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Case Report

Nivolumab and Adverse Eye Events: A Case Report

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Keywords

- Metastatic renal cell carcinoma; Immunotherapy; Side effects; Uveitis; Retinopathy

Abstract

Background: Nivolumab is a human antibody used to treat several types of cancer, including renal cell carcinoma. We report the case of a man who developed bilateral anterior uveitis and retinal complications during treatment with nivolumab for metastatic renal cancer.

Case Presentation: 77-year-old man treated with nivulomab for metastases of the right piriform sinus (lateral wall of the right pharynx), following pT2G2 clear cell renal cell carcinoma (right nephrectomy in 1999), and left renal cell carcinoma clear cell pT1G2 (left renal tumorectomy in 2007), developed a sudden bilateral deficit in visual acuity and painless bilateral redness of the eyes several days after the third administration of nivolumab (the first two fifteen days apart and the third after twenty-eight days). The examination showed a significant decrease in visual acuity (ODV:4/10,OSV:1/10). The slit lamp revealed the presence of bilateral granulomatous keratic precipitates, bilateral anterior synechiae cells. Cortical cataracts OU (OS>OD), were already present two years earlier. Discrete hypotony was present (10 mm Hg in OU). Infrared fundusoscopy, possible only in OD, revealed light papilledema, macular edema with subretinal deposits of granular appearance in the perimacular area and a round serous retinal detachment of 1 ½ diameter of the papilla in the superior temporal paramacular area. The Optical Coherence Tomography (OCT), showed the presence in the macular area of a diffuse lamellar thickening with the appearance of a hyperreflective band at the level of the RPE and the formation of granules in the external segment of the photoreceptors, moderate subretinal subfoveal fluid. Infrared funduscopy and OCT of the OS they was scarcely available. Treatment with topical and oral corticosteroids was initiated and nivolumab was stopped. After 3 weeks the evolution was favorable with a decrease in ocular inflammation and treatment with oral corticosteroids was stopped after 4 weeks of treatment. The normalization of the OCT images and the improvement in visual acuity (ODV:5/10,OSV:2/10), were appreciated two months after the onset of the adverse event. Topical corticosteroid therapy was continued and nivolumab was restarted after two months of suspension and repetition for three cyclically every 28 days. There was no recurrence of bilateral uveitis and retinopathy.

Conclusion: Ophthalmological manifestations following nivolumab should be rapidly recognized and adequately treated with oral and topical corticosteroids. Resumption of nivolumab is possible after previous adverse events wich don,t form an absolut contraindication to restarting the use of nivolumab.

ABBREVIATIONS

irAE: immune-related adverse events; OCT: Optical Coherence Tomography; PD-1: Programmed Cell death Protein 1; PD-L1: Programmed death Ligand 1

BACKGROUND

"Immune Checkpoint Inhibitors" (ICI), have led to a new immunotherapy that stimulates our immune system to attack tumor cells. nivolumad is a human IgG4 monoclonal antibody against PD-1 (programmed cell death protein 1), receptors on T cells. PD-L1 (programmed death ligand 1), instead is produced by tumor cells. Nivolumad is directed against the PD-1 receptor by blocking PD-1/PD -L1 and so that the "T" cells are not inactivated and consequently the activation of this system of Immuno Checkpoint Inhibitors (IcIs), can at last lead to the death of tumor cells. Clinical studies have demonstrated the effectiveness of these Checkpoint Inhibitors (ICIs), in the treatment of metastatic tumors. The risk of immune-related adverse events (irAEs) affects various organs and is becoming increasingly more frequent

PRESENTATION OF THE CASE

A 76-year-old Caucasian man who had undergone a right nephrectomy for pT2 G2 clear cell renal cell carcinoma in 1999 and a left renal tumorectomy for pT1 G2 clear cell carcinoma in 2007, developed subsequent appearance of metastases to the ileal loops, to the thyroid, to the left thigh, to the right lateral cervical lymph nodes, to the left maxillary sinus, and lastly (January 2023), to the right piriform sinus (pharyngolarynx cavity). Since a surgical procedure was not indicated, burdened by considerable risks, he was subjected to a initial immunotherapy treatment with Nivolumab programmed as follows: a first cycle of three infusions (the first two spaced 15 days apart and the third 28 days after the second), with the possibility of recycling every 28 days if necessary. After the third infusion the patient complained of sudden bilateral deficit in visual acuity and painless bilateral redness of the eyes. Visual acuity examination revealed ODV:4/10,OSV:1/10 and slit lamp revealed the presence of bilateral granulomatous keratic precipitates, anterior chamber

cells+++, bilateral synechiae.The presence of cataract OU was detected two years earlier before treatment with nivolumab, and OS surgery was already scheduled. In consequence of cataract and of the anterior segment infiammation, the examination of the ocular fundus was possible on OD. Fluorangiography and the indocyanine green werent'accepted from patient. Infrared funduscopy revealed a slight macular edema, the presence of fine yellowish subretinal deposits with a granular appearance in the macular area and a bubble of serous retinal detachment of approximately 1 diameter and 1/2, located temporally and superiorly to the fovea. The papilla appears with slightly diseappeared margines.

The OCT (optical coherence tomography) (Figure 1), possible in OD but not in OS, confirmed the presence of liquid under the fovea and the presence of a small central intraretinal cyst and moreover there was a hyperreflective band between the retinal pigmented epithelium (RPE), and the external segment of the photoreceptors with granular formations. The choroid appeared, like the retina, with a wavy appearance. The examination of the peripapillary nerve fibers (OCT RNFL), revealed a certain degree of peripapillary retinal edema. Common cause of bilateral granulomatous uveitis were excluded. Topical corticosteroid eye drops with dexamethasone sodium phosphate were started three times a day and after a consultation with the oncologist, oral treatment with prednisone (1 mg/kg), was started and nivolumad was stopped. The patient was followed every week and the oral corticosteroid was progressively reduced and definitively suspended after 4 weeks in consideration of the decrease in ocular inflammation and the recovery of visual acuity (ODV=5/10, OSV=2/10). The drops were not stopped because the eye pressure was constantly low (10 mmHg). On the contrary nivolumab was suspended for 2 cycles and restarted with 3 cycles every 28 days without recurrence of IrAE. Two months after the start of oral cortisone therapy, the serous retinal detachment and the hyperreflective band disappeared and the OCT appearance was almost normal (Figure 2). At last small foci of depigmentation of the RPE appeared at the posterior pole. Six months after the onset of ocular symptoms, the ocular picture was stable, the cataract and vision were still stationary and the patient continued local therapy with corticosteroid eye drops.

DISCUSSION AND CONCLUSION

Anti-PD1 therapy selectively modulates the inflammatory response of T cells at tumor sites therefore has a localized effect mainly in the microenvironment of the tumor and a low frequency of adverse events and immune complications. These latter appeared reversible after discontinuation of nivolumab treatment and the use of systemic steroid drugs. Anti-PD1 therapy can be reintroduced with precautions of topical corticosteroid treatment with low risk of recurrence of immune adverse events. As regards these it is likely that the T cells activated by nivolumab can attack not only tumor cells but also normal ocular structures such as the uvea and RPE and that leading to a cellular immune response may compromise their functionality. Specifically, the reduced pumping function of the RPE could lead to elongation of the outer segment of the photoreceptors and to a decreased phagocytic function of the RPE cells with the formation of serous detachment of the retina and thickening of the band detectable with OCT [2]. Others cases similar to ours have already been reported [3] but, if managed correctly and observed closely, it has been possible monitor iRAEs and overcome them with oral and topical corticosteroids without interrupting nivolumab . Indeed, further research is needed on the mechanism underlying ocular adverse events following the use of ICIEs. The purpose of this report is anhoter: don't forget to performe an ocular check-up at the first symptoms and to begin a rapid and adequate management. The continuous use of topical cortisone has proven useful in preventing recurrences of ocular adverse events after resumption of nivolumab and on the other hand its use does not constitute a problem when the cataract is already present and the eye pressure is very low.

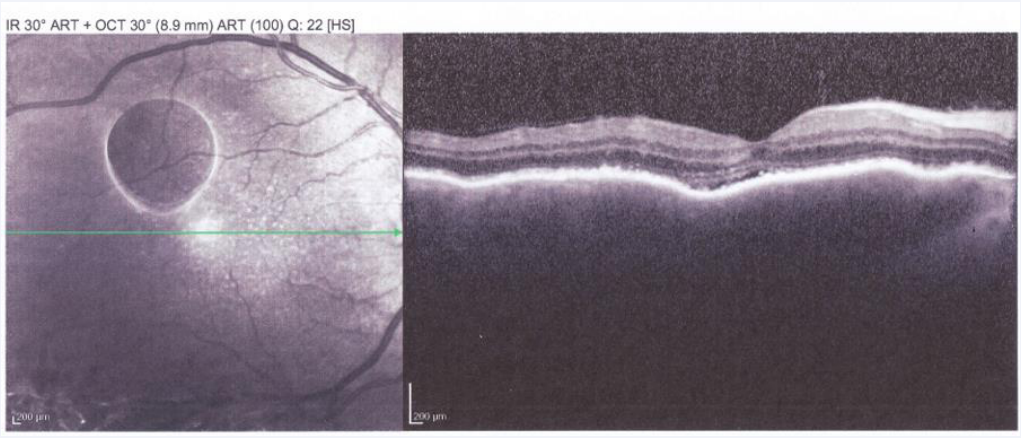

Figure 1 Optical coherence tomography: liquid under the fovea,small central intraretinal cyst,hyperreflectivw band between RPE and photoreceptor

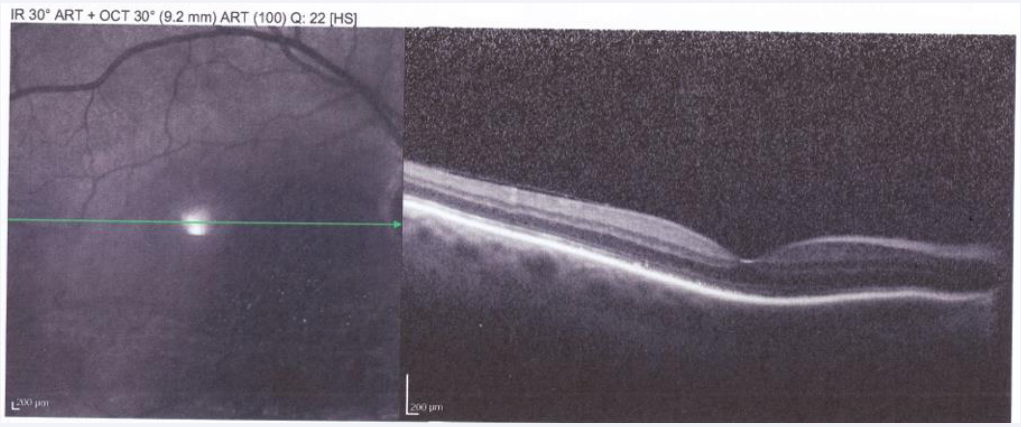

Figure 2 OCT appearance after two months from the start of oral prednisone therapy

Consent to publication

A copy of the written consent is available for review by the editor of this journal.

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