Strategies for Minimizing Radiation Maculopathy

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Choroidal melanoma is an ominous malignant tumor of the eye, with propensity for hematogenous metastasis to the liver, lung, and other sites. The management of choroidal melanoma is primarily with enucleation or forms of radiotherapy, including plaque radiotherapy or proton beam radiotherapy. Twelve-year results of the Collaborative Ocular Melanoma Study (COMS) revealed no difference in survival for patients with medium-size melanoma treated with enucleation vs those treated with plaque radiotherapy. Shields et al noted impressive local melanoma control with plaque radiotherapy in 97% of cases by 5-years follow-up. Despite excellent control, radiotherapy for choroidal melanoma can lead to visually disabling radiation side effects, particularly in patients with macular involvement. These side effects include cataract, retinopathy, papillopathy, and maculopathy. Radiation maculopathy is one of the most common causes of visual loss following radiotherapy and can lead to irreversible blindness.

Radiation retinopathy/maculopathy typically develops when radiation exposure extends beyond tissue tolerance. The earliest clinical sign of radiation maculopathy is non-ischemic macular edema which can lead to ischemic maculopathy. Once ischemic maculopathy has evolved, then visual improvement is unlikely. Several protocols have been used to treat radiation maculopathy. However, the novel approach is to prevent maculopathy with methods including panretinal photocoagulation (PRP) to the ischemic radiation bed, scheduled intravitreal injections of bevacizumab (Avastin, Genentech) or ranibizumab (Lucentis, Genentech), and intravitreal or sub-Tenon fascia injections of triamcinolone. In this report, we describe treatment of choroidal melanoma using plaque radiotherapy with secondary intention of prevention of radiation maculopathy through prophylactic treatments.

CASE
A 51-year old white man presented with 3 months of intermittent photopsia in the left eye. Medical history was unremarkable. The patient had extensive professional exposure to arc welding. On examination, best corrected visual acuity (BCVA) was 20/20 OU. The anterior segment was unremarkable. Fundus examination of the right eye was normal. Fundus examination in the left eye revealed a medium-size choroidal melanoma superior to the optic disc measuring 10 x 8 mm in basal dimensions and 4.7 mm in thickness. There was overlying orange pigment and shallow serous retinal detachment (Figure 1A). Optical coherence tomography (OCT) confirmed overlying subretinal fluid with preservation of the retinal pigment epithelium (RPE) and retinal layers (Figure 1B). Autofluorescence showed hyperautofluorescence of orange pigment and subretinal fluid surrounding the mass (Figure 1C). B-scan ultrasonography disclosed acoustically hollow tumor mass of 4.7 mm.
The melanoma was treated with 15-mm round plaque with 7185 cGy to the apex and 17,023 cGy to the base of the tumor. An estimated 3355 cGy was delivered to the foveola and 4235 cGy to the optic disc. At the time of plaque placement, fine needle aspiration of the lesion was taken for genetic molecular testing. At plaque removal, bevacizumab was injected into the vitreous cavity, and transpupillary thermotherapy (TTT) was performed to the treated tumor. Molecular testing revealed disomy of chromosomes 3, 6, and 8.

Following treatment, the patient was given prophylactic intravitreal bevacizumab injections at 4-month intervals and later sector PRP. Three sessions of TTT for tumor scar consolidation were delivered. At nearly 2 years' follow-up, the tumor scar was 10 x 8.8 x 3.3 mm (Figure 2 A and B), with resolved subretinal fluid by OCT (Figure 2C) and with tumor thickness of 3 mm by B-scan ultrasonography (Figure 2D). Visual acuity has remained 20/20 OU.

DISCUSSION

Radiation maculopathy with secondary vision loss is a significant complication of plaque radiotherapy for choroidal melanoma.4 Visual acuity following plaque radiotherapy has been reported by Shields et al in a cohort of 1106 eyes and by the COMS in a cohort of 623 eyes.8,9 Shields et al showed that eyes with medium melanoma were found to have visual acuity of 20/200 or worse in 3%, 31%, and 69% of patients at follow-up of 1, 5 and 10 years, respectively.8 Important risk factors for poor vision included increasing tumor thickness, location within 5 mm of the foveola, tumor recurrence, patient age more than 60 years, subretinal fluid, cobalt isotope, tumor anterior margin located postequatorial, and worse initial visual acuity.9 Similarly, in an analysis by COMS, visual acuity was found to be less than 20/200 in 45% of patients at 3 years, with median visual acuity of 20/125.9 While the COMS study shared similar risk factors of increasing tumor thickness, less distance from foveola, and poor initial visual acuity with the study by Shields et al, it also included factors of diabetes mellitus, related retinal detachment, and lack of dome-shaped tumor.9

Our patient possessed several of these risk factors for poor visual outcome including tumor margin less than 5 mm from foveola, anterior margin posterior to equator, retinal detachment, and subretinal fluid. Considering these risk factors and the preserved visual acuity of 20/20 at 2-years follow-up, it appears that our patient is among only 16.8% of patients who maintain 20/20 vision at 2-year follow-up.9 This outcome could be somewhat related to the prophylactic treatments for prevention of radiation maculopathy, including intravitreal bevacizumab, TTT to the necrotic tumor, and PRP to the radiation field.

There are several strategies to identify and prevent radiation-related vision loss secondary to macular edema. Horgan et al studied onset of macular edema using OCT and found that macular edema was detected in 17% of patients at 6 months, 40% at 12 months, 57% at 18 months, and 61% at 24 months (n=135).10 The mean time to OCT-evident radiation maculopathy was 12 months.10 The mean time to clinical signs of radiation maculopathy was 17 months, occurring 5 months later than OCT-detectable macular edema.10 Thus it is apparent that OCT documents onset of macular edema several months before the patient becomes visually symptomatic.

The strategies for treatment of radiation maculopathy include laser photocoagulation,11 sub-Tenon triamcinolone,12 intravitreal triamcinolone,13 and intravitreal bevacizumab.7,14 Focal laser therapy may have moderate benefits in improving visual acuity from radiation-related macular edema at 6 months (n=19), but Hykin et al showed that this effect was not lasting at 2 years.11 Similarly, Shields et al established that intravitreal triamcinolone injections can improve or stabilize visual acuity in 91% of patients at 1 month and 45% of patients at 6 months (n=31), but long-term data are not available.13 In a retrospective study, Mason et al showed that intravitreal bevacizumab injections decreased macular edema and showed moderate...
early increases in visual acuity, but failed to show lasting effects.\textsuperscript{13} In 21 patients with radiation retinopathy, an average of 3.8 intravitreal injections of bevacizumab (1.25 mg in 0.05 mL) every 6 to 12 weeks improved or maintained visual acuities in 86%, with 14% gaining 2 or more Snellen lines of visual acuity, but long-term effects were not available.\textsuperscript{5}

 Few reports have focused on the prevention of radiation maculopathy. Horgan et al evaluated 55 patients following plaque radiotherapy for uveal melanoma in which sub-Tenon triamcinolone was delivered at the time of plaque removal, and then at 4 months’ and 8 months’ follow-up, with the intention to minimize radiation maculopathy. They found that pericentral triamcinolone injections lowered the risk for macular edema but did not prove to significantly affect visual outcomes at 2-year follow-up.\textsuperscript{13} Our group is currently investigating the use of bevacizumab for prevention of radiation maculopathy, and results are forthcoming. However, there is early enthusiasm that this approach could reduce maculopathy in the 2-year period as witnessed in this patient.

 From the data published by Horgan et al,\textsuperscript{6} our patient is expected to have a 69% chance for radiation macular edema by 2 years, but with prophylactic therapies of intravitreal bevacizumab, PRP, and TTT, he has avoided macular edema.

 Another prophylactic treatment is PRP to the sector of the radiation ischemic bed. Laser photocoagulation of radiation retinopathy in areas outside of the macula delays the progression to radiation maculopathy.\textsuperscript{9} In a study by Finger et al, prophylactic PRP was provided to 16 patients who were labeled as high risk for radiation maculopathy from tumors close to the optic disc and located in the parafoveal region. Of these 16, only 3 developed radiation retinopathy by mean follow-up of 16.5 months. Furthermore, PRP is effective in early radiation maculopathy. In a separate group of 45 patients with early onset retinopathy, treatment with sector argon laser photocoagulation showed regression of retinopathy in 64% of patients.\textsuperscript{7} An additional study by Materin et al, prophylactic sector PRP and sub-Tenon triamcinolone injections in 29 cases resulted in only 24% of patients developing OCT evidence of macular edema at 2 years follow-up.\textsuperscript{15} This evidence suggests that scatter argon laser PRP could be beneficial for prevention of radiation maculopathy with ultimate improvement in visual outcome.

 There could be a beneficial effect of TTT in visual outcome, although this is unproven. With TTT, the partially necrotic tumor scar is consolidated for improved control. Secondary effects are thought to be completion of tumor necrosis and reduction in toxic tumor syndrome, with subsequent reduction in vitreous cytokines and VEGF factors. Damato et al explored toxic tumor syndrome and speculated that complete removal of the tumor scar with methods of tumor resection in his hands,\textsuperscript{10} or by TTT in our hands, could ultimately prove beneficial to patient visual outcome.

 In summary, we present a case of choroidal melanoma controlled with iodine-125 plaque radiotherapy and TTT and vision protected with prophylactic PRP and intravitreal bevacizumab injections to prevent radiation maculopathy. The patient maintains visual acuity of 20/20 with no radiation complications. However, long-term follow-up is necessary to establish the full benefit of this approach.

 The authors have no financial interest in the devices or medications in this document.

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