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CASE STUDY

Two cases of acute-onset cystoid macular edema and serous retinal detachment associated with combined use of encorafenib and binimetinib for advanced melanoma: A possible confounding risk for drug intolerance

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Abstract

While combined use of BRAF/MEK inhibitors has elicited dramatic clinical efficacy in incurable melanoma, drug-associated retinopathy has become an emerging adverse event. We present two Japanese men with advanced melanoma who developed visual impairment due to serous retinal detachments (SRDs) with cystoid macular edema (CME) immediately after initial administration of encorafenib/binimetinib, a BRAF and MEK inhibitor. One case had drug-intolerable retinopathy on repeat dosing. Both cases were switched to another BRAF/MEK inhibitors, dabrafenib/trametinib, with no recurrence of SRDs. Co-existing CME may be a confounding risk for the early development of SRDs with encorafenib/binimetinib therapy, providing attention during drug administration.

KEYWORDS
BRAF, cystoid macular edema, melanoma, oncoimmunology, serous retinal detachment

1 | INTRODUCTION

In Japan, an encorafenib/binimetinib combination therapy was approved in 2019 for BRAF-mutated, advanced melanoma, following dabrafenib/trametinib. While the BRAF/MEK inhibitors have evoked dramatic clinical efficacy on incurable melanoma, serous retinal detachments (SRDs), a subset of serous retinopathy, have now been recognized as a distinct entity of adverse event, termed MEK inhibitor-associated retinopathy (MEKAR).[1] SRDs mostly represent a reversible even with ongoing treatment but often alert the requirement of dose reduction or withdrawal.[2,3] We described two cases with advanced melanoma who immediately developed SRDs with cystoid macular edema (CME) after starting encorafenib/binimetinib, one of whom had drug-intolerable retinopathy to repeated drug administration. We discuss the possible risk of CME, which may be a possible underrecognized confounder in the development of MEKAR.

2 | CASE REPORT

Case 1 was a 77-year-old Japanese man with BRAF V600E mutation-positive advanced melanoma of the left lower leg (pT4bN3bM1c

Stage IV; Figure 1A), who had undergone encorafenib/binimetinib therapy. No ocular diseases were found on optical coherence tomography (OCT) prior to administration (Figure 1B). The next day following the initiation of encorafenib/binimetinib, he complained of bilateral blurred vision with CME and SRD on OCT (Figure 1C), thus discontinuing the treatment. After 1 week of drug withdrawal, both ocular symptoms and abnormal OCT findings improved. However, restarting the drugs in accordance with the guidelines for proper use suddenly relapsed the ocular symptoms (Figure 1D). We gave up continuing the treatment and switched to dabrafenib/trametinib after the improvement of ocular symptoms and OCT findings. Thereafter, no ocular symptoms appeared at least during 2 years of follow-up.

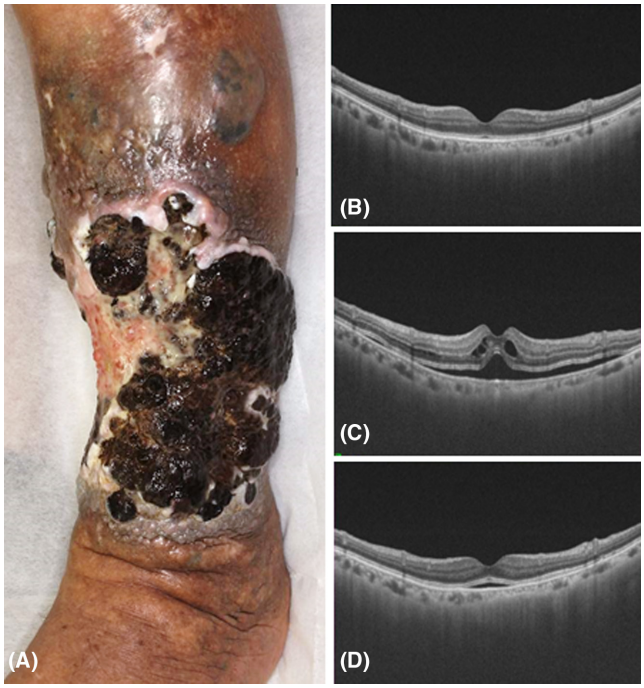

FIGURE 1 Clinical and OCT findings of case 1. Multiple melanotic masses with ulceration and satellite lesions on the left lower leg (A). Despite of no OCT findings before treatment (B), CME and SRDs appeared in both eyes on the next day of initial encorafenib/binimetinib administration, (C) and improved 1 week after changing to dabrafenib/trametinib (D).

Case 2 was a 66-year-old Japanese man with BRAF V600E mutation-positive unresectable melanoma of the abdominal skin (pT4aN2cM0 Stage IIIc; Figure 2A). He was treated with encorafenib/binimetinib, followed by anti-PD-1 antibody. On the same day, diplopia suddenly appeared with OCT findings of CME and SRD (Figure 2C), compared to those before treatment (Figure 2B), which improved within 1 week of drug withdrawal. After switching to dabrafenib/trametinib, he had no relapsing of ocular symptoms and abnormal OCT findings (Figure 2D).

3 | DISCUSSION

The global phase III study (CMEK162B2301) reported that among 192 patients who underwent the encorafenib/binimetinib combination therapy, 78 (40.6%) had adverse events in eyes,[4] as was the equivalent occurrence in three preceded trials for phase Ib-II (40%–65%),[5] and more than 60% of whom developed eye events within 1 month of treatment. Notably, most patients with binimetinib monotherapy (46/51, 90%) developed mild subretinal edema as a causative of SRDs, which was reversible with continued dosing, supporting the possible acquisition of drug tachyphylaxis with continuous exposure.[6] The current consensus, therefore, states the proper consideration of either continuation or discontinuation and later readministration at a lower dose of binimetinib.[7] Dose reduction and interruption of dabrafenib/trametinib, another combination of BRAF/MEK inhibitors, did not affect the overall disease survival of the Japanese melanoma cohort,[8] albeit with not applicable to the encorafenib/binimetinib therapy.

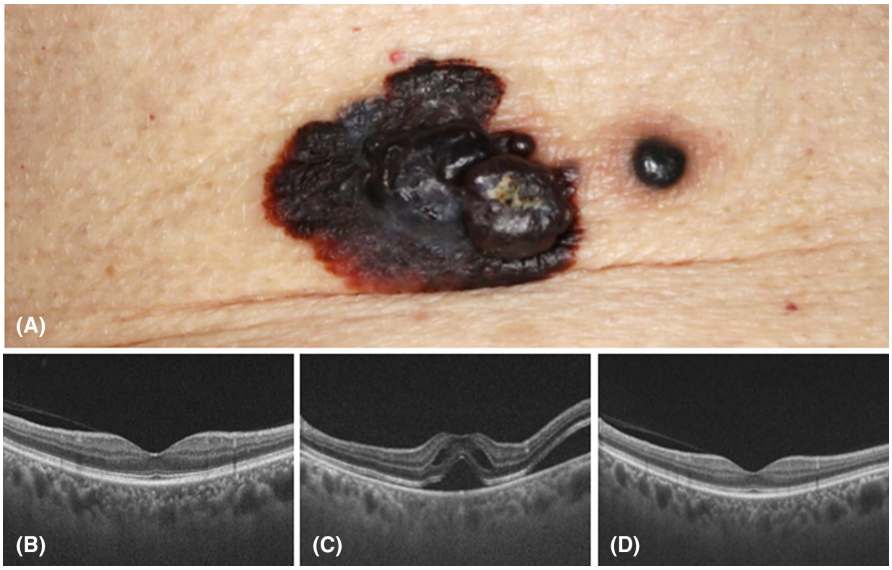

FIGURE 2 Clinical and OCT findings of case 2. An irregular melanotic maculonodule with a satellite lesion on the abdomen (A). No OCT findings before encorafenib/binimetinib treatment (B). On the same day of initial administration, CME and SRDs suddenly appeared in both eyes (C) and disappeared 1 week after discontinuation of the treatment (D).

Binimetinib can be highly toxic to retinal pigment epithelial cells in a dose-dependent manner.[5,9] The resultant retinal cell damage directly collapses the maintenance of proper local fluid gradient. Another mechanism of action arises the possibility of the excess water permeability across retinal cells via a channel-forming membrane protein aquaporin 1 (AQP1)[10]; that is, suppression of MEK/ERK signaling activity leads to the increase of AQP1 expression in retinal cells and subsequent water hyperpermeability and the influx into fragile subretinal tissue, contributing to detachment of the outermost retinal pigment epithelium from the underlying choroidal layer. Besides, it remains unknown as to why binimetinib causes more ocular damage than trametinib, although both are similar MEK inhibitory agents.

Our retrospective review reported from Japan found only nine cases of SRDs caused by BRAF/MEK inhibitors, including ours; all of them had ocular symptoms by the next day of treatment. Only three cases described ophthalmological symptoms, including visual impairment, dyschromatopsia, and narrowing visual field. Six cases (66.7%) were achieved to continue the treatment with reduced doses of encorafenib/binimetinib, but our two cases were finally switched to dabrafenib/trametinib, providing a relapse-free of SRDs. A study using other MEK inhibitors demonstrated a higher risk for the development of MEKAR in subjects with a possible association of age, impaired renal function, and previous inflammatory eye diseases.[11] Besides, little is known about what clinical parameter(s) are significant for symptomatic MEKAR that is intolerable to the continued or repeated drug, although the co-existing CME on OCT might be a confounding risk,[12] like our cases. Further investigation is warranted regarding the relationship between drug-intolerable MEKAR and the presence of the CME finding on OCT, to ensure that more specific ophthalmologic assessments benefit patient subgroups when taking BRAF/MEK inhibitors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

None.

ETHICS STATEMENT

Approval of the research protocol: No human participant was involved in this study.
Informed Consent: N/A.
Registry and the Registration No.: N/A.
Animal Studies: N/A.

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