Bilateral anterior uveitis after immunotherapy for malignant melanoma

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Abstract:
Immune checkpoint blockade therapy is relatively a new treatment for cancer which has shown promising results. However, immune-related side effects including uveitis have occasionally been reported during this therapy. Herein, we report the case of a 65-year-old male who suffered bilateral anterior uveitis after immune checkpoint blockade therapy with pembrolizumab and ipilimumab for malignant melanoma. His symptoms and signs improved after topical treatment with corticosteroids. Clinicians should be aware that uveitis can be an immune-related adverse event of immunotherapy.

Keywords:
Immune checkpoint blockade, ipilimumab, pembrolizumab, uveitis

Introduction
Uveitis is a sight-threatening disease which is defined as intraocular inflammation involving the iris, ciliary body, or choroid. More than 30 etiologies have been reported to cause uveitis,¹ and treatment and outcomes are mainly associated with its etiology and clinical course. Although uncommon, various local and systemic medications including antimicrobial drugs, bisphosphonates, vaccines, and antiglaucomatous drugs can cause uveitis.²

Immune checkpoint blockade therapy was developed and approved by the Food and Drug Administration in the United States to treat cancer in 2011. It enhances human autoimmune reactions against cancer cells by blocking checkpoint signals, which are the inhibitory signals of T-cell-mediated adaptive immunity.³⁴ However, inhibition of these pathways may result in persistent T-cell activation, increased cytokine production, and enhanced T-cell-mediated immune responses.⁵⁶ Various immune-related adverse events have been reported, including those affecting the skin, gastrointestinal tract, kidneys, central nervous system, liver, pancreas, and endocrine system. The severity of these events ranges from minor symptoms to life-threatening complications.⁷⁻¹⁰ In addition, ocular side effects including dry eyes and noninfectious uveitis have also been reported.⁷¹³¹²

Herein, we present a patient with skin and brain melanoma who developed bilateral anterior uveitis accompanied with systemic signs after immunotherapy.

Case Report
A 65-year-old male presented with acute blurring, redness, and discomfort in both eyes for 3 days. His visual acuity was 6/10 in the right eye and 6/8.6 in the left eye. The intraocular pressure was 7 mmHg in the right eye and 8 mmHg in the left eye. A slit-lamp examination showed bilateral anterior uveitis with congested conjunctiva, corneal edema, multiple
whitish keratic precipitates, 2+ inflammatory cells, 1+ of flare, and focal iris posterior synechia in both eyes [Figure 1a]. Mild cataract was also observed. No vitreous cells, haze, or focal chorioretinal lesions were noted in either eye. Optical coherence tomography revealed normal macula contours and normal ellipsoid zones.

Tracing back the patient’s history, he had been diagnosed with skin malignant melanoma and received surgical treatment in 2012. Unfortunately, brain and lung metastases were found 3 years after the diagnosis, and he had been receiving immune checkpoint blockade therapy with intravenous infusions of pembrolizumab (Keytruda; Merck) 100 mg in combination with ipilimumab (Yervoy; Bristol-Myers Squibb) 50 mg since then. This episode of blurred vision occurred 2 weeks after the third infusion of immunotherapy. At the presentation of uveitis, he reported a skin rash and an itching sensation. Systemic workup revealed mild anemia (hemoglobin: 9.9 g/dL), impaired renal function (serum creatinine level: 1.55 mg/dL), and a slightly elevated level of serum C-reactive protein (0.58 mg/dL). A chest radiograph showed lung metastasis without lymphadenopathy. Other blood tests including human leukocyte antigen B27 were all negative.

He was treated with a topical 1% prednisolone (Pred Forte; Allergan) every 2 h and topical 1% atropine sulfate (Antol) twice a day. In addition, 10 mg of oral prednisolone was prescribed for 3 days due to his skin reaction. After 1 month of treatment, his vision recovered to 6/6 in the right eye and 6/7.5 in the left eye. Moreover, all signs of uveitis including conjunctival congestion, edematous cornea, keratic precipitates, anterior chamber cells, and iris synechiae subsided [Figure 1b].

He subsequently received a few more courses of pembrolizumab (Keytruda; Merck) monotherapy. No signs of progression or metastasis of his malignant melanoma were noted during the following 1 year, and there was no recurrence of any uveitis. However, poliosis and vitiligo developed and progressed during follow-up [Figure 2].

**Discussion**

Immune checkpoint blockade therapy is a novel treatment for melanoma, nonsmall cell lung cancer, and renal cell carcinoma. An immune checkpoint pathway is a pathway that downregulates immune functions to maintain immune homeostasis. Two components are involved in this pathway: programmed cell death protein-1 (PD-1) and PD-1 ligand 1 (PDL-1) receptor–ligand pair, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4). Cancer cells seem to induce immune checkpoint pathways to evade immune attack. Nivolumab and pembrolizumab are antibodies that block PD-1, and ipilimumab is used to block CTLA4. These antibodies are approved for human use as cancer treatment.

Several adverse effects of immune checkpoint blockade have been reported, including uveitis. Robinson et al. reported two cases who received CTLA4 blockade therapy for metastatic melanoma and developed bilateral anterior uveitis and vitritis after treatment. They were treated with topical steroids and CTLA4 blockade therapy was discontinued, after which their uveitis resolved; however, one of the patients was found to have progression of melanoma. Abdel-Wahab et al. performed a systematic review of adverse effects associated with immune checkpoint blockade and found that uveitis was reported in 10.3% of patients who received ipilimumab and in 10% of patients who received pembrolizumab although no ophthalmologic side effects were reported in patients who received nivolumab. Once uveitis occurs, treatment includes discontinuation of the immunotherapy, topical steroids with 1% prednisolone, and an oral form in severe cases, and immunomodulatory agents such as...
Melanocytes, melanin, and pigment in the human uvea tissues and retina share many surface proteins with skin melanocytes. Since immune checkpoint blockade is typically used to treat patients with melanoma via enhancing immune reactions, it is possible that such therapy may trigger autoantibodies against normal melanocytes in uvea tissue, leading to uveitis. Both ipilimumab and pembrolizumab have been reported to cause immune-related side effects including uveitis.\(^7\) Our patient suffered from acute onset of uveitis (<3 days) 2 weeks after the third infusion of a combination of these two medications. His uveitis resolved after topical steroid treatment and discontinuation of ipilimumab. He received a few more courses of pembrolizumab alone, and no uveitis was noted even without topical steroids. Hence, we suspect that ipilimumab caused uveitis in this patient. Although no uveitis was noted after subsequent courses of pembrolizumab therapy, the occurrence of poliosis and vitiligo supports autoimmune reactions to systemic normal melanocytes.

**Conclusion**

Immune checkpoint blockade used to treat cancer patients may be a cause of uveitis. Although the severity of ocular side effects is usually minor, topical or systemic anti-inflammatory treatments including steroids, immunomodulatory agents, and biologic drugs can be used to control these immune-related side effects. Drug discontinuation should be considered if the adverse events are too severe although subsequent recurrence or metastasis of the malignancy is possible.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

The authors declare that there are no conflicts of interests of this paper.

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