Rapid onset of radiation maculopathy after whole-brain radiation therapy
A case report

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Abstract
Background: Radiation maculopathy is a phenomenon that occurs after radiation exposure. The rapid onset of unilateral macular atrophy without peripheral retinopathy after radiation has rarely been described.

Methods: A case report and literature review.

Results: We report a case of stage 4 non-small cell lung cancer under targeted therapy using Gefitinib who presented with severely impaired visual acuity related to rapid onset of unilateral macular atrophy and diminished photoreceptor inner segment/outer segment (IS/OS) junction 1 month after whole-brain radiation therapy. The fundus fluorescein angiography revealed an enlarged diamond-shaped clear-cut foveal avascular zone in the macula without peripheral retinal vascular changes that differed from typical radiation retinopathy. We confirmed the diagnosis by evaluating the total radiation dosage and by excluding target therapy-induced maculopathy based on a review of the medical literature.

Conclusion: Current therapeutic interventions for macular atrophy after radiation therapy remain a challenge. Vasodilators or antplatelet medication may be beneficial; however, long-term follow-up is needed. Further studies are required to support the use of early aggressive therapy for the prevention of radiation retinopathy.

Abbreviations: BBB = blood-brain barrier, EGFR = epidermal growth factor receptor, ERG = full-field electoretinogram, FFA = fundus fluorescein angiography, Gy = Gray, ICG = indocyanine green chorioangiography, IS/OS junction = inner segment/outer segment junction, MRI = magnetic resonance imaging, SD-OCT = spectral-domain optical coherence tomography, VEP = visual-evoked cortical potential.

Keywords: gefitinib, radiation maculopathy, whole-brain radiation therapy

1. Introduction
Radiation retinopathy is a well-established, dose-dependent complication after radiation therapy. The most characteristic signs result from vascular decompensation caused by radiation damage. The rapid onset of unilateral macular atrophy without peripheral retinopathy after radiation has rarely been reported in the literature. In this report, we describe an unusual case of radiation maculopathy in a stage 4 lung cancer patient receiving targeted therapy that was initially thought to be caused by ocular toxicities. We present the clinical ocular findings and describe the manifestation of ischemic radiation maculopathy, which may be of value to ophthalmologists and radiation oncologists.

2. Case report
A 55-year-old female presented to our eye clinic because of blurred vision in the right eye for 1 month. She had a medical history of stage 4 nonsmall cell lung cancer which was treated using targeted therapy with Gefitinib and had finished whole-brain radiation therapy 2 months earlier (40Gray [Gy] in 16 fractions) for brain metastasis (Fig. 1A and B). There was no history of diabetes, hypertension, or systemic vascular disease. There was no other ocular history of note. At the initial assessment, she had best-corrected visual acuity of finger counting at a distance of 30 cm in the right eye and 6/6 in the left eye. The intraocular pressure, anterior segment, optic disc, and retinal vessels were unremarkable bilaterally. No relative afferent pupillary defect was noted in either eye. Fundus examination showed loss of foveal light reflex of the right eye (Fig. 2). Spectral-domain optical coherence tomography (SD-OCT) showed macula atrophy with diminished photoreceptor IS/OS junction of the right eye with a central retinal thickness of 229 μm and several intraretinal cystic spaces, compared with 278 μm in the left eye (Fig. 3A and B). She scored 0/15 on color plates for the right eye. The standard automated perimetry showed paracentral scotoma visual field defect of the right eye in contrast to the left eye (Fig. 4A and B). Fundus fluorescein angiography (FFA) of the right eye revealed an enlarged diamond-shaped clear-cut foveal avascular zone in the macula that was disc-sized with peripheral surrounding microaneurysms and telangiectatic vessels in the zone margin (Fig. 5A). The FFA of the left eye presented with normal foveal avascular zone (Fig. 5B). Indocyanine green chorioangiography (ICG) showed normal choroidal vessels. No latency or reduced amplitude of the P100
component of the visual-evoked cortical potential (VEP) was observed. The full-field electroretinogram (ERG) response of the right eye showed no markedly reduced amplitude or significant abnormality. A review of the patient’s medical history did not reveal anything of concern with respect to diabetic retinopathy. Taken together, the severe ischemic macular change and the findings of clinical examinations suggested a diagnosis of radiation maculopathy. The high dose of radiation delivered further supports the diagnosis. She was regularly followed up in our clinic. No cotton wool spots or blot hemorrhages, retinal neovascularization, or vitreous hemorrhage were noted, and visual acuity of both eyes remained the same after 6 months. Antiplatelet medication (low-dose aspirin, 100 mg per day) was considered appropriate at this stage.

Our case report was waived from the ethical approval or institutional review board of Tri-Service-General-Hospital, based upon their policy to review case report including >3 cases. An informed consent has been explained to this patient and signed by herself.

3. Discussion

This case report describes the development of unilateral fulminant maculopathy after whole-brain radiation therapy without underlying medical or drug history. The area of the eye that appears to be most sensitive to radiation damage is the posterior pole. Radiation maculopathy typically develops when radiation exposure extends beyond tissue tolerance. The earliest and most common clinical feature of radiation maculopathy is macular edema,[1,2] which can lead to ischemic maculopathy. Initially, the capillary endothelial damage from ionizing radiation results in patches of capillary nonperfusion. Subsequent ophthalmoscopic and angiographic changes reflect features of vascular occlusion in the retina layers and choroid, including microaneurysms, retinal hemorrhages, intraretinal exudation, nerve fiber layer infarcts, perivascular sheathing, and retinal or optic disc neovascularization.[1] The primary event is probably endothelial cell damage with secondary loss of pericytes. This histologic picture is similar to that seen in diabetic retinopathy. The macular edema after radiation generally precedes ischemic change. Once ischemic maculopathy has evolved, visual improvement is unlikely. In contrast to typical evolved vascular change patterns in radiation maculopathy, the OCT of this patient revealed attenuation of central macular thickness with loss of photoreceptor IS/OS junction rather than macular edema. The FFA in our case further showed unilateral ischemic maculopathy without other extramacular abnormality as the only manifestation in the unilateral eye.
It has been reported that the total cumulative dose of radiation, the fraction size, concomitant chemotherapy, the presence of diabetes mellitus, collagen vascular disease, or pregnancy are important in the development of retinopathy.[3] A reported safe dose is 3000 rads/30 Gy, 1000 rads/10 Gy per week in 5 fractions (200 rads/2 Gy per session).[3] Absence of radiation retinopathy was observed in eyes receiving <40 Gy, whereas the incidence of retinopathy was 10% and 50% in eyes receiving doses of 40 to 60 and >60 Gy, respectively.[4] Parsons and colleagues[5] recommend that individual dose fractions should not exceed 1.8 to 1.9 Gy. In the recent Cochrane database review of radiotherapy for macular degeneration, no retinopathy or optic

Figure 3. (A) SD-OCT showed atrophy of central macular with diminished IS/OS junction of right eye. (B) SD-OCT of left eye. IS/OS junction = inner segment/outer segment junction, SD-OCT = spectral-domain optical coherence tomography.

Figure 4. (A) The standard automated perimetry using central 30–2 program showed paracentral scotoma visual field defect of right eye. (B) The standard automated perimetry of left eye.
Nerve damage was reported in 1154 patients treated with doses up to 24 Gy.\(^6\) The latent period before the onset of clinically significant retinopathy is typically 6 months to 3 years, but has been known to occur \(>15\) years after radiotherapy.\(^7\) The latent period is shorter after higher dose radiotherapy.\(^8\)

A higher than recommended radiation dose was prescribed in our case (2.5 Gy per session) due to multiple brain metastases. The retinal photoreceptors are radio-resistant and retinal atrophy usually develops after long-standing retinal detachment or macular edema. However, in this case, the macular ischemia and atrophy of the IS/OS junction developed rapidly without peripheral retinopathy. There were no other underlying vascular diseases that have a potentiating effect in the pathogenesis of vascular impairment of retina. Moreover, the rapid onset of unilateral maculopathy developing 1 month after completing treatment with whole-brain radiation therapy has rarely been reported.\(^8\)

Gefitinib is an orally bioavailable small molecule inhibitor of epidermal growth factor receptor (EGFR). It is administered daily during radiation therapy and continued daily after the completion of radiation therapy as the target therapy for metastatic lung cancers. Reported ocular and periocular adverse reactions of EGFR inhibitors include trichomegaly, periorbital rash with associated ectropion, and persistent corneal epithelial defect formation. Posterior ocular segment toxicities have not been reported.\(^9\) Preclinical and clinical studies have demonstrated the radiation-sensitizing effects of gefitinib in brain tumors. However, there is poor drug penetration to brain tumors owing to the existence of the blood–brain barrier (BBB).\(^10\) Hence, the concentration of gefitinib in retina vessels was likely not responsible for the development of maculopathy.

Different treatment regimens have been advocated in the management of radiation maculopathy. Focal laser photocoagulation, intravitreal anti-VEGF injections, and intravitreal dexamethasone implant have been used for radiation-induced macular edema and retinal or choroidal neovascularization.\(^11,12\) However, improvement in visual acuity after injection appears to be short term and is seen only in a few patients. Oral pentoxyphylline has been reported to increase visual acuity and decrease the number of hemorrhage dots and cotton wool spots of the macular nonperfusion area. A possible explanation is the unique rheologic properties of pentoxyphylline, which cause an increase in blood flow and oxygenation to the damaged retina.\(^13\) Current therapeutic interventions for radiation maculopathy place greater emphasis on macular edema. In our case, severe macular nonperfusion with impaired photoreceptor cells caused rapid visual loss, and thus, the treatment modality for macular edema was not appropriate. Low-dose aspirin was prescribed to increase retinal circulation. During the following 6 months, however, the visual acuity showed no improvement.

4. Conclusion
This case serves to remind both ophthalmologists and radiation oncologists that radiation maculopathy may increase the risk of rapid progression of vision loss. Counseling and fundus examination should be offered in all cases at risk of visual loss before receiving whole-brain radiotherapy. The use of antiplate-
let medication that was prescribed in our case may need to be reviewed during long-term follow-up. Further studies are required to determine whether the use of early aggressive therapy for the prevention of radiation retinopathy is beneficial.

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