow JS and associates successfully treated pembrolizumab-associated retinal vasculitis with pars plana vitrectomy. They discussed that removal of metastatic melanoma in the vitreous might alleviate retinal vasculitis.[9] Aaberg MT and Aaberg TM Jr. effectively managed pembrolizumab-associated retinal vasculitis with a repeated intraocular dexamethasone implantation. Both cases did not need pembrolizumab discontinuation or systemic corticosteroid administration.[10] The consequences of these 3 cases imply that continuing pembrolizumab with the aid of local corticosteroid therapy is a promising treatment option for retinal vasculitis associated with pembrolizumab.

Although this is a case of retinal vasculitis which occurred as an irAE during pembrolizumab therapy, it is unclear whether it was induced by pembrolizumab therapy or not. Unfortunately, no clinical information on eye conditions before pembrolizumab therapy was available as the patient had been first referred to an ophthalmologist 2 weeks after the initiation of pembrolizumab therapy. However, systemic work-up revealed no remarkable findings suggestive of systemic disorders which may cause uveitis. In addition, there were no obvious signs of previous ocular inflammation such as posterior synechiae, chorioretinal scars, or disorganized retinal layers on OCT. Therefore, we suppose that pembrolizumab is responsible for retinal vasculitis in this case.

4. Conclusions

We have reported here the first case of retinal vasculitis occurred as an irAE of pembrolizumab in a patient with metastatic lung cancer. Retinal vasculitis affected both arteries and veins and subsided with transient pembrolizumab discontinuation and one-month administration of oral corticosteroid. Then, pembrolizumab was restarted with the help of local corticosteroid therapy. As the benefit of continued immune checkpoint inhibitor therapy might outweigh the risk of visual loss caused by ocular irAEs, the management of ocular irAEs should be determined on a case-by-case basis.

Patient consent

Consent to publish the case report was obtained. Moreover, this report does not contain any personal information that could lead to the identification of the patient. This study complied with the tenets of the Declaration of Helsinki. Approval by the IRB was exempted as this is a single case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

None of the authors have financial disclosures or conflicts of interest relating to this topic.

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