



Multimodal imaging in radiation retinopathy following orbital metastasis

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ABSTRACT

Background: Radiation retinopathy is a major cause of vision loss in patients receiving radiotherapy to the head and orbit. Diabetic retinopathy is one of the differential diagnosis owing to similar clinical features, including microaneurysms, cotton-wool spots, hard exudates, and macular edema. The only significant pathological difference is that radiation retinopathy spares pericytes, unlike in diabetic retinopathy. Multimodal imaging helps diagnose and predict the prognosis of radiation retinopathy, which is presented in this case report.

Case Presentation: A 55-year-old woman diagnosed with stage-4 metastatic breast carcinoma presented with gradual diminution of vision in the left eye (OS) over 5 months. Vision in the right eye was lost because of orbital radiotherapy for orbital metastasis. The patient underwent multiple sessions of chemotherapy and radiotherapy. Examination of the left eye revealed a best-corrected distance visual acuity (BCDVA) of 20/30. Fundus examination of the OS revealed multiple cotton-wool spots and retinal hemorrhages. Fundus fluorescein angiography (FFA) showed diffuse macular leakage with capillary nonperfusion. Multicolor imaging (MCI) with Spectralis™ revealed black dots in the blue and green reflectance images, corresponding to capillary dilatation on FFA. Darker dots were more evident in the infrared images. BCDVA improved to 20/20 in OS after tapering the dose of oral steroids for 2 months, with improvements in hemorrhages and cotton-wool spots. Focal laser photocoagulation was recommended for the treatment of persistent macular edema. The patient declined further treatment, was lost to follow-up, and passed away 6 months later.

Conclusions: This case highlights the importance of multimodal imaging for the identification and classification of radiation retinopathy. MCI using Spectralis™ has been described for the first time in radiation retinopathy and can be used to complement existing imaging modalities. Future studies involving more patients and a longer follow-up duration may provide better results for the applicability of these imaging modalities in the clinical setting.

KEYWORDS


radiations, macula luteas, imaging, multimodal, multimodal imaging, multi-color imaging, fluorescence angiography, optical coherence tomography, cystoid macular edema

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INTRODUCTION

Radiation retinopathy is a vision-threatening and devastating complication of radiotherapy in patients with malignancies of the eyeball, orbit, head, and neck [1, 2]. The occurrence of radiation retinopathy depends on several factors, including the total radiation dosage, fraction radiation dosage, adjuvant chemotherapy, and concomitant vascular disorders, such as diabetes mellitus [1, 3].

Diabetic retinopathy (DR) is a risk factor for radiation retinopathy and also included in the differential diagnosis owing to similar features, such as microaneurysms, cotton-wool spots, hard exudates, and macular edema [1, 4]. Both diseases progress in a similar fashion from non-proliferative to proliferative stages and share similar ischemic complications, including capillary nonperfusion (CNP) areas, retinal neovascularization, vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma [1].

However, the pathogeneses of these two diseases show one difference. Pericytes are primarily affected in DR [5] but rarely affected in radiation retinopathy, which is hypothesized to cause preferential loss of vascular endothelial cells instead of pericytes [5, 6]. This leads to alterations in the retinal microvasculature because of a compromised blood-retinal barrier, followed by vascular occlusion and CNP. Exposure to high concentrations of free radicals indirectly damages endothelial cells [5].

Other vascular differential diagnoses include hypertension, retinal vein occlusion, ocular ischemic syndrome, hypertensive retinopathy, Coats disease, and parafoveal telangiectasia [7]. Concomitant chemotherapy can accentuate retinal vascular damage caused by radiation exposure by increasing oxygen-derived free radicals [1].

Clinically differentiating radiation retinopathy from the aforementioned differential diagnoses may be difficult, and various imaging modalities may help to a certain extent. Multimodal imaging has become an indispensable tool for the identification, classification, and prognosis of radiation maculopathy [8]. This case highlights the importance of multimodal imaging in radiation retinopathy following radiation exposure for orbital metastases from breast carcinomas.

CASE PRESENTATION

A 55-year-old Asian Indian woman presented with painless, mild, and non-progressive blurring of vision in the left eye (OS) for 5 months. She had been diagnosed with stage 4 metastatic breast carcinoma 2 years before, for which she had received multiple sessions of chemotherapy (5-fluorouracil, epirubicin, and cyclophosphamide), radiotherapy, and oral letrozole therapy. She had a history of vision loss in the right eye (OD) 11 months prior because of orbital metastasis, which was treated with multiple sessions of orbital radiation (35 Gray [Gy] in ten fractions). Further details regarding the duration or last radiation session are unavailable. The patient was diagnosed with hypothyroidism and hypertension. She had no history of diabetes mellitus. Positron emission tomography (PET) performed 8 days before her eye consultation had shown a relatively stable metabolically inactive soft tissue nodule in the inferolateral quadrant of the left breast with stable subcentimeter left axillary and deep pectoral metastatic lymph nodes. There was no evidence of orbital metastasis. The general physical examination revealed no palpable lymph nodes, and systemic examination revealed a palpable mass in the left breast.

On ocular examination, the best-corrected distance visual acuity (BCDVA) using the Snellen chart (auto chart projector CP 670; Nidek Co., Ltd., Gamagori, Japan) was denial of perception of light (OD) and 20/30 (OS). Slit-lamp examination (Topcon Corporation, Tokyo, Japan) of the anterior segment revealed a pseudo-cornea with a flat anterior chamber in OD and normal findings in OS. Fundus examination using binocular indirect ophthalmoscopy (Keeler Instruments Inc., PA, USA) and a +20-diopter ancillary lens (VOLK Optical Inc., Mentor, OH, USA) of OS revealed clear media, multiple cotton-wool spots (Figure 1A), and a few retinal hemorrhages at the posterior pole. Intraocular pressure measured using a Goldmann applanation tonometer (Haag Streit, Koeniz, Switzerland) at 12:30 PM was 14 mmHg in OS.

Spectral-domain optical coherence tomography (SD-OCT; Heidelberg Spectralis SD-OCT; Spectralis software version 5.3.2; Heidelberg Engineering, Inc., Dossenheim, Germany) of OS showed hyperreflective dots in the posterior vitreous with cystoid changes and intraretinal deposits in the macula (Figure 1B). The central macular thickness and macular thickness in the greatest dimension were 208 and 424 μm , respectively. Enhanced-depth imaging OCT revealed a normal choroid morphology. Diffuse macular leakage with a distorted and enlarged foveal avascular zone (FAZ) suggestive of macular edema, perivascular leakage at the macula, and localized CNP areas (Figures 2A-E and 3A, B) were noted on the fundus fluorescein angiography (FFA; Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany) of OS.

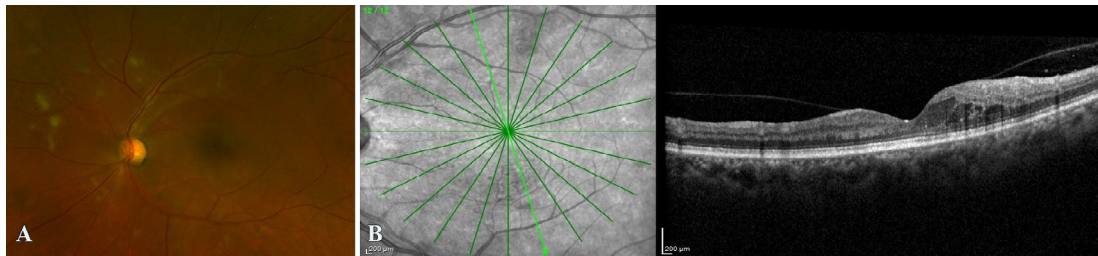


Figure 1. (A) Color fundus photograph (Optos™, Optos Carfortina®, Optos Inc., Dunfermline, United Kingdom) of the left eye on presentation showing prominent multiple cotton-wool spots (yellowish irregular lesions). (B) Spectral-domain optical coherence tomography (Heidelberg Spectralis SD-OCT; Spectralis software version 5.3.2; Heidelberg Engineering, Inc., Dossenheim, Germany) of the left eye on presentation showing cystoid macular edema.

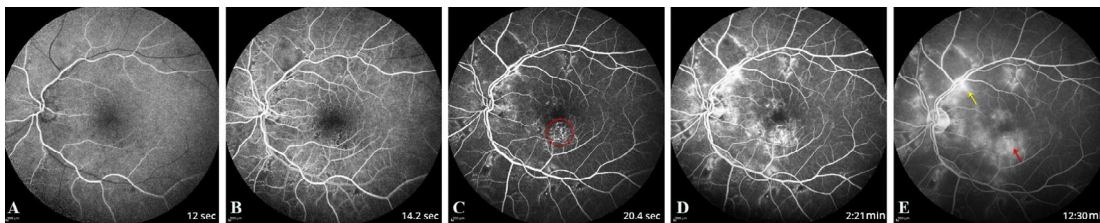


Figure 2. (A-E) Fundus fluorescein angiography (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany) on presentation showing enlarged and distorted foveal avascular zone with (C-E) capillary dilatations (C, red dashed circle) in the venous phase and leakage in the macula (E, red arrow) and perivascular area (E, yellow arrow) in the posterior pole in the late phase.

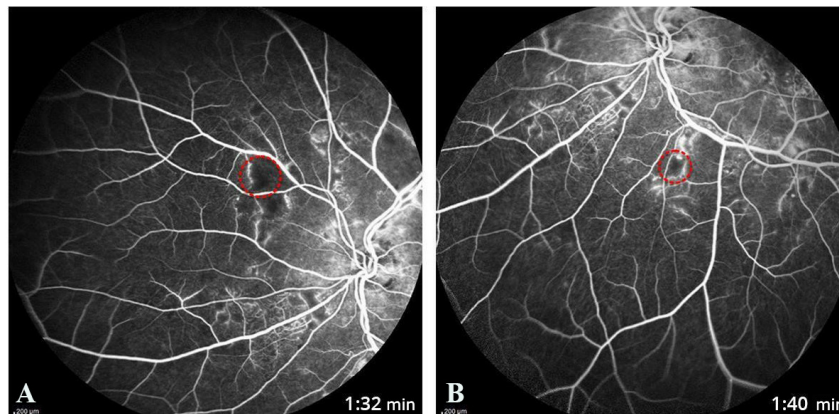


Figure 3. (A, B) Fundus fluorescein angiography (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany) on presentation showing localized areas of capillary nonperfusion (red dashed circles).

Multicolor imaging (MCI) with Spectralis™ (Heidelberg Engineering™, Heidelberg, Germany) revealed black dots in the blue and green reflectance images corresponding to capillary dilatation on FFA. Darker dots were more evident in the infrared images (Figure 4A-D). We hypothesized that this could be because of a swelling in the inner retinal layers on SD-OCT, which casts a shadow on the deeper layers. A few hyperreflective outpouchings were observed in the parafoveolar area on blue reflectance (Figure 4D), corresponding to leakage at the macula with a distorted FAZ on FFA. Blood investigations showed (Table 1) an elevated erythrocyte sedimentation rate (ESR; 28 mm/h; Table 1). Because signs of retinal vascular inflammation were present, an immunologist's opinion was sought. The autoimmune workup revealed positivity for the anti-Ro-52 antibody (52 KDa) [9]. No evidence of blood dyscrasia or anemia, which could have contributed to similar fundus findings, was found.

The patient was started on topical difluprednate 0.05% (Durezol ophthalmic emulsion, Alcon Laboratories, Inc., Fort Worth, TX, USA) and nepafenac 0.1% suspension (Nevanac; Alcon Laboratories, Inc., Fort Worth, TX, USA) thrice daily for cystoid macular edema. Since ESR was raised with vascular leakage on FFA, inflammatory

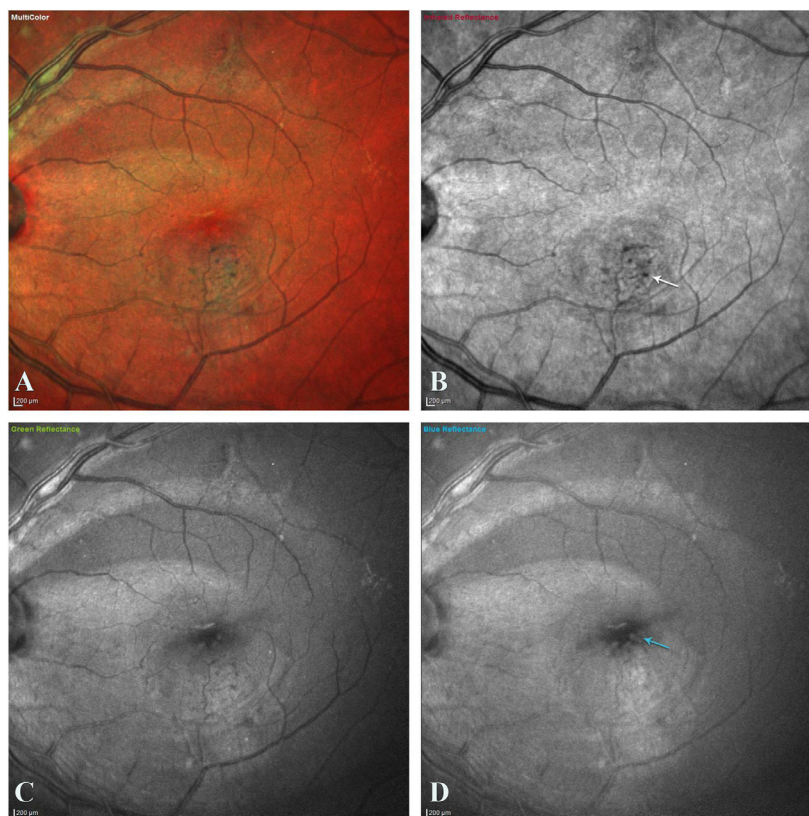


Figure 4. (A-D) Spectralis™ multimodal imaging (Heidelberg Engineering™, Heidelberg, Germany) on presentation showing (A) dark dots inferior to the fovea in the pseudocolor image, (B) black dots in infrared (white arrow) and (C) green reflectance image, and (D) a few hyperreflective outpouchings in the blue reflectance image (blue arrow).

Table 1. Laboratory parameters

Laboratory parameters	Report	Normal values
RBC count	$4.40 \times 10^{12}/L$	$3.8-4.8 \times 10^{12}/L$
Hb	12.0 g/dL	12.0–15.0 g/dL
PCV	35.9%	36–46%
MCV	81.6 fL	83–101 fL
MCH	27.3 pg	27–32 pg
MCHC	33.4 g/dL	31.5–34.5 g/dL
RDW	14.5%	11.5–14.5%
ESR	28 mm/h	< 20 mm/h
RBS	78 mg/dL	< 180 mg/dL
Anti-Ro-52-antibody (52 KDa)	Positive	-
cANCA	Negative	-

Abbreviations: RBC, red blood cell; Hb, hemoglobin; g/dL, grams per deciliter; PCV, packed cell volume; %, percentage; MCV, mean corpuscular volume; fL, femtoliters; MCH, mean corpuscular hemoglobin; pg, picograms; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; ESR, erythrocyte sedimentation rate; mm/hour, millimeters per hour; RBS, random blood sugar; mg/dL; milligrams per deciliter; cANCA, antineutrophil cytoplasmic autoantibody. Note: Abnormal blood parameters are shown in bold.

etiology was considered. Further, 40 mg of tablet prednisolone (Wysolone oral tablet, Pfizer Ltd., USA) was added in consultation with an immunologist with weekly tapering over 4 weeks.

At the 3-month follow-up, hemorrhages and cotton-wool spots had improved (Figure 5A). Topical steroid- or nepafenac-related side effects (raised intraocular pressure or corneal melting) were not observed. BCDVA in OS had improved to 20/20. However, repeat SD-OCT revealed persistent macular edema (Figure 5B)

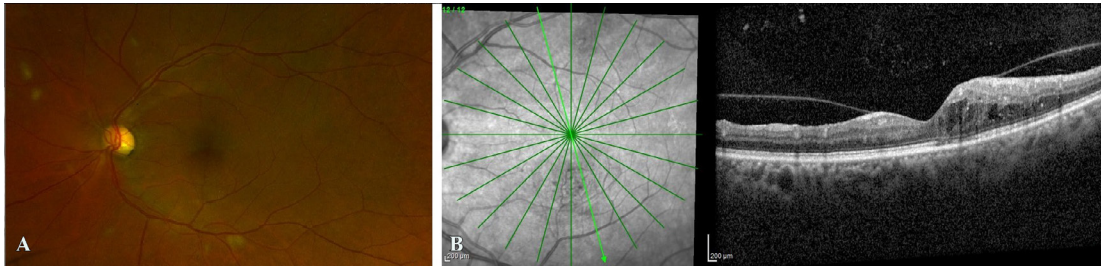


Figure 5. (A) Color fundus photograph (Optos™, Optos Carifornia®, Optos Inc., Dunfermline, United Kingdom) of the left eye at the final visit showing prominent reduction in the number of cotton-wool spots. (B) Spectral-domain optical coherence tomography (Heidelberg Spectralis SD-OCT; Spectralis software version 5.3.2; Heidelberg Engineering, Inc., Dossenheim, Germany) of the left eye at the final visit showing persistence of cystoid macular edema.

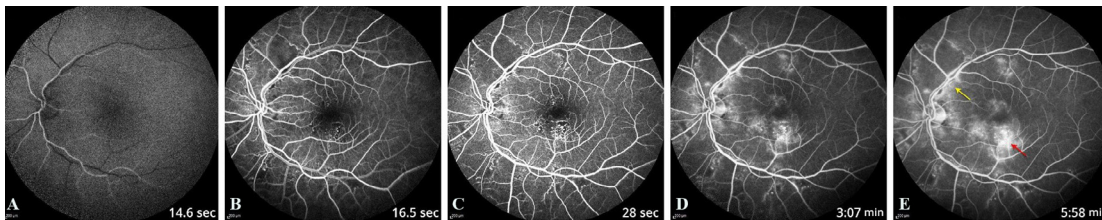


Figure 6. (A-E) Fundus fluorescein angiography (Heidelberg Retinal Angiograph; Heidelberg Engineering, Inc., Dossenheim, Germany) at the final visit showing reduction in perivascular leakage (E, yellow arrow) with persistence of macular leakage (E, red arrow).

and corresponding persistent focal leaks on FFA (Figure 6A-E). The central macular thickness and macular thickness in the greatest dimension increased to 226 and 469 μm , respectively. Focal laser photocoagulation was advised, but the patient did not consent. Topical steroids and nepafenac were continued. The patient was lost to follow-up and died 6 months later.

Ethical approval for the publication of this case report was received from the Ethics Committee of Vitreo-Retinal Department, Narayana Nethralaya Super Specialty Eye hospital and Post Graduate Institute of Ophthalmology, Bangalore, Karnataka, India in April 2023.

DISCUSSION

Here, we described the case of a middle-aged woman diagnosed with retinopathy in OS following radiotherapy for metastatic breast cancer on multimodal imaging, with other causes of retinal hemorrhages being ruled out. Macular edema was observed on SD-OCT, for which topical and oral steroids were started with a possible inflammatory etiology. At the 3-month follow-up, although hemorrhage had improved significantly, macular edema persisted on SD-OCT, with focal leaks on FFA. Focal laser therapy was advised for these leaks. However, the patient did not consent and was lost to follow-up.

Radiation retinopathy is a major cause of vision loss in patients undergoing radiotherapy for head and neck malignancies, including those of the globe and orbit [1, 10]. Several imaging modalities for the diagnosis of radiation maculopathy have been described in the literature. Moreover, various classification systems for radiation retinopathy have been proposed based on different imaging tools [8, 11, 12].

Finger and Kurli's classification [11] is based on ophthalmoscopic and FFA findings. FFA is a useful imaging modality for detecting vascular occlusive changes in radiation retinopathy, including CNP areas, microaneurysms, nerve fiber layer infarcts, neovascularization, and macular leakage. However, this classification is no longer used because it does not include OCT findings [11].

Horgan et al. in 2010 [12] proposed an OCT-based classification for macular edema. Nonetheless, this was a qualitative classification system excluding the quantitative OCT analysis [12]. Moreover, atrophic retinal changes associated with macular edema were not considered.

Recently, Parrozzani et al. [8] conducted a study on the classification of radiation maculopathy using a multimodal imaging approach by identifying the most relevant macular morphological biomarkers and correlating them with the visual acuity of patients. They assessed various OCT parameters, including the vertical thickness of the thickest macular cyst, foveal retinal pigment epithelium (RPE) atrophy, and inner/

outer segment layer disruption, to characterize radiation maculopathy [8]. Cystoid macular edema was noted in the present patient, although without RPE atrophy.

To the best of our knowledge, this is the first report of radiation retinopathy using MCI. MCI is a noninvasive retinal imaging tool developed by Spectralis™ (Heidelberg Engineering, Heidelberg, Germany). Three individual lasers with different wavelengths (blue, 488 nm; green, 515 nm; and infrared, 820 nm) are used to produce three reflectance images of the retina. Information from different retinal structures can be generated based on different depths of tissue penetration. Information from these three images are integrated to produce a pseudocolor image [13].

The total radiation dose and fraction size play critical roles in the development of radiation retinopathy [1]. A safe recommended dose of 3000 rads/30 Gy and 1000 rads/10 Gy per week in five fractions (200 rads/2 Gy per session) has been reported. The risk of developing retinopathy due to radiotherapy is up to 5% with doses between 30 Gy in 10 fractions and 40 Gy in 20 fractions [14]. The present patient received radiotherapy for the orbital metastasis at a dose greater than the recommended dose because of the aggressive nature of the metastasis.

Letrozole is a nonsteroidal aromatase inhibitor that acts by inhibiting estrogen synthesis. Further, anastrozole, a selective nonsteroidal aromatase inhibitor, causes retinal hemorrhages [15]. However, to date, no case has been reported regarding the retinal side effects of letrozole. Since the present patient received letrozole for the management of breast carcinoma, retinal hemorrhage could be partly attributed to the long-term use of letrozole. However, further studies with longer observation periods and the recruitment of more patients are required to verify this hypothesis.

Various treatment options for radiation retinopathy have been described in the literature, including intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy, laser photocoagulation, steroids, and intravenous diuresis [16-18]. Kinyoun et al., Amaoku et al., and Hykin et al. have outlined the importance of focal laser therapy in cases of radiation maculopathy [1]. In the present patient, focal laser therapy was advised in view of the non-resolving macular edema on SD-OCT to prevent vision deterioration. However, this was deferred because the patient refused treatment.

Steroids perform both anti-inflammatory and anti-VEGF actions and help reduce macular edema [19]. In the present case, clinical resolution occurred in the form of BCDVA improving to 20/20, and soft exudates and retinal hemorrhages improved with oral steroid therapy, although macular edema was persistent on SD-OCT. Therefore, multimodal imaging was employed to plan the appropriate management for complete patient recovery.

A case of radiation retinopathy detected using multimodal imaging has been reported. However, it was limited by the case report design. Focal laser therapy could not be applied because of the patient's refusal; therefore, the effect of focal laser therapy on focal leaks could not be determined. Future studies involving more patients and a longer follow-up duration to address these limitations may provide better results for applicability in the clinical setting.

CONCLUSIONS

The present case suggests that multimodal imaging of the posterior segment of the eye in radiation retinopathy helps in treatment planning, monitoring the progression, and predicting the outcomes. The clinical resolution may not always correspond to the resolution observed on imaging. MCI using Spectralis™ has been described for the first time in radiation retinopathy and can be used to complement existing imaging modalities. Inflammation can coexist in cases of radiation retinopathy, which responds well to steroids. Focal laser therapy is an additional option for cases of non-resolving macular edema.

ETHICAL DECLARATIONS

Ethical approval: Ethical approval for the publication of this case report was received from the Ethics Committee of Vitreo-Retinal Department, Narayana Nethralaya Super Specialty Eye hospital and Post Graduate Institute of Ophthalmology, Bangalore, Karnataka, India in April 2023.

Conflict of interests: None

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