OBSERVATION

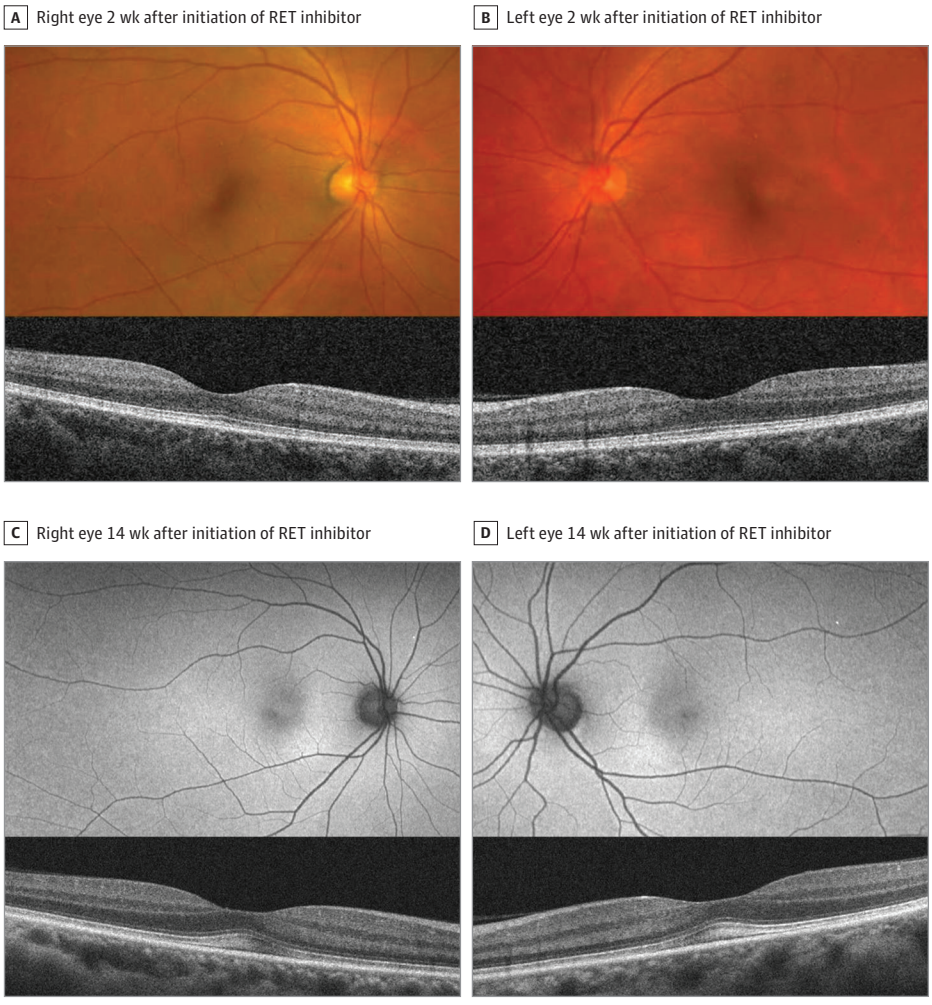
Fovea-Involved Outer Retinal Abnormality Induced by a Novel RET Inhibitor

Report of a Case | A 52-year-old female was diagnosed with right lung adenocarcinoma (T3N2M0IIIA) complicated by cervical lymph and hilar lymph node metastasis 5 months previously. Genetic testing revealed a *RET* gene fusion, and she was enrolled in a phase 1/2 clinical trial in which a novel tyrosine kinase inhibitor called KL590586 was used orally to inhibit the proliferation of tumors with *RET* gene mutations. After 2 weeks of the medication, her ophthalmic examination showed a best-corrected visual acuity (BCVA) of 20/20 OU. Slitlamp examination and fundus photography showed no anterior or posterior segment abnormalities. Optical coherence tomography (OCT) of the macular area is shown in **Figure 1**A and B. The central subfield thickness was 254 µm OD and 240 µm OS, and the central subfield volume was 10.5 mm^3 OD and 10.3 mm^3 OS.

Fourteen weeks after starting the medication, the patient had a second ophthalmic examination. Her BCVA and fundus photographs remained the same as before, whereas the high-definition OCT showed thickening of the interdigitation zone (IZ) without an obvious change of autofluorescence (Figure 1C and D). The patient was asked to follow up while continuing to take the medication.

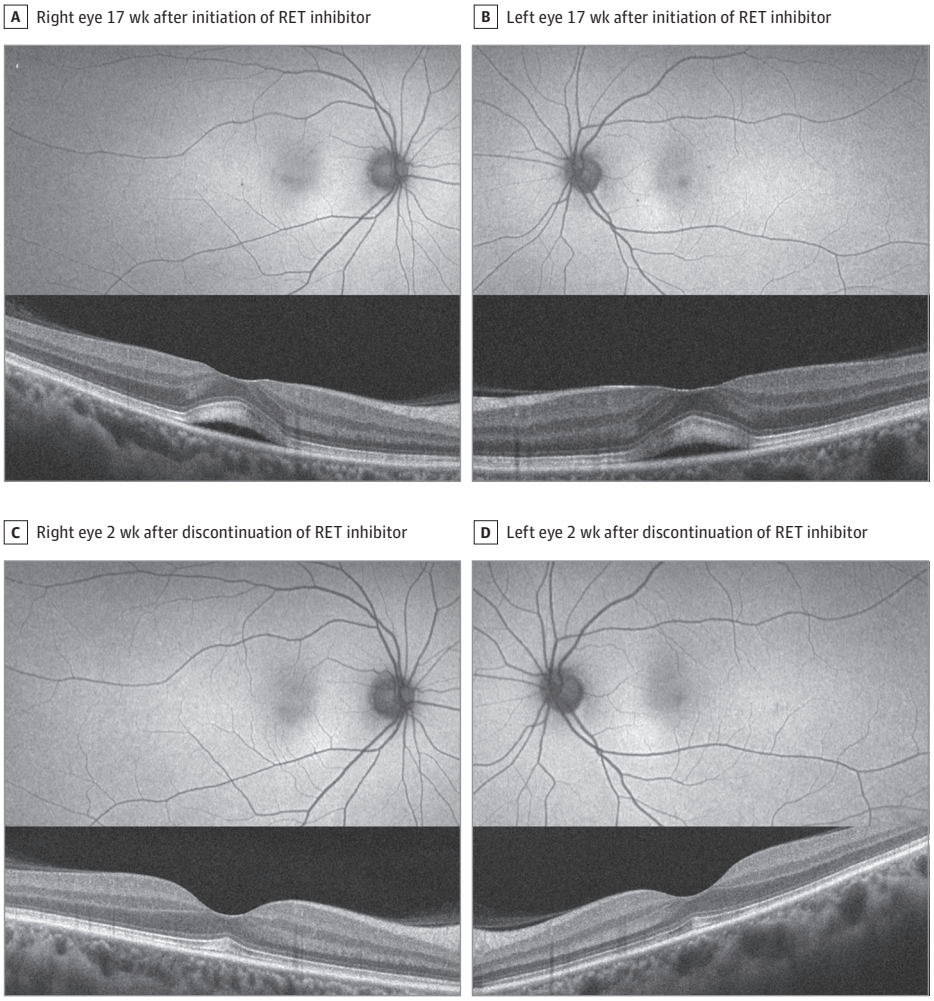
Three weeks later, she reported a mild yellowish central scotoma in both eyes. Her BCVA was still 20/20 OU and the autofluorescence remained normal, but the OCT showed further thickening of the IZ combined with a fovea-involved focal neurosensory retinal detachment bilaterally. The maximum width and height of the detached area were 1412 µm and 78 µm OD and 1451 µm and 60 µm OS, respectively

Figure 1. First 2 Fundus Images Captured After the Initiation of Treatment With the RET Inhibitor



A, Bilateral fundus color photographs and optical coherence tomography (OCT) B scans (512 × 128–volume scans, Cirrus HD5000; Zeiss) displaying normal macular structures. B, Bilateral autofluorescence fundus photographs showing no abnormal hyperautofluorescence or hypoautofluorescence. High-definition OCT B scans reveal bilateral thickening of the interdigitation zone.

Figure 2. Last 2 Fundus Images Captured After the Initiation of Treatment With the RET Inhibitor



A, Bilateral autofluorescence fundus photographs showing no abnormal hyperautofluorescence or hypoautofluorescence. High-definition optical coherence tomography (OCT) B scans (Cirrus HD5000; Zeiss) show further thickening of the interdigitation zone combined with a fovea-involved focal neurosensory retinal detachment bilaterally. B, Bilateral autofluorescence fundus photographs showing no abnormal hyperautofluorescence or hypoautofluorescence. Bilateral high-definition OCT B scans show the central macular abnormality had resolved, leaving a focal slight enhancement of the interdigitation zone.

(**Figure 2**A and B). After reporting this issue to the oncologist, the patient was told to temporarily discontinue the medication.

Two weeks later, her symptoms disappeared and visual acuity remained unchanged. The OCT revealed that the central macular abnormality had resolved, leaving a slight focal enhancement of the IZ (Figure 2C and D). The patient was then told to resume the treatment and continue regular follow-up.

Discussion | RET is a receptor tyrosine kinase that plays an important role in the development of neurons and kidneys. *RET* gene fusions, which lead to increased oncogenic signaling, are a targetable alteration in patients with *RET* fusion-positive solid tumors. Recent phase 3 clinical trials have confirmed the efficacy of RET inhibitors in lung and thyroid cancers, with adverse events mainly related to the digestive, cardiovascular, and hematological systems.[1,2] To our knowledge, retinopathy has not been reported to be related to RET inhibitors in humans. Nevertheless, previous experiments have demonstrated that retinas from RET hypomorphic mice were both functionally and anatomically abnormal, and specific damage to the photoreceptor cell synapses was indicated.[3,4] Previously, Francis et al[5] reported a case series of mitogen-activated protein kinase–associated retinopathy (MEKAR), characterized by bilateral multifocal subretinal fluid foci with undisturbed retinal pigment epithelium (RPE).

In this case, the outer retinal abnormality associated with the RET inhibitor bears a resemblance to that observed in MEKAR; however, only a single center-involved lesion was identified. Notably, we observed that IZ thickening occurred before the onset of neurosensory detachment, a feature not previously highlighted in cases of MEKAR. Given that the damage in this RET-associated maculopathy was restricted to the outer segments of the photoreceptors, with the RPE remaining intact and visual acuity preserved throughout the observation period, we question the presence of fluid accumulation in the space between the IZ and the RPE. Moreover, Francis et al[5] reported no leakage on fluorescein angiography in cases of MEKAR.

In summary, a reversible isolated macular outer retinal segment abnormality was associated with a novel RET inhibitor. Therefore, patients undergoing RET inhibitor treatment should be observed carefully with macular OCT.

Nevertheless, further investigations are warranted to determine whether this RET-associated maculopathy could cause permanent visual loss or share the same entity with MEKAR.

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