American Journal of Ophthalmology Case Reports 27 (2022) 101631

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Delayed onset anterior uveitis and macular edema after cessation of pembrolizumab

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ARTICLE INFO

Keywords:
Uveitis
Immune checkpoint inhibitor
Macular edema
Anterior uveitis
Oncology

ABSTRACT

Purpose: To report a case of macular edema and anterior uveitis that developed 5 months after discontinuation of pembrolizumab, an immune checkpoint inhibitor.

Observations: A 67-year-old man with a history of metastatic clear cell renal cell carcinoma was referred for evaluation of bilateral macular edema and anterior uveitis, potentially attributed to his recently initiated belzutifan and lenvatinib chemotherapy regimen. Upon further review, he had previously been on pembrolizumab and axitinib for 20 months but had stopped five months prior due to cancer progression. Symptoms resolved on difluprednate 0.05% drops, and he restarted his belzutifan and lenvatinib treatment with no recurrence of uveitis.

Conclusion and Importance: Ocular immune-related adverse events secondary to immune checkpoint inhibitor therapy can occur months after stopping the medication. It is important for clinicians to recognize the delayed immune-related effects of immune checkpoint inhibitors.

1. Introduction

Immune checkpoint inhibitors (ICPIs) are known to cause several types of ocular immune-related adverse effects (irAEs), including uveitis.[1] We present a case of anterior uveitis and macular edema presenting 5 months after discontinuation of pembrolizumab (a PD-1 inhibitor) after having been on the regimen for 20 months. Although uveitis associated with ICPI is a well-known occurrence, our case is an important example demonstrating the phenomenon termed delayed immune-related events, or DIRE, which has not been previously well-described in cases of uveitis.[2]

2. Case report

A 67-year-old male was referred for evaluation of new-onset bilateral macular edema. He was diagnosed with metastatic clear cell renal cell carcinoma (RCC) two and a half years ago when a T8 mass was discovered, causing mid-back pain and right abdominal numbness. Diagnosis was confirmed after biopsy of T6-T8 surgical resection. At the time, he also had metastases to the lung, mediastinum, spine, and pelvis. He was started on pembrolizumab, axitinib, and one month of external beam radiation therapy to the spine, but briefly suspended treatment after 9 months due to development of colitis. After resolution of the diarrhea, he restarted pembrolizumab and axitinib, continuing the regimen for 20 total months until it was stopped due to cancer progression. Three months later, he started belzutifan and lenvatinib, which was discontinued after two months due to onset of his ocular symptoms characterized by worsening blurry vision and mild photosensitivity.

Five days prior to presentation, he had been started on prednisolone acetate 1% four times a day in both eyes by his referring ophthalmologist. On exam, his visual acuity was 20/50 in both eyes. Slit lamp examination demonstrated 1+ anterior chamber cell in both eyes without any keratic precipitates or posterior synechiae. Dilated funduscopic examination was unremarkable without any vitreous inflammation or chorioretinal lesions. Optical coherence tomography (OCT) revealed bilateral cystoid macular edema (Fig. 1A and B) with intraretinal and subretinal fluid. Fluorescein angiography demonstrated angiographic evidence of macular edema without vasculitis in both eyes (Fig. 1C and D).

Given the presence of inflammation at presentation while on prednisolone acetate 1%, he was switched to difluprednate 0.05% four times a day in both eyes. Additionally, he underwent a uveitis workup

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https://doi.org/10.1016/j.ajoc.2022.101631
Received 24 May 2022; Received in revised form 17 June 2022; Accepted 21 June 2022
Available online 23 June 2022

including Treponema pallidum particle agglutination (TP-PA), rapid plasma reagin (RPR), QuantiFERON, and chest x-ray which were unremarkable. After two weeks of treatment with difluprednate 0.05%, his visual acuity improved to 20/25 right eye and 20/20 left eye, with resolution of anterior chamber cells and improvement of his symptoms and macular edema. Given his improvement on topical steroids, he was restarted on belzutifan and lenvatinib. After another two weeks while tapering difluprednate 0.05%, his macular edema had fully resolved in both eyes. Two and a half months after his initial presentation, his visual acuity was 20/20 in both eyes and he had tapered off of difluprednate 0.05%, and his OCT showed no recurrence of his macular edema (Fig. 1E and F). He remained on belzutifan and lenvatinib course with no recurrence of his symptoms or ocular inflammation at 6 months after tapering off difluprednate.

3. Discussion

Adverse effects resulting from ICPI therapy are well-documented, but DIRE in the form of uveitis are not well-described. Our case emphasizes the importance of recognizing the potential of DIRE in any patient that previously received treatment with ICPI. ICPIs inhibit down-regulators of immunity which in turn increase antitumor activity of T cells. The resulting inflammatory side effects have been termed irAEs, which can involve excessive immune reactions against any organ or system.[3] As an example, ICPIs are known to cause oral mucositis and xerostomia similar to other types of chemotherapy and radiation therapies.[1] Our patient did experience oral sores while he was on pembrolizumab.

With regards to uveitis, both CTLA-4 inhibitors and PD-1 inhibitors are associated with ocular adverse events.[4] One study shows up to 1% of patients on CTLA-4 and PD-1 inhibitors reporting ocular irAEs, with the

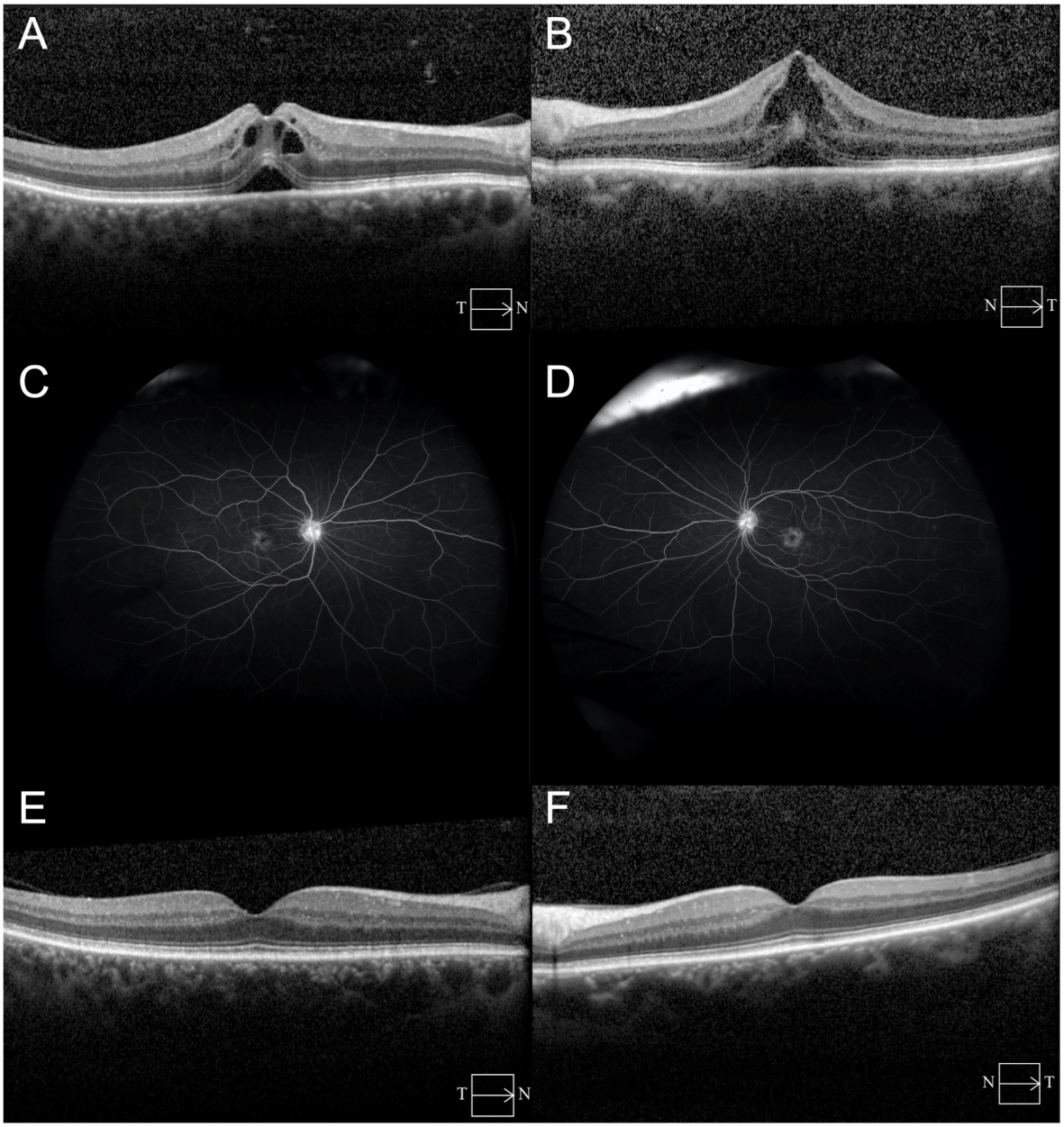

Fig. 1. Imaging at initial presentation. Optical coherence tomography demonstrating cystoid macular edema with intraretinal and subretinal fluid in right eye (A) and left eye (B). Fluorescein angiogram with leakage in the macula consistent with angiographic evidence of macular edema, but otherwise there is no evidence of vasculitis in right eye (C) and left (D). Macular edema fully resolved two and a half months after presentation, completely tapered off difluprednate in right eye (E) and left eye (F).

most common being uveitis and dry eye.[5] Within uveitis as an ocular irAE from ICPIs, anterior uveitis is the most common type.[6] A review of ICPI-associated uveitis showed a mean interval between PD-1 inhibitor initiation and uveitis diagnosis of 161.2 days.[7]

In contrast to these reports of irAE onset during ICPI treatment, delayed immune-related events, or DIRE, have been defined as new irAEs occurring at least 90 days after termination of the immunotherapy.[2] A compilation of DIRE cases found the median time between ICPI discontinuation and irAE onset to be 6 months, with a maximum of 28 months. As examples of particularly long delays, one patient presented with immune-related colitis 23 months after stopping pembrolizumab treatment, and another developed neurosarcoidosis two years after the last ICPI dose. In both these cases, early diagnosis and treatment were significantly hampered because effects from the ICPIs were not initially considered.[2]

Specifically regarding PD-1 inhibitors, one case describes onset of autoimmune hepatitis as an irAE 8 months after PD-1 inhibitor discontinuation.[8] Another patient experienced new onset type 1 diabetes mellitus and diabetic ketoacidosis 4 months after PD-1 inhibitor discontinuation.[9] One study of patients with melanoma on PD-1 inhibitors found the incidence of irAEs across all organ systems that onset over 3 months after ICPI cessation was 14%. Additionally, authors found no significant difference in the severity of the irAE depending on whether the patient was still on the PD-1 inhibitor or not.[10] There was a reported case of uveitis occurring 157 days after the cycle completion of ICPI therapy as part of a Phase 1 clinical trial, which was attributed to tremelimumab, but no clinical details were provided.[11] This is a similar period of time that elapsed from our patient's last pembrolizumab infusion to onset of his visual symptoms. There was another reported case of a patient with melanoma in remission after 8 cycles of pembrolizumab, who developed bilateral anterior uveitis 120 days after the last cycle, but few clinical details are available. Of note, this patient was also diagnosed with sarcoidosis during the pembrolizumab course.[12]

While few cases of uveitis onset after ICPI discontinuation have been published, the chronicity of irAEs secondary to ICPI therapy and theoretically very long-lasting ICPI effects have been better described. Although a benefit in terms of treating cancer, ICPIs are known to have long-lasting, sometimes indefinite antitumor activity. Preliminary studies show that patients on ICPIs have a broadened T-cell repertoire, and heightened dominance of memory T cells. Because the therapeutic effects of ICPIs often last after discontinuation, irAEs can also be triggered on a delayed basis.[13]

At the onset of his ocular symptoms, our patient was taking belzutifan and lenvatinib as part of a clinical trial. Belzutifan is a HIF-2α inhibitor used as a monotherapy for renal cell carcinoma (RCC), and may lead to side effects associated with hypoxia-induced pathway inhibition.[14] Lenvatinib is a multikinase inhibitor (MKI) for RCC, and its mechanism of action is by inhibiting tumor growth and angiogenesis; it may induce hypertension by blocking VEGFR-2.[15] To the best of our knowledge, neither medications' mechanism of action is related to the pathogenesis of uveitis.

In conclusion, our patient's uveitis was most likely a delayed result of his 20 months of pembrolizumab treatment. Since the onset was 5 months after stopping pembrolizumab, this falls under the criteria for DIRE. In cases such as these, it is important to be aware of the potential for delayed adverse effects even long after discontinuation of ICPIs to avoid misattributing adverse effects to other medications, preventing patients from reaping the benefits of these lifesaving therapies. To minimize this, ophthalmologists should routinely inquire about previously discontinued medication regimens, in addition to current ones.

4. Patient consent

Consent to publish this case report has been obtained from the patient.

5. Acknowledgements and disclosures

This work was supported by an Unrestricted Grant from Research to Prevent Blindness to the UCLA Department of Ophthalmology.

6. Authorship

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

Declaration of competing interest

ET: Cylite Pty Ltd, Kowa Company Ltd, EyePoint Pharmaceuticals.
MM: No conflicts.

Acknowledgments

None.

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