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【 CASE REPORT 】

Bilateral Serous Retinal Detachment Associated with a Mitogen-activated Protein Kinase Kinase Inhibitor in a Patient with *BRAF*-mutant Colorectal Cancer

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Abstract:

We herein report a 73-year-old woman with *BRAF* V600E-mutated colon cancer treated with encorafenib plus cetuximab with binimetinib as standard salvage therapy for patients with advanced colorectal cancer. She developed bilateral serous retinal detachment the next day, and the regimen was discontinued, resulting in complete resolution by the third day. Doublet therapy without binimetinib was initiated along with a weekly ophthalmologic examination for 10 weeks without recurrence of retinal detachment. Thus, binimetinib was presumed to have been the cause of the retinal detachment. This clinical course suggests the need for close monitoring of patients for vision impairment and close collaboration with ophthalmologists.

Key words: colorectal cancer, BRAF, MEK inhibitor, retinal detachment

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Introduction

The BRAF serine/threonine protein kinase is a downstream protein in the epidermal growth factor receptor-mediated mitogen-activated protein kinase pathway. The mutation of codon 600 within the *BRAF* kinase domain causes constitutive activation. *BRAF* V600E-mutated colorectal cancer is associated with right-sided primary tumors, older women, high-grade tumors, and precursor sessile serrated adenomas (1).

Retrospective studies of Japanese patients with metastatic colorectal cancer (mCRC) have shown that a *BRAF* V600E mutation is a significant indicator of a poor prognosis (2) with a lower prevalence rate among Japanese than among Caucasian patients (5.4-6.7% vs. 5-12%) (3). Therefore, multiple Asian oncology organizations have reported agreement with the European Society for Medical Oncology consensus guideline, which recommends initial *BRAF* testing and first-line therapy using 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab for patients with *BRAF*-mutant mCRC (4).

BRAF, mitogen-activated protein kinase kinase (MEK), and EGFR inhibition strategies were developed through several clinical trials, although the biology of CRC with a *BRAF* mutation is complex and heterogenous (5). In this combination therapy, MEK inhibitors can cause different degrees of retinal, uveal, and adnexal ocular adverse events, leading to visual disturbances or discomfort (6). Recently, a global phase 3 trial demonstrated the efficacy of the combination of encorafenib and binimetinib for patients who experienced failure with one or two prior regimens with *BRAF* V 600E mutant mCRC. In this trial, 0.9% of patients developed serous retinal detachment (7), although information on the clinical course is limited.

We herein report a case of bilateral serous retinal detachment caused by a MEK inhibitor in a patient with *BRAF* V 600E mutant mCRC.

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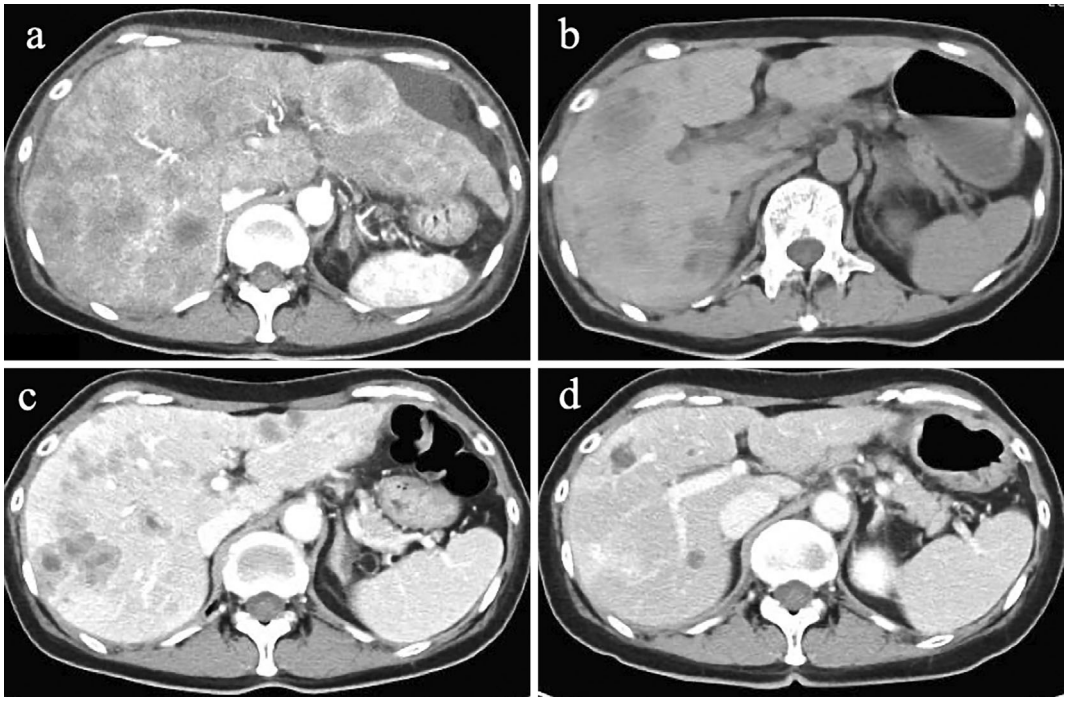

Figure 1. **Computed tomography findings before chemotherapy (a), after the fourth cycle of mFOLFOX plus bevacizumab (b), and before and fourth cycle of encorafenib and cetuximab (c and d, respectively).**

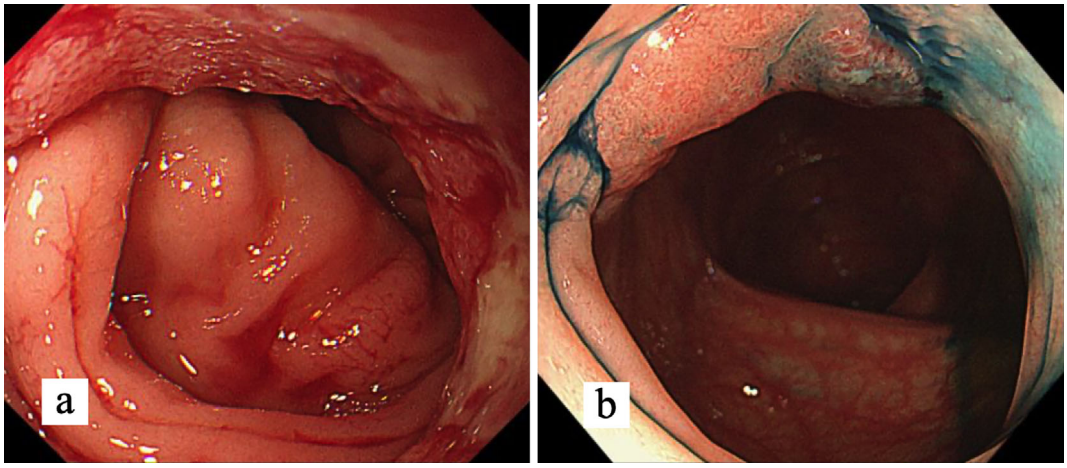

Figure 2. **Colonoscopy findings before chemotherapy (a) and after the second cycle of encorafenib and cetuximab (b).**

Case Report

A 73-year-old woman consulted her previous doctor because of loss of appetite and weight loss for the past 2 months. In addition, she was also suspected to have cancerous peritonitis and transverse colon cancer. The patient was referred to our hospital, where she was diagnosed with advanced transverse colon cancer with *BRAF* V600E mutation, hepatic metastases, and peritoneal dissemination (T3N2M1b; Hep, P; cStage IV) and hospitalized (Fig. 1a, 2a). She initially developed disseminated intravascular coagulation (DIC) because of the advanced disease stage.

As first-line chemotherapy, bevacizumab (5 mg/kg on day 1) followed by modified FOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and fluorouracil 400 mg/m^2 intravenous bolus on day 1 and then 2,400 mg/m^2 over 46 hours of continuous infusion) was administered. The patient's condition improved, and she was discharged and continued chemotherapy as an outpatient.

However, on the third day after the fourth cycle, the patient was rushed to the emergency department due to impaired consciousness and diagnosed with posterior reversible encephalopathy syndrome (PRES) based on hypertension and brain MRI findings. She regained consciousness the next morning with observation alone, and oxaliplatin or

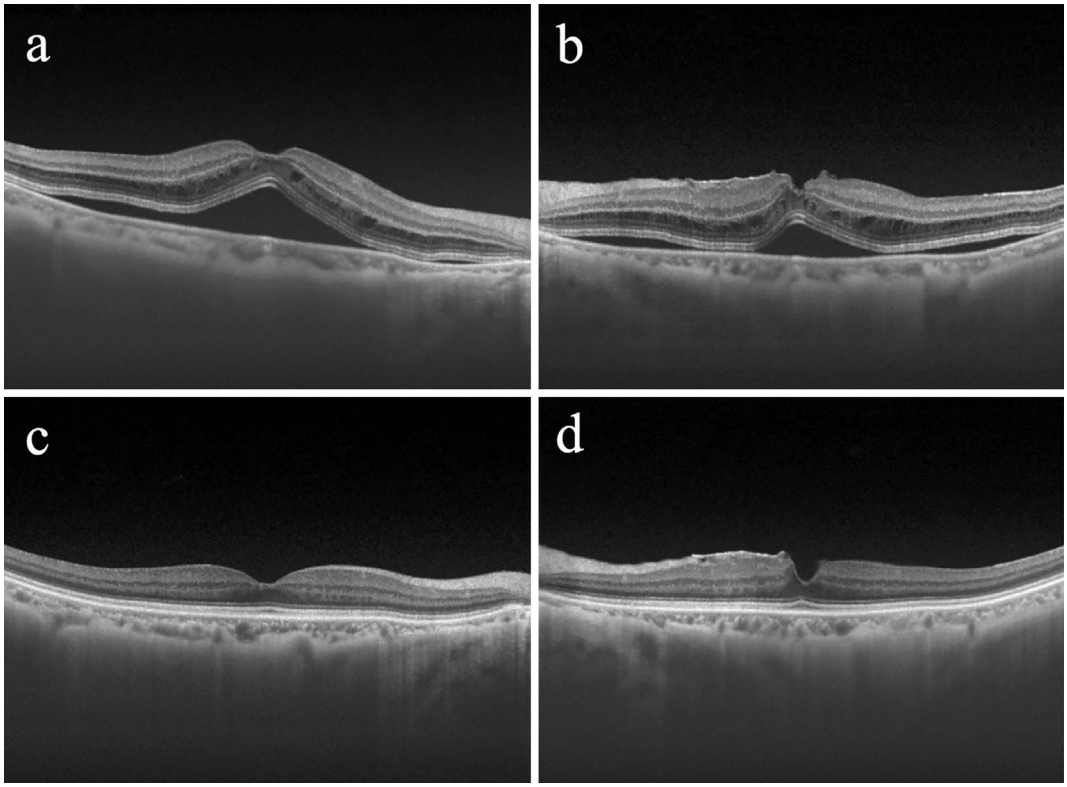

Figure 3. Optical coherence tomography findings (a, c: right eye; b, d: left eye). Foveal subretinal fluid was observed in both eyes (a, b), which was completely resolved on the third day in both eyes (c, d).

bevacizumab was suspected of being the cause of the PRES. Although mFOLFOX6 as first-line chemotherapy was effective and reduced the hepatic metastasis (Fig. 1b), the regimen was discontinued because of this adverse event.

Since this was a case of advanced CRC with a *BRAF* V 600E mutation, aggressive treatment was considered desirable. Encorafenib (300 mg daily) plus cetuximab (400 mg/m^2 as an initial dose and then 250 mg/m^2 weekly) with binimetinib (45 mg twice daily) was selected as second-line treatment. The patient was hospitalized, and the second chemotherapy regimen was started. Twelve hours after the oral administration of encorafenib and binimetinib, the patient complained of acute-onset visual impairment.

On a clinical examination by an ophthalmologist, her decimal visual acuity was 0.7 in both eyes. Optical coherence tomography (OCT) revealed sub-foveal neurosensory serous retinal detachment (Fig. 3a, b). Binimetinib, encorafenib, and corticosteroid as a premedication were suspected of having caused the retinal detachment, and the chemotherapy was discontinued.

The next morning, the patient's vision improved slightly, and on the third day, the abnormal findings had completely resolved on OCT (Fig. 3c, d). The decimal visual acuity improved to 1.2 in the right eye and 1.0 in the left eye. This ocular toxicity was assessed as Common Terminology Criteria for Adverse Events (CTCAE) Grade 2, which resolved to Grade 0. These clinical courses suggested that the same treatment could be reinstituted with or without dose reduction, but the patient did not consent to receive the same regimen. In addition, ocular adverse events have been reported more frequently in binimetinib plus cetuximab with encorafenib regimen than in those without binimetinib (7). Therefore, only a regimen consisting of encorafenib and cetuximab was administered.

In the present case, the utmost care was exercised to prevent subsequent retinal detachment. The patient was therefore hospitalized again for a week to undergo a daily ophthalmologic examination in order to detect vision impairment and retinal detachment promptly. Although the patient received weekly follow-up for 10 weeks, with the examination interval gradually increased up to 3 weeks, no ocular adverse events were observed during the follow-up period of 6 months. Grade 2 nausea was the only adverse event to occur during the doublet therapy. After two cycles of the doublet therapy, computed tomography (CT) and colonoscopy showed shrunken tumors (Fig. 1c, 2b). The best response to the therapy was a partial response (Fig. 1d), and the progression-free survival was about six months (Fig. 4).

Discussion

The regimen consisting of encorafenib plus cetuximab with or without binimetinib is accepted as standard therapy for patients with advanced CRC with a *BRAF* V600E mutation who experience failure with one or two prior regimens (7). Our present findings suggest that patients receiv-

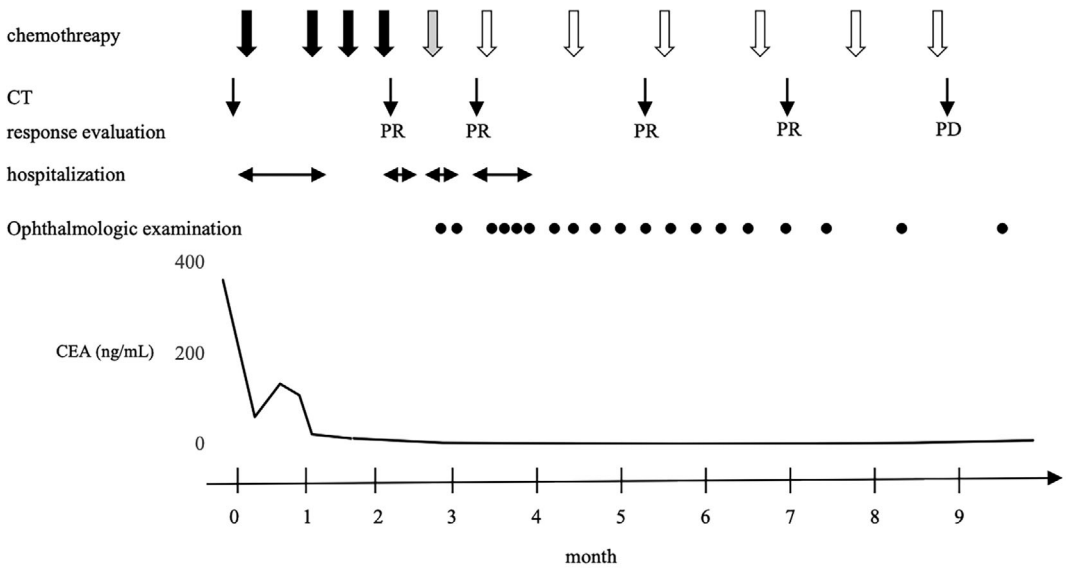

Figure 4. **The clinical course of chemotherapy. Black arrow: modified FOLFOX6. Gray arrow: encorafenib plus cetuximab with binimetinib therapy. White arrow: encorafenib and cetuximab therapy.**

ing MEK inhibitors need to be closely monitored for vision impairment.

The efficacy of the regimens that we administered to the patient in this report have been demonstrated in a previous study (7). In an open-label, phase 3 trial, 665 patients with *BRAF* V600E-mutated mCRC that progressed after 1 or 2 previous regimens were randomly assigned to receive encorafenib, binimetinib, and cetuximab (triplet therapy group); encorafenib and cetuximab (doublet therapy group), or cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil, and irinotecan; control group). The median overall survival was 9.0 [95% confidence interval (CI), 8.0 to 11.4] months in the triplet therapy group, 8.4 (95% CI, 7.5 to 11.0) months in the doublet therapy group, and 5.4 (95% CI, 4.8 to 6.6) months in the control group. The objective response rate was 26% (95% CI, 18% to 35%) in the triplet therapy group and 20% (95% CI, 13% to 29%) in the doublet therapy group, both of which were significantly higher than in the control group ($p<0.001$). Although no significant difference was found in the best percentage change in the size of the target lesions, the triplet therapy showed better results than the doublet therapy in cases with high baseline levels of C-reactive protein, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1, an incompletely resected primary tumor, and involvement of ≥3 organs (8). In the present case, the patient had *BRAF*-mutated mCRC with multiple liver metastases and severe peritoneal dissemination with a PS of 1. We suspected that intensive therapy was needed and thus selected the triplet therapy. After the improvement of serous retinopathy, doublet therapy (encorafenib and cetuximab without binimetinib) was initiated. Based on previous reports (7, 9, 10), the triplet therapy may have been able to be continued with or without dose reduction, but the patient did not provide her consent to continue the triplet therapy because binimetinib, a mitogen-activated MEK inhibitor, has been associated with ocular adverse events (11-14). In addition, the risk of retinal detachment was reported to be associated with the age, glomerular filtration rate, and history of ocular disease (particularly inflammatory eye disease). In the present case, age was the most relevant factor (6). Furthermore, CT performed two months after starting doublet therapy showed shrunken tumors, indicating the efficacy of this regimen. Thus, the patient continued receiving the doublet therapy.

The mechanism underlying MEK inhibitor-associated retinopathy (MEKAR) is poorly understood. The mitogen-activated protein kinase (MAPK) pathway plays an important role in the maintenance, protection, and repair of the retinal pigment epithelium. An *in vitro* study (15) showed that MAPK signaling regulates the density of fluid transport channels (aquaporins) between retinal pigment epithelial cells, indicating that MAPK signaling regulates the permeability of the retinal pigment epithelium and thus the accumulation of subretinal fluid (9, 15). As these events usually arise in the early phase after dosing, the toxicities were suspected of being related to the maximum serum concentration (16).

Future studies should explore the association between MEKAR and anti-tumor efficacy, as an anti-EGFR agent-induced skin rash has been associated with efficacy in patients with mCRC (17). However, our literature review did not uncover any studies evaluating the correlation between MEKAR severity and the anti-cancer efficacy of binimetinib.

In patients with melanoma, fluid accumulation in the retina resulting in retinal detachment is a common adverse event during treatment with BRAF and MEK inhibitors (18). This adverse event is a known class effect of MEK inhibi-

tors (11). In previous reports, 0.6-27% patients with advanced melanoma developed serous retinopathy reactions to MEK inhibitors (10, 18, 19). A phase 3 study of malignant melanoma using the same doses of encorafenib and binimetinib as for colorectal cancers reported a 1% incidence of retinal detachment (10). Most retinopathy incidents arise quickly after the start of treatment (within 1 day to 1 month) (9, 13). In a previous study, most patients with serous retinal detachment found by an ophthalmologic examination were asymptomatic or showed only mild symptoms. Patients with CTCAE Grade 1 event continued the chemotherapy, and all retinopathic events resolved (9, 12). However, 0.9% of patients with mCRC with a *BRAF* mutation treated by encorafenib and cetuximab plus binimetinib developed serous retinal detachment. These events were CTCAE Grade 1 or 2 and did not require dose reduction (7). Among the safe lead-in results from the phase 3 study, two patients developed grade 2 serous retinal detachment but remained in the study after the interruption of binimetinib dosing (20). Although patients with mCRC additionally received cetuximab, the incidence and severity were similar to those of patients with melanoma. In the present case, retinal detachment was diagnosed because of the patient's complaint of blurred vision and resolved within three days. This clinical course is similar to that in previous reports in patients with other cancers besides mCRC (9, 11, 13).

In the protocol of the clinical trial of mCRC (7), the ophthalmologic examination was performed at the screening phase, on cycle 2 day 1 (i.e., on day 29), and then every 8 weeks from cycle 2 day 1 as well as at the end of treatment. A 30-day follow-up examination is required if a clinically significant abnormality is noted at the end of the treatment. Thus, an ophthalmologic examination was performed at intervals of at least one month. Of note, retinal detachment tends to occur in the early phase of treatment with MEK inhibitors, and there has been a report of non-resolving MEKAR (21), so more frequent ophthalmologic examinations may be necessary, particularly in the early phase.

This report describes the clinical course of serous retinal detachment associated with the use of a MEK inhibitor in a patient with *BRAF*-mutant mCRC. Ocular toxicities can affect the activities of daily life and patients' quality of life. Patients receiving MEK inhibitors therefore need to be closely monitored for vision impairment through close collaboration with ophthalmologists.

The authors state that they have no Conflict of Interest (COI).

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