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Radiation Retinopathy

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Abstract

Purpose of the Review. In this review, we bring together recent developments in the detection and management of radiation retinopathy.

Recent Findings Research into OCT-angiography for radiation retinopathy has led to the identification of biomarkers of early radiation-induced changes in the retinal microvasculature including focal capillary loss and vascular remodeling. These microvasculature changes are detectable after exposure to radiation but prior to the emergence of classical clinical markers historically used to diagnose radiation retinopathy. The ability to detect subclinical changes may present the need to redefine radiation retinopathy diagnostic criteria which may ultimately impact management. Additionally, explorations into prophylactic treatment following radiation exposure and development of newer anti-VEGF agents may present more options for retinal specialists to prevent or treat vision loss and retinal vasculopathy from radiation exposure.

Summary Currently, anti-VEGF injections and/or intravitreal steroids remain the primary treatment following a diagnosis of radiation retinopathy. However, a mainstay treatment and management strategy have not yet been identified. In the future, new anatomical endpoints for radiation retinopathy may be identified with OCT-angiography while prophylactic treatment with anti-VEGF agents following radiation therapy may reduce initial vision loss and changes to the retina.

Keywords Eye · Retina · Vascular · Ionizing radiation · Choroidal melanoma · Ocular lymphoma

Introduction

Radiation retinopathy (RR) is a chronic and progressive vasculopathy resulting from endothelial cell damage at the level of the retinal microvasculature [1]. RR encompasses a broad range of ischemic and non-ischemic changes to the retina and can result from any exposure to radiation including exposure to therapeutic radiation for ocular neoplasms, non-ocular neoplasms, and some non-neoplastic ocular lesions like wet age-related macular degeneration (AMD) or ocular sequalae of systematic diseases like Graves' ophthalmopathy [2]. Risk of complications secondary to radiation therapy, especially the development of RR, has been demonstrated to be dependent upon radiation dose, fractionation, and volume of irradiation [3]. The evaluation of radiation retinopathy primarily includes fundus biomicroscopy, fluorescein angiography, and optical coherence tomography (OCT). Medical management of RR includes anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections, intravitreal corticosteroids, and laser photocoagulation to halt disease progression and prevent further vision loss [4–6].

Further exploration of new anti-VEGF medications and prophylactic anti-VEGF administration has expanded treatment options for managing RR [7–10]. Moreover, OCT-angiography (OCT-A) identification of early clinical biomarkers has improved detection changes in retinal microvasculature, such as focal capillary loss and vascular remodeling, after exposure to radiation, but before classical clinical markers such as cotton wool spots and retinal hemorrhages are detected [11, 12].

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Radiation Retinopathy

Clinical Features and Diagnosis

RR phenotypically results from microvascular occlusion and leaking capillaries between 6 and 36 months after

radiation exposure [13, 14]. Classical findings include macular edema, retinal hemorrhages, telangiectatic vessels, and microaneurysms, as well as hard exudates, cotton-wool spots, and disc swelling (Figs. 1 and 2) [15]. RR is also associated with neovascularization of the retina, optic disc, and iris as well as optic atrophy, choroidal vasculopathy, and cataract (Fig. 1 and 2) [16]. Fundoscopy findings on dilated exam, in conjunction with a history of radiation exposure, support clinical diagnosis of RR [13, 14].

Radiation retinopathy can present variably including elements of ischemia, hemorrhage, exudation, and atrophy [13]. Ischemic RR is due to retinal vascular ischemia while exudative RR results from endothelial tight junction damage allowing serous and lipid-laden fluid to freely pass incompetent vascular barriers. Hemorrhagic RR is defined by capillary rupture yielding multifocal intraretinal hemorrhages or neovascularization allowing for frank vitreous hemorrhages. Thinning of the retinal pigment epithelium, retina, and choroid are hallmarks of atrophic RR [13, 17].

Diagnostic Imaging

Fluorescein Angiography

Fluorescein angiography (FA) is particularly most sensitive to detect vasculopathy in RR. Widefield FA reveals microaneurysms, capillary dropout, and neovascularization throughout the posterior segment [18]. Findings on fluorescein angiography in RR have previously been classified into four grades based upon microvascular changes as observed by Amoaku et al. [19, 20]. Grade 1 is defined as small foci of irregular retinal capillaries with clustered microaneurysms without capillary incompetence; grade 2 as multiple foci of telangiectatic capillaries and closure up to one optic disc area with capillary leakage; grade 3 as widespread, diffuse capillary dilation, microvascular incompetence, up to four disc areas of non-perfusion, and significant macular edema; grade 4 as extensive microvasculature disorganization, non-perfusion in greater than four disc areas, retinal neovascularization, and vitreous hemorrhage [20]. Similarly, Finger et al. proposed a classification based upon stages of RR including stage 1 of peripheral non-perfusion and ischemic changes [19, 21]. Stage 2 progresses to macular non-perfusion and ischemic changes while stage 3 possesses the addition of macular edema and peripheral retinal neovascularization. Stage 4 comprises the previous stages and vitreous hemorrhage and five or more disc areas of retinal ischemia [21]. Regardless of staging scheme for vasculopathy in RR, the vascular dysfunction is proportional to radiation dose and proximity to the radiation source.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a noninvasive imaging modality with sensitive detection of early RR [19]. Macular edema is an initial sign of RR detected on OCT and can occur as macular thickening without cystoid spaces

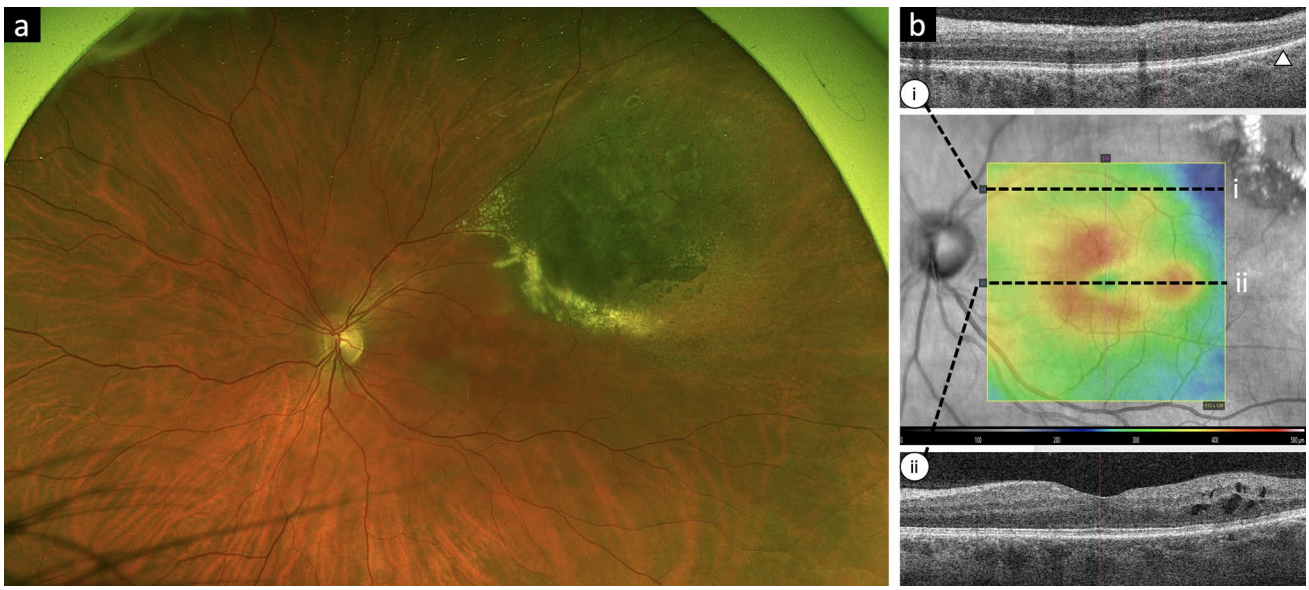

Fig. 1 43-year-old male with a history of choroidal melanoma of the left eye, treated 3 years previously with plaque radiotherapy. **A** Color fundus photograph of the left eye demonstrating regressed melanoma with exudates along the inferonasal margin; **B** OCT images demonstrating retinal atrophy (i) adjacent to the treated melanoma (white arrowhead) and macular thickening from macular edema (ii)

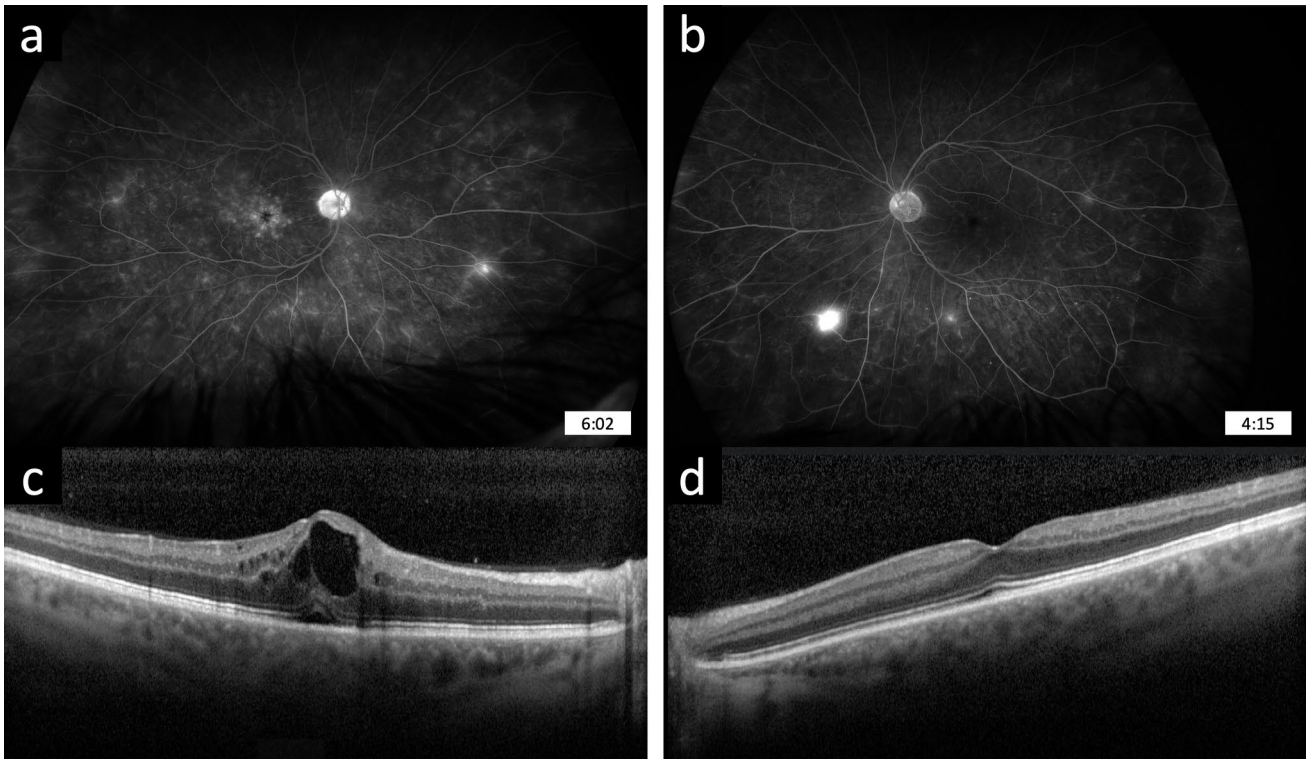

Fig. 2 60-year-old male with a lymphoma treated with whole body radiation and bone marrow transplant 9 years prior. **A** and **B** Late phase fluorescein angiography demonstrating small foci of peripheral neovascularization in both eyes, diffuse vascular leakage in both eyes, and petaloid macular leakage in the right eye; **C** and **D** Optical coherence tomography demonstrating macular edema in the right eye and a grossly normal macula in the left eye

as early as 4 months following radiation therapy [22]. Horgan et al. found that macular edema can be identified in a third of irradiated eyes with no clinical manifestations of RR and created a classification scale for grading severity of macular edema changes in RR with grade 1 defined as extra-foveolar non-cystoid edema; grade 2 as extra-foveolar cystoid edema; grade 3 as foveolar non-cystoid edema; grade 4 as mild-moderate foveolar cystoid edema; and grade 5 as severe foveolar cystoid edema [22]. Macular edema identified on OCT may precede clinically significant visual acuity loss but is limited by inability to identify vascular changes [23]. OCT-angiography (OCT-A) has recently been utilized to address this limitation [24, 25]. Additionally, spectral-domain and swept-source OCT provide improved scanning speeds and higher-resolution images than older time-domain OCT units [26].

Laser Speckle Flowgraphy

Laser speckle flowgraphy (LSFG) is a noninvasive tool that uses laser to create a quantitative estimate of intraocular blood flow across multiple eye structures. LSFG evaluates dynamic blood flow in the optic nerve head, choroid, and retina with high reproducibility [27]. Decreases in laser speckle blood flow have been observed in both retinal and choroidal vasculature in irradiated eyes, a possible early marker of microvasculopathy following radiation [27, 28]. LSFG is not widely available.

Recent Improvements in Understanding and Detecting Radiation Retinopathy

Biomarkers and Automation

Recent studies have identified that prior to development of a clinically detectable phenotype, OCT-A can identify capillary loss and vascular remodeling as early biomarkers for RR. Tamplin et al. used quantitative approaches to establish that microvascular damage and visual field changes were detected earlier than changes to inner retinal structure after brachytherapy [24]. Furthermore, evolving microvascular alterations are detectable on OCT-A over time [29]. Focal capillary loss and foveal avascular zone enlargement progressed over time despite improvements in cotton wool spots and retinal hemorrhages [29]. Torkashvand et al. used OCT-A to identify changes to the macular microvasculature following brachytherapy, revealing larger avascular zones in

both the superficial and deep fovea in irradiated eyes. Foveal and parafoveal vascular area density were decreased in both the superficial and deep capillary plexus for irradiated eyes. Radiation dose at the fovea and optic disc had high predictive values for macular microvasculature burnout [30].

Radiation also alters choroidal anatomy. Gilli et al. detected choriocapillaris microvascularization on OCT-A as an early biomarker of RR, and this correlated with disease severity [31]. Decreases in retinal and choroidal blood flow detected on LSFG within 6 months following brachytherapy may also constitute early markers of radiation-induced microvascular damage [28]. Kase et al. postulated that choroidal circulation disorder may play a role in the pathogenesis of RR upon finding choroidal circulation and perfusion in the macula was notably reduced at the onset of RR using LSFG [27].

Improvements to OCT-A including wider field of view and availability of automated measurement software further expand the ability to detect radiation-induced retinal damage before classical clinical signs of RR present. Preziosa et al. investigated extended field imaging OCT-A (EFI-OCTA) and found extensions of retinal and choroidal areas of nonperfusion. Vessel density also appeared significantly different with EFI-OCTA where vessel density in both the retina and choroid negatively correlated with areas of nonperfusion [32]. To compare nonirradiated fellow eyes, eyes without RR, and eyes with RR after brachytherapy for uveal melanoma, de Carlo et al. used automated AngioVue AngioAnalytics OCT-A software quantifications of foveal avascular zone size, perimeter size, and capillary density (Optovue Inc., Fremont, CA, USA). Eyes without RR had significantly decreased superficial capillary plexus density when compared to nonirradiated fellow eyes in some regions of the OCT-A. Whole-scan density for full retina thickness decreased per year after radiation exposure [12].

Moreover, automation methods validated on datasets of more common retinovascular disease, such as diabetic retinopathy, may also find translational application for RR. Small hyperreflective retinal foci (HRF) detected on OCT may represent aggregates of activated microglial cells and signal in vivo markers of retinal inflammation; however, clinical usage is currently limited by technical difficulty in counting and tracking HRF. Midena et al. created a semi-automatic method for detecting HRF to overcome quantification limitations in diabetic retinopathy [33]. Application may extend to RR in the future as the number and location of HRF have been previously correlated with central subfield thickness and intraretinal inflammation in RR [34].

Radiation Delivery and Thresholds

Studies have validated that total radiation dose as well as fractionation of dosages contribute to the development of RR [35]. Literature had previously proposed the threshold dose for development of RR at 30 Gy, where therapeutic radiation doses above 30 Gy have been associated with more observations of RR [36]. A recent systematic review of fifteen retrospective and prospective studies examined the local recurrence rate and median dosage of iodine-125 brachytherapy for uveal melanoma, finding that the mean and median radiation doses to the tumor apex ranged between 62.5 and 104 Gy. The review found that local recurrence rates ranged from 0 to 24% and postulated an association between each Gy increase and decimal decrease in local recurrence rate [37]. Depending on apical tumor height, the optimal dose of radiation may vary with some single-institution studies proposing lower doses of radiation for tumors of apical height less than 5.0 mm [38, 39]. Similarly, a study stratified by radiation dose such as less than 65 Gy or greater than 85 Gy established a direct relationship between radiation dose and tissue toxicity, verifying the relationship previously proposed in literature. Moreover, the study did not find an association between tumor apex and rate of local failure, advocating for a lower dose at tumor apex such as less than 85 Gy for tumors less than 5 mm in height [40].

Recent publications suggest modified guidance for safe doses of radiation therapy. Adding to literature on radiation thresholds, a recent Kaplan–Meier analysis demonstrated significantly increased incidence of RR following brachytherapy radiation dose greater than 52 Gy to the macula and 42 Gy for the optic disc. Previous reports had indicated higher thresholds for optic disc radiation damage [41]. Also, Chan et al. reported the development of RR following low-dose whole brain radiation therapy at 30 Gy in 10 fractions [42].

Management

Anti-VEGF Agents

There is currently no FDA-approved treatment for RR. The primary management goal in RR is to halt the progression and prevent further vision loss. Historically, restoration of vision has been difficult to achieve. VEGF is a protein secreted during local hypoxia that induces angiogenesis; however, the nascent blood vessels are prone to leakage, resulting in edema and loss of visual acuity [4]. Intravitreal anti-VEGF agents including bevacizumab, ranibizumab, and aflibercept have been have demonstrated to improve macular edema and confer sustained visual acuity preservation with short-term reduction in neovascularization [43–45]. Continuous therapy with anti-VEGFs may be necessary to preserve vision over the long-term, and higher doses may be needed at shorter intervals in refractory cases [43, 46]. Emerging developments in the management of RR also center on

prophylactic therapy to preempt the difficult, progressive course. Anti-VEGF agents, while all used off label to treat RR include pegaptinib sodium, ranibizumab, bevacizumab, aflibercept, brolucizumab, and faricimab-svoa.

Steroids

Intraocular steroids including dexamethasone, fluocinolone, and triamcinolone have been used for macular edema associated with RR. Corticosteroids downregulate cytokines and are often used in conjunction with anti-VEGF agents [47]. Moreover, corticosteroids stabilize endothelial tight junctions and reduce leukocyte migration, resulting in decreased capillary incompetence [2]. More recently, intravitreal dexamethasone implant has also been shown to provide benefits in visual acuity and reduction in central foveal thickness with variable sustainability [48, 49]. Corticosteroids are also mainstay treatment for other disease entities including radiation optic neuropathy and dysthyroid optic neuropathy [50, 51].

Retinal Laser Photocoagulation

Laser photocoagulation was an early innovation in the treatment of RR and delivers clinical marker improvement such as regression of neovascularization and reduction in edema, but is limited in efficacy due to lack of change or worsening of visual acuity [21, 52]. Laser photocoagulation also reduces VEGF production which may possess a benefit for prophylactic therapy [21]. The use of extensive laser photocoagulation in ischemic retinal disease may result in worsening macular edema, vision decline, and progressive retinal pigment epithelium atrophy [53, 54].

Recent Developments in Management

Investigations Into Brolucizumab

Use of brolucizumab as intravitreal injections is currently off-label for refractory macular edema including in the setting of RR. Murray et al. reviewed brolucizumab use for patients who have failed prior anti-VEGF therapy across three indications including RR and found that macular edema significantly improved, visual acuity improved or remained, and no anticipated severe adverse events occurred [8]. Though adverse events remain a serious concern, prior anti-VEGF exposure may potentially reduce the risk of brolucizumab acting as a vision "rescue" [8]. Villegas et al. also reported that brolucizumab was helpful in a case of RR-associated macular edema refractory to bevacizumab [9].

Hematopoietic Stem Cells

Prevention of retinal cellular atrophy and vasculopathy has been studied using hematopoietic stem cells. A rat model receiving ophthalmic irradiation and treated with intravitreal injection of human umbilical cord-derived CD133 + CD34 + hematopoietic stem cells demonstrated some protection against retinal endothelial and ganglion cell damage after radiation exposure [55]. The grafted cells are distributed along retinal vessels and into the ganglion cell layer. Higher numbers of CD31 + retinal endothelial cells and Brn3a + ganglion cells survived following irradiation. Co-culture of human umbilical cord-derived CD133 + CD34 + hematopoietic stem cells attenuated damage to human retinal microvascular endothelial cells in vitro as well [55].

Potential Disease Prophylaxis

Previous studies explored anti-VEGF treatment upon completion of radiation therapy as prophylaxis for the development of RR. Building upon previous literature, Powell et al. conducted a review of anti-VEGF therapy immediately after plaque removal stratified for patients at the highest risk of developing RR based upon tumor location and radiation dose [56–58]. The authors found that increasingly earlier initiation of anti-VEGF therapy at first clinical signs of RR correlated with greater vision preservation and restoration of macular anatomy; correspondingly, this was also the case for the highest-risk patients but upon treatment with no clinical signs for RR. The authors posit that this prophylactic benefit in high-risk patients without visible clinical signs for RR may be associated with recent research in OCT-A identifying radiation-induced subclinical focal capillary loss and microvascular remodeling [58].

Prior studies of prophylactic anti-VEGF injections had been conducted at a long interval of four months between injections [56, 57]. Powell et al. describe a current-practice regimen of initiation of prophylactic anti-VEGF treatment at the time of plaque removal for patients meeting the outlined stratification criteria [58].

Observations

To the authors of this review, recent research into OCT-A and the identification of subclinical biomarkers of early radiation-induced retinal damage and microvasculopathy represent important progress in RR. Early-onset microvascular changes identified on OCT-A occurring after radiation exposure but prior to emergence of classical clinical markers may redefine

the diagnostic criteria of RR and subsequently management of RR. Gilli et al. have called for a new approach to RR classification to include previously elusive minimal forms of RR [59].

The development of new pharmacologics has expanded treatment options for RR where there had previously been a dearth of possibilities for vision-saving treatment. However, treatment strategies remain empirical due to the lack of randomized controlled trials. Multiple anti-VEGF agents possess individual benefits such as the cost-effective advantage of first-line bevacizumab. Yet newer anti-VEGF agents are also potential candidates for RR treatment by improving visual acuity with reduced treatment frequency. Different roles for each anti-VEGF agent are taking form as some are used first-line while newer evidence shows the advantage of using a different anti-VEGF as possible rescue therapy. Due to the progressive nature of RR, there exists a high patient burden of intravitreal injections to improve or sustain the vision. Monthly injections may be inaccessible for some patients and while treat-and-extend protocols provide logistical convenience, the latter regimen may not preserve visual gains sufficiently in RR [10].

Further exploration of prophylactic treatment with anti-VEGF agents may address challenges associated with RR by preventing vision loss in the initial stages following radiation exposure and preserving retinal architecture. The use of OCT-A to monitor early changes in vascular anatomy with and without prophylactic therapy may offer an informative anatomical endpoint. The time to initiate RR therapy may precede macular edema and symptomatic vision loss and retinal specialists may have a larger range of treatment options at their disposal.

Declarations

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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