Dexamethasone 0.7 mg Implant for the Treatment of Recalcitrant Radiation Maculopathy after Proton Radiotherapy for Carcinoma of the Maxillary Sinus

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Abstract: *Purpose*: To report the efficacy of dexamethasone 0.7 mg intravitreal implant in recalcitrant radiation retinopathy. *Method*: Retrospective case report of a single case describing successful treatment of radiation retinopathy with dexamethasone 0.7 mg intravitreal implant following multiple failed attempts with both bevacizumab and focal laser. *Results*: After the first injection of 0.7 mg dexamethasone the best corrected visual acuity (BCVA) improved from 20/400 to 20/250 and central macular thickness (CMT) decreased. BCVA continued to improve after a second injection to 20/125 and remained stable through the third and fourth injection at 20/150, respectively. The intraocular pressure remained within normal limits. *Conclusion*: 0.7 mg dexamethasone implant showed benefit in a recalcitrant case of radiation retinopathy.

Keywords: Corticosteroids, cystoid macular edema, intravitreal implant, macular edema, Ozurdex, radiation retinopathy, steroids.

INTRODUCTION

Radiation-induced retinopathy is a predictable complication of local or external beam radiation therapy in and around the eye [1-3]. The clinical manifestations are similar to those of diabetic retinopathy and include macular edema, nerve fiber layer infarcts, exudation, neovascularization, hemorrhage, and retinal atrophy [4-8]. Macular edema is the most common manifestation, and its effects can be devastating [9]. Macular edema from radiation-induced retinopathy has consistently been shown to lead to permanent visual loss in a large percentage of patients and has proven to be very difficult to treat [10-12].

Several modalities have been reported as treatment options for radiation-induced macular edema including laser photocoagulation [13,14], intravitreal bevacizumab [15-19], photodynamic therapy [20,21], pentoxifylline [22], hyperbaric oxygen treatment [23], intravitreal triamcinolone [19,24,25], and most recently, intravitreal dexamethasone implants (Ozurdex™) [26,27]. There is currently no consensus on the best available treatment.

Corticosteroids are highly effective anti-inflammatory agents. Though their mechanism in resolving macular edema isn't clear, they have been shown to restore a damaged inner blood-retina barrier by increasing the density of tight junctions, inhibiting the expression and metabolic activity of VEGF, and reducing the osmotic swelling of Muller cells [28-30]. Dexamethasone is six times more potent than triamcinolone [31], and the recent development of a sustained-release dexamethasone implant (Ozurdex™) means that patients require less frequent injections, lowering the risk for potential complications like cataracts, glaucoma, or infection. Although the data is limited for its use in radiation-induced macular edema, the 0.7 mg dexamethasone implant (Ozurdex™) has been proven as a successful treatment for macular edema due to a variety of other causes [32-36].

There are two reports in the literature on the use of dexamethasone in the treatment of radiation maculopathy following choroidal melanoma [26,27], but none following radiation for carcinoma of the maxillary sinus. This case report describes such a successful treatment following failed attempts with both bevacizumab and focal laser.

CASE REPORT

A pseudophakic 78-y/o woman was diagnosed with radiation induced retinopathy in the right eye in 2006, 31 months after receiving radiation treatment for adenocystic carcinoma of the right maxillary sinus. The

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total radiation dose was 5000 cGy and was delivered in 22 treatments over 35 days in 2002. She was initially treated with bevacizumab (Avastin^{TM}), which improved the cystoid macular edema (CME) with a reduction of central retinal thickness from 381 µm to 264 µm 6 months following the injection. However, her best corrected visual acuity (BCVA) failed to improve and remained stable at 20/400.

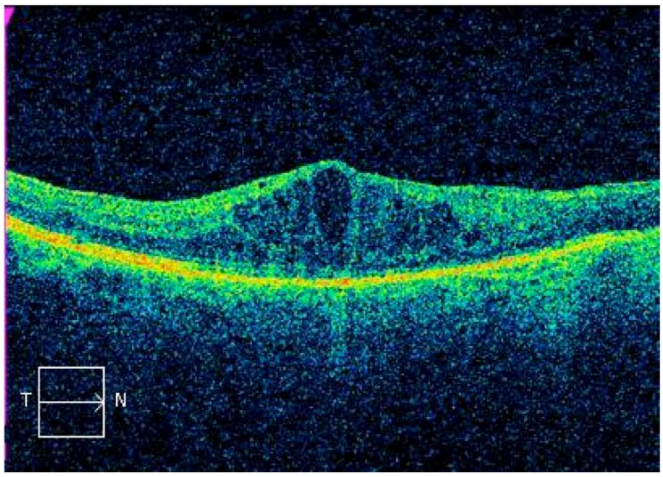

Figure 1: OCT image of the patient after failing treatment with bevacizumab and laser and before the first dexamethasone injection. CMT was 486 µm and BCVA was 20/400.

For the next three years she was treated with several focal argon lasers with temporary moderate improvements in visual acuity. In 2009 she resumed bevacizumab injections every five months and continued to receive periodic focal argon laser treatment. By 2012 her BCVA had dropped to counting fingers at three feet (20/400 on the day of the first injection) and the CME worsened, with a mean retinal thickness of 486 µm (Figure **1**). At this time the decision was made to treat with intravitreal dexamethasone injection.

Four months following the first injection of 0.7 mg dexamethasone there was only moderate improvement of the CME (mean retinal thickness 415 µm), but the BCVA improved to 20/250. The patient received a second injection and one month later mean retinal thickness was 332 µm (Figure **2**), and BCVA was 20/125. After four months, mean retinal thickness was 307 µm, and BCVA was 20/150.

With the third injection BCVA was 20/200 at one and three months, and mean retinal thickness was 301µm and 342µm, respectively. Most recently BCVA improved to 20/150 one month following a fourth injection (Figure **3**, Table **1**). The intraocular pressure remained within normal limits throughout.

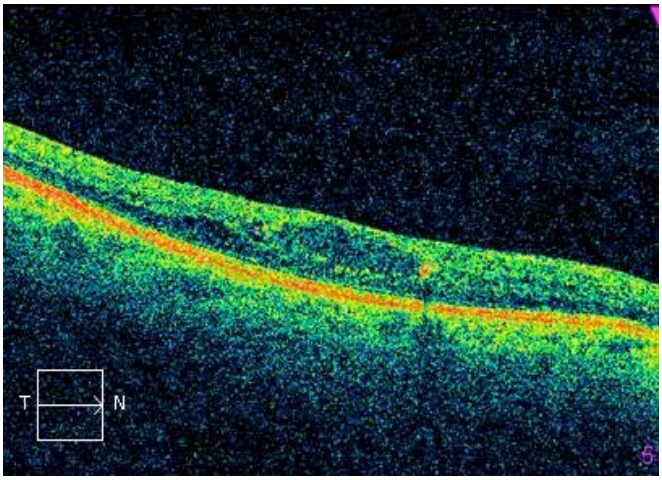

Figure 2: OCT image one month after patient received a second dexamethasone injection. CMT was 332 µm and BCVA was 20/125.

DISCUSSION

Macular edema is a common cause of vision loss in patients who have received radiation in and around the eye, and it is difficult to treat. Several treatments have been proposed, though it is not clear which one is ideal. Some less commonly used modalities that have shown success in small case series include photodynamic therapy [20,21], pentoxifylline [22], and hyperbaric oxygen treatment [23]. More frequently used methods include focal argon laser treatment, anti-VEGF agents, and intravitreal corticosteroid injections.

Two studies have examined the effects of laser photocoagulation in the treatment of radiation-induced macular edema. Kinyoun demonstrated that median visual acuity improved from 20/100 to 20/75 in twelve eyes after a mean of 39 months [13]. In a study of 19 patients, Hykin showed that 42% of patients who received laser therapy experienced ≥ 1 Snellen line improvement at 6 months *vs*. 0% in the 23 observed patients [14]. However, there was no significant difference in BCVA at two years. Our case study supports this finding as our patient initially showed a moderate response to focal laser therapy that decreased over time with repeated treatment.

The data on bevacizumab is mixed, but it has been shown to be moderately effective in the treatment of radiation-induced macular edema. Concerns are that the effect is modest and short lasting [19]. Gupta showed that only two of five patients treated with

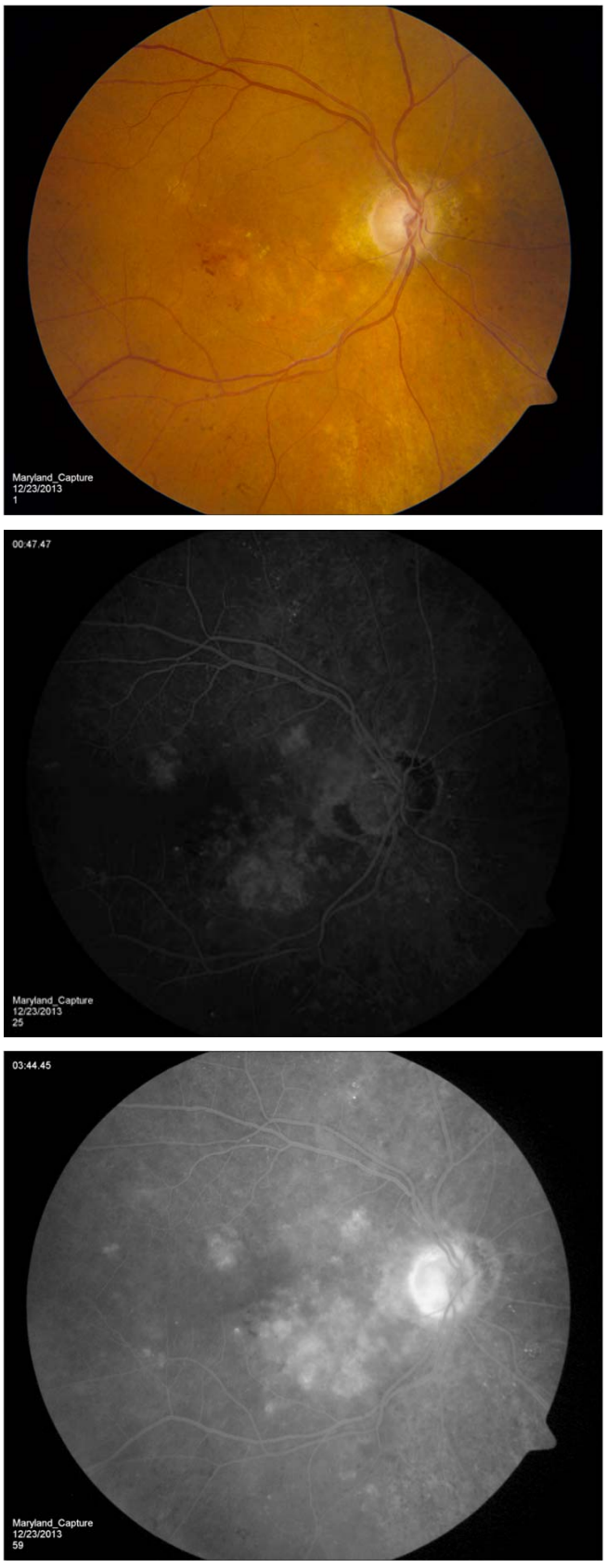

Figure 3: Retinal imaging after 4 Dexamethasone 0.7 mg (Ozurdex) implant injections. A- Color picture showing intraretinal hemorrhage and previous macular laser scars. B – Early Fluorescein angiography (FA). C- Late FA showing minimal leakage and macular hyper fluorescence.

Table 1: Best Corrected Visual Acuity and central Retinal Thickness 1, 3, and 4 Months Following 4 Injections of 0.7 mg Dexamethasone Implant

	Pre-injection	1 Month	3 Months	4 Months
1st Injection				
BCVA	20/400			20/250
CRT	486			415
2nd Injection				
BCVA	20/250	20/125		20/150
CRT	415	332		307
3rd Injection				
BCVA	20/150	20/200	20/200	
CRT	307	301	342	
4th Injection				
BCVA	20/200	20/150		
CRT	342			

BCVA – Best Corrected Visual Acuity, CRT – Central Retinal Thickness

bevacizumab showed improvement of visual acuity and resolution of macular edema, and the improved BCVA was mild (from 20/30 to 20/25 and from 20/25 to 20/20) [15]. In a series of ten patients, Mason showed a modest improvement in BCVA (20/100 to 20/86) and mean foveal thickness (482 μm to 284 μm) at six weeks, but essentially a return to baseline at four months (mean BCVA 20/95 and central foveal thickness 449 μm) [16]. Bakri showed that only one of five patients responded to bevacizumab injections and this response diminished following successive injections. As in our case report, two patients in that study demonstrated a resolution of CME on OCT without an improvement in BCVA [19]. On the other hand, Finger showed an improved or stabilized visual acuity in 16 of 18 patients after a mean of 3.8 injections of bevacizumab roughly every eight weeks [18]. Our case report supports the idea that bevacizumab's effect is moderate and diminishes with repeated use.

Intravitreal triamcinolone acetonide has been shown to be more effective than both bevacizumab [37] and macular grid laser photocoagulation [38] for the treatment of macular edema secondary to diabetic retinopathy, and evidence suggests that this may be true for radiation-induced maculopathy as well. Sutter published a case report of a patient who, after failing to respond to laser therapy, improved BCVA from 20/50 to 20/25 three months following an injection of

triamcinolone. He had a similarly positive response to a second injection when the CME recurred nine months later [24]. Shields looked at 31 patients with radiation-induced maculopathy and found that 91% showed stable or increased visual acuity at one month and 45% at 6 months. Mean foveal thickness was 417 μm at initial injection, 207 μm at one month, and 292 μm at 6 months. 10% of patients required cataract surgery and 10% required topical medications for increased intraocular pressure [25].

Although adverse events were relatively low in these studies, triamcinolone injections are associated with the development of cataracts, glaucoma, and endophthalmitis [39,40]. In a study of the use of intravitreal triamcinolone for refractory macular edema secondary to diabetic retinopathy, glaucoma medication was required in 44% of patients receiving intravitreal triamcinolone injections and cataract surgery was required in 54% [39]. In a recent case series on five patients with radiation-induced retinopathy, 40% of patients required medication for increased intraocular pressure and 80% developed cataracts. In that study, three of five patients showed improved visual acuity with triamcinolone injections after failing treatment with bevacizumab [19].

The anti-inflammatory effect of dexamethasone is six times greater than that of triamcinolone and due to its increased hydrophilicity, it acheives higher vitreous concentrations [41]. The dexamethasone implant delivers high levels of the drug to the posterior segment with a reduced need for repeat injections. The first reported use of dexamethasone for the treatment of radiation-induced maculopathy was from Russo, who presented a patient refractory to bevacizumab with an improvement in BCVA from 0.3 to 0.5 four weeks following injection. Central retinal thickness was reduced from 498 μm to 224 μm [27].

The second report comes from Baillif *et al.*, who looked at five patients with radiation macular edema following proton beam therapy for choroidal melanoma. BCVA improved in three of five patients two months following injection (+4, +9, and +15 Early Treatment Diabetic Retinopathy Study letters) with a mean gain of six letters. Central retinal thickness was reduced from 487.1 μm to 331 μm. At five months central retinal thickness had increased but only one patient had a BCVA worse than baseline. Two patients underwent an additional injection with comparable results to the first. Twenty percent of patients required topical medication for increased intraocular pressure [26].

In response to dexamethasone, our patient showed a remarkable improvement in visual acuity and a decrease in central retinal thickness following failure of multiple rounds of both bevacizumab and focal laser therapy. Visual acuity has been maintained for the past year with three subsequent 0.7 mg dexamethasone implant injections, showing that multiple injections continue to be efficacious.

More research is needed to determine the ideal treatment for radiation-induced macular edema. This case report is limited by its size and retrospective nature, and it is difficult to draw conclusions from it. However, we believe that the 0.7 mg dexamethasone implant should be considered for the treatment of radiation-induced macular edema.

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