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Case report

Is it melanoma-associated retinopathy or drug toxicity? Bilateral cystoid macular edema posing a diagnostic and therapeutic dilemma

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ABSTRACT

Purpose: To report the clinical presentation, multimodal imaging, and management of a patient with metastatic melanoma who presented with cystoid macular edema (CME).

Observations: We report a case of a 71-year-old Caucasian male with metastatic melanoma who presented with bilateral cystoid macular edema after being on treatment with a programmed T cell death ligand 1 inhibitor, MPDL3280, for 1 year. Multimodal imaging techniques, including color fundus photographs, autofluorescence, spectral domain optical coherence tomography (OCT), fluorescein angiography (Spectralis, Heidelberg, Germany), and spectral-domain OCT angiography (Zeiss; California, USA) were performed to evaluate the etiology of his CME and to monitor his response to treatment. Clinical examination and multimodal imaging revealed 1 + chronic vitreous cells, an epiretinal membrane, and mild macular edema in both eyes. Fundus autofluorescence showed paravenous hypoautofluorescence in the right eye and scattered hypoautofluorescent spots in the left eye. Optical coherence tomography angiography (OCTA) revealed mild drop out of superficial vessels in the peri-foveal region bilaterally. These findings were concerning for melanoma-associated retinopathy, drug-related uveitis, or activation of a previous chronic autoimmune process. The patient was started on prednisone 30 mg oral daily and ketorolac tromethamine 0.5% 1 drop four times daily. He was then treated with bilateral sustained-release dexamethasone intravitreal implants (Ozurdex). He had complete resolution of CME, and was tapered off of oral steroids within 6 weeks.

Conclusions and Importance: Melanoma-associated retinopathy can be accompanied by CME, which presents a diagnostic and therapeutic dilemma in cases where a new drug has been recently initiated. By treating the condition locally, the ophthalmologist may be able to taper systemic immunosuppression more quickly.

1. Introduction

The use of monoclonal antibodies for the treatment of melanoma has resulted in higher survival rates but also substantial side effects and visual disturbances.[1,2] Here, we report a case of cystoid macular edema (CME) in a patient after initiation of treatment with the biological modifier MPDL3280A for which it was unclear if the CME was due to MAR or to the medication itself, resulting in a diagnostic and therapeutic dilemma.

2. Case report

A 71-year-old Caucasian male, with a history of metastatic melanoma that was in clinical remission with treatment under a clinical trial with a programmed T cell death ligand 1 (PD-L1) inhibitor MPDL3280A and vemurafenib, and with ocular history significant only for bilateral cataracts recently having undergone surgery, was referred with the complaint of increased blurry vision bilaterally. He had been on these medications for 1 year with gradual bilateral vision changes and floaters. Thirty days after cataract extraction with intraocular lens insertion in the right eye, the patient was found to have anterior chamber cells and flare in both eyes for which he was treated with oral prednisone 40mg daily, tapered over 1 week to 30mg four times daily, as well as topical prednisolone acetate 1% four times daily in the right eye and twice daily in the left eye, and cycloplegic drops. He had been off his anti-neoplastic agents for 6 days prior to referral due to the onset of these symptoms and because his clinical trial prevented use of anti-neoplastic agents while on prednisone.

On presentation best-corrected visual acuity (BCVA) was 20/125 in the right eye and 20/50 in the left eye. Intraocular pressures, visual

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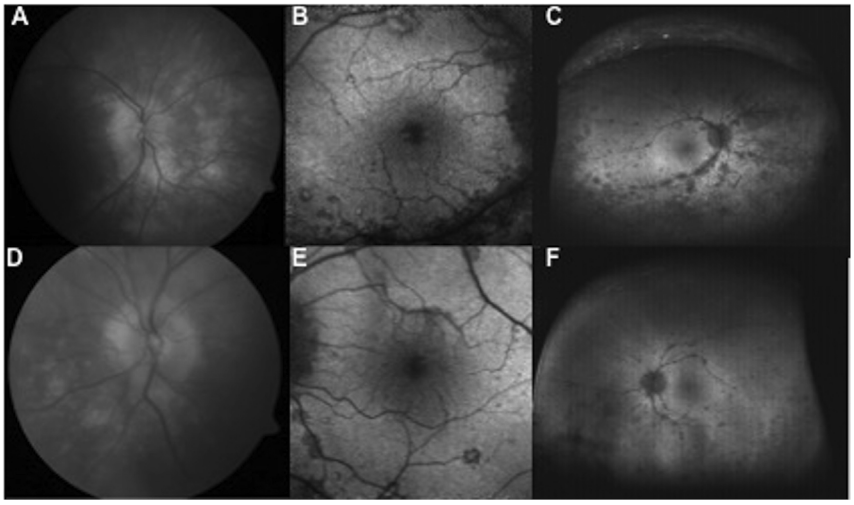

Fig. 1. A. Fundus photograph of the right optic nerve showing peripapillary atrophy and pigmentary changes nasal to the disc. B. Fundus autofluorescence of the right eye showing peripapillary hypoautofluorescence as well as paravenous hypoautofluorescence. C. Optos ultrawidefield autofluorescence of the right eye showing multiple round areas of well-circumscribed hypoautofluorescence, most predominantly in the paravenous region and also in between vessels in the periphery. D. Fundus photograph of the left optic nerve showing peripapillary atrophy and round pigmentary changes near the optic disc. E. Fundus autofluorescence of the left eye showing peripapillary hypoautofluoresence and multiple round foci of hypoautofluoresence tracking along the vessels, with fewer areas than the right eye. F. Optos ultra-widefield autofluorescence of the left eye showing multiple round areas of well-circumscribed hypoautofluorescence, most predominantly paravenous and also in between vessels in the periphery, less prominent than the right eye.

fields, and motility were within normal limits bilaterally. Slit lamp exam of the right eye demonstrated a well-centered posterior chamber intraocular lens implant in the right eye, while the left eye had rare pigmented cells in the anterior chamber with inferior posterior synechiae and a mild nuclear sclerotic cataract. Fundus examination revealed mild epiretinal membranes (ERM) and peripheral pigmentary changes bilaterally (Fig. 1 A, E).

Optical coherence tomography (OCT) confirmed the presence of the ERMs with mild cystic intraretinal fluid, an intact ellipsoid zone (EZ) and retinal pigment epithelium (RPE) in both eyes, distortion of the foveal contour in the left eye, and relative preservation of the foveal contour in the right eye (Fig. 2A–D). Autofluorescence showed paravenous hypoautofluorescence in the right eye (Fig. 1B and C) and scattered hypoautofluorescence in the left eye (Fig. 1E and F).

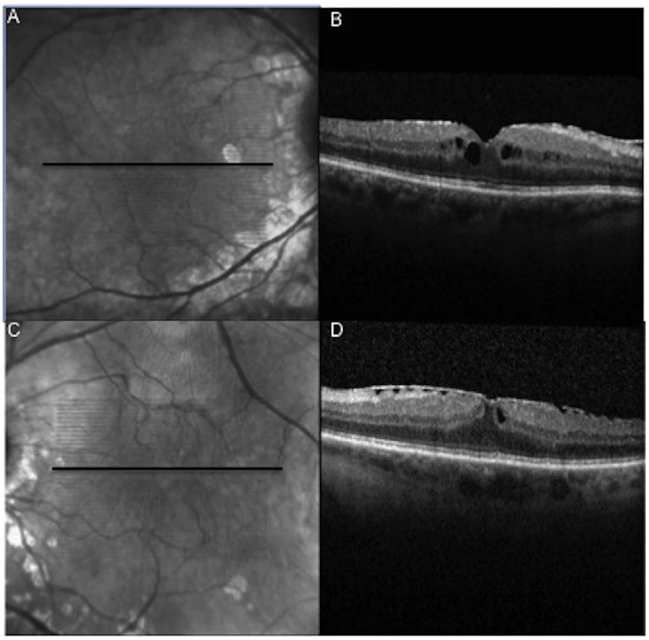

Fig. 2. A. Infrared photo of the macula of the right eye, denoting the slice through which spectral domain optical coherence tomography (SD-OCT) imaging was performed. B. SD-OCT through the macula of the right eye, showing epiretinal membrane with relative preservation of the foveal contour and cystic intraretinal fluid. C. Infrared photo of the macula of the left eye, denoting the slice through which SD-OCT imaging was performed. D. SD-OCT through the macula of the left eye, showing epiretinal membrane with distortion and loss of the foveal contour and a solitary area of cystic intraretinal fluid subfoveally.

Fluorescein angiography showed bilateral window defects without vasculitis and weak signal likely secondary to media opacity from the cataract in the left eye. Optical coherence tomography angiography (OCTA) revealed mild drop out of superficial retinal vessels perifoveally (Fig. 3A–F). Based on the clinical exam and multimodal imaging, the patient's differential diagnoses included panuveitis with bilateral CME concerning for melanoma-associated retinopathy, drug-related uveitis, pseudophakic macular edema, or activation of a previous chronic autoimmune process.

As the panuveitis improved, prednisone was tapered to 25 mg PO daily for 1 week and then 20 mg PO daily. He was also started on topical ketorolac tromethamine 0.5% 1 drop four times daily in the right eye. Fourteen days later BCVA improved to 20/30 in the right eye and 20/70 in the left eye, without change to the bilateral CME. To treat the CME and allow for local immunosuppression and to reduce time spent off of his chemotherapy regimen, an intravitreal dexamethasone implant (Ozurdex, Allergan Inc., Irvine, CA) (IVO) 0.7 mg was injected into the right eye and one week later into the left eye. One week after IVO, the BCVA had remained stable at 20/30 in the right eye and improved to 20/50 in the left eye with improvement in CME bilaterally. His prednisone was lowered to 5 mg a day and tapered off within 5 weeks, and the ketorolac was also tapered and stopped over a period of two months.

He underwent additional IVO ten weeks later bilaterally and again seven weeks after that in the right eye with near resolution of his CME within two weeks, and the decision was made with the patient's oncologist to restart his anti-neoplastic medications (Fig. 4A–D). After restarting the medications, he did not have a recurrence of CME, and blood testing revealed positive anti-retinal antibodies against 30-kDa (carbonic anhydrase II), 33-kDa (at very high titer), and 35-kDa (GAPDH) proteins. Prednisolone acetate 1% drops twice daily bilaterally were continued as a maintenance treatment. He then underwent cataract extraction with intraocular lens implantation in his left eye, and had a BCVA of 20/40 in the right eye and 20/30 in the left eye on last follow-up. Unfortunately, during this period of time, there was noted to be a relapse of his melanoma, for which he was treated with dabrafenib and trametinib. Systemic immunosuppression thus remained contraindicated, necessitating continued local intravitreal injections to control his uveitic process.

3. Discussion

CME is defined as macular thickening as a result of a dysfunctional blood-retinal barrier that allows for fluid accumulation within the retina.[3] CME is most commonly associated with cataract surgery, diabetes, retinal vein occlusion, and uveitis, but it can also be found as a