

Radiation Retinopathy; A Journey With Intravitreal Injections Through 12.5 Years of Treatment and Follow-Up

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ABSTRACT

The records of a patient who has been treated for radiation retinopathy following the administration of external radiotherapy for Graves ophthalmopathy was reviewed retrospectively. A total of 60 intravitreal injections were administered into the patient's right eye during a period of 12.5 years (triamcinolone acetonide, pegaptanib, bevacizumab, ranibizumab, aflibercept, dexamethazone implant). Visual acuity of the right eye remained the same as baseline visual acuity of 0.2 with the Snellen chart during the follow up. Macular edema related to radiation retinopathy could not be fully controlled during the course of follow-up. Various agents were administered during the follow-up period due to persistent nature of the macular edema. The clinical course reflects the relatively negative character of the disease and also proves that radiation maculopathy is a very resistant disease requiring almost continuous intravitreal therapy.

Keywords: Aflibercept, Bevacizumab, Dexamethasone implant, Radiation retinopathy, Ranibizumab.

INTRODUCTION

Radiotherapy is a treatment modality preferred in some head-neck tumors, intraocular tumors and Graves ophthalmopathy; however, it may have ocular adverse effects observed on extra-ocular muscles, cornea, conjunctiva, sclera, iris, lens, retina and optic nerve.¹⁻³

The first report on radiation retinopathy was published by Stallard in 1933.⁴ Stallard reported edema at optic nerve head, optic atrophy, exudates, retinal hemorrhages and changes in retinal pigment epithelium in patients received radiotherapy for retinal capillary hemangioma and retinoblastoma.

Total radiation dose and extent of the area exposed to radiation are major factors that increase risk for radiation retinopathy.⁵ Clinical findings include micro-aneurysms at fundus, soft exudates, capillary dilatation, telangiectasia and capillary occlusion and posterior pole is affected more commonly than retina.⁵ The increased vascular permeability may cause macular edema while ischemia can lead neovascularization and subsequent intravitreal hemorrhage and retinal detachment. Unlike

diabetic retinopathy, vascular endothelial cells are preferentially injured in radiation retinopathy while damage initially starts at pericytes in diabetic retinopathy.⁷ Micro-aneurysms are less commonly seen in radiation retinopathy when compared to diabetic retinopathy. Mean time from radiotherapy to retinopathy onset ranges from 6 months to 3 years; however, it may occur earlier or later.⁸ Chemotherapy, diabetes mellitus and vascular disorders such as hypertension can exacerbate retinopathy.⁹ In addition, pregnancy may accelerate retinopathy.¹⁰

Albeit rare, spontaneous recovery can occur in retinopathy.¹¹ In radiation retinopathy, treatment options include laser photocoagulation, photodynamic therapy, intravitreal triamcinolone, intravitreal pegaptanib, intravitreal bevacizumab, intravitreal ranibizumab and intravitreal aflibercept used either alone or in combination. In addition, systemic bevacizumab and pentoxifylline can also be used.¹²⁻¹⁷

In this case report, the case with a follow-up of 12.5 years was presented to summarize challenges and longer duration of treatment in radiation retinopathy into attention of retina specialists.

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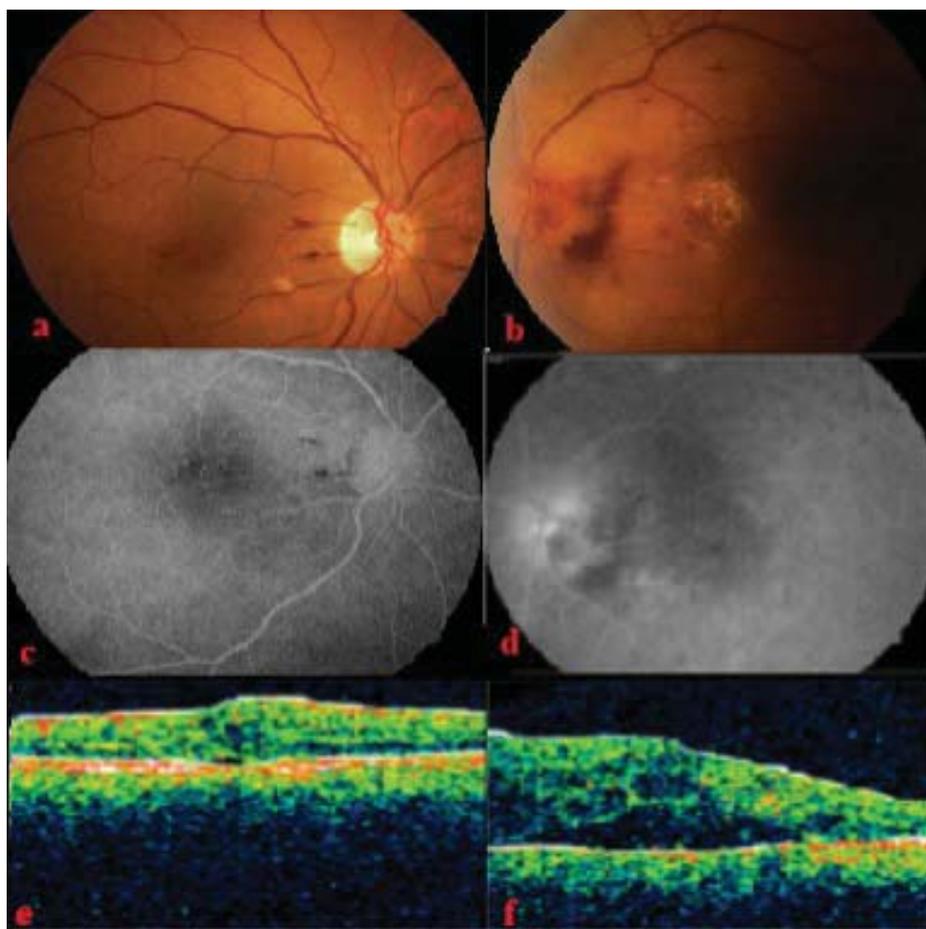
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CASE REPORT

A 53-years old man presented to our clinic with impaired vision in both eyes at March, 2006. In his history, it was found out that he received radiotherapy for thyroid ophthalmopathy (Graves) in 2003 and his complaints started at 2004. It was also found out that he underwent vitrectomy in the left eye with diagnosis of central retinal vein occlusion in 2005.

In the examination, best-corrected visual acuity was finger counting at 4 meters in the right eye and at 2 meters in the left eye. Biomicroscopy revealed normal anterior segment with normal intraocular pressure in both eyes. In fundus examination, edema at posterior pole, exudates and occasional punctate hemorrhages were detected. Presence of faded optic nerve in left eye suggested additional optic neuropathy (Picture 1a and 1b). On fluorescein

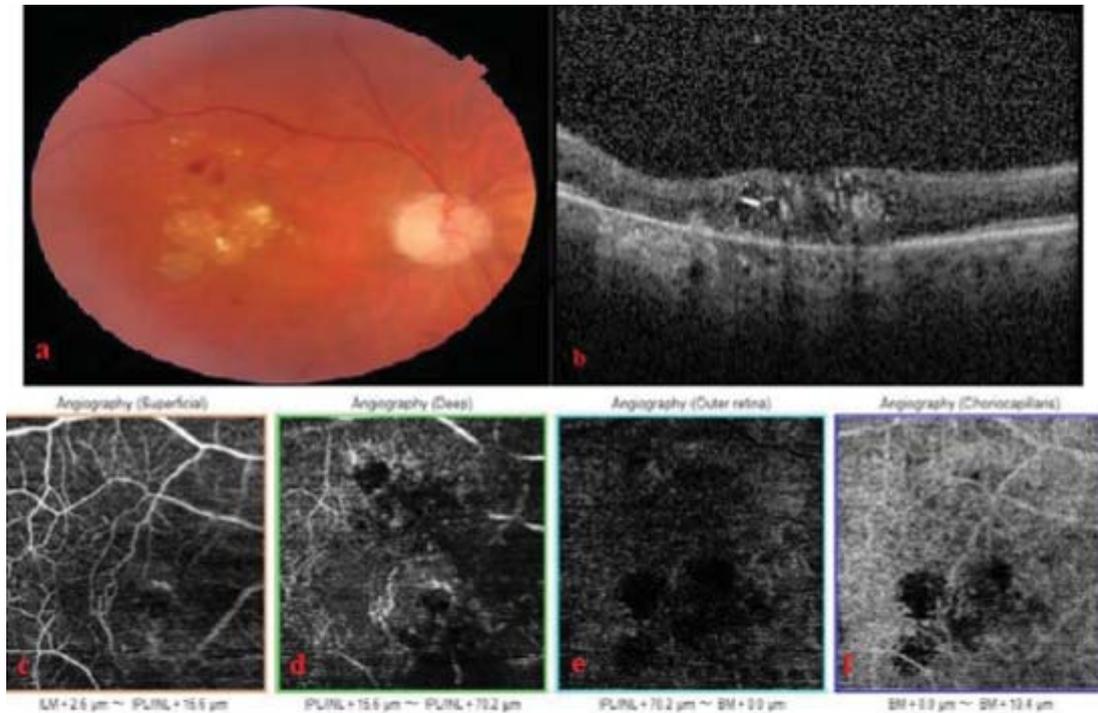
angiography, bilateral macular edema was detected (Picture 1c and 1d). Macular thickness was measured as 417 μ in right eye and 585 μ in the left eye (Picture 1e and 1f) (This case was reported in part in a case series).¹⁷ Simultaneous bilateral intravitreal triamcinolone acetonide (2 mg/0.1 ml, Kenacort A, Bristol-Myers Squibb) plus bevacizumab (1.25 mg) was administered to the patient. In the patient, 6 simultaneous combined treatment (triamcinolone plus bevacizumab), 1 pegaptanib, 4 triamcinolone acetonide, 17 bevacizumab, 3 ranibizumab, 24 aflibercept and 5 dexamethasone implant were administered to right eye during 12.5 years of follow-up. In addition, the patient also underwent minimal focal laser photocoagulation (100 mW, 100 ms, 14 shots) in the right eye. In 2018, intraocular lens implantation was performed via phacoemulsification surgery due to development of cataract in the right eye. In the right eye, dexamethasone implant therapy is ongoing



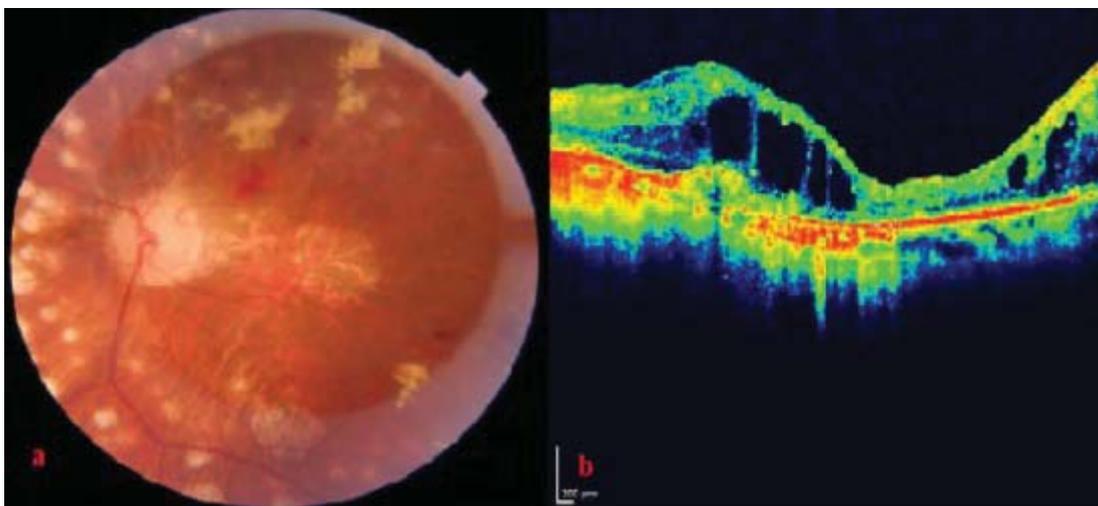
Picture 1: At presentation; A) color fundus image of right eye; peri-papillary and intraretinal hemorrhages; B) color fundus image of left eye, intraretinal hemorrhages accumulated at peri-papillary region and macular exudation; C) fluorescein angiography of right eye; venous phase, masking due to retinal hemorrhages and foveal hyper-fluorescence secondary to edema; D) fluorescein angiography of left eye; late venous phase, masking due to retinal hemorrhages, leakage from optic disc and foveal hyper-fluorescence secondary to edema; E) right eye; stratus optical coherence tomography; macular cystoid edema; F) left eye; stratus OCT; macular edema and serous macular elevation.

as it is pseudophakic. As of November, 2019, Picture 2 and 3 shows clinical presentation of right and left eye, respectively. Figure 1 and 2 shows treatments administered to right eye.

In the left eye, simultaneous combined treatment (triamcinolone plus bevacizumab) was administered at presentation; however, no further treatment was given to left eye given that there would be no visual gain due



Picture 2: After 12.5-years of follow-up, right eye; A) color fundus image; retinal macular hemorrhages, hard exudates and enlarged laser scars at fovea and partial pallor at optic disc; B) Heidelberg SD-OCT image; intra-retinal hyper-reflective dots and cystic macular edema; C) Topcon SS OCT angiography; superficial retinal plexus section; non-perfusion areas; D) deep capillary plexus section; non-perfusion areas; E) avascular retina section; black spots belonging to laser scars; F) choriocapillaris section; black spots belonging to laser scars.



Picture 3: After 12.5-years of follow-up, left eye; A) color fundus image; laser spots in retina and occasional retinal hemorrhages; large geographic atrophy at macula and pallor at optic disc; B) Heidelberg SD-OCT image; macular thinning and irregular retinal layers secondary to intraretinal cystoid degeneration.

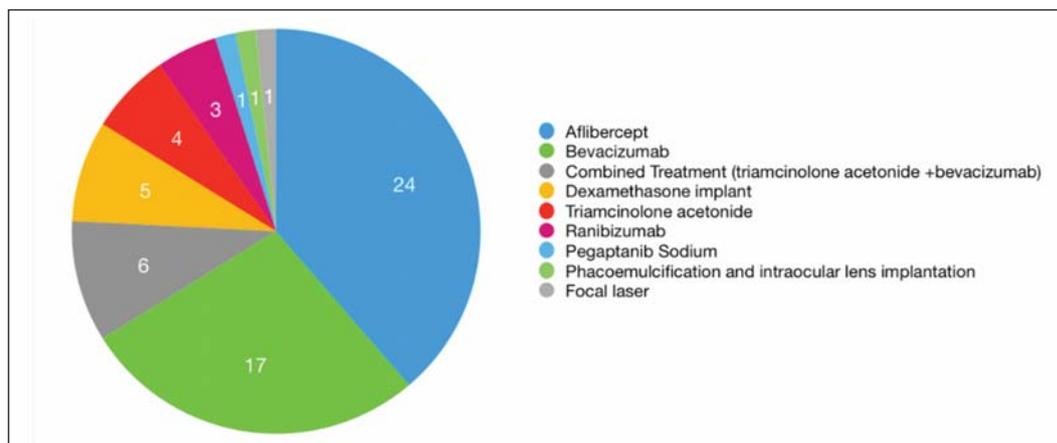


Figure 1: Graphic of treatment given at 2006-2019.

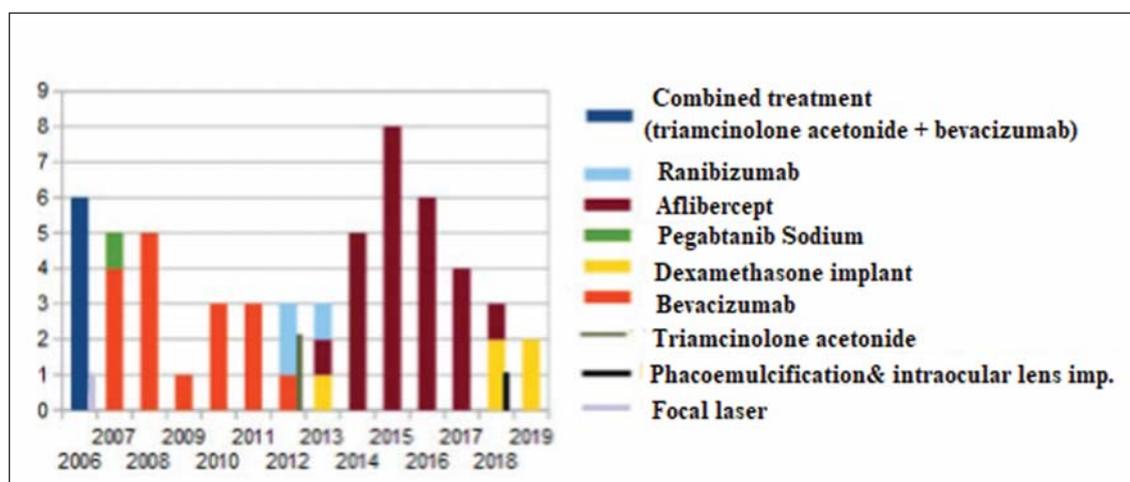


Figure 2: Yearly distribution of treatments.

to previous radiation optic neuropathy and that patient declined treatment based on poor visual prognosis.

DISCUSSION

Although pathogenesis and clinical presentation are relatively well-known in the radiation retinopathy, there is no consensus on treatment algorithm and several treatment modalities have been used so far.

Laser panretinal photocoagulation is used in the proliferative stage of radiation retinopathy, focal or grid laser for treatment of macular edema is less commonly used today.¹⁸

Today, intravitreal anti-VEGF agents are most commonly used treatment modalities in the treatment of macular edema. There are many studies on this issue in the literature (Table 1). In a study by Finger et al. which has a long follow-up period, 120 patients who were treated with anti-VEGF agents (bevacizumab and ranibizumab) for radiation retinopathy were followed over 10 years.²³ In

this cohort including patient received plate radiotherapy for uveal melanoma and developed radiation retinopathy during follow-up, bevacizumab (at doses of 1.25 mg/0.05 mL, 2.0 mg/0.08 mL, 2.5 mg/0.1 mL or 3.0 mg/0.12 mL) and ranibizumab (0.05 mg/0.05 mL or 2.0 mg/0.05 mL) were administered by 4-12 weeks intervals. In the study, doses were given by 4-weeks intervals and escalated based on response in macular edema. The goal of treatment was defined as protection of macular anatomy and improvement in visual acuity. Although macular thickness was decreased at end of year 10 when compared to baseline, the likelihood of maintaining visual acuity within 2 lines was 69% at year 5 which was decreased to 38% at year 8. In addition, full recovery of retinopathy without relapse was rarely observed. Authors concluded that visual loss could be delayed, at least in part, by continuous VEGF suppression. Although visual acuity can be preserved at long-term and regression in macular edema can be achieved by repeated intravitreal anti-VEGF injections, macular anatomy continues to be damaged in general.²²⁻²³

Table.						
	Year	Anti-VEGF	N*	Duration of follow-up (mean))	Number of injections*	Outcome
Mason et al. ¹⁵	2007	Bevacizumab	10	4 months	1	Stable BCVA *stabil and CMT reduction
Finger et al. ¹⁹	2007	Bevacizumab	21	7.8 months	3.8	Stable BCVA / increase retinal edema**
Finger et al. ²⁰	2010	Ranibizumab	5	8 months	8.2	Improved BCVA and CMT reduction
Jutley et al. ²¹	2012	Ranibizumab	1	-	7	Improved BCVA and CMT reduction
Finger et al. ²²	2013	Ranibizumab***	10	12 months	12	Stable/improved BCVA and CMT reduction in 70%
Finger et al. ²³	2015	Bevacizumab/ Ranibizumab	120	81 months	-	Stable/improved BCVA and CMT reduction in 80%
Khan et al. ²⁴	2017	Aflibercept	10ϕ	12.8 months	9	Lower CMT and better BCVA when compared to control group
Fallico et al. ²⁵	2019	Aflibercept	9	24 months	4.4	Improved BCVA and CMT reduction

*N: number of patients treated; BCVA: best-corrected visual acuity; CMT: central macular thickness; number of injections: mean number of injections given during follow-up. **ophthalmoscope, fundus imaging and angiography were used during follow-up; ***High-dose (2 mg) intravitreal therapy; ϕ 5 patients in treatment group and 5 patients in untreated group; u: high-dose (2 mg) intravitreal treatment.

In retinopathy, it is attempted to address progression and recurrences by escalating anti-VEGF dose or switch to another anti-VEGF agent.

Eleni et al. administered intravitreal aflibercept treatment in a patient not responded to bevacizumab injections (overall 5 injections in right eye and 7 injections in the left eye) given over one year for radiation retinopathy.³² Reduction in macular thickness was achieved after 3 doses of bilateral intravitreal aflibercept injections by 4-weeks interval.

Intravitreal corticosteroid injections, either alone or in combination, are also used in radiation retinopathy. Shield et al. administered intravitreal triamcinolone injections (4 mg) in patients with radiation retinopathy and achieved stable visual acuity in 45% of cases.²⁶ However, glaucoma and cataract were developed in 10% of cases during follow-up. Shah et al. achieved recovery in maculopathy by intravitreal triamcinolone in combination with bevacizumab.²⁷ Kaplan et al. used intravitreal triamcinolone injection (4 mg) in combination in cases refractory to high-dose bevacizumab therapy.³¹ In the study, 10 sessions of bevacizumab therapy was given to 8 eyes of 8 patients within 6 months prior to combined therapy and 7 doses of triamcinolone acetonide was administered yearly.

Russo et al. found regression in edema by intravitreal dexamethasone implant in a patient with maculopathy refractory to bevacizumab therapy and observed that implant was effective until month 5.²⁸ Owing to prolonged

effect, dexamethasone implant achieves more stable visual acuity and macular anatomy at long-term when compared to anti-VEGF treatment.^{29, 30, 33}

As suggested in the literature, radiation retinopathy is a disorder requiring multi-dose treatments and switch between treatments due to clinical unresponsiveness. In our case, bevacizumab plus intravitreal triamcinolone injections were used after diagnosis. However, our protocol was altered as novel agents such as ranibizumab and aflibercept have been proven to be safe and effective. In our case, dexamethasone implant was preferred, particularly after cataract surgery, due to its prolonged duration of action. During 12.5 years of follow-up, overall 60 intravitreal treatments were given to the patient but it was failed to stop progression in retinopathy and macular edema. The unresponsiveness closely associated with pathophysiology of retinopathy and resistance to different treatment modalities was also observed in our case.

Prophylactic anti-VEGF administration has also been attempted before onset of retinopathy. Shields et al. started prophylactic intravitreal bevacizumab therapy concurrently with plate radiotherapy in 1131 of 1248 patients receiving radiotherapy with diagnosis of uveal melanoma and compared outcomes with 117 patients not received prophylactic anti-VEGF therapy.³⁴ The patient received prophylactic intravitreal bevacizumab injections (1.25 mg/0.05 mL every 4 weeks) over 2 years. At 2-years follow-up, it was found that rates of cystic macular edema

detectable on OCT, radiation maculopathy, radiation papillopathy and proliferative retinopathy in bevacizumab group. In addition, it was found that visual acuity was better in prophylactic bevacizumab group. Based on the study, a novel treatment modality has been developing, which suggested that prophylactic anti-VEGF therapy before onset of progressive clinical findings resistant to treatment in radiation retinopathy.

Radiation retinopathy has a clinical course which is generally progressive and refractory to treatment and treatment with any intravitreal agent alone mostly results in treatment failure. Different treatment options, either alone or in combination should be used to protect anatomy and visual function. In the presented case, all known treatment modalities and agents were used during 12.5 years of follow-up but achieved visual and anatomic outcomes remained to be limited.

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