A Case of Radiation-Induced Optic Neuropathy and Retinopathy after Radiation Therapy, Chemotherapy, and Immunotherapy for Brain Metastasis

Brittney Jimenez OD,
Angelina Tran OD, FAAO,
Yun-Ting Lisa Huang OD, FAAO,
Bhagya Segu OD, MPH, FAAO

Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA

Abstract

Radiation-induced optic neuropathy and retinopathy are associated with high-dose radiation therapy and can lead to devastating vision loss. This case report follows a 72-year-old Hispanic male with extensive stage IV small cell lung cancer and brain metastasis who presented with radiation-induced optic neuropathy and retinopathy. The patient's cancer treatment included whole-brain external radiation therapy, chemotherapy, immunotherapy, and thoracic radiation therapy prior to his eye examination. When managing radiation-induced ocular sequelae, consideration should be given to the size of individual fractions administered during radiation therapy, particularly in patients concomitantly undergoing chemotherapy and immunotherapy.

KEYWORDS:
radiation retinopathy, optic disc edema, radiation optic neuropathy, external beam radiation, chemotherapy

INTRODUCTION

Radiation therapy used in the treatment of brain and intraocular tumors can lead to radiation-induced optic neuropathy (RION) and retinopathy.[1] External beam radiation greater than 35 gray (Gy) increases the risk for developing radiation-induced ocular sequelae with associated vision loss.[2,3] The patient described in this case report received 30 Gy of whole-brain external radiation therapy (WBXRT) delivered in ten 3 Gy fractions (fx) in conjunction with chemotherapy and immunotherapy. He subsequently developed optic neuropathy and retinopathy, presumably due to his cancer treatments.

CASE REPORT

A 72-year-old Hispanic male with a history of extensive stage IV small cell lung cancer (SCLC) and brain metastasis presented for a comprehensive eye examination on October 27, 2021. The patient had a chief complaint of floaters and occasional photopsia in the left eye (OS) for two weeks; however, he denied recent ocular trauma, shadows, or dark curtains over his field of vision. His last eye examination was three years prior. He had a history of bilateral cataract extraction with intraocular lens placement, as well as ocular allergies and dry eyes, which were well-controlled with ophthalmic ketotifen and preservative-free artificial tears.

In addition to SCLC, his medical history was significant for hypertension, chronic obstructive pulmonary disease (COPD), Barrett's esophagus, benign prostatic hyperplasia, hyperlipidemia, and seasonal allergies, which were medically managed with amlodipine, albuterol, omeprazole, simethicone, docusate, finasteride, pravastatin, and cetirizine, respectively.

The patient's SCLC treatment included WBXRT delivered in ten 3 Gy fx (completed July 2, 2019), chemotherapy (completed December 3, 2019), im-

munotherapy (completed August 20, 2021) and thoracic radiation therapy (completed October 22, 2021). Magnetic resonance imaging (MRI) of the brain (September 1, 2021) showed no evidence of brain metastasis, new mass lesions, or abnormal enhancements of any structures, and a positron emission tomography (PET)-computed tomography (CT) scan (March 25, 2021) showed no signs of metastatic disease. After WBXRT, he was started on palliative chemotherapy and immunotherapy consisting of carboplatin, etoposide, and pembrolizumab for six cycles. The patient was on maintenance pembrolizumab, a checkpoint inhibitor, from December 31, 2019, until August 20, 2021. At the time of his eye examination, the patient's cancer was in remission and being observed by oncology.

His best corrected visual acuities (BCVA) were 20/25 right eye (OD) and 20/25 OS. Pupils were equally round and reactive to light with no obvious afferent pupillary defect. Extraocular movements and confrontation visual fields were full. Intraocular pressures measured by Goldmann applanation tonometry were 21 mmHg OD and 20 mmHg OS. The evaluation of the anterior segment was unremarkable in both eyes (OU).

Dilated fundus exam (DFE) revealed a well-perfused optic nerve without signs of disc edema or neovascularization OD (Figures 1a and 2a). There were two cotton wool spots (CWS) along the superior nasal (SN) and inferior temporal (IT) arcades OD (Figure 1a). Grade 1 optic disc edema was evident OS (using the Modified Frisén scale, see Table 1) with peripapillary hemorrhages, elevation of the superior border, and vascular congestion, but no sign of optic disc neovascularization (Figures 1b and 2b). Venous distension adjacent to the disc OS was also noted (Figure 2b). Both maculae were flat and evenly pigmented OU. There were no retinal breaks or detachments in the periphery OU. Vitreous findings included syneresis OU.

Figure 1: *Fundus photograph of the right (a) and left (b) eyes at the initial visit. Note the two cotton-wool spots along the superior and inferior temporal arcade in the right eye, and the venous distension adjacent to the optic disc in the left eye.*

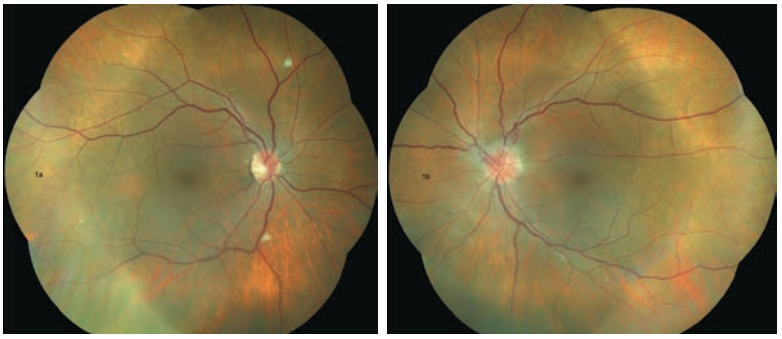


Figure 2: *Closer views of the right (a) optic nerve with no signs of disc edema and the left (b) optic nerve with Grade 1 disc edema and increased elevation of the superior rim.*

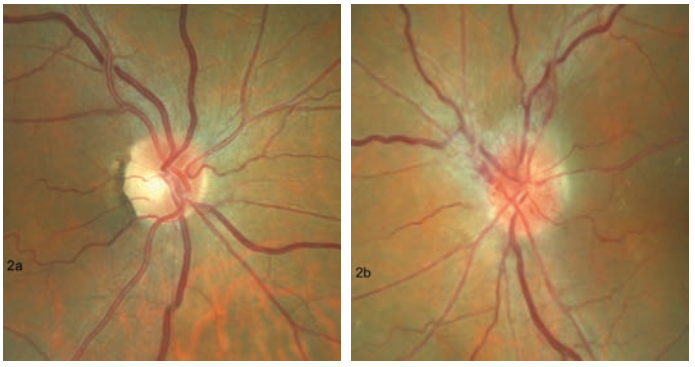


Table 1: *Modified Frisén Scale for grading papilledema*[4]

Grade	Characteristics
0 (Normal)	Normal optic disc
1 (Minimal)	Subtle C-shaped halo of disc edema with a normal temporal disc margin
2 (Low)	Circumferential halo of disc edema
3 (Moderate)	Obscuration of one or more segments of the major blood vessels leaving the disc
4 (Marked)	Partial obscuration of a segment of major blood vessels on the disc
5 (Severe)	Partial or total obscuration of all blood vessels on the disc

Due to the presence of the CWS OD and optic disc edema OS in the setting of previous WBXRT for extensive stage IV SCLC and brain metastasis, the patient was diagnosed with radiation-induced retinopathy OU and radiation-induced optic neuropathy OS. Hypertension was an unlikely etiology as the patient's blood pressure was historically well-controlled on medications. The patient was to return to the eye clinic within 2 weeks for a spectral domain optical coherence tomography (SD-OCT) of the retinal nerve fiber layer (RNFL) and macula, and fluorescein angiography (FA).

First follow-up visit: one month after the initial presentation

At his one-month follow-up eye exam, the patient reported no new visual complaints; his floaters were stable, and he was no longer symptomatic for photopsia. BCVA and all preliminary testing at this visit remained stable OU. On dilated fundus exam, the previous SN CWS were resolved and one CWS remained along the IT arcade, with new optic disc edema OD seen (Figure 3). In the left eye, Grade 1 optic disc edema without radiation-induced retinopathy was noted. SD-OCT of the RNFL revealed asymmetric RNFL global values of 101 mm OD and 138 mm OS, with displacement of the scan circle resulting in an overestimation of the IT RNFL thickness (Figure 4). SD-OCT of the macula revealed no macular edema OD, and peripapillary intra-retinal fluid with scattered hard exudates OS (Figure 5). FA demonstrated optic nerve edema OS>OD, with OS having greater hyperflourescence than OD. It was recommended that the patient continued to be observed and to return to the clinic within 4 weeks for a repeat FA with transit OS.

Second follow-up visit: two months after the initial presentation

At his second follow-up exam, the patient had no new complaints, and his BCVA and all preliminary testing remained stable. Grade 1 optic disc edema with mild blurring of the neural retinal rim superiorly with vascular congestion and peripapillary hemorrhages was observed OD (Figure 3). Grade 1 optic disc edema OS was resolving based on the clinical appearance. The CWS was still noted along the IT arcade OD. A SD-OCT of the RNFL revealed a global value of 116 mm OD, and a more significantly reduced global value of 90 mm, with inferior temporal thinning at 75 mm OS (Figure 6), likely due to the difference in the delineation of the circumpapillary scan circle between the first and second scans. The FA revealed no leakage OS.

Figure 3: *Fundus photograph of the right eye with grade 1 disc edema with peripapillary hemorrhages and elevation of the superior border of the disc.*

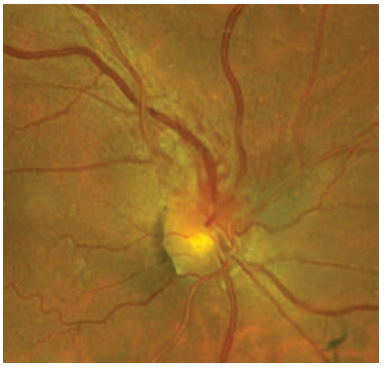


Figure 4: *Spectral domain optical coherence tomography (SD-OCT) of the retinal nerve fiber layer (RNFL) of both eyes at the first follow-up visit.*

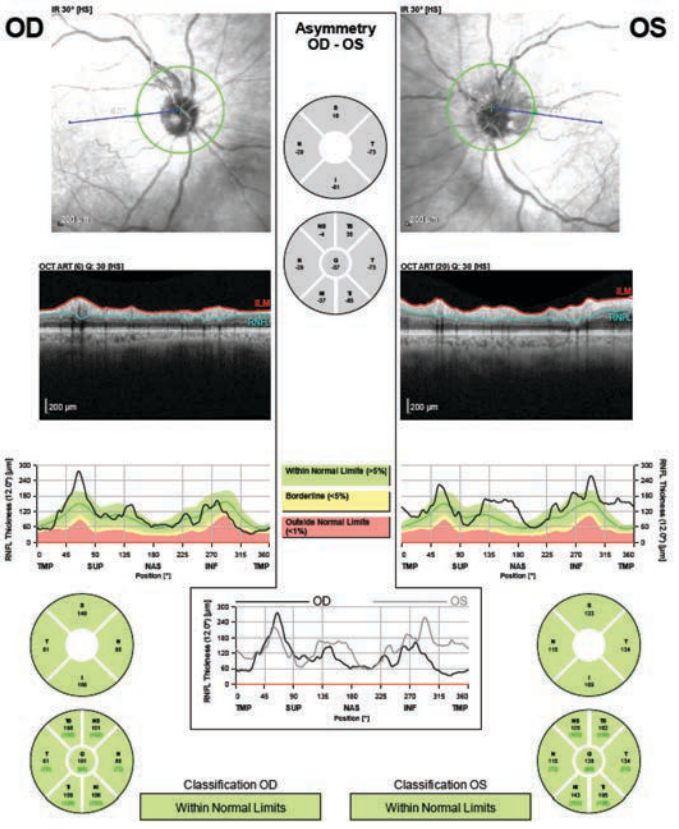


Figure 5: *SD-OCT of the macula with peripapillary intra-retinal fluid of the left eye at the first follow-up visit.*

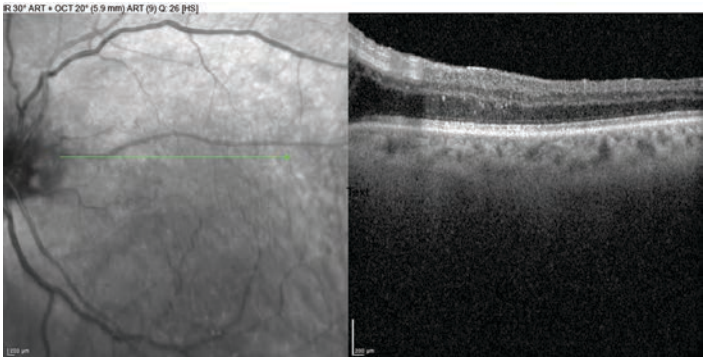
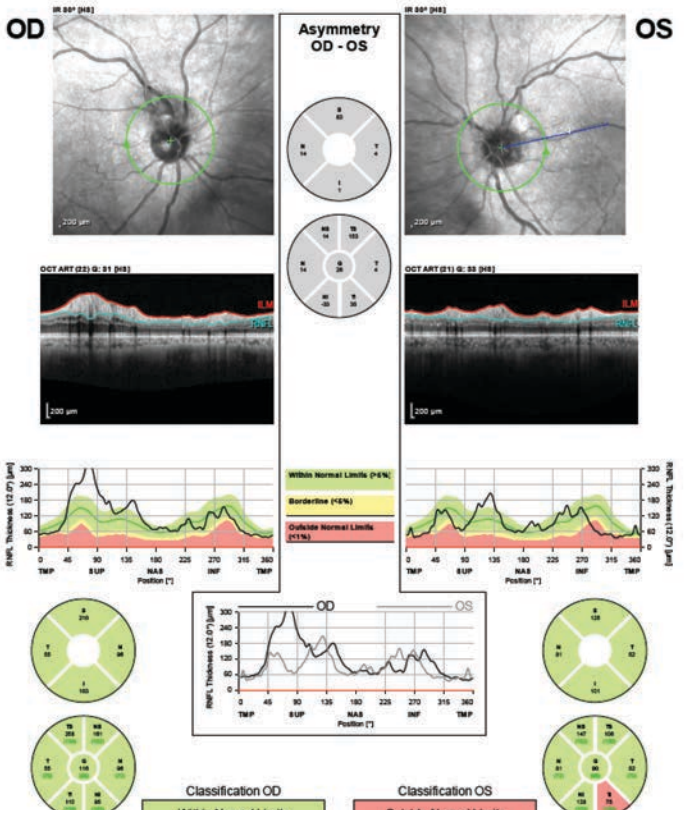
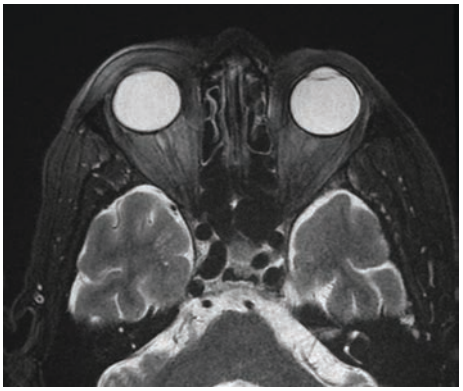


Figure 6: *SD-OCT of the retinal nerve fiber layer (RNFL) of both eyes at the second follow-up visit.*



Due to the development of optic disc edema with superior temporal vascular congestion OD, potential metastasis versus infectious etiologies were also considered. The patient was referred to neuro-ophthalmology for evaluation of bilateral optic nerve edema and an infectious disease lab work-up was ordered to rule out other potential causes of the optic nerve head edema, including Rapid Plasma Reagin (RPR), Microhemagglutination Assay for Treponema Pallidum (MHA-TP), Bartonella, and QuantiFERON-TB Gold. The specialists from hematology, oncology, and neuro-ophthalmology teams subsequently recommended a repeat MRI of the brain and orbits to rule out acute infarction, intracranial hemorrhage, intracranial disease, metastatic disease, mass effect, or abnormal enhancements on the orbits (Figure 7).

Figure 7: *MRI of the brain and orbits: There is no evidence of acute infarction intracranial hemorrhage or acute intracranial disease, and no evidence of metastatic disease. High-resolution images reveal no mass, mass effect or abnormal enhancement.*



Third follow up visit: two and a half months after the initial presentation

At the neuro-ophthalmology visit, the patient noted no new complaints, and BCVA and all preliminary testing remained stable. No changes were seen on dilated fundus exam OU. HVF 24-2 SITA (Swedish Interactive Testing Algorithm). Faster testing revealed a superior depression OD related to superior lid interference and global depression, with an enlarged blind spot and probable rim artifact 360 OS (due to the absolute sensitivity scores of less than zero around the peripheral edge) (Figures 8 and 9). A repeat HVF should be performed to clarify these findings. The patient continues to be off all cancer-related medications, and his lab work was negative for QuantiFERON-TB gold, RPR, MHA-TP, and Bartonella. Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) laboratory tests were ordered to rule out Giant Cell Arteritis (GCA) as a potential etiology for the optic disc edema, though it was thought to be unlikely in the absence of GCA symptoms, such as scalp tenderness, jaw pain, fever, or a persistent headache.

PET-CT scans on January 31, 2022 revealed no evidence of intracranial metastasis. An MRI of the brain and orbits with contrast was completed February 2, 2022, and showed no evidence of acute infarction, intracranial hemorrhage, acute intracranial disease, metastatic disease, mass effect, or abnormal enhancements on the orbits.

The patient was to return to the clinic within 4 weeks for a review of the lab results and SD-OCT RNFL for continuing resolution of the disc edema. His follow-up visits are currently ongoing.

Figure 8: *Humphrey Visual Field 24-2 SITA Faster OD at the third follow-up visit.*

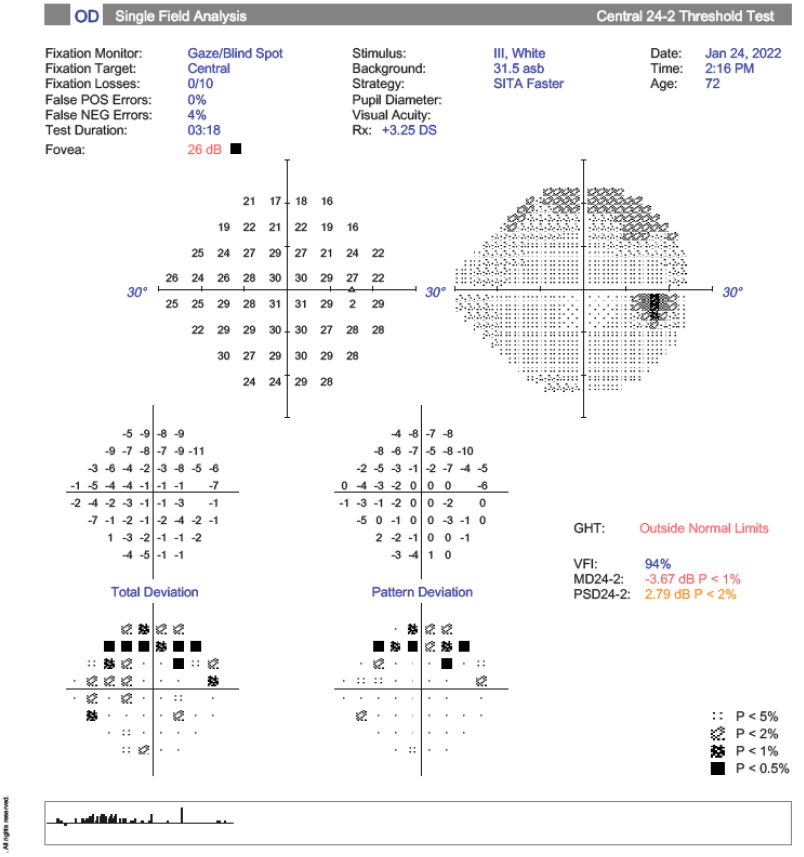
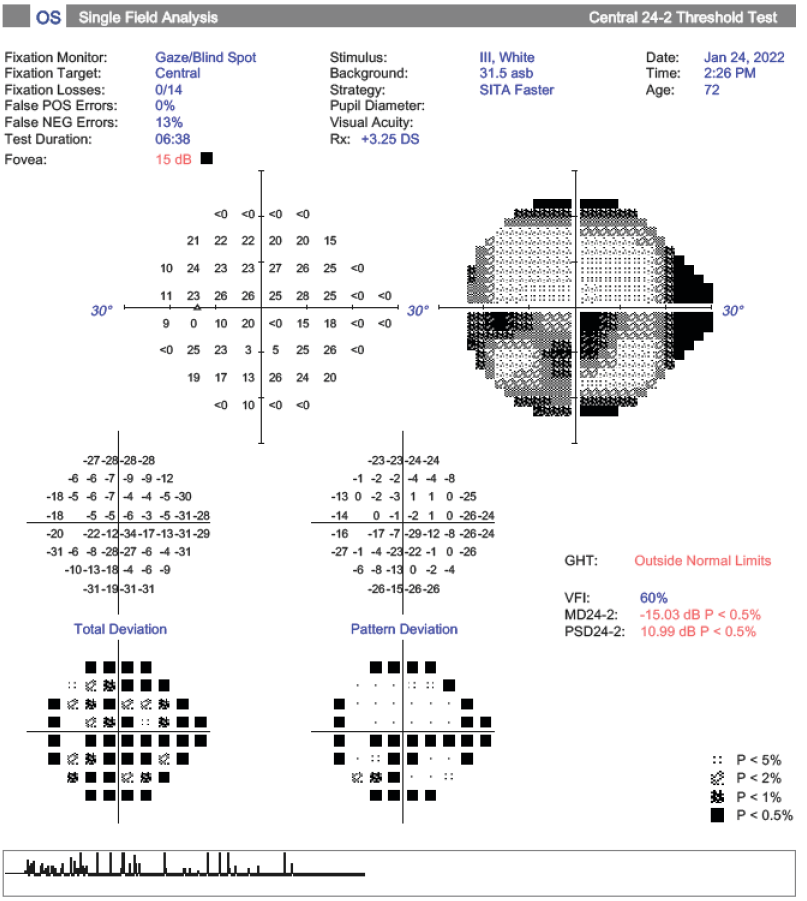


Figure 9: *Humphrey Visual Field 24-2 SITA Faster OS at the third follow-up visit.*



DISCUSSION

Review of the literature

RION and radiation-induced retinopathy are rare complications of external radiation therapy (XRT).[5] This case report focuses on a patient who had WBXRT two years prior to having clinical manifestations of bilateral optic disc edema and radiation-induced retinopathy: this timeline is not surprising, as RION and radiation-induced retinopathy manifest an average of 18 months after radiation exposure.[2,3,6,7]

While the pathophysiology of RION is not fully understood, it is thought to be a white matter disorder due to delayed radionecrosis in the central nervous system.[8] Radiation disrupts molecular bonds and produces free radicals which, in turn, promote cellular necrosis.[8-10]

Radiation-induced retinopathy is thought to originate from radiation-induced microangiopathy associated with endothelial cell loss.[9,10] Radiation has been reported to damage endothelial cells, cell membranes, organelles, and deoxyribonucleic acid (DNA).[9-11] The tight junctions between endothelial cells subsequently lose their integrity, making the blood vessels more permeable to retinal vascular leakage and edema.[9,10]

The total amount of radiation exposure, the fraction size that was given, and treatment with concomitant chemotherapy or immunotherapy are factors to consider when determining the underlying causes of RION and radiation-induced retinopathy.[5,8,10] The presence of concurrent pre-existing vascular conditions such as hypertension, hyperlipidemia, and diabetes mellitus can also increase the likelihood of radiation-induced retinopathy.[5,8]

Current studies suggest that the total dose of radiation administered to the brain or body should be below 35 Gy to prevent retina or anterior visual pathway sequelae.[12] There is a 50% chance of developing radiation-induced retinopathy with a dose of 60 Gy and an 85-90% chance with a dose of 70-80 Gy; the average dose for a cancer patient is 45-60 Gy.[2] However, many cases of ocular complications have been reported with much lower levels of radiation than in our patient, who had an accumulated dose of 30 Gy of WBXRT.[2,12] Therefore, another consideration is the amount of radiation exposure per radiation time, which should not exceed 1.8-1.9 Gy per time.[1,2.] Our patient received 3 Gy of radiation per radiation time and subsequent chemotherapy and immunotherapy, increasing the risk of ocular complications. Carboplatin, a type of chemotherapy agent given to this patient, is a radio-sensitizing agent that crosses the blood brain barrier and sensitizes the optic apparatus, which may potentiate radiation injury.[13] Co-management with oncology is imperative to prevent visually devastating outcomes from RION and radiation-induced retinopathy.

Clinical features

RION commonly presents with sudden, painless, monocular vision loss 3 weeks to more than 7 years after radiation exposure.[2,3,6-8] RION is a retrobulbar process in which the optic nerve will appear normal on fundus examination in the acute phase.[8] However, if the ischemic insult occurs anterior to the lamina cribrosa, the optic nerve head (ONH) will appear swollen, and optic nerve atrophy and pallor (signs of retinal ganglion cell death) begin to develop between 6-8 weeks following onset of the ONH edema.[8] Patients with RION involving the chiasm develop a bitemporal hemianopsia and eventual retrograde optic atrophy.[8] FA in patients with ONH edema show filling of the capillaries at the ONH, while those without ischemia will appear to have unremarkable FA results.[8]

Clinical manifestations of radiation-induced retinopathy are frequently similar to vascular abnormalities of diabetic retinopathy.[3] Microaneurysms, retinal hemorrhages, capillary non-perfusion, and CWS all tend to appear first with radiation-induced retinopathy, followed by retinal edema, hard exudates, telangiectasia, and vascular sheathing.[3] Neovascularization may develop later, with subsequent vitreous hemorrhages and tractional retinal detachments similar to those seen in diabetic retinopathy.[3] One feature of radiation-induced retinopathy that distinguishes it from diabetic retinopathy is the atrophy of the retinal pigment epithelium evident after radiation exposure.[3]

Stages and prognosis for radiation-induced retinopathy

This patient was classified as having stage 1 radiation-induced retinopathy, which is characterized by a mild risk of vision loss. Stage 1 radiation-induced retinopathy includes CWS, retinal hemorrhages, retinal micro-aneurysms, ghost vessels, exudates, uveal effusion, chorioretinal atrophy, choroidopathy, and retinal ischemia less than 5 disc-diameters in size. In stage 1, patients are generally asymptomatic since the macula is unaffected and there is a minimal risk of vision loss.[14]

Stage 2 includes the same signs as stage 1, but there is macular involvement, and the risk of vision loss is greater.[14]

Stage 3 includes any of the same signs as above, as well as retinal neovascularization and macular edema. Symptoms during stage 3 are more severe, with both extramacular and macular involvement increasing the risk of severe vision loss.[14]

Stage 4 includes all the signs in stages 1, 2 and 3 plus vitreous hemorrhage and retinal ischemia equal to or greater than 5 disc-diameters in size. Symptoms are severe and signs are extramacular, macular, and in the vitreous with a significant risk of severe vision loss.[14]

Prognosis for RION

The visual prognosis is poor for patients with RION, which is associated with an ultimate visual acuity range of <20/200 to light perception.[8,15,16] There is a potential for permanent blindness with RION, which is why radiation exposure should be carefully considered when treating patients with tumors adjacent to visual pathways.[8,15,16]

Differential diagnoses

Differential diagnoses for RION include ONH compression, infiltrative optic neuropathy, toxic optic neuropathy secondary to chemotherapy, checkpoint inhibitor-induced optic neuritis, and giant cell arteritis. Differential diagnoses for radiation-induced retinopathy include diabetic retinopathy, branch retinal vein occlusion, central retinal vein occlusion, and hypertensive retinopathy. Patients with early radiation retinopathy and optic neuropathy may initially be asymptomatic, but more advanced disease can present with decreased vision or floaters. An important factor to consider is the patient's history of radiation therapy around the optic apparatus, which can include WBXRT. The clinical diagnosis is based on a thorough case history, DFE, HVF, SD-OCT, and FA which can be helpful in showing microvascular features of radiation-induced retinopathy. An OCT-angiography can also be used to

aid in diagnosis, as it can visualize vascular damage in both the retina and choroid, however FA remains the diagnostic gold standard to document retinal edema and the breakdown of the inner blood retinal barrier.[17,18]

MRI of the brain and orbits may also be beneficial when differentiating between radiation-induced optic neuropathy and other forms of optic neuropathy. PET-CT scans have a higher sensitivity for lung nodule characterization compared to an MRI and can be ordered periodically to track the response to therapy.[5]

Management

Radiation-induced retinopathy and optic neuropathy can lead to devastating vision loss with unpredictable treatment outcomes. Management of radiation-induced retinopathy has been directed towards the reduction of macular edema and neovascularization. Pan-retinal photocoagulation (PRP) remains the gold standard in the treatment of ischemic retinopathies, including radiation-induced retinopathy, and the use of PRP prophylactically is being studied.[12] Anti-vascular endothelial growth factor (anti-VEGF) injections are the gold standard to effectively reduce radiation-induced macular edema and ocular neovascularization. Currently, bevacizumab and ranibizumab are the two most effective intravitreal anti-VEGF agents used to treat macular edema in patients with radiation-induced retinopathy.[19] In contrast, the use of intravitreal anti-VEGF therapy for patients with optic neuropathy showed no statistically significant difference for visual outcome versus those who were only observed.[15] Another treatment option for radiation-induced retinopathy is intravitreal corticosteroids, such as dexamethasone and triamcinolone acetonide, alone or in conjunction with anti-VEGF therapy.[19] It has been reported that a single intravitreal corticosteroid injection could stabilize or improve visual acuity in 91% of patients one month post-injection.[19] Coupling of corticosteroids and anti-VEGF injections has also been used to improve vision.[19]

Other treatment options include photodynamic therapy, hyperbaric oxygen therapy, and oral pentoxifylline; however, all of these result in limited visual improvement in comparison to previously mentioned therapies.[12]

Prevention

Eliminating radiation exposure to prevent radiation-induced retinopathy and optic neuropathy is not always possible for patients who need cancer treatment to survive. Therefore, co-management with an oncologist regarding radiation dosage and fraction sizes of radiation per dose is imperative for preventing devastating vision loss associated with later stages of radiation-induced retinopathy and optic neuropathy.

CONCLUSION

Although radiation-induced retinopathy and optic neuropathy are rare, it is important to recognize these conditions, and determine the exact cumulative dosage with the individual fraction size of radiation when managing a patient who has previously been (or is currently being) exposed to radiation. Co-management with oncology and ophthalmology is necessary to ensure optimal visual outcome. Furthermore, patients who are not actively undergoing cancer treatment should be followed at regular intervals to monitor for the development of remote ocular toxicity secondary to radiation and/or chemotherapy treatment. ●

FINANCIAL DISCLOSURES

The authors have no propriety or commercial interest in any material discussed in this article.

CORRESPONDING AUTHOR

Brittney Jimenez, OD – brittneyjimenez11@gmail.com

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