Very delayed onset, asymmetrical radiation retinopathy after external beam irradiation for nasopharyngeal carcinoma: a case report

Sivakami A. Pai[1*]

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ABSTRACT

Background: Radiation retinopathy is a chronic, gradually progressive retinal microangiopathy that can occur with variable latency after exposure to radiation of head and neck. Nasophargeal carcinoma is a frequent head and neck tumor of the south-East Asian countries.

Case Presentation: A 54-year old Asian male presented with decreased vision for 2 years in left eye. He had diffuse cystoid macular edema, retinal hemorrhages, exudates, and telangiectatic vessels. In the right eye, he had focal macular edema, exudates, and micro-aneurysm. He had undergone external beam radiation for nasopharyngeal carcinoma 32 years ago. He was treated with several injections of Anti-vascular endothelial growth factors elsewhere for persistent macular edema secondary to vein occlusion in the left eye, and had fewer response.

Conclusion: The chronic maculopathy responded to treatment with intra vitreal sustained-release dexamethasone implant (Ozurdex®) and laser photo coagulation.

Keywords: Case report, radiation retinopathy: external beam radiation, cystoid macular edema, dexamethasone implant, anti-VEGFs.

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Correspondence to: Sivakami A. Pai
*Vitreo-Retinal Surgeon, Alzahra Private Hospital, Dubai, UAE.
Email: shivsudhir@gmail.com
Full list of author information is available at the end of the article.

Introduction

Radiation retinopathy is a chronic, predictable complication following exposure to any source of radiation. The latency period varies between 3 months and 8 years, with a peak at 1 to 1.5 years [1]. It is a slowly progressive vaso-occlusive complication of ionizing radiation exposure to the retina. Nasopharyngeal carcinoma is a frequent head and neck tumor in South-East Asian countries. Radiation therapy is the primary treatment modality with or without chemotherapy for advanced Nasopharyngeal carcinoma [2]. Current treatment strategy of radiation retinopathy is thermal laser photocoagulation, intravitreal anti-vascular endothelial growth factor, and intravitreal steroid injections [3].This is a case report of very delayed onset, asymmetrical radiation retinopathy. Wherein, the retinopathy, in the right eye, occurred 32 years after exposure to external beam radiation therapy for nasopharyngeal carcinoma.

Case Presentation

A 54-year Asian gentleman presented with a decrease in vision in the left eye in the past 2 years. He was treated for branch retinal vein occlusion with cystoid macular edema elsewhere. He had received peripheral scatter laser and several injections of Anti-VEGFs. It showed no significant resolution of macular edema. Eventually, the macular edema responded to intravitreal sustained-release dexamethasone implant (Osurdex®). He had received External beam radiation therapy for nasopharyngeal carcinoma 32 years ago in the United Kingdom. He did not have any other comorbidities, such as diabetes, hypertension, or any collagen vascular disease. He had sustained Pathological fracture of the clavicle two years ago, for which he had undergone surgery. He had wasting of muscles of the neck and lower jaw. On examination, the Best correct corrected vision in the right eye (OD) was 1.0 and the left eye (OS) was 0.6. Intraocular pressure was normal. Anterior segment examination was unremarkable in both eyes. OD fundus examination showed microaneurysms with focal edema involving the posterior pole and nasal quadrant (Figure 1A). Left eye (OS) fundus examination showed dense hard exudates, microaneurysms, retinal hemorrhages involving the superior- temporal quadrant and involving the posterior pole with macular edema (Figure 2A). There were few scatter laser marks in the far periphery. Fundus fluorescein angiography (FA) of the OD revealed multiple microaneurysms and telangiectatic vessels involving the posterior pole and nasal quadrant. Late frame showed leakage. The foveal avascular zone was normal (Figure 1E and F). Left eye FA revealed enlargement of the foveal avascular zone, attenuated

superior-temporal branch vein. Capillary telangiectasia involving the posterior pole, and superior- temporal quadrant, focal areas of capillary non-perfusion, and venous beading (Figure 2B). Late frame showed staining of vessels with leakage.

Optical coherence tomography (OCT) of the OD showed a focal area of extramacular thickening with a normal central retinal thickness (CRT) (Figure 1B–D).

In OS, there was diffuse cystoid macular edema with CRT of 560 microns, there no vitreomacular interface abnormality (Figure 2C). He underwent two intravitreal injections of ranibizumab (Novartis—Lucentis®) on the monthly interval, there was no response to Anti-vascular endothelial growth factor (VEGF) treatment. After 2 months, Argon green laser photocoagulation was performed to the involved temporal quadrant and paramacular areas in both eyes. The microaneurysm was targeted when seen. After 4 months of follow up, there was a minimal decrease in CRT (520 microns) with no improvement in vision (Figure 2D). Intravitreal sustained-release dexamethasone implant (Osurdex®) was injected in the OS. There was a decrease in CRT to 310 microns with Improvement of vision by one line (0.7) after 2 months (Figure 2-E).

Discussion

Radiation retinopathy (RR) is a slowly progressive, irreversible, delayed onset occlusive microangiopathy of the retinal vasculature that occurs with variable latency (peak-1–1.5 years) after exposure of the retina to ionizing radiation. Ionizing radiation can cause a variety of damaging effects on tissues in the body. Damage occurs directly through the blockage of cellular mitotic activity and indirectly through damage to the vasculature, which nourishes the tissue. Within the eye, the retina and optic nerve are relatively radioresistant tissues, but the damage may develop secondary to disruptions in their vascular supply [3]. Following radiation, the destruction of endothelial cells and capillary closure induces ischemic and proliferative changes similar to those found in other retinal vascular diseases such as diabetic retinopathy [4]. The loss of capillary cellularity leads to the development of microaneurysms, and hemodynamic alterations produce fenestrated telangiectatic retinal vessels. Larger retinal vessels become involved later in the course of the retinopathy. Closure of blood vessels is the single most characteristic finding on Fluorescein angiography [5].

Radiation retinopathy occurs secondary to treatment of cephalic, nasopharyngeal, orbital, and paranasal tumors as well as intraocular tumors, such as uveal melanoma and retinoblastoma [6]. Nasopharyngeal carcinoma is a frequent head and neck tumor in South-East Asian countries [2]. Many factors are now known to influence the incidence of radiation retinopathy, including total dosage, daily fraction size, field design, type, and rate of administration of radiation. Presence of comorbidities, such as diabetic, hypertensive, adjuvant chemotherapy, and pregnant women are more susceptible to radiation retinopathy [7,8].

In the 1980s, a total dose to the primary lesion was 60–75 Gy in 6–8 weeks and, in few cases, over 80 Gy was used and 50 Gy was applied to the cervical lymphatic chain [3]. More than 50% of the patients that receive 65 Gy to the healthy retina will develop radiation retinopathy [9]. There is a single case reported on delayed onset radiation retinopathy, which occurred 10 years following external beam irradiation for nasopharyngeal carcinoma [10]. The Medline search revealed, probably this case could the most delayed onset, asymmetrical radiation retinopathy. Where the retinopathy in OD occurred 32 years following exposure to radiation, OS developed symptomatic retinopathy with macular edema, 30 years following exposure to radiation. At the time of presentation, the patient had advanced retinopathy in the left eye, he was treated earlier as a primary branch retinal vein occlusion with macular edema.

Early retinopathy changes in fellow-OD, and history of radiotherapy provided a possible clue to the diagnosis of

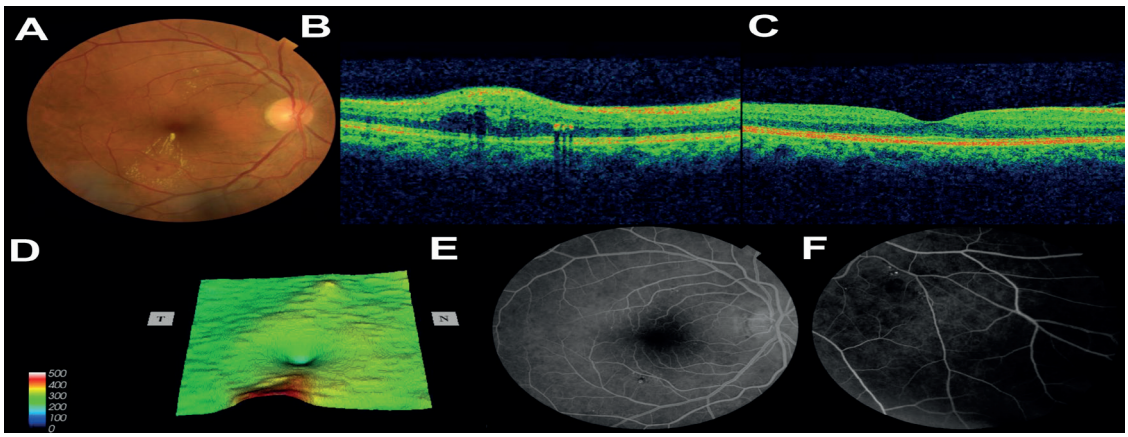

Figure 1. *(A) OD fundus examination showing microaneurysms with focal edema involving the posterior pole and nasal quadrant; (B, C and D) OCT of the OD showing a focal area of extramacular thickening with a normal CRT; (E and F) FA of the OD revealing multiple microaneurysms involving the posterior pole and nasal quadrant with telangiectatic vessels in the posterior pole. Late frame showing leakage.*

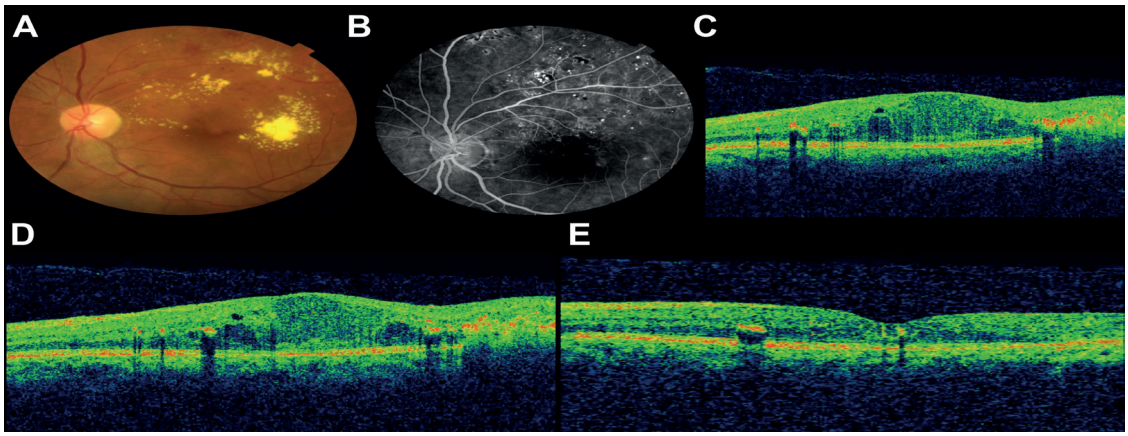

Figure 2. *(A) OS fundus examination showing dense hard exudates, microaneurysms, retinal hemorrhages involving the superior- temporal quadrant and involving the posterior pole with macular edema; (B) FA of the OS showing enlargement of the foveal avascular zone, superior-temporal branch vein attenuation, capillary telangiectasia involving the posterior pole and superior-temporal quadrant; (C) OCT of OS showing a diffuse cystoid macular edema with CRT of 560 microns with no vitreomacular interface abnormality; (D) OCT of OS at first follow up showing a minimal decrease in CRT (520 microns); (E) OCT of OS at second follow up showing a decrease in CRT to 310 microns.*

radiation retinopathy in the absence of other comorbidities. The patient also ran through a series of investigations to rule out other retinovascular disorders. Without careful history, cases of RR can be easily misdiagnosed.

Possible asymmetrical Leber's multiple miliary aneurysms were also considered. Leber's miliary aneurysm is a congenital malformation, a form of primary retinal telangiectasia characterized by the presence of multiple miliary aneurysms associated with intraretinal lipid exudates. It is a unilateral condition with a male predilection. It is not associated with any other systemic or ocular disease. The condition is usually unilateral, only rarely bilateral. There are only a few reported bilateral cases [11–13]. Radiation-induced damage to the macula, "radiation maculopathy," is characterized by edema, hemorrhage, telangiectasia, microaneurysm formation, nerve fiber layer infarcts, capillary nonperfusion, and atrophy of the retinal pigment epithelium. It is a slowly progressive condition with guarded visual prognosis.

After irradiation, the resulting environment of inflammation and ischemia may stimulate the production of many numbers of growth factors and cytokines in response to the injury, including VEGF [14,15]. Hypoxia resulting from initial radiation damage to the retinal vasculature stimulates increased VEGF expression in the retina, leading to changes in microvascular permeability and resultant macular edema. Laser photocoagulation, Photo dynamic therapy and pharmacologic therapies such as corticosteroids and anti-VEGF agents have been investigated for the treatment for radiation maculopathy.

Conclusions

With the history of receiving high dose of radiation 32 years ago and no other systemic or ocular co-morbidities, ionizing radiation could be the most probable cause of secondary branch retinal vein occlusion in the OS. The microvascular changes and focal edema in the OD, more evident on fluorescein angiography, also could be explained secondary to radiation. But, the fact that the retinopathy is asymmetrical and occurring almost three decades following exposure to radiation raises speculation for any other underlying cause. Therefore, he was investigated in detail and no other cause determined.

This report probably would be the most delayed onset, asymmetrical Radiation retinopathy. In this case, the sustained-release dexamethasone implant (Osurdex®) following scatter laser photocoagulation was effective in the resolution of macular edema and stabilizing the retinopathy in the fellow eye. Although there was not much improvement in the vision due to macular ischemia.

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Dr. P. Mahesh Shanmugam, DO, FRCSEd, PhD, FAICO(VR), Head, Vitreoretinal & Ocular Oncology Services, Sankara Eye Hospitals, India

List of Abbreviations

OCT	Optical coherence tomography
CRT	Central retinal thickness
FA	Fundus fluorescein angiography

Consent for publication

Written informed consent was obtained from the subject.

Ethical approval

Ethical approval is not required by our institution to publish an anonymous case report.

Author details

Sivakami A. Pai[1]

1. Vitreo-Retinal Surgeon, Alzahra Private Hospital, Dubai, United Arab Emirates

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Summary of the case

1	**Patient (gender, age)**	Male, 54 years
2	**Final Diagnosis**	Bilateral asymmetrical radiation retinopathy
3	**Symptoms**	Left eye gradual decrease in vision.
4	**Medications**	OS: 2 intravitreal injections of lucentis and 1 Ozurdex
5	**Clinical Procedure**	OS: Scatter laser photocoagulation
6	**Specialty**	Vitreo-retina