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Clinical and Morphologic Characteristics of MEK Inhibitor–Associated Retinopathy

Differences from Central Serous Chorioretinopathy

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Purpose: To investigate the clinical and morphologic characteristics of serous retinal disturbances in patients taking mitogen-activated protein kinase kinase (MEK) inhibitors.

Participants: A total of 313 fluid foci in 50 eyes of 25 patients receiving MEK inhibitors for treatment of their metastatic cancer, who had evidence of serous retinal detachments confirmed by optical coherence tomography (OCT).

Design: Single-center, retrospective cohort study.

Methods: Clinical examination and OCT were used to evaluate MEK inhibitor–associated subretinal fluid. The morphology, distribution, and location of fluid foci were serially evaluated for each eye. Choroidal thickness was measured at each time point (baseline, fluid accumulation, and fluid resolution). Two independent observers performed all measurements. Statistical analysis was used to correlate interobserver findings and compare choroidal thickness and visual acuity at each time point.

Main Outcome Measures: Comparison of OCT characteristics of retinal abnormalities at baseline to fluid accumulation.

Results: The majority of patients had fluid foci that were bilateral (92%) and multifocal (77%) and at least 1 focus involving the fovea (83.3%). All fluid foci occurred between the interdigitation zone and an intact retinal pigment epithelium. The 313 fluid foci were classified into 4 morphologies, as follows: 231 (73.8%) dome, 36 (11.5%) caterpillar, 31 (9.9%) wavy, and 15 (4.8%) splitting. Best-corrected visual acuity at fluid resolution was not statistically different from baseline; and no eye lost more than 2 Snellen lines from baseline at the time of fluid accumulation. There was no statistical difference in the choroidal thickness between the different time points (baseline, fluid accumulation, and fluid resolution). A strong positive interobserver correlation was obtained for choroidal thickness measurements ($r = 0.97$, $P < 0.0001$) and grading of foci morphology ($r = 0.97$, $P < 0.0001$).

Conclusion: The subretinal fluid foci associated with MEK inhibitors have unique clinical and morphologic characteristics, which can be distinguished from the findings of central serous chorioretinopathy. In this series, MEK inhibitors did not cause irreversible loss of vision or serious eye damage. *Ophthalmology 2017;■:1–11 © 2017 by the American Academy of Ophthalmology*

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Human cancers commonly have dysregulation of the mitogen-activated protein kinase (MAPK), and may be amenable to treatment with targeted agents that block this pathway, such as mitogen-activated protein kinase kinase (MEK) inhibitors.[1–4] Targeted agents have a different toxicity profile compared with traditional chemotherapy.[5] Specifically, MEK inhibitors have been associated with self-limited serous detachments of the neurosensory retina, which have been designated MEK inhibitor–associated retinopathy (MEKAR).[6–12]

Some groups and authors have labeled these neurosensory detachments with the description of "central serous retinopathy (CSR)" or "CSR-like."[11,13–15] A recent editorial has suggested MEKAR is intriguing owing to "its similarity to central serous chorioretinopathy" and its potential to deepen our understanding of this latter visually-threatening disease.[16] The authors of this published editorial dedicate a paragraph to discussing the differences between MEKAR and central serous chorioretinopathy (CSC), and others have also commented on these distinctions.[9,10,16]

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However, the discussion of these differences is limited to a few points: the "presentation and location" of the fluid are distinct and retinal pigment epithelial detachments (PEDs) and fluorescein leakage are absent in MEKAR. In some reports, there is no further elaboration on these statements, or the assertion is based on fewer than a handful of patients or simply represents a citation of another paper.

In an effort to better understand this topic, this study systematically explored additional characteristics that may differ between these 2 disease entities (MEKAR and CSC). By carefully evaluating over 300 fluid foci in eyes of cancer patients on MEK inhibition, this study analyzed the clinical and morphologic characteristics and the associated retinal, retinal pigment epithelium (RPE), and choroidal changes. Through this analysis, the differences between MEKAR and CSR are discussed: known findings are confirmed and new findings are described.

Methods

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center. This retrospective, single-center study included 25 patients recruited from Memorial Sloan Kettering Cancer Center, New York, New York, between October 2012 and February 2017. Patients were enrolled in a prospective MEK inhibitor study for treatment of their metastatic cancer and exhibited subretinal fluid on optical coherence tomography in 1 or both eyes.

Examination

All enrolled patients received an ophthalmologic examination complete with best-corrected visual acuity (BCVA), automated refraction, intraocular pressure, dilated fundus examination, and fundus photography. Enhanced-depth imaging optical coherence tomography (OCT) images were obtained with the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering). A scan of 9 mm was used and a 32-line cross-scan patterns were chosen in the horizontal direction, consisting of a maximum of 50 averaged scans. Patients were examined at baseline, followed by examinations either required by the study protocol (in all but 1 protocol) or conducted if the patient was symptomatic. All but 1 patient was on a protocol that required scheduled examinations irrespective of symptoms (Table S1, available at www.aaojournal.org).

Data Collection

Demographic data were collected on each patient, including gender, age, and primary cancer diagnosis. Treatment data included the initial drug, dose, route, frequency, duration, number of cycles, concomitant drugs, and any alterations in this plan over the treatment course. Clinical data included best-corrected visual acuity (in Snellen and logMAR) at baseline, fluid accumulation and fluid resolution, and whether the patient was symptomatic at the time of fluid accumulation. Further data included time from medication start to initial subretinal fluid detection by OCT, the cycle number during which subretinal fluid was initially detected by OCT, and time to resolution of subretinal fluid by OCT (evaluable in 39 eyes: for 5 patients [10 eyes] there were no adequate images available at the time of fluid resolution and 1 eye developed no serous detachment).

By OCT, the foci of fluid were carefully examined for each eye: details on the number of foci, laterality of foci, location within the fundus, location within OCT layers, configuration/morphology of fluid, caliber of the OCT layers, and other chorioretinal abnormalities (intraretinal cysts, presence of PED, hyperreflective dots) were all recorded. Two independent observers performed grading of the fluid foci morphology and an interobserver correlation was calculated.

Choroidal thickness was measured on enhanced-depth imaging OCT with the caliper tool, as the vertical distance from the hyperreflective line (corresponding to the Bruch membrane) to the chorioscleral border. Two independent observers performed manual segmentation of the choroid at all measurement points, and the mean of both measurements was used for analysis. Choroidal thickness was measured in the location corresponding to the focus of subfoveal subretinal fluid and was evaluable for 32 eyes. In 2 eyes with nonfoveal foci, a location corresponding with an adjacent fluid focus was measured. Choroidal thickness was compared from baseline to fluid accumulation (evaluable in 32 eyes), fluid accumulation to resolution (evaluable in 31 eyes), and baseline to fluid resolution (evaluable in 29 eyes). Eyes were deemed inevaluable if no images were available or if the OCT image was not enhanced-depth, which is preferred for assessment of choroidal thickness.

Statistical Analysis

Choroidal thickness was expressed as mean ± standard error of the mean. Interobserver correlation for all measurements was determined using Pearson correlation. The mean choroidal thickness measurements, and grading of fluid foci morphologies, between observer 1 and observer 2 were used for comparison and statistical analysis. Choroidal thickness was analyzed with a paired 2-tailed *t* test and confirmed with a 2-way analysis of variance. A *P* value less than or equal to 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad software (GraphPad Software, Inc, La Jolla, CA).

Results

Fifty eyes of 25 patients with MEK inhibitor–associated subretinal fluid were evaluated. Details regarding patient characteristics and drug information are provided in Table 1. Primary cancer diagnoses included cutaneous melanoma, ovarian cancer, gastrointestinal stromal tumor, colon cancer, uveal melanoma (1 patient; included fellow eye), and thyroid cancer. The mean patient age was 59 years (median, 61 years; range, 22–81 years). Seventeen of 25 patients (68%) were female.

The median duration of the first cycle was 1 day (range, 1–7 days) and the median frequency of the cycles was 4 weeks (range, 3–5 weeks). The median time from medication start to initial subretinal fluid detection by OCT was 14 days (mean, 28.0 days). The abnormal OCT findings were found after a median of 1 cycle of drug (mean, 1.4 cycles of drug, range, 1–4 cycles): 80% of patients had abnormal OCT findings after a single cycle of drug. The overall median time to resolution of the subretinal fluid by OCT was 32 days (mean, 47.4 days; range, 5–182 days). Of evaluable eyes receiving 5 cycles or less, the median time to resolution was 21 days (mean, 35 days, n = 24 eyes). Of evaluable eyes receiving more than 5 cycles, the median time to resolution was 54 days (mean, 65.1 days; n = 15 eyes). In all cases of bilateral fluid foci, resolution occurred at the same time for both eyes. In all eyes, the fluid was self-limiting and did not require discontinuation of the drug.

Concomitant drugs in 7 of the protocols included panitumumab, dabrafenib, ribociclib, imatinib, atezolizumab, encorafenib, and buparlisib. There was no difference in the mean number of foci