LETTER TO THE EDITOR

PSEUDOVITELLIFORM MACULOPATHY SECONDARY TO BRAF AND MEK INHIBITORS IN A PATIENT WITH METASTASIC MELANOMA

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To the Editor,

Malignant melanoma is the seventh most common cancer worldwide and the main cause of skin cancer deaths. Sun exposition and type 1 phenotype are the major risk factors for this illness. Its incidence has been rising faster than other types of cancer in the last decade, but fortunately we have also seen the dawn of a new era in the treatment options available for patients with metastatic disease (1).

Combination regimens of BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) have improved clinical benefit. Combinations approved for the management of metastatic melanoma are cobimetinib plus vemurafenib (1) and dabrafenib plus trametinib (2). Treatment with BRAFi and MEKi can lead to serious iatrogenic responses such as rash, diarrhea or pyrexia (3). Ocular toxicity has been reported in clinical trials as serous retinopathy and, rarely, central vein occlusion or retinal detachment (3).

The aim of this report is to describe a case of a patient treated with the combination vemurafenib-cobimetinib who suffered ocular adverse effects and was under observation in our ophthalmology department. The patient read, understood and signed informed consent to participate in the study.

Clinical case

A 55-year-old man was diagnosed in 2013 of anteriorcervical intradermal nodular melanoma with liver metastasis. As it was positive for V600E mutation (gene BRAF), in October 2017, the patient started oral treatment with vemurafenib (960 mg oral administration) and cobimetinib (60 mg oral administration) in a continuous regimen.

The ophthalmologic examination carried out prior to the treatment did not reveal any alteration. During the first ophthalmologic examination, one month after the beginning of the treatment, the patient reported a slight decrease of his visual acuity with a feeling of blurred vision and metamorphopsia. Visual acuity was 20/25 (Snellen chart) in the right eye (OD) and 20/20 in the left eye (OS). Funduscopy exam revealed the presence of a yellowish deposit at foveolar level in both eyes that was rated as vitelliform material (Fig. 1). Optical Coherence Tomography (OCT) revealed a bilateral subfoveal neuroepithelial retinal detachment of 202 microns in OD and 167 in OS (Fig. 2). Together with the oncology department it was decided not to suspend the treatment and close observation of the patient.

During the second ophthalmologic examination,

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3 months after the beginning of the treatment, the patient reported improvement in the symptoms. Visual acuity was 20/20 for both eyes. Slight alteration of the retinal pigment epithelium could be seen in the retinography.

The new OCT examination reported a neurosensorial detachment of 125 microns for OD and 150 microns for OS (Fig. 3).

DISCUSSION

New combination therapy of BRAFi and MEKi in metastatic melanoma has improved survival in this cohort of patients (4). One of the combinations used nowadays is cobimetinib plus vemurafenib, as in reported. Despite the benefit of this combination being well known, it is not exempted from systemic and ocular adverse events. The most described one is serous neuroepithelial detachment, and in severe cases, retinal vein occlusion (5).

Cancer, as a disease itself, can cause visual disturbances and affects up to 12% of patients (6). Retinopathy can also develop in patients with melanoma as an autoimmune complication (7). Opthalmologist advise is crucial to achieve a better management of this kind of patients and their possible complications. We report a clinical case of serous neuroepithelial detachment with pseudovitelliform macular deposit.

Optical coherence tomography is useful to detect and characterize the fluid distribution pattern and to distinguish it from corticosteroids-related subretinal fluid accumulation of central serous corioretinopathy (CSC), as glucocorticoids are often taken by oncologic patients, although sometimes it is necessary to carry out a fluoresceine angiography in case of doubt.

Serous detachment related to BRAFi and MEKi have different qualities, being multifocal, bilateral, not associated to retinal pigment epithelium (RPE) detachment and not necessarily dome-shaped, in contraposition of serous detachment in CSC (8).

Choroidal thickness was within normal range in our patients. This suggests that MEK inhibitor-induced serous detachments may not be associated with a pachychoroid phenotype, highlighting another distinction between CSC and MEKi-BRAFi serous detachment (9).

Other causes of pseudoviteliform deposition, such as choroidal folds, macular degeneration or chronic macular edema, should be ruled out as well as real vitelliform deposit secondary to retinal dystrophy.

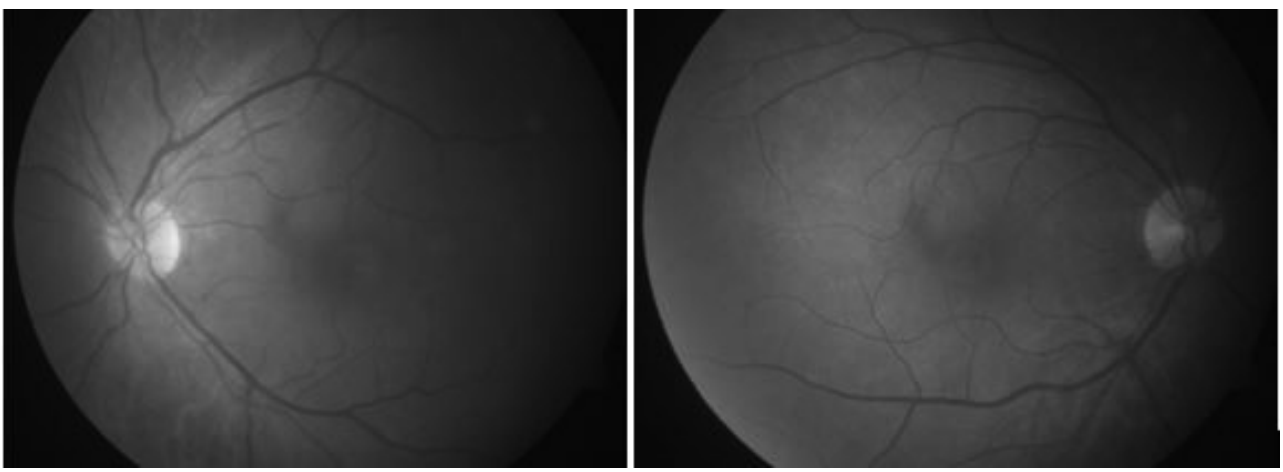

Fig. 1. *Fundus photography of OD and OS showing pseudovitelliform macular deposit.*

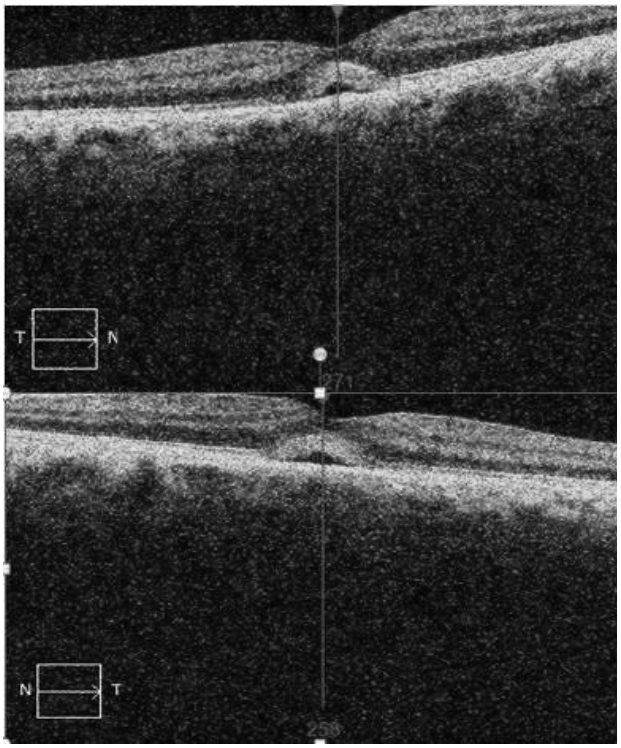

Fig. 2. *OCT of OD and OS in the first exam.*

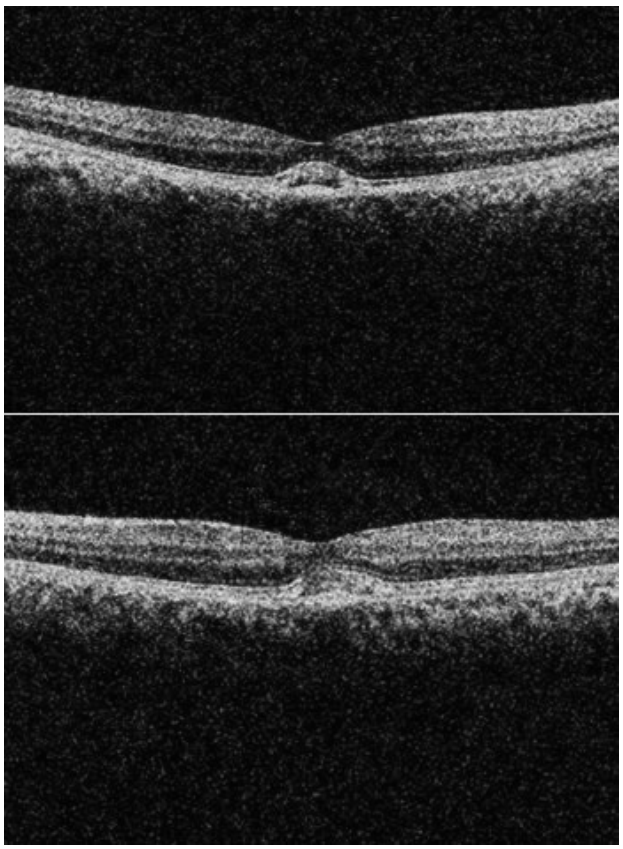

Fig. 3. *OCT of OD and OS in the second exam.*

In the trial by Stjepanovic (Phase 3, coBRIM or GO28141)**,** forty-nine percent (49%) of patients receiving the combination treatment experienced grade ≥2 CTCAE scale toxicity that occurred before study day 12 in 52% of patients and resolved after dose interruption, reduction or discontinuation of cobimetinib in 75% of the patients at the time of presentation of the results (10).

We agree with these results, as in our case, retinopathy was established 30 days after drug administration but we decided to continue with the treatment due to risk-benefit situation in our patient.

In our experience, as metastatic melanoma is a very aggressive neoplasia and new combined therapies of MEKi and BRAFi have changed survival prognosis, patients should be monitored, but it is not necessary to stop drug administration as these ocular adverse events are mild and usually reversible. A risk-benefit and an individualized decision must be taken.

Therapy expansion in oncology is just beginning. Clinicians should pay attention to detect new ocular adverse events and learn how to manage them properly.

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