Case report: Bilateral uveitis and papillitis secondary to treatment with pembrolizumab

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Pembrolizumab is a programmed cell death protein 1 (PD-1) monoclonal antibody used in the treatment of metastatic melanomas. Severe ocular complications appear in less than 1% of the patients and require early treatment. We present the case of a patient diagnosed with a BRAF mutated metastatic melanoma. Ocular pain and a blurred vision appeared after treatment and the patient visited the ophthalmology emergency room, where he was diagnosed with acute anterior uveitis (AAU), synechiae, and bilateral papillitis. The patient was treated with topical corticosteroids, prednisone, and mydriatics, which immediately improved the patient's status. Therefore, when an ocular inflammatory disease exists, immune checkpoint inhibitor treatments must be ruled out as possible causes.

Key words: CTLA-4, melanoma, papillitis, PD-1, pembrolizumab, uveitis

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Pembrolizumab is a humanized IgG4 monoclonal antibody that is selective against the PD-1 receptor on the cell surface. It is used in the treatment of unresectable metastatic melanomas. The response rate of this treatment is about 40%.[1] Although the frequency of adverse effects is high, in majority of the cases these are mild and easily treated.[2,3] These side effects are known as immune-related adverse

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events because they are caused by the lack of inhibition of T lymphocytes.

Ocular complications appear in less than 1% of the patients and are severe and require early treatment.[1]

Case Report

A 38-year-old male, Caucasian, diagnosed with a BRAF-mutant melanoma with locoregional recurrence, a satellite nodule, and adenopathies. Treatment with pembrolizumab was initiated. After 6 cycles of treatment, the patient began to experience ocular pain and blurred vision for which he visited the ophthalmology emergency room of the hospital, where he was diagnosed with AAU with synechiae and bilateral papillitis. He had a visual acuity (VA) of 20/20, Tyndall +++ in the right eye (OD) and Tyndall++++ in the left eye (OS) with multiple inferior iridocrystalline synechiae in both eyes (OU) and no hypopyon. Edema of the bilateral papilla without vitritis was observed in the fundoscopy [Fig. 1]. Treatment with dexamethasone eye drops and 40 mg of prednisone every 24 hours was initiated in the emergency room. Cyclopentolate, tropicamide, and phenylephrine eye drops were also prescribed to break the synechiae. The examination after 24 hours revealed Tyndall++ in OD and Tyndall + in OS and no synechiae were found. There was an improvement of the bilateral papillitis. The oncologist in charge of the patient and an ophthalmologist expert in uveitis considered the pembrolizumab to be the primary cause of ocular inflammation since the mechanism of action of the drug can induce ocular inflammation and there are similar cases reported in the literature. They discontinued the treatment with pembrolizumab because of grade 3 ocular toxicity and was replaced by vemurafenib and cobimetinib. A head CT scan was performed without any relevant findings.

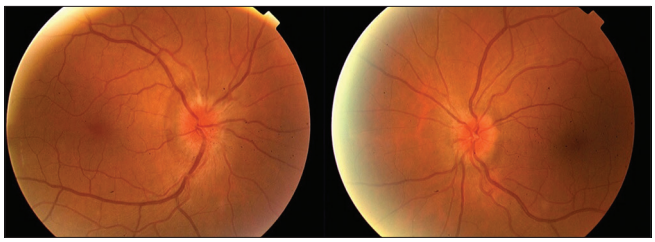

Figure 1: Bilateral papillitis

The ophthalmologists continued the topical treatment with dexamethasone eye drops every 6 hours and cyclopentolate drops every 8 hours. The oral prednisone was lowered to 30 mg/day for a week. The results of the assessment a week after the episode was Tyndall+ in OD and Tyndall+/- in OS and an improvement of disc edema. An optical coherence tomography (OCT) of the layer of the nerve fibers was performed to assess the edema [Fig. 2]. After this examination, a treatment plan was set up which consisted of reducing the topical corticoids and prednisone until their elimination. The patient was reassessed after a month, with the following outcomes 20/20 VA OU, no Tyndall or synechiae, and normal papillae [Figs. 3 and 4]. The patient continues receiving check-ups every 4 months by the ophthalmologist. Moreover, 2 years after the pembrolizumab was stopped, no similar episodes have been observed in this patient.

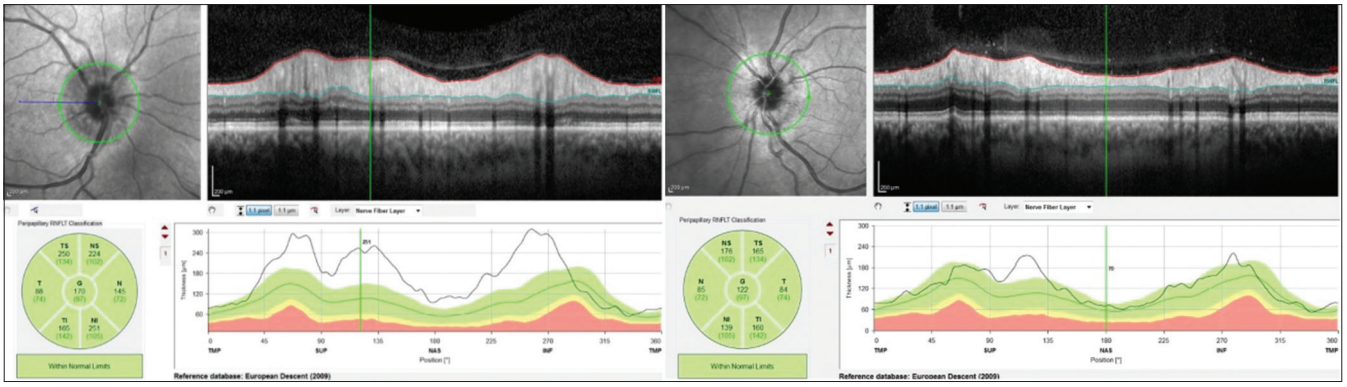

Figure 2: OCT: showing disc edema at presentation

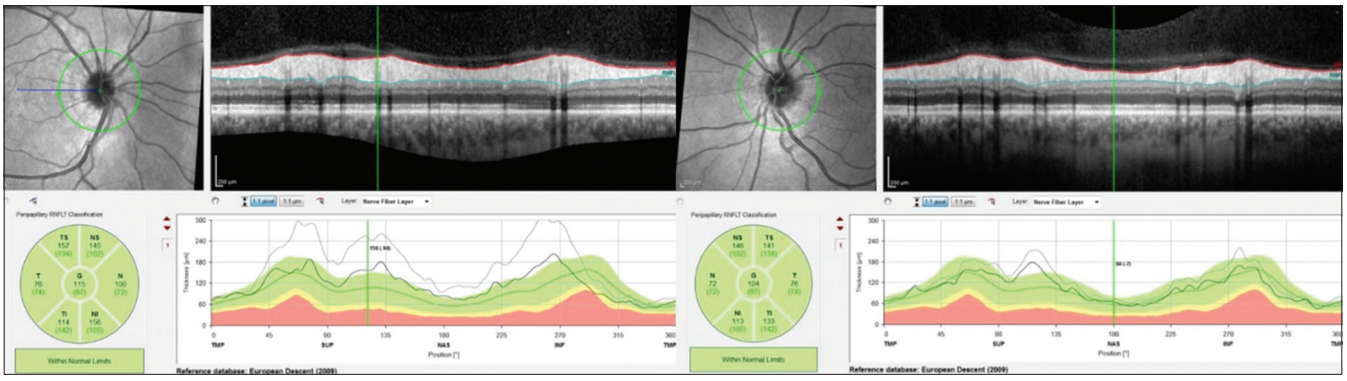

Figure 3: OCT: showing improvement in disc edema after treatment

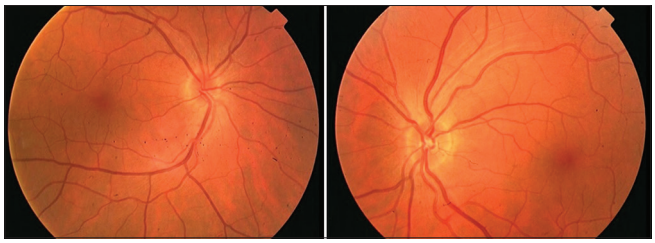

Figure 4: Resolved disc edema

Discussion

Few cases found in the literature describe the association of pembrolizumab with anterior uveitis but only one case associated it with bilateral papillitis.[4,5] In the present case report, we have included new evidence for the association of the use of pembrolizumab with the development of anterior uveitis and papillitis.

The activation of T cells is the principal immunological mechanism against cancer. To avoid activating the immune system, T cells have receptors that inhibit activation. Two of these receptors are CTLA-4 and PD-1. The metastatic cells of the melanoma are capable of expressing ligands for these receptors and hence, inhibit the activation of the immune system. Ipilimumab was the first of this family of drugs known as an immune checkpoint inhibitor, which acts by inhibiting the ligands of the CTLA-4 tumor cells and therefore T cells proliferate, invade the tumor cells, and help in the process of regression. Pembrolizumab acts in the same way but on PD-1 ligands.[6]

The mechanism that explains the development of ocular inflammation during the use of pembrolizumab is as follows: The presence of PD-1 ligand in ocular cells has been demonstrated and it is believed that the expression of these PD-1 ligands mediates in the ocular inflammation by inhibiting the proinflammatory cytokines produced by T cells. Thus, it is believed that the presence of PD-1 inhibitors can contribute to the development of ocular inflammation.[1]

In our case, the withdrawal of pembrolizumab was definitive, and treatment with systemic and topical corticoids was necessary over a period of 2 months to completely solve the problem. However, in two of the similar cases described in the literature, the treatment was not totally discontinued and intermittent treatment with pembrolizumab was maintained to try to control the progression of the melanoma and thus required treatment with intravitreal, topical, and systemic corticoids over a period of 6 months to prevent relapses.

Conclusion

With this case, we reinforce the fact that when an ocular inflammatory disease appears in oncological patients, it is important to rule out treatments known as immune checkpoint inhibitors as possible causes. Although the incidence of these complications is low at present, an increase of uveitis in oncological patients is to be expected due to an increase in the use of these drugs on different kinds of tumors.

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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