Synergism between diabetic and radiation retinopathy: case report and review

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Abstract
It is suspected that radiation retinopathy is more likely to develop in an eye with pre-existing diabetic retinopathy than in a normal eye. However, there is only one report of this occurring, at a radiation dose of 4500 rads. We present a woman with minimal diabetic retinopathy who had breast carcinoma which was treated with chemotherapy but metastasised to the choroid. Within nine months of external beam radiation (3000 rads in fractions of 200 rads) a fulminant retinopathy evolved in that eye, while the non-radiated eye showed no change. The histopathology of radiation and diabetic retinopathy and causes for possible synergism are discussed. As this case report shows, radiation oncologists and ophthalmologists need to be aware of the risk that patients with minimal diabetic retinopathy who have undergone chemotherapy may suffer a dramatic visual loss from radiation therapy despite a radiation dose which is considered adequate, safe, and properly fractionated.

Radiation damage in tissues may result from direct parenchymal damage, usually in a rapidly dividing cell system such as intestinal epithelium, or from delayed effects caused by damage to vascular and interstitial support structures. In the eye, radiation retinopathy is a disease resulting from damage to retinal blood vessels. Gass states that, clinically and angiographically, radiation retinopathy is virtually identical to diabetic retinopathy.

Several authors have noted that patients with diabetes or hypertension may be particularly susceptible to radiation induced vascular damage. However, we could find only one case report of this occurring. In this case a moderate radiation dose (4500 rads was given to the fovea by cobalt-60 plaque irradiation) caused radiation retinopathy in a diabetic patient. Chemotherapy is also thought to augment the damaging effects of radiation to the posterior segment of the eye even if it is not concomitant with radiation.

In this paper we describe a case of a woman in which the combined effects of pre-existing minimal diabetic retinopathy, previous chemotherapy, and radiation therapy led to a slimmer retinopathy despite a dose of external beam radiation which was considered adequate, safe, and properly fractionated.

Case report
The patient is a 54-year-old woman with known insulin dependent diabetes mellitus for 16 years and minimal background diabetic retinopathy. She is otherwise healthy and has no cardiovascular or carotid artery disease. At the age of 45 she underwent a modified radical mastectomy for breast cancer. Since the tumour had spread to adjacent lymph nodes the patient received a full course of cyclophosphamide, methotrexate, and 5-fluorouracil. She developed a cough seven years later, and a mediastinoscopy confirmed the presence of metastatic adenocarcinoma, which has been treated with tamoxifen since.

Nine years after diagnosis of the primary tumour the patient noted photopsias in the right eye. Examination showed a best corrected visual acuity of 20/30 and 20/25 in the right and left eye respectively. There was slight congestion of episcleral vessels of the right eye nasally. Both eyes showed minimal background diabetic retinopathy with a few microaneurysms and dot haemorrhages (Figs 1 and 2). In the right fundus a creamy white choroidal lesion between 3 and 5

Figure 1 Red-free photograph of the right eye shows minimal background diabetic retinopathy changes with a few microaneurysms and dot haemorrhages.

Figure 2 Fluorescein angiogram of the right eye shows microaneurysms and blockage of background choroidal fluorescence by intraretinal haemorrhages (242 seconds after dye injection).
fluorescein angiogram showed o'clock in the far inferonasal periphery with secondary shallow retinal detachment was noted, consistent with metastatic carcinoma (Fig 3). A fluorescein angiogram showed very early leakage from this mass lesion which continued throughout the course of the study. A diagnosis of choroidal metastasis from primary breast carcinoma was made. With the 4 MeV linear accelerator the lesion was treated with a total of 3000 rads over three weeks, in fractions of 200 rads.

One month after treatment the secondary retinal detachment had disappeared. The visual acuity and the appearance of mild background diabetic retinopathy were unchanged. Six months after radiotherapy the visual acuity remained unchanged but the retinopathy had markedly increased in the right eye. Cotton-wool spots were now present as well as increased haemorrhages and oedema. Seven months after radiation visual acuity in the right eye had decreased to 20/80, and a fluorescein angiogram showed early perifoveal capillary loss as well as haemorrhages and peripheral capillary loss (Figs 4 and 5). Nine months after radiotherapy the vision in the right eye, was hand motions and severe capillary dropout was seen (Figs 6 and 7). The left eye remained unchanged with 20/25 visual acuity and minimal background diabetic retinopathy (Fig 8).

Discussion
The first report of radiation retinopathy was published in the 1930s in a case of implantation of radon seeds for the treatment of a retinoblastoma. Subsequent reports have described the typical clinical and angiographic changes of radiation retinopathy. Clinically one may see microaneurysms, intraretinal oedema, exudation, and haemorrhage. Retinal telangiectasis, neovascularisation, cotton-wool spots, and vascular sheathing are also seen. Ischaemic optic neuropathy may occur as well as vitreous haemorrhage and retinal detachment. The posterior pole of the eye appears to be the area most sensitive to radiation damage. On fluorescein angiography the most striking finding is severe retinal capillary non-perfusion. Histologically the walls of small retinal vessels are thickened, and there is loss of endothelial cells. In experiments on monkeys Irvine and Wood demonstrated that the retinal capillaries are damaged first. In their trypsin digest flat bed preparations there was initial...
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Figure 7. The fluorescein angiogram of the right eye shows marked capillary non-perfusion nine months after radiation therapy (30.6 seconds after dye injection).

Figure 8. The left eye remains unchanged, exhibiting minimal background diabetic retinopathy changes with a few microaneurysms and dot haemorrhages (red-free photograph).

endothelial cell loss and then loss of pericytes, resulting in large areas of capillary non-perfusion. Microaneurysms, closure of bigger vessels, recanalisation, and neovascularisation in the retina and to a smaller degree in the choriocapillaris can be observed later. Electron microscopy confirmed new endothelial cell growth within thickened, recanalised vessels. However, Irvine et al had found in an earlier study that endothelial cells initially appeared to be less damaged than pericytes on electron microscopy, contrary to the findings in trypsin digest preparations.

Clinically, radiation retinopathy may develop after ionising radiation reaches the posterior segment of the eye by either local treatments (for example, application of a radioactive plaque) or external beam radiation. The radiation may be given for local intraocular lesions (for example, retinoblastoma, choroidal melanoma, metastatic disease) or for adjacent extraocular lesions (for example, nasopharyngeal or sinus carcinoma, or intracranial tumours). The severity of the retinopathy is thought to be related to total radiation dosage and to the fractionation of that dosage. The total time of the treatment is also of significance.

There is general agreement that 3000 rads with a standard fractionation of 1000 rads per week in five fractions (200 rads per treatment session), is a safe total dose of external beam radiation, though there are reports in which radiation retinopathy occurred at lower doses. However, these dosages were reconstituted, and a low energy 220 KV machine was used which has a higher incidence of complications than contemporary radiotherapeutic emitters. The time course of retinopathic changes is variable, with an onset between six months and three years after radiotherapy, but earlier and later changes have been noted. Higher doses of radiation are not known to be associated with a shortened latency period, but the use of adjunct chemotherapy may be. Conditions thought to enhance the development of radiation vasculopathy include vascular diseases like diabetes, hypertension, collagen vascular disease, or chemotherapy. However, we found only one previous report in the literature in which a moderate dose of radiation (4500 rads was given to the fovea by cobalt-60 plaque irradiation) caused radiation retinopathy in a diabetic patient. In this study the authors noted that eyes which progressed to total blindness from radiation damage had received chemotherapy more frequently than eyes with less damage. The chemotherapy does not have to be given concurrently with radiation to show this effect.

This case report describes unilateral development of a fulminating retinopathy after orbital radiation and chemotherapy in the setting of minimal background diabetic retinopathy. The patient received 3000 rads in fractions of 200 rads over a three-week period. With our current understanding it is unlikely that in an otherwise normal eye this conservative radiation dose would have led to the described severe and blinding retinopathy. Likewise, the dramatic visual loss was probably not due to mere progression of the pre-existing diabetic retinopathy alone, since the fellow eye was stable throughout the period of observation. This case suggests that pre-existing minimal diabetic retinopathy and prior chemotherapy had a potentiating effect in the pathogenesis of radiation retinopathy. Since both diabetes and radiation primarily cause damage to retinal capillaries, this potentiating effect may not be surprising. In diabetes it has been shown that there is, among other changes such as thickening of basement membrane, an early loss of pericytes. In contrast to this, in radiation induced retinopathy endothelial cells may be disproportionately affected. Since endothelial cells and pericytes are the primary cells making up retinal capillaries, destruction of both these elements by the combined effect of diabetes and radiation would leave little cellular support for capillaries and facilitate changes of capillary closure, aneurysms, vessel leakage, and haemorrhage.

As this case report shows, radiation oncologists and ophthalmologists need to be aware of the risk that patients with minimal diabetic retinopathy who have undergone chemotherapy may suffer a dramatic visual loss from radiation therapy despite a radiation dose which is considered adequate, safe, and properly fractionated.

This study was presented at the West Coast Retina Study Club, 26-27 January, 1987, Kona, Hawaii.
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