Bilateral Uveitis and Papillitis During Metastatic Melanoma Treatment with Dabrafenib and Trametinib

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ABSTRACT

Purpose: To report a patient who developed bilateral uveitis and papillitis during dabrafenib and trametinib treatment for metastatic cutaneous melanoma.

Material and Methods: Retrospective chart review.

Results: A patient under treatment for metastatic cutaneous melanoma with dabrafenib and trametinib presented to our clinic with 1 month of bilateral visual blurring complaint. At ophthalmological examination, bilateral uveitis and papillitis were observed. After stopping dabrafenib and trametinib and initiating topical steroid administration, intraocular inflammation and papillitis improved in 2 months. Final visual acuities were 20/20 in both eyes.

Conclusion: Mitogen activated protein kinase (MAPK) inhibitors Dabrafenib anf trametinib can lead to ocular toxicity. Patients should be informed for the need of consecutive eye examinations.

Keywords: Dabrafenib; Trametinib; Uveitis; Papillitis; Melanoma.

New chemotherapeutics prolong overall and progression-free survival time in metastatic cutaneous melanoma. BRAF gene coded protein and mitogen/extracellular signal regulated kinase (MEK) are effectors of the mitogen activated protein kinase (MAPK) pathway. This pathway is important in melanoma development. BRAF and MEK mutations cause an increase in melanoma cell survival and proliferation.[1] Here, we reported a case of bilateral uveitis and papillitis during metastatic cutaneous melanoma therapy with a BRAF inhibitor (Dabrafenib) and a MEK inhibitor (Trametinib) combination. Combining BRAF and MEK inhibitors reduces resistancy and lowers toxicity. Nevertheless, side effects such as intraocular inflammation can be seen during treatment with these agents.[2] Although this intraocular inflammation is mostly manageable via steroid administration and drug cessation[3], patients under treatment with these agents should be informed that regular ophthalmological examinations are important.

CASE REPORT

A 37 years old female patient with metastatic cutaneous melanoma stage IV in her back under treatment with Dabrafenib 150 mg twice a day and Trametinib 2 mg once a day for 11 months presented with blurred vision in both eyes for 1 month. Her previous axillary lymph node biopsy revealed $BRAF^{V600E/V600E2/V600D}$ mutations. Her visual acuity was 16/20 with Snellen chart (0.1 logMAR) in both eyes. On slit lamp examination, there were small keratitic precipitates and 3+ anterior chamber cellular reactions, bilaterally. Fundoscopy revealed retinal vascular tortuosity and papillitis in both eyes (Figure 1). There were no choroidal thickening or serous retinal detachments on optical coherence tomography. (Figure 2) Fundus florescein angiography showed bilateral optic disc and vascular leakage through temporal vascular arcades, peripheral retina was normal (Figure 3). Uveitis work-up including blood tests (serology for viral infections, syphilis, lyme disease, ANCA, ANA, cardiolipin antibodies, Lupus anticoagulant, serum protein electrophoresis), tuberculin

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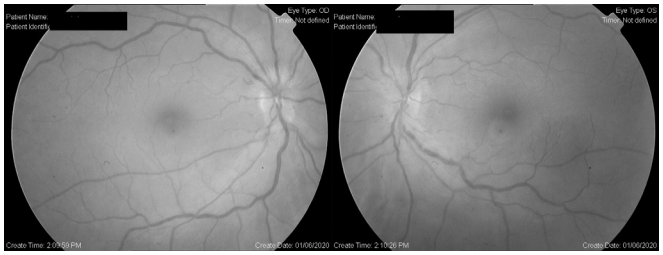

Figure 1: *Fundus photography of right and left eyes at presentation showing swollen optic disc as a sign of papillitis.*

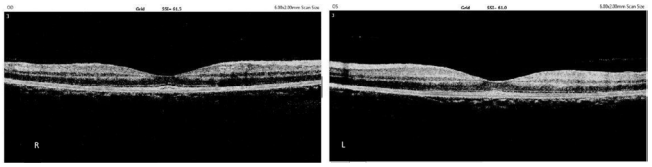

Figure 2: *Normal macula optic coherence tomography findings of both eyes.*

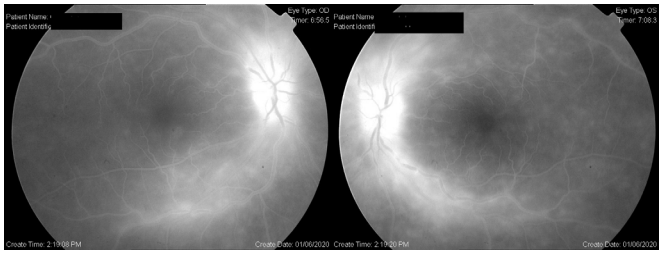

Figure 3: *Fluorescein angiography of right and left eyes showing disc leakage and blurred disc margins.*

test and chest X-ray were negative. She was started on prednisolon %1 topical eye drops hourly, mydriatic agent once a day and dexamethasone0.1% eye ointment at bedtime. Trametinib and Dabrafenib were discontinued in agreement with the oncologist. A good response was obtained within a week. Anterior chamber reaction, the degree of papillitis and vascular leakage decreased. After 2 months, final visual acuity was 20/20 bilaterally and there was no anterior chamber inflammation, papillitis or panuveitis findings.

DISCUSSION

Drug relation is important in the differential diagnosis of uveitis. Besides other drugs, MAPK inhibitors are known inductors of uveitis.[4,5] Some newer MAPK inhibitors, Dabrafenib and Trametinib are used in the treatment of metastatic cutaneous melanoma and are also known to induce uveitis.[6]

Our patient had panuveitis, vasculitis and papillitis. The exact mechanism for this side effect is still unknown. The MAPK pathway leads cellular proliferation and MAPK inhibition can cause an inflammatory response with breakdown of the blood-retinal barrier. [6] After cessation of MAPK inhibitors and administration of topical steroids in our patient vasculitis, uveitis and papillitis disappeared in 2 months.

Some authors also published case reports of patients under Dabrafenib and Trametinib treatments with uveitis[7], papillitis[3], multiple serous retinal detachment[8] and retinal vein occlusion.[9]

Huang et al administered the MEKI PD0325901 to rabbits by intravitreal injection to investigate the ocular toxicity mechanism and demonstrated potential mechanisms for retinal vein occlusion and central serous chorioretinopathy in MEK inhibitor treated humans.[10]

In conclusion, consecutive eye examinations are important in metastatic cutaneous melanoma patients under Dabrafenib and Trametinib treatments. Optical coherence tomography and fluoerescein angiography are important imaging techniques to identify subclinical inflammation of the posterior segment. Physicians should be alert for the ocular side effects of these drugs. These side effects including uveitis, are mostly reversible with drug cessation or replacement and topical treatments but some amount of resistancy and need for systemic treatment also exists.[11] Further studies are needed to enlighten the induction mechanisms, dose-related effects and patients under risk.

DECLARATION OF INTEREST

Author reports no conflicts of interest and is alone responsible for the content and writing of this article.

REFERENCES

1. Menzies AM, Long GV, Murali R. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther 2012;6:391-405.

2. Moorthy RS, Moorthy MS, Cunningham ET Jr. Drug-induced uveitis. Curr Opin Ophthalmol. 2018;29:588-603.

3. Woltsche N, Kruger MA, Weger M, Wolf IH, Seidel G. Intravitreal steroid treatment for uveitis associated with Dabrafenib and Trametinib for metastatic cutaneous melanoma. Ocular Immunol Inflamm 2020; 6;1-3.

4. Naranjo CA, Busto U, Sellers EM, Sandor P, Rui I, Roberts EA, Janecek E, DomecqC, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45

5. Guedj M, Queant A, Funck-Brentano E, Kramkimel N, Lellouch J, Monnet D, Longvert C, Gantzer A, Brezin A. Uveitis in patients with late stage cuyaneous melanoma treated with Vemurafenib. JAMA Ophthalmol 2014;132:1421-25.

6. Dy GK, Adjei AA. Understanding, recognizing and managing toxicities of targeted anticancer therapies. CA Cancer J Clin. 2013;63:247-79.

7. Joshi L, Karydis A, Gmenetzi M, Shao EH, Taylor SR. Uveitis as a result of MAP Kinase pathway inhibition. Case Rep Ophthalmol. 2013;4:279-82.

8. Mc Cannel TA, Chmielowski B, Finn RS, Goldman J, Ribas A, Wainberg ZA et al. Bilateral subfoveal neurosensory retinal detachment associated with MEK inhibitor use for metastatic cancer. JAMA Ophthalmol. 2014;132:1005-9.

9. Mozo Cuadrado M, Tabuenca Del Barrio L, Compains Silva E. Bilateral Drug-Induced Uveitis and Epiretinal Membrane during the Treatment of a Metastatic Cutaneous Melanoma. Ocul Immunol Inflamm. 2019 Nov 22:1-3.

10. Huang W, Yang AH, Matsumoto D, et al. PD0325901, a mitogen-activated protein kinase kinase inhibitor, produces ocular toxicity in a rabbit animal model of retinal vein occlusion. J Ocul Pharmacol Ther. 2009;25:519-30.

11. Lim J, Lomax AJ, McNeil C, Harrisber B. Uveitis and papillitis in the setting of Dabrafenib and Trametinib therapy for metastatic melanoma:a case report. Ocul Immunol Inflamm. 2018;26:628-31.