Letter to the Editor

Bilateral neurosensory retinal detachments secondary to ERK inhibitor use for metastatic lung adenocarcinoma

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Targeted immunotherapy for the treatment of solid tumours has progressed with many ongoing trials of novel anti-cancer therapies. Inhibitors of the Ras-RAF-mitogen-activated kinase (MEK) kinase-extracellular signal-regulated kinase (ERK) pathway, in particular MEK inhibitors, have been associated with a number of ocular toxicities.¹ We describe a case of bilateral neurosensory retinal detachment after commencement of an ERK inhibitor for metastatic lung cancer.

A 64 year-old Caucasian female with metastatic KRAS mutant non-small cell lung adenocarcinoma was enrolled in a Phase 1b clinical trial of an ERK inhibitor (LTT462 300mg orally daily) in combination with a pan-RAF inhibitor (LXH254 200mg orally daily). She had a past ocular history of hyperopia, right esotropia and mild amblyopia.

At baseline examination one week prior to commencing therapy, her best corrected visual acuities were 6/7.5 and 6/4.8 in the right and left eyes respectively. Ocular examination including macular and retinal vascular evaluation was normal. Optical coherence tomography (OCT) of the maculae and retinal nerve fibre layers were also normal.

The patient presented four days after commencing trial medications with painless bilateral central metamorphopsia and photopsia. Visual acuities were 6/12 in the right eye and 6/7.5 in the left eye. Examination revealed bilateral neurosensory detachment of the maculae accompanied by cystoid macular oedema (CMO) surrounding the fovea. Peripheral retinal examination was unremarkable bilaterally. OCT imaging showed bilateral sub macular fluid and CMO (Figure 1A). Autofluorescence imaging showed hypoautofluorescence at the inferior margins of the neurosensory detachments bilaterally and subtle changes consistent with CMO (Figure 1B). Both trial medications were ceased.

Figure 1: A) OCT imaging showing neurosensory retinal detachment with subretinal fluid and CMO bilaterally. Central foveal thickness measures 539microns and 531microns in right and left eyes, respectively. B) Autofluorescence imaging demonstrating CMO and hypoautofluorescence at inferior margins of macular detachment.

One week later, ocular symptoms had resolved with recovery of visual acuities to 6/9 and 6/6 in the right and left eyes respectively. Fundal evaluation and OCT findings showed resolution of all signs (Figure 2A). Autofluorescence showed persistent hypo autofluorescence along the inferotemporal arcades (Figure 2B).

Figure 2: A) OCT imaging demonstrates normalisation of retinal changes shown in Figure 1A. B) Autofluorescence imaging showing persistent hypo autofluorescence at inferior margin of detachment.

The Ras-RAF-mitogen-activated kinase (MEK) kinase-ERK pathway is one of many mitogen-activated protein kinase pathways (MAPK) involved in fundamental cellular processes including cellular proliferation, differentiation and survival.² Mutations in BRAF and KRAS genes leading to preferential hyperactivation of this MAPK pathway are frequently involved in oncogenesis, including many cases of lung cancer.³ ERK 1/2 is directly downstream of MEK 1/2 in the phosphorylation cascade.²

Maculopathies including including bilateral neurosensory retinal detachment distinct from classic central serous chorioretinopathy secondary to the use of MEK inhibitors have been well described.^{1,4,5} Fluorescein angiography in two reported patients with MEK inhibitor-associated retinopathy has shown a lack of fluorescein leakage.⁴ The mechanism of MEK inhibitor maculopathy is poorly understood.

Macular neurosensory retinal detachments have not been described in association with RAF inhibitors alone.⁵ Furthermore, ERK is more closely related to MEK in the MAPK pathway. Therefore, the complication described here was more likely secondary to the use of the ERK inhibitor rather than the pan-RAF inhibitor. However, we cannot exclude this as a possibility.

The case presented here showed a greater degree of macular detachment than seen with patients in our institution with MEK inhibitor-associated retinopathy.

To the best of our knowledge, there have been no previously published case reports in the literature describing bilateral neurosensory retinal detachment associated with ERK inhibitor use. However, one such case has been presented (Bakri SJ, American Society of Retina Specialists, Vancouver, July 2018).

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Figure1.tiff

Figure2.tiff

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