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Teaching Case

Damage to the Superior Retinae After 30 Gy Whole-Brain Radiation

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Abstract

Purpose: The most common treatment protocol for whole-brain radiation therapy (WBRT) is 30 Gy in 10 fractions. This regimen entails a low risk of radiation retinopathy, with fewer than a dozen reported cases. We describe a case of radiation retinopathy that was confined to the superior retinae. These regions were the only portions of the eyes that were included in the treatment field.

Methods and Materials: Observational case report consisting of clinical examination, review of radiation treatment planning and implementation, computerized visual field testing, and fundus photography.

Results: A 36-year-old man with metastatic lung adenocarcinoma developed radiation retinopathy 16 months after WBRT to 30 Gy in 10 fractions. The retinopathy was largely confined to the superior halves of the retinae. There was corresponding geographic inferior visual field loss in both eyes. Review of the patient's treatment protocol revealed that the superior retinae received a substantial radiation dose, approaching 30 Gy, whereas the inferior retinae were essentially outside the treatment field.

Conclusions: In this patient, the correlation between the treatment field and the resulting local development of radiation retinopathy demonstrated unequivocally that the relatively low dose used in routine WBRT (ie, 30 Gy in 10 fractions) can induce radiation retinopathy.

Introduction

Whole-brain radiation therapy (WBRT) is a common palliative measure for patients with brain metastases. A dose of 30 Gy in 10 fractions is a widely used treatment regimen. A common risk of WBRT is neurocognitive impairment, which is partially mitigated by hippocampal avoidance.[1,2] Another risk is radiation retinopathy, a rare but sometimes unrecognized sight-threatening condition with delayed onset after irradiation. It is characterized by a progressive, occlusive microvasculopathy that resembles the findings associated with diabetic retinopathy. Common manifestations include cotton wool spots, microaneurysms, hard exudates, dot-blot hemorrhages, telangiectasis, cystoid macular edema, and neovascularization.

Fewer than a dozen cases of radiation retinopathy from WBRT have been reported.[3-8] Only a single case report has been published describing radiation retinopathy after a dose of 30 Gy in 10 fractions.[5] The patient was a 55-year-old woman with metastatic breast carcinoma who developed vision loss 6 years after treatment. The absence of any other cases in the literature raises some doubt whether radiation retinopathy can truly occur at a dose of only 30 Gy, which is generally thought to be safe. We corroborate

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the conclusion that 30 Gy can injure the eyes, by describing the regional development of radiation damage limited to retinal zones exposed to this dose.

Case Presentation

A 36-year-old man with a 17 pack-year smoking history and no other significant past medical history presented to his primary care physician with cellulitis of the right foot, followed by bilateral calf pain and swelling one week later. He was found to have bilateral deep venous thromboses. Anticoagulation treatment was started with rivaroxaban. Several weeks later, he presented to urgent care with neurologic symptoms. Magnetic resonance (MR) imaging 2 days later revealed greater than 50 scattered brain metastases. Treatment was started with oral dexamethasone. Computed tomography (CT) of the chest, abdomen, and pelvis showed a left pleural effusion with nodular pleural thickening, bilateral pulmonary nodules, hepatic hypodensities, and multiple lytic and sclerotic osseous lesions throughout the spine, clavicle, sternum, pelvis, and right proximal femur. Cytology from thoracentesis of the left pleural effusion revealed an adenocarcinoma, positive for thyroid transcription factor 1 (TTF-1) and monoclonal antibody 31. A core biopsy guided by CT imaging of the left lower lobe mass confirmed the diagnosis of adenocarcinoma, which was positive for thyroid transcription factor and Napsin A, consistent with a lung primary. Fluorescence in situ hybridization showed c-ros oncogene 1 (ROS1) gene rearrangements. The programmed death-ligand 1 tumor proportion score was 1%.

Ten days after MR imaging revealed brain metastases, WBRT was started. The patient received 30 Gy divided in 10 fractions during a period of 12 days. Treatment was administered using a Varian 2100 iX linear accelerator with on-board imaging and daily kV-kV image matching to ensure proper alignment of the radiation field. The treatment couch did not have 6 degrees-of-freedom capability to facilitate application of angular corrections. The treatment field included the cribriform plate; this resulted in a radiation dose gradient across the superior halves of the retinae (Fig 1). The 30 Gy isodose line intersected the superior retina. Isodose contours were tightly stacked through the upper half of the eyes, with a sharp drop in the planned dose to only 7.5 Gy in the middle of the globes. On a sagittal image the 30 Gy isodose line was tangent to most of the superior retinae. The inferior retinae were nearly fully outside the treatment field.

One month after WBRT, the patient started treatment with crizotinib 250 mg twice daily. Six weeks later a follow-up MR scan showed a marked decrease in the size and number of supra- and infratentorial lesions. Three months after initiation of crizotinib, positron emission tomography showed resolution of hypermetabolic activity in previously noted bony, mediastinal, and hepatic metastases, indicating a good response to therapy.

Unfortunately, 8 months after WBRT, a brain MR scan showed progression of disease with development of new lesions, enlargement of previously noted lesions, and leptomeningeal involvement. The patient was subsequently evaluated at our institution. Treatment with crizotinib was discontinued in favor of lorlatinib 100 mg per day.[9] One month later, follow-up MR imaging showed a modest improvement. It was decided to continue treatment with lorlatinib and to maintain close surveillance without any additional radiation therapy.

Sixteen months after WBRT, the patient noticed intermittent double vision. An MR scan showed enhancement

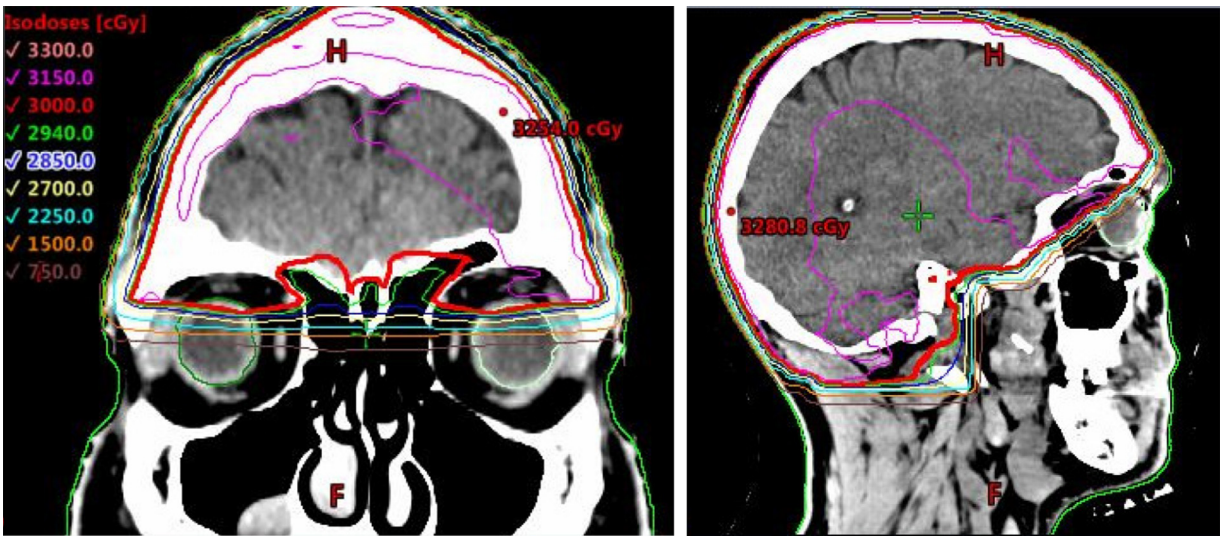

Figure 1 Radiation isodose contours on coronal and sagittal views demonstrating irradiation of the cribriform plate and the superior globes. There is a steep drop-off in the amount of planned radiation to the eyes. Note on the sagittal image that the 30 Gy isodose line follows closely the arc of the superior retina. Below the horizontal meridian of the globes, the dose is less than 7.5 Gy.

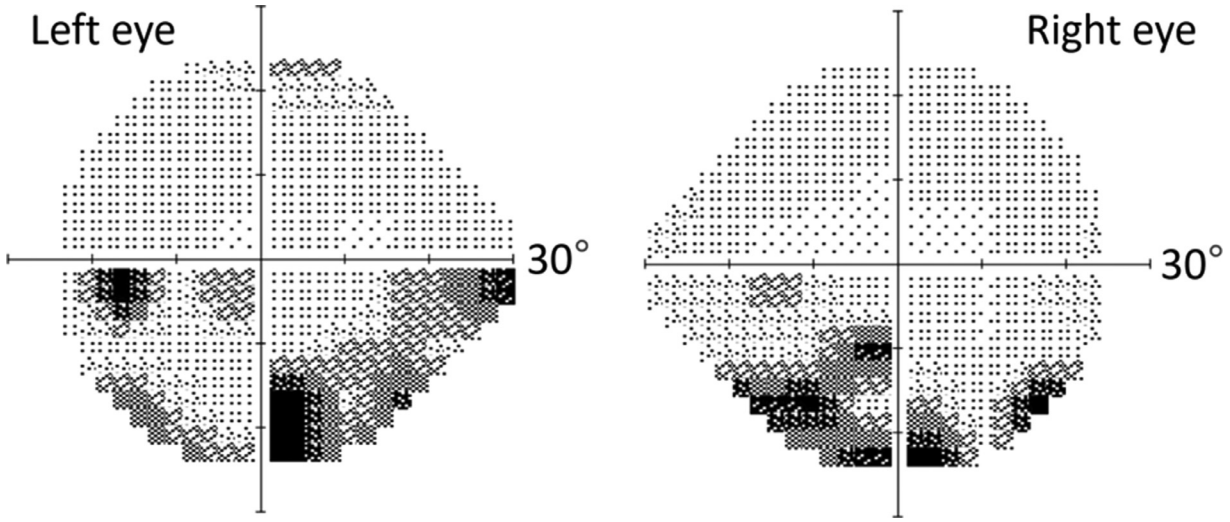

Figure 2 Humphrey threshold tests showing patchy inferior visual field loss in both eyes. Foveal sensitivities: 35 dB (left eye); 28 dB (right eye). Mean deviations: −7.92 dB (left eye); −7.48 dB (right eye).

of both oculomotor nerves. He was referred to the Neuro-ophthalmology Service for further evaluation of his symptoms. In our clinic, the patient was noted to have a best-corrected visual acuity of 20/20 in both eyes. No afferent pupillary defect was noted. The extraocular eye movements showed slight limitation in upgaze. His diplopia, which was his main concern, was attributed to mild, asymmetrical oculomotor nerve impairment.

Automated perimetry showed patchy visual field loss in both eyes on Humphrey 24-degree threshold testing (Fig 2). The striking feature of the defects was that they were entirely confined to the inferior visual fields. Dilated fundoscopic examination revealed a normal appearance of the optic discs in both eyes. There were typical signs of radiation retinopathy, with cotton wool spots, exudates, and dot-blot hemorrhages (Fig 3). The radiation damage was concentrated superiorly in both retinae, corresponding to his inferior visual field deficits. The patient was essentially unaware of this visual field loss. His radiation retinopathy has been monitored without treatment and has not progressed during a 6-month period of follow-up care.

Discussion

Although whole-brain radiation fields commonly encompass portions of the eyes, radiation retinopathy is a rare complication of whole-brain radiation therapy (WBRT).[8] At the conventional dose of 30 Gy in 10

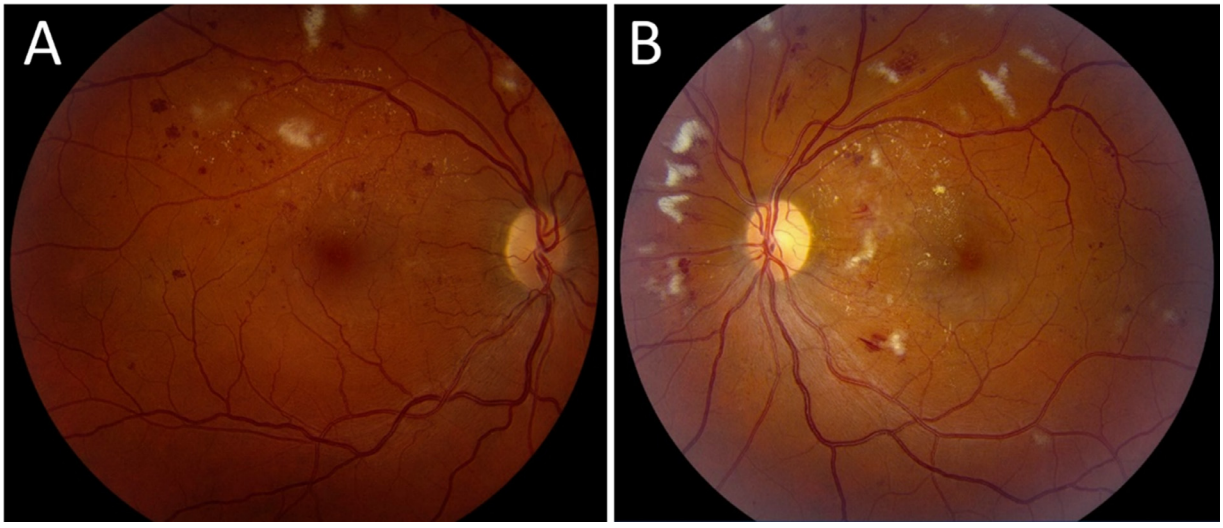

Figure 3 Fundus photos on presentation. (A) Right eye fundus showing cotton-wool spots, hard exudates, venous beading, microaneurysms, and splinter/dot-blot hemorrhages. Radiation retinopathy is localized predominantly to the superior hemiretina. (B) Similar findings in the left eye.

fractions, only a single case has been reported previously.[5] In that patient no other factor that might explain retinopathy, except for mild hypertension, could be identified. Our patient developed radiation retinopathy 16 months after administration of WBRT to 30 Gy in 10 fractions. Evidence that radiation retinopathy can result from this treatment regimen is adduced by the crucial finding that the damage was largely confined to the upper half of the retina in each eye, with corresponding inferior visual field loss. To our knowledge, this is the first documented case of radiation retinopathy from WBRT occurring in a bilateral superior hemiretinal distribution. The correspondence to the radiation isodose contours suggests that the superior retina in each eye was exposed to a substantial dose of radiation, whereas the inferior retinae were spared. The fact that retinopathy subsequently developed only in the superior retinae establishes a cause-and-effect relationship between the radiation treatment and the tissue damage. It makes it unlikely that a systemic condition, such as undetected diabetes mellitus or hypertension, was responsible for the retinopathy.

The precise threshold for the amount of focused radiation that can produce retinopathy is not known and likely varies with factors such as radiation target location, modality, fractionation, concurrent chemotherapy, and medical comorbidities. Some articles cite a higher risk of radiation retinopathy at doses greater than 45 Gy,[10] doses greater than 30 Gy,[11] and even at doses between 20 and 30 Gy.[12] Elsås et al[6] reported a case of bilateral radiation retinopathy in a 32-year-old man who received WBRT to 54 Gy in 30 fractions for an oligodendroglioma of the left frontal lobe, with a calculated dose of 11 Gy to the retina. The authors stated that this was the lowest retinal dose of radiation documented to produce retinopathy. Hong et al[3] described a case of a 37-year-old woman with breast cancer that metastasized to the brain who received 30 Gy over 10 fractions WBRT and 12 Gy local boost irradiation to the tumor bed in the right frontal area. The patient developed radiation retinopathy predominantly affecting the left eye; the authors suggested that shielding also be provided contralateral to the site of irradiation. These patients did not have any known risk factors predisposing them to radiation retinopathy. Hsu et al[4] described a case of unilateral radiation maculopathy without peripheral retinopathy in a patient with non-small cell lung cancer who had been treated with gefitinib and WBRT to 40 Gy in 16 fractions. Ko et al[7] reported a case of radiation retinopathy after WBRT to 35 Gy (number of fractions unspecified) for metastatic breast cancer, with resolution of bilateral macular edema after intravenous diuresis with furosemide for pleural effusion.

Our patient did not have any microvascular comorbidities such as hypertension, diabetes mellitus, or other systemic vascular diseases that would predispose him to radiation retinopathy. Concurrent or prior treatment with conventional chemotherapy may increase tissue sensitivity to radiation.[10,13,14] Our patient received only tyrosine kinase inhibitors: crizotinib and later lorlatinib, after completing WBRT. Crizotinib is a first-generation inhibitor used to treat non-small cell lung cancer caused by defects in anaplastic lymphoma kinase (ALK) or ROS1. It has a low rate of central nervous system penetration.[15] Crizotinib has been reported to cause visual disturbances such as flashes of light or shadows.[9,16] A single case has been reported of a patient receiving crizotinib who developed optic neuropathy and blindness after WBRT,[17] but no cases link crizotinib and retinopathy. Similarly, there are no documented reports of retinopathy associated with use of lorlatinib, a third-generation ALK tyrosine kinase inhibitor with a high rate of central nervous system penetration. Nonetheless, as new agents become available and patients live longer, there will be much to learn about how various systemic therapies may increase risks of radiation therapy.

There are currently no widely accepted treatments for radiation retinopathy, but given its similarities to diabetic retinopathy, therapies such as intravitreal antivascular endothelial growth factor (VEGF) agent injections (eg, bevacizumab), intravitreal steroid injections (eg, triamcinolone acetonide), and laser photocoagulation for cases with neovascularization have been studied as possible treatments with variable success.[18] A recent randomized phase 2 prospective clinical trial by Schefler et al[19] showed that monthly intravitreal injections with ranibizumab, an anti-VEGF agent, may improve visual acuity in patients with radiation retinopathy-related macular edema. Fortunately, our patient has not required treatment.

Despite daily pretreatment portal imaging in our patient to ensure proper alignment of the radiation field, this case illustrates that the relatively low dose used in routine whole-brain radiation can cause radiation retinopathy. Improvements in systemic therapy are prolonging survival in patients who previously would not have lived long enough to experience late toxicity,[20] heightening the importance of sparing normal tissue in treatment planning. In our patient, the globes were exposed to a substantial dose of radiation to include the cribriform plate, a sanctuary site for certain neoplasms, in the treatment field.[21-23] Shielding the eyes reduces the risk of developing ocular complications, such as radiation retinopathy, keratoconjunctivitis sicca, keratitis, and radiation-induced cataracts. Radiation oncologists must carefully balance the risk of radiation retinopathy against the risk that aggressive shielding may lead to undertreatment of the cribriform plate and cancer recurrence.

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