A novel side effect of mitogen-activated protein kinase inhibitor cobimetinib: Acute corneal decompensation

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A 38-year-old man with a diagnosis of BRAF-mutated metastatic melanoma was referred to our clinic. He had been under treatment with 60-mg oral cobimetinib daily for 21 days/7 day off in combination with 960 mg vemurafenib twice daily. The patient had symptoms of blurred vision and photophobia in his right eye. A slit-lamp examination revealed bilateral central corneal stromal opacity and epithelial microcystic edema Involvement was more severe in the right eye compared with the left eye. Fourteen days after the first visit, the patient's symptoms and slit-lamp findings were largely resolved. We suggest that endothelium pump failure was involved in this acute corneal decompensation case similar to the mechanism in retinal pigment epithelium.

Key words: Corneal decompensation, cobimetinib, MEK inhibitor

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Malignant melanoma is a steadily increasing, significant health problem. It is a dangerous form of skin tumor that causes 90% of skin cancer-related mortality.[1] At diagnosis, metastases are present in approximately 2–5% of patients.[2] The

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mitogen-activated protein kinase (MEK) inhibitor cobimetinib and V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor vemurafenib have significantly improved the prognosis of BRAF-mutated unresectable-metastatic melanoma.[3] One of the most commonly reported ocular adverse effects of this treatment is called MEK inhibitor-associated retinopathy. Herein, we describe a case of acute corneal epithelial and stromal edema with normal retinal findings after MEK inhibitor treatment and BRAF inhibitor immunotherapy, which has never been reported before.

Case Report

A 38-year-old man with a diagnosis of BRAF-mutated metastatic melanoma was referred to our clinic. He had been under treatment with 60 mg oral cobimetinib daily for 21 days/7 day off in combination with 960 mg vemurafenib twice daily at Corum Erol Olcok Research and Education Hospital Oncology department. The patient had symptoms of blurred vision and photophobia in his right eye. His visual acuity was 3/10 and 9/10 according to the Snellen chart in his right and left eyes, respectively. The intraocular pressure was 14 mm Hg in the right eye and 17 mm Hg in the left eye. A slit-lamp examination revealed bilateral central corneal stromal opacity and epithelial microcystic edema [Fig. 1a and b]. Involvement was more severe in the right eye compared with the left eye. There were no cells/flare in the anterior chamber. The fundoscopic examination was normal, bilaterally. Topical preservative-free lubricant drops were administered for symptomatic relief. Fourteen days after the first visit, the patient's symptoms and slit-lamp findings were largely resolved [Fig. 1c and d]. The patient's visual acuity was 10/10 bilaterally.

Discussion

Several ocular signs and symptoms have been observed following this treatment. It was reported that vemurafenib caused ocular adverse effects in 22% of subjects in patients with advanced-stage melanoma, including uveitis, dry eye, and conjunctivitis as the most common toxicities.[4] Retinal vein occlusion (RVO)[5] and iritis[6] have been reported less frequently.

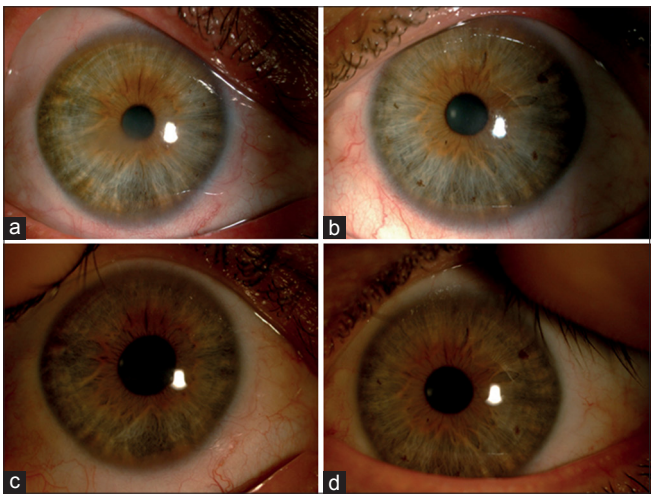

Figure 1: (a) Central corneal stromal opacity and epitelial microcystic edema in the right eye. (b) Central corneal stromal opacity and epitelial microcystic edema in the left eye. (c) Corneal edema nearly resolved after 2 weeks in the right eye (d) Corneal edema resolved after 2 weeks in the left eye

When we reviewed through the literature, we found that one of the most reported adverse effects of this treatment involved the posterior segment of the eye, called MEK inhibitor- associated retinopathy. It is characterized by retinal pigment epithelium (RPE) dysfunction and neurosensorial retinal detachment.[7] The main mechanism of this phenomenon still remains unresolved. There are some reports suggesting that dysfunction of RPE may play a major role in the pathogenesis.[8] Several preclinical studies showed that MEK inhibition led to acute RPE toxicity, which resulted in RPE hyperpermeability and breakdown of the retinal–blood barrier.[9,10] It was reported that most adverse effects occurred within the first treatment cycle, and these could be managed through observation alone. It was shown that symptoms resolved with continuation of the treatment without dose modification.[11] Urner-Bloch *et al*. showed that MEK inhibitor-associated retinopathy was dose–time dependent and reversible in all patients.[12] Gavric *et al*. claimed that MEK inhibitor-associated retinopathy lesions had no or only mild influence on visual function and needless interventions including the discontinuance of the treatment should be avoided.[13] Likewise, in our case, at the end of the first treatment cycle of the drug therapy, corneal symptoms were apparent but were substantially relieved in 2 weeks, during the intertreatment interval.

Different from the entire related literature, we describe a different ocular adverse effect of cobimetinib–vemurafenib combination treatment. We strongly suggest that MEK inhibitors damage the RPE pump and affect corneal endothelial function, which could lead to acute corneal stromal and microcystic epithelial edema. Just as the retinopathy adverse effect of this anticancer therapy was reported as reversible; similarly, the corneal edema resolved in our case despite continuation of the drug therapy. We could suggest that corneal endothelium pump failure was involved in this case, similar to the mechanism in RPE. However, more cases should be reported to gain a certain opinion.

There are some limitations in this study. If we had had specular or confocal microscopy in our clinic, it would have made a significant contribution to this case. The patient also rejected being transferred to another ophthalmology clinic for specular/confocal microscopy due to his poor state of health. Nevertheless, we think that this side effect of treatment with cobimetinib–vemurafenib combination is self-resolving and cessation of a life-prolonging treatment should be avoided.

Conclusion

We report a novel side effect of acute corneal epithelial and stromal edema with normal after MEK inhibitor treatment and BRAF inhibitor immunotherapy, implying the need for baseline ophthalmic evaluation and follow-up of such patients by an ophthalmologist.

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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Conflicts of interest

There are no conflicts of interest.

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