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Posterior-scleritis: Case report of an uncommon immune-related adverse event in the treatment of advanced endometrial cancer

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ABSTRACT

As Immune checkpoint inhibitors are being expanded for use in gynecologic malignancies, rare immune-related adverse events are more frequently being reported. Here we describe a 63-year-old with Stage IIIB mismatch repair deficient uterine adenocarcinoma who underwent six cycles of carboplatin and paclitaxel with partial response but persistent disease. She was then started on single agent pembrolizumab. After six cycles of pembrolizumab, she developed bilateral vision changes and was diagnosed with posterior scleritis. Pembrolizumab was held and she was treated with oral prednisone, with rapid resolution of symptoms. One month after completion of prednisone, vision changes were again reported and she was restarted on a longer oral prednisone course. She then underwent definitive surgical management consisting of a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, with final pathology of benign endometrial hyperplasia. She has completed her steroid course without any symptoms. Given her complete pathologic response, she was subsequently placed into surveillance and is currently without evidence of disease. Prompt recognition and treatment of this rare immune-related adverse event led to the prevention of potential permanent, debilitating outcomes.

1. Introduction

Since it was first approved for advanced melanoma in September 2014, the role for pembrolizumab has expanded use for multiple cancers, including gynecologic malignancies. In March 2022, pembrolizumab was approved as a single-agent line of immunotherapy for microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) endometrial cancer, following disease progression from primary systemic therapy. (O'Malley et al., 2022) Tumors that are dMMR accumulate high mutation rates and subsequently develop mechanisms to avoid the innate immune system. One of these mechanisms is through the expression of the programmed death-ligand (PD-L1), which inactivates T-cells when it meets the PD-1 receptor on T- cells. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor preventing its interaction with the PD-L1 ligand on tumor cells, and subsequently preventing the innate immune system from being inactivated. (Cho et al., 2021; Cao et al., 2021; Mechanism of Action, 2023) As such, common treatment limiting toxicities of immunotherapy with pembrolizumab are immune-mediated adverse reactions. However, due to the nature of the mechanism of action, immune-mediated reactions can impact any organ system and can occur at any time after starting or discontinuing treatment. The most common immune mediated toxicities include thyroiditis (with subsequent hyper- and hypo-thyroid states), pneumonitis, colitis, and dermatologic reactions. (Severe and Fatal Immune-Mediated Adverse Reactions, 2023) Here, we describe a case of immune-mediated posterior scleritis after initiation of pembrolizumab in the setting of MSI-H/dMMR endometrial cancer following primary chemotherapy.

2. Case report

A 63-year-old with a history of hypertension, type II diabetes mellitus, hyperlipidemia, and class III obesity was diagnosed with clinical FIGO Stage IIIB uterine adenocarcinoma in April 2022. At the time of diagnosis, her pelvic exam was remarkable for an irregular cervical mass and cervical biopsies demonstrated a moderately differentiated

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adenocarcinoma, with endometrioid features. Immunohistochemistry was ER, PR positive, with tumor loss of nuclear expression of MLH1 and PMS2, with retained expression of MSH2 and MSH6. Methylation of MLH1 promoter region was detected in the tumor. She was referred to our gynecology oncology practice in May 2022 and bimanual exam revealed a mobile normal-sized uterus, with nodularity palpated on the left rectovaginal septum and visible tumor replacing 50 % of cervix. A CT of the chest, abdomen, and pelvis confirmed no evidence of intra-thoracic metastatic disease or intra-abdominal disease. MRI pelvis showed a 4x4 cm mass involving the uterine cervix and extending to the upper vaginal canal with focal involvement of the posterior vaginal wall at the posterior fornix without associated parametrial invasion. PET CT confirmed the above findings and demonstrated no suspicious metabolic activity or enlarged retroperitoneal, pelvic, or inguinal lymph nodes. Given the locally advanced disease and risk of occult distant metastases, she underwent neoadjuvant chemotherapy with three cycles of carboplatin/paclitaxel with a demonstrated partial response followed by three additional cycles. A subsequent PET CT again demonstrated a partial radiologic response with no abnormal hypermetabolic activity in the cervix or uterus and no metastatic disease. MRI at this time showed that the previously measured 4 cm mass was now 2.4 cm, which was consistent with her physical exam showing reduced cervical tumor size, but with continued nodularity along the left rectovaginal septum. Given her persistent disease burden and MSI status, the decision was then made to proceed with immunotherapy with pembrolizumab monotherapy. She received four cycles (12 weeks) without any adverse effects. A follow up MRI showed a stable residual treated cervical mass with no evidence of parametrial involvement and no evidence of metastatic disease in the pelvis. Therefore, she was dispositioned to an additional 12 weeks of immunotherapy. One week after receiving cycle six, she reported having blurred vision bilaterally, causing her inability to operate her motor vehicle. She saw an ophthalmologist who subsequently referred her to a retina specialist due to concern for an immune related toxicity. Her retinal exam revealed significant bilateral thickening of the posterior sclera with resulting choroidal folds and retinal distortion, consistent with immune-mediated posterior scleritis (Figs. 1, 2). Decision was then made to discontinue the pembrolizumab at this point, receiving six of the eight planned cycles. She was started on an oral prednisone course as follows: 40 mg for three days, 20 mg for three days, 10 mg for three days, 5 mg for 7 days and then discontinued. An

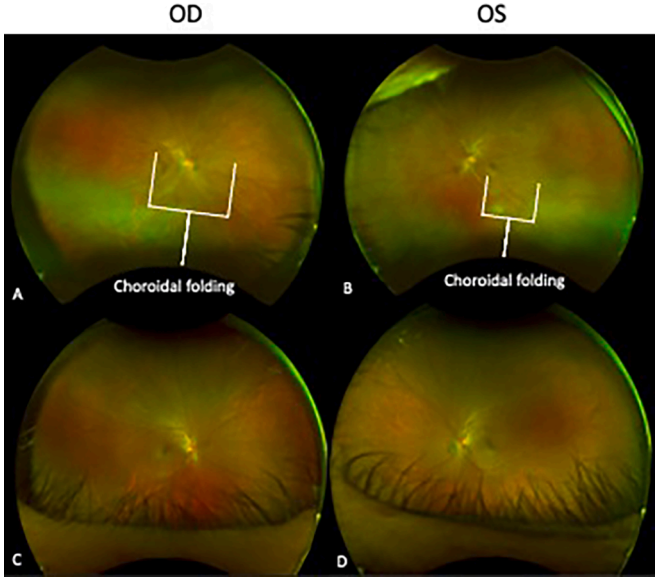

Fig. 1. Color Fundus photograph. A and B show choroidal thickening in the right and left eye respectively on initial presentation. C and D show significant improvement two weeks later following steriod initiation.

MRI of the brain confirmed no enhancing intracranial metastasis and follow-up with the retina specialist two weeks after the start of steroids confirmed that the posterior scleritis was improving on exam (Figs. 1, 2). Her pelvic examination at this time was only significant for a small polypoid lesion at the external os with a biopsy of the lesion identifying only fragments of endocervical polyp with squamous metaplasia and no residual malignancy. Similarly, a PET CT was negative and pelvic MRI confirmed stable appearance of the hyperintense heterogeneous lesion on the cervix, significantly decreased compared to initial pelvic MRI one year prior. One month after completing the steroid course, the patient presented again with blurry vision and scleral thickening, more significant in her left eye, consistent with a relapse (Figs. 3, 4). The steroid course was then restarted at 40 mg daily and then reduced to 20 mg when her vision improved seven days later (Figs. 3, 4). Her steroid course was continued at 20 mg daily for an additional 21 days. During this time, she underwent surgical resection consisting of a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with final pathology demonstrating only a foci of residual atypical and non-atypical endometrial hyperplasia, an endometrial polyp, uterine leiomyomas, and Nabothian cysts of the cervix. Given her complete pathologic response, she was subsequently placed into surveillance. Due to the short interval of the scleritis relapse, she was put on a longer tapered prednisone course, starting with 10 mg daily for two weeks postop, 5 mg daily for three weeks, 2.5 mg daily for four weeks, 1 mg daily for 4 weeks, and then discontinued. She is currently without evidence of disease 14 months after her initial diagnosis and two months after surgery.

3. Discussion

Here, we presented a rare case of posterior scleritis following the administration of pembrolizumab for MSI-H/dMMR endometrial cancer in a patient who had persistent disease after systemic chemotherapy. Ocular immune-mediated adverse reactions are found in less than 1 % of patients who received pembrolizumab for advanced MSI-H/dMMR cancers. (Reactions and Advanced, 2023) Though rare, it has been reported more frequently in patients treated with anti-PD1 agents for metastatic melanoma, with anterior uveitis being the most common. (Chaudot et al., 2022) Compared to anterior scleritis, posterior scleritis has a higher risk for severe vision impairment if not treated in a timely manner. (Lee et al., 2022) Most commonly, posterior scleritis manifests in a unilateral fashion and is remarkably painful. Common etiologies are infectious, idiopathic or rheumatologic. This case was unusual in that the thickening of the sclera/choroid was painless, bilateral, and widespread. This, along with the temporal presentation of her symptoms within four months of treatment, suggests that it was likely induced by the immune checkpoint inhibitor.

As immune-checkpoint inhibitors are becoming more frequently used for a broad spectrum of malignancies, the American Society of Clinical Oncology (ASCO) published a statement in 2021 on how to manage the most common immune-related adverse events (irAE). Immunotherapy is typically continued for grade 1 toxicities with close monitoring, suspended for grade 2 toxicities with consideration for restarting once symptoms revert to grade 1, suspended for grade 3 toxicities with initiation of high-dose corticosteroids that should be tapered over 4–6 weeks, and then permanently discontinued for grade 4 toxicities. (Schneider et al., 2021) While posterior scleritis is not specifically included in the ASCO schema for irAE, it is reasonable to consider it in keeping with the grading of uveitis and iritis, which, in this case, would be considered a grade 3 toxicity, especially given the involvement of the choroidal folds. (Schneider et al., 2021).

There have been multiple case reports that discuss uveitis as an irAE of pembrolizumab, but only one specifically addressed nodular posterior scleritis. The patient was being treated with pembrolizumab for an ependyoma for two months prior to her development of nodular posterior scleritis. The agent was discontinued, and dexamethasone 8 mg

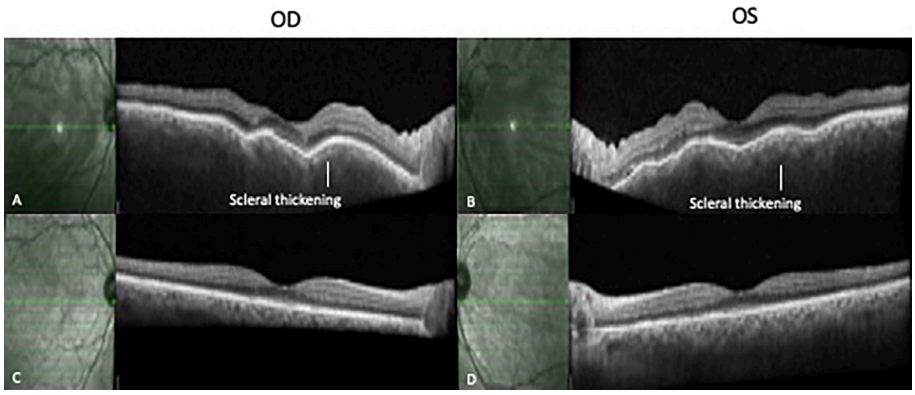

Fig. 2. Optical Coherence Tomography. A and B show scleral thickening in the right and left eye respectively, on initial presentation. C and D show significant improvement two weeks later following steriod initiation.

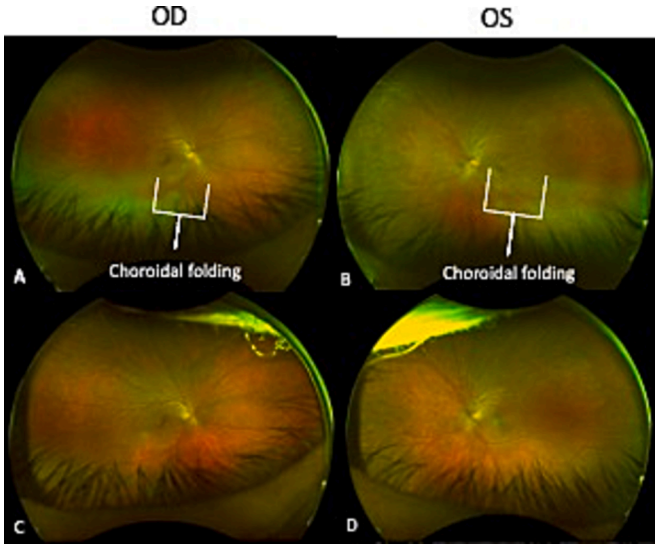

Fig. 3. Color Fundus photograph. A and B show relapsed choroidal thickening in the right and left eye respectively, one month following one month following steroid cessation. C and D show recovery after steroids reinitiated.

twice daily was administered. Improvement was seen two days later, then complete resolution 14 days after discontinuation. Dexamethasone was then tapered over 3 weeks. (Mcnelly et al., 2023) In our case, discontinuation of pembrolizumab and initiation of systemic corticosteroids led to quick improvement in physical findings. She was then tapered off steroids over the course of two weeks. One month after the completion of her steroids, she noticed blurry vision again and was started on prednisone 40 mg daily and then transitioned to 20 mg once symptoms improved seven days later. This was followed by a longer tapered course.

Most irAEs occur within the first six months of initiating PD-1 antibody therapy. (Martins et al., 2019) With symptoms seen at almost four months after initiation of therapy, there were no clear inciting events. While risk factors for immune related toxicities are known, there are no strict contraindications to initiating the immunotherapy. The patient did not have a history of any of the known risk factors for irAEs such as connective tissue or autoimmune diseases, vasculitis, combination immunotherapy regimens, or intrinsic tumor factors. (Martins et al., 2019).

As with chemotherapy monitoring, surveillance strategies have been proposed which include general pre-treatment labs and antibody testing in suspected irAEs.(Martins et al., 2019) Given that irAEs often quickly resolve upon cessation of the immune checkpoint inhibitor, and that timing of onset is unpredictable, it is debatable whether these tests are necessary and informative for treatment. More data is needed to develop a standardized, cost-effective monitoring system. In the interim, empowering our patients to take ownership in recognizing known irAEs can ensure that they receive the necessary treatment in a timely manner to avoid any permanent deficits.

4. Conclusion

Pembrolizumab and other anti-PD1/PDL1 immune checkpoint inhibitors are increasingly being used as a therapeutic option as both a

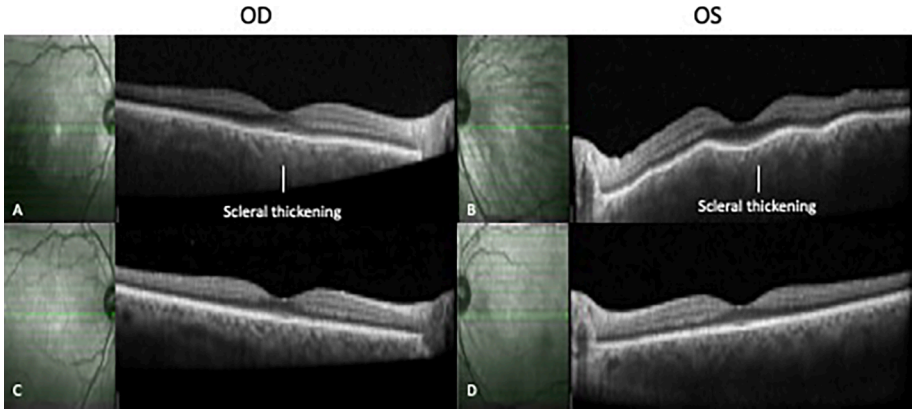

Fig. 4. Optical Coherence Tomography. A and B show relapsed scleral thickening in the right and left eye respectively, one month following steroid cessation. C and D show recovery after steroids reinitiated.

single agent and combination therapy for advanced endometrial and other gynecologic cancers. As it is utilized more in practice, it is important to recognize and promptly address even the rarest forms of irAEs such as posterior scleritis; failure to do so could lead to permanent consequences. Having a multi-disciplinary mindset when it comes to addressing patient symptoms, as in ophthalmology in this case, will help to effectively diagnose and treat suspected irAEs. Discontinuation of pembrolizumab and quick initiation of systemic corticosteroids led to reversal of posterior scleritis. The timing of when to reinitiate pembrolizumab following an irAE is still unclear but in this case, definitive management with a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy confirmed no residual disease without any further pembrolizumab cycles. Validating patient concerns and actively responding to any suspected irAEs will ensure the best patient outcomes.

CRediT authorship contribution statement

Brandon I. Ing: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Derek Kuhl:** Resources, Investigation, Visualization, Writing – review & editing. **Deanna Glassman:** Investigation, Writing – review & editing. **Cynae A. Johnson:** Investigation, Writing – review & editing. **Shrina Patel:** Investigation, Writing – review & editing. **Amir A. Jazaeri:** Conceptualization, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Amir A. Jazaeri reports clinical trial funding from Merck to the institution. All other authors have no conflict of interests to disclose.

References

Cao, W., Ma, X., Fischer, J.V., et al., 2021. Immunotherapy in endometrial cancer: rationale, practice and perspectives. Biomark Res. 9, 49.

Chaudot, F., Seve, P., Rousseau, A., et al., 2022 Nov. Ocular Inflammation Induced by Immune Checkpoint Inhibitors. J. Clin. Med. 4993.

Cho, Y.A., Lee, H., Kim, D.G., et al., 2021 Sep 16. PD-L1 Expression is Significantly Associated with Tumor Mutation Burden and Microsatellite Instability Score. Cancers (basel). 13 (18), 4659.

Lee, D.H., Cho, H., Choi, E.Y., et al., 2022 Nov. Clinical features and long-term treatment outcome of posterior scleritis. Ann. Transl. Med. 10 (21), 1162.

Martins, F., Sofiya, L., Sykiotis, G.P., 2019 Sep. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat. Rev. Clin. Oncol. 16 (9), 563–580.

Mcnelly, C.L., Haider, A.A., Wann, R.C., 2023 Apr 10. Pembrolizumab-Induced Nodular Posterior Scleritis. Sage J. https://doi.org/10.1177/24741264231163396.

Mechanism of Action: Keytruda (pembrolizumab: PD-1 Receptor Blockade). Merck & Co, 2023. Available at https://www.keytrudahcp.com/resources/mechanism-of-action/. Accessed June 8, 2023.

O'Malley, D.M., Bariani, G.M., Cassier, P.A., et al., 2022 Mar 1. Pembrolizumab in Patients with Microsatellite Instability- High Advanced Endometrial Cancer: Results from KeyNote-158 Study. J. Clin. Oncol. 40 (7), 752–761.

Selected Adverse Reactions. Advanced MSI-H/dMMR Cancers. Merck & Co, 2023. Available at https://www.keytrudahcp.com/safety/adverse-reactions/msi-h-dmmr/. Accessed on June 8, 2023.

Schneider, B.J., Naidoo, J., Santomasso, B.D., 2021 Dec 20. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J. Clin. Oncol. 39 (36), 4073–4126.

Severe and Fatal Immune-Mediated Adverse Reactions. Merck & Co, 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s110lbl.pdf. Accessed on June 8, 2023.