Case Report

Serous Retinal Detachment without Leakage on Fluorescein/Indocyanine Angiography in MEK Inhibitor-Associated Retinopathy

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Keywords
Serous retinal detachment · Mitogen-activated protein kinase kinase inhibitor · Electro-oculography · Retinal pigment epithelium

Abstract
The aim of this paper was to report the cases of 3 consecutive patients with mitogen-activated protein kinase kinase inhibitor (MEKi)-associated retinopathy with characteristic multiple serous retinal detachments (SRDs). A functional analysis of the retinal pigment epithelium was performed in 2 patients by electro-oculography (EOG). In all 3 patients, SRD lesions were observed in the posterior pole including the fovea of both eyes. Interestingly, neither obvious leakage in fluorescein/indocyanine angiography nor abnormal fundus autofluorescence was associated. SRDs and associated cystoid macular edema in one case rapidly resolved with the cessation of MEKi but recurred quickly after treatment resumption. In EOG tests, three of four eyes with multiple SRDs showed a marked decrease in the light-peak-to-dark-trough ratio (LP:DT ratio). The LP:DT ratio in EOG reflects the transepithelial potential of the retinal pigment epithelium, suggesting the involvement of disrupted tight junctions and impaired active transport of fluid/ions in MEKi-associated retinopathy. The latter may be the major cause of SRDs as we observed that fluid leakage in angiography was absent in the areas of the patients' SRDs.
Introduction

Mitogen-activated protein kinase kinase inhibitor (MEKi)-associated retinopathy has been advocated as a new ocular complication of molecular targeted cancer therapy [1–4]. The therapeutic efficacy of MEKi has been demonstrated in various types of metastatic cancer [1, 3, 5], but adverse events including diarrhea, nausea, and visual disturbances due to serous retinal detachments (SRDs) are frequently associated with MEKi treatment. In a clinical trial of a MEKi for metastatic malignant melanoma, the reported incidence of SRD was high at 77% [5, 6]. Multiple SRDs that appear and resolve rapidly along with MEKi administration and cessation are the characteristic feature of MEKi-associated retinopathy, and fortunately, the visual prognosis is fair with vision deterioration developing only in 23% of the clinical trial patients, and the deterioration did not lead to permanent vision loss [5]. Cystoid macular edema may be also found together with SRDs [7–9].

A striking feature of MEKi-associated SRD is the lack of leakage from either the retinal vessels or the retinal pigment epithelium (RPE), meaning choroid in fluorescein and indocyanine angiography (FA/IA) [2–4, 6–8, 10]. Typical multiple SRD lesions associated with other retinochoroidal diseases (e.g., central serous chorioretinopathy [CSC]) are accompanied by fluorescein leakage [4, 9]. By using electro-oculography (EOG), van Dijk et al. [5] observed the reduced light-peak potential in eyes with MEKi-associated SRD. These findings suggest that RPE dysfunction rather than increased vascular permeability may be involved in the pathogenesis of MEKi-associated retinopathy.

A combination therapy of a MEKi, an epidermal growth factor receptor inhibitor (EGFRi), and a BRAF inhibitor (BRAFi) recently showed promising results for metastatic BRAF V600E-mutated colorectal cancer [5], and it has been approved in Japan as the second-line treatment following unsatisfactory effects of the first-line chemotherapy. At our hospital, 3 patients with BRAF V600E-mutated colorectal cancer have undergone this combination therapy so far, and all 3 patients developed multiple SRDs in both eyes. One patient also showed cystoid macular edema. Here, we provide the detailed assessments of MEKi-associated retinopathy and discuss the potential mechanisms.

Case Series

Case 1

An 89-year-old Japanese female was diagnosed with transverse colon cancer with multiple distant metastases. After four lines of chemotherapy, she received a combination therapy including a MEKi (binimetinib, 300 mg/day). Within 2 days, the patient noticed chromatopsia and blurred vision in both eyes, in addition to severe gastrointestinal side effects. The MEKi was thus discontinued. The patient was referred to our department 3 days after the cessation of the binimetinib. She was under glaucoma treatment with a β-blocker eye drop but had no history of retinochoroidal diseases. Her subjective ocular symptoms had improved slightly, but the best-corrected visual acuity (BCVA) was 20/50 in the right eye and 20/40 in the left eye. Slit-lamp biomicroscopic examination showed no obvious abnormalities in the anterior segments.

Infrared fundus photographs showed multiple SRDs and stellate-figured macular edema in the left eye (shown in Fig. 1a). Optical coherence tomography (OCT) revealed foveal SRD and cystoid macular edema (shown in Fig. 1b). Similar findings were observed in the right eye (shown in Fig. 1c, d). A MEKi-free interval of only 6 days led to the rapid resolution of the SRD and cystoid macular edema in both eyes (shown in Fig. 1e–h). The BCVA accordingly improved to 20/20 in the right eye and 20/25 in the left eye.
Interestingly, FA/IA at the patient’s initial visit had shown no apparent leakage in either the early (shown in Fig. 2a, b) or late phase (shown in Fig. 2c, d), while there were multiple SRDs and cystoid macular edema. OCT angiography (OCTA) exhibited no obvious abnormal findings. Fundus autofluorescence (FAF) revealed no abnormal hyper- or hypo-autofluorescence, indicating no apparent defect in RPE (shown in Fig. 2e, f). Infrared fundus photographs and OCT and OCTA images were obtained with RS-3000 (NIDEK, Gamagori, Japan). FA/IA and FAF were obtained using the SPECTRALIS HRA device (Heidelberg Engineering Inc, Dossenheim, Germany). Fundus photographs were obtained with a TRC-50DX fundus camera (Topcon, Tokyo, Japan). Although the ocular symptoms subsided, the MEKi was not resumed because the patient could not bear the systemic adverse events.

Fig. 1. An 89-year-old female treated with the MEKi binimetinib (300 mg/day) for metastatic colorectal cancer suffered from vision deterioration and chromatopsia (case 1). The fundus photograph of the left (a) and the right (c) showed stellate-figured macular edema (between arrows) with multiple SRDs (arrows) on the initial visit. OCT showed SRDs and prominent macular edema, which corresponded to stellate-figured macular edema in the left (b) and the right (d). After cessation of the MEKi for 6 days, stellate-figured macular edema and SRDs resolved in both eyes (e–h).
Fig. 2. FA/IA on the initial visit (Case 1). Early-phase FA (a) and IA (b) (48 s) revealed no apparent leakage. Late-phase FA (c) and IA (d) (6 min) still did not show apparent leakage or pooling while there were multiple SRDs and stellate-figured macular edema as demonstrated in Fig. 1. FAF showed no abnormal hyper- or hypo-autofluorescence, indicating no apparent anatomical defect or damage in the RPE (e, f).
Case 2

A 51-year-old Japanese female was diagnosed with ascending colon cancer with multiple distant metastases and received first-line chemotherapy. However, peritoneal dissemination progressed, and a recently approved combination therapy that included a MEKi (binimetinib, 300 mg/day) was started. Seven days later, the MEKi was discontinued because of severe gastrointestinal side effects including diarrhea. Since a yellow circular patch appeared in the center of the visual field of both eyes, the patient was referred to our department. The BCVA was 20/20 in both eyes. Anterior segments were unremarkable, but there was a dome-shaped SRD in the fovea of both eyes and shallow SRDs along the arcades in the right eye. There was no thickening of the choroid or dilation of the choroidal vessels. FA/IA showed no apparent leakage, and there was no abnormality in FAF or OCTA. SRD was evaluated as grade 2 in the Common Terminology Criteria for Adverse Events (CTCAE), and the MEKi was discontinued until 2 weeks after the complete resolution of the SRDs.

The MEKi was resumed at a reduced dose (binimetinib, 275 mg/day), and 1 week after its resumption, a fundus examination showed multiple SRD lesions along the arcade vessels. An EOG was obtained, and the LP:DT ratio was reduced to 1.25 in the left eye, which had shown multiple prominent SRDs covering a wide range (shown in Fig. 3). In the right eye with mild SRDs spreading less range, the LP:DT ratio was subnormal or on the lower limit of the normal range at 1.97. Thavikulwat et al. [11] reported that the normal range of LP:DP ratio

![Fig. 3. Electro-oculogram of the right (a) and the left (b) eyes (case 2). A schematic of the distribution of SRDs. The left eye with multiple prominent SRDs showed a reduced LP:DT ratio (1.25), suggesting diffuse RPE dysfunction. In the right eye, the SRD was relatively mild, and the LP:DT ratio was on the lower borderline of the normal range (1.97).](image-url)
differs depending on age and gender. They described that the lower limit of normal for the LP:DP ratio reported across studies varies, ranging from 1.5 to 2.0 [11]. Throughout the entire course, the BCVA remained good in both eyes.

**Case 3**

A 68-year-old Japanese female with metastatic colorectal cancer underwent a combination therapy of a MEKi (binimetinib, 300 mg/day), a BRAFi, and EGFRi. Although she tolerated the combination treatment very well and there were no subjective symptoms, physicians referred her to our department to check for any ocular adverse events. The BCVA was 20/20 in both eyes. Anterior segments were unremarkable. Infrared fundus photographs showed SRDs, and OCT revealed a shallow SRD in the fovea of both eyes (Fig. 4). FA/IA did not show any apparent leakage. The LP:DT ratio of EOG was decreased in both eyes that was 1.66 in the right eye and 1.61 in the left eye. The combination treatment with MEKi was thus continued, and we advised the patient to visit our outpatient clinic immediately if she noticed any vision deterioration.

![Fig. 4. The fundus photographs of the right (a) and the left (b) are unremarkable, but the infrared fundus photograph demonstrates scattered SRD (arrows) (c, d). OCT showed SRDs but no cystoid macular edema in both eyes of case 3 (e, f).](image-url)
Discussion/Conclusion

A combination therapy of MEKi, BRAFi, and EGFRi was recently approved for metastatic colorectal carcinoma in Japan. In the 3 months since approval, 3 patients underwent this combination therapy at our hospital, and all 3 patients developed MEKi-associated retinopathy with unique bilateral multiple SRDs.

Although some reports have referred to these MEKi-associated SRDs as CSC-like events, there are several distinct differences. In CSC, FA shows prominent leakage from the choroid through the RPE defect in the lesions of SRD, and IA shows hyperpermeability of choroidal vessels [9]. Although similar SRDs, sometimes associated with CME, are found in MEKi-associated retinopathy, there is no leakage in FA [1, 4]. In all three cases presented herein, FA/IA showed no leakage or vascular abnormalities. Francis et al. [4] performed enhanced depth imaging of PCT for the cases with MEKi-associated retinopathy, and they reported that thickening of the choroid was not observed. In the three cases of MEKi-associated retinopathy described herein also, conventional OCT images showed no apparent pachychoroidal findings. Although a steroid, which is often administered in the process of chemotherapy, may induce CSC, we thus excluded CSC from the 3 patients' diagnoses.

The mechanisms of multiple SRDs in MEKi-associated retinopathy remain unclear. EOG abnormalities were demonstrated in patients with MEKi-associated retinopathy [5]. Consistently, three eyes of 2 of our patients with multiple SRDs showed a decreased LP:DT ratio in EOG tests, and one eye with fewer SRDs showed an LP:DP ratio on the lower borderline of the normal range. The EOG response reflects the transepithelial potential of the RPE cells, and together with the unremarkable FA, IA, and FAF findings, these data suggest that RPE dysfunction is the major cause of MEKi-associated SRD. Unremarkable FAF also suggests that MEKi does not affect RPE structures including autofluorescence substances such as lipofuscin, but it does affect RPE function.

The mitogen-activated protein kinase (MAPK) pathway is essential for maintaining the homeostasis of the RPE. The MAPK pathway regulates tight junctions between RPE cells, which form the outer blood-retinal barrier [9]. MAPK also regulates water channels such as aquaporins [12], thereby mediating the fluid-pump function of the RPE. Therefore, a MEKi may interfere with the outer retinal barrier and pump function of the RPE, resulting in the accumulation of fluid in the retina and subretinal space. Because fluid leakage in angiography was absent in the areas of our patients' SRDs, we postulate that the impaired active transport of fluid/ions may be the major cause of SRD.

Clinical trials for MEKi for various types of metastatic cancer are undergoing, and indications for treatment with a MEKi can be expected to spread to a wide variety of intractable metastatic cancers. MEKi-associated retinopathy should be taken into consideration as a differential diagnosis in patients with unexplained SRDs during the treatment of metastatic cancer. If such patients show unremarkable FA/IA findings, EOG may be a useful examination when considering a diagnosis of MEKi-associated retinopathy.

Statement of Ethics

All clinical procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from 3 patients for publication of their relevant medical data and any accompanying images. For solely reporting of cases, this retrospective review of patient data did not require ethical approval in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.
Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Chihiro Murata, Yusuke Murakami, Takuma Fukui, and Sakurako Shimokawa contributed to the data acquisition and drafting of the manuscript. Koh-Hei Sonoda and Kimihiko Fujisawa contributed to the design of the work and data analysis.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. McCannel 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(8):1005–9.
2. Urner-Bloch U, Urner M, Stieger P, Galliker N, Winterton N, Zubel A, et al. Transient MEK inhibitor-associated retinopathy in metastatic melanoma. Ann Oncol. 2014;25(7):1437–41.
3. AlAli A, Bushehri A, Park JC, Krema H, Lam WC. Pimasertib and serous retinal detachments. Retin Cases Brief Rep. 2016;10(2):191–6.
4. Francis JH, Habib LA, Abramson DH, Yannuzzi LA, Heinemann M, Gounder MM, et al. Clinical and morphologic characteristics of MEK inhibitor-associated retinopathy: differences from central serous chorioretinopathy. Ophthalmology. 2017;124(12):1788–98.
5. van Dijk EH, van Herpen CM, Marinkovic M, Haanen JB, Amundson D, Luyten GP, et al. Serous retinopathy associated with mitogen-activated protein kinase kinase inhibition (Binimetinib) for metastatic cutaneous and uveal melanoma. Ophthalmology. 2015;77122(9):1907–16.
6. Francis JH, Canestraro J, Haggag-Lindgren D, Harding JJ, Diamond EL, Drilon A, et al. Clinical and morphologic characteristics of extracellular signal-regulated kinase inhibitor-associated retinopathy. Ophthalmol Retina. 2021;5(12):1187–95.
7. Duncan KE, Chang LY, Patronas M. MEK inhibitors: a new class of chemotherapeutic agents with ocular toxicity. Eye. 2015;29(8):1003–12.
8. Gavric AU, Ocvirk J, Meljavic PJ. Ocular changes in metastatic melanoma patients treated with MEK inhibitor cobimetinib and BRAF inhibitor vemurafenib. Radiol Oncol. 2018;52(2):213–9.
9. Fukuyama H, Komuku Y, Gomi F. Characteristics and treatment responses of cystoid retina associated with central serous chorioretinopathy. Jpn J Ophthalmol. 2021;65(3):372–9.
10. Weber ML, Liang MC, Flaherty KT, Heier J. Subretinal fluid associated with MEK inhibitor use in the treatment of systemic cancer. JAMA Ophthalmol. 2016;134(8):855–62.
11. Thavikulwat AT, Lopez P, Caruso RC, Jeffrey BG. The effects of gender and age on the range of the normal human electro-oculogram. Doc Ophthalmol. 2015;131(3):177–88.
12. Jiang Q, Cao C, Lu S, Kvlin R, Wallin B, Chu W, et al. MEK/ERK pathway mediates UVB-induced AQP1 downregulation and water permeability impairment in human retinal pigment epithelial cells. Int J Mol Med. 2009; 23(6):771–7.