Articles

Radiation Retinopathy

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Radiation therapy is effective against many cancerous and noncancerous disease processes. As with other therapeutics, side effects must be anticipated, recognized, and managed appropriately. Radiation retinopathy is a vision-threatening complication of ocular, orbital, periorbital, facial, nasopharyngeal, and cranial irradiation. Factors that appear important in the pathogenesis of radiation retinopathy include total radiation dosage, fraction size, concomitant chemotherapy, and preexisting vascular disorders. Clinical manifestations of the disorder include macular edema and nonproliferative and proliferative retinopathy, similar to changes seen in diabetic retinopathy. Argon laser photocoagulation has proved efficacious for managing macular edema and fibrovascular proliferation in some of these patients.

Ongoing basic laboratory and clinical research efforts have led to a better understanding of the pathogenesis, natural history, and treatment response of radiation retinopathy. The ultimate goal of this knowledge is to improve the prevention, recognition, and management of this vision-threatening complication.

(Zamber RW, Kinyoun JL: Radiation retinopathy. West J Med 1992 Nov; 157:530-533)

On November 8, 1895, Wilhelm Röntgen availed to the world new and powerful diagnostic and therapeutic potential with his discovery of x-rays. Remarkably, within two months of Röntgen's discovery, a patient with cancer of the breast began receiving daily radiation treatment administered by Chicago medical student Emil Grubbé.[1] As greater understanding of the nature, power, and possible pathogenicity of x-rays emerged, refinements in delivery techniques evolved. In 1922 Claudius Regaud and Henri Contard developed fractionation techniques that greatly reduced the side effects of radiotherapy.[1] In the 1930s and 1940s, "super voltage" and "megavoltage" units were produced in the United States,[1] and the evolution and development of radiotherapy accelerated to become a fundamental cornerstone of cancer treatment.

The retinopathic effects of radiation exposure have been recognized for more than 50 years, dating back to Stallard's initial description in 1933.[2,3] He reported the occurrence of radiation retinopathy following radon seed treatment of retinoblastoma. Three to six weeks after irradiation, Stallard noted retinal hemorrhages and exudates in a circinate pattern followed by the development of disc edema, vascular sheathing, and ultimately optic atrophy. Because ionizing radiation is being used more frequently for many ocular, orbital, periorbital, and intracranial disease processes, radiation retinopathy continues to be a sight-threatening complication of radiation treatment despite technologic advances in radiation delivery and dosage calculations.

Studies of the retinal vaso-occlusive complications following ionizing radiation are especially enlightening because of this disorder's similarity to the retinal vascular abnormalities seen in other ocular and systemic diseases, particularly diabetes mellitus.[4-14] In addition, the vascular abnormalities consequent to radiation treatment ultimately may lead to severe visual impairment or blindness as in diabetic retinopathy. Thus, insightful analysis of clinical and laboratory studies of radiation retinopathy and its treatment may yield important information relevant to other ischemic and vasoproliferative retinal vascular disorders.

Pathogenesis

Radiation retinopathy has been reported following local irradiation with cobalt 60 plaques and external beam irradiation with megavoltage linear accelerators for the treatment of retinoblastoma,[4,15] choroidal melanoma,[4,5,7] choroidal metastases from breast carcinoma,[16] nasopharyngeal carcinoma and paranasal sinus tumors,[4,6,11,17-19] periorbital basal cell carcinoma,[11] Graves' ophthalmopathy,[9,20-22] and intracranial lesions[4,6,12,23,24] and following prophylactic cranial irradiation in patients with leukemia.[25] Typical radiation retinopathic changes also have been reported in 50% of survivors of the atomic bombing of Hiroshima and Nagasaki.[26]

Although 3,500 cGy had previously been accepted as the upper limit of safe total dosage,[27] cases of radiation retinopathy have been reported after much lower levels of irradiation. Doses as low as 1,100 cGy,[24] 1,200 cGy,[25] 1,700 cGy,[28] 2,000 cGy,[9,21] and 2,080 cGy[22] have resulted in radiation retinopathy. Patients seem to vary considerably with respect to susceptibility for retinal complications of radiation exposure; however, there is no question that increased radiation dosage increases the likelihood of retinal injury.[8,18,19,21,23,27,29] De Schryver and co-workers reported that patients receiving 2,500 cGy or more had a much higher incidence of retinal complications than patients receiving less than 2,500 cGy.[29] Shukovsky and Fletcher reported that nine of ten eyes in patients receiving more than 6,800 cGy suffered complete loss of vision[19]; the loss of vision was attributed to proliferative retinopathy in six eyes and to profound optic nerve atrophy in the other three eyes. In addition, Howard noted that patients receiving a second course of radiotherapy to their eyes for retinoblastoma suffered a more severe radiation retinopathy.[30] Reports also suggest that higher doses of local radiation therapy, as compared with external beam, must be given to produce radiation retinopa-

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Supported by National Institutes of Health research grant EY01730, by the Chatlos Foundation, and by a departmental award from Research to Prevent Blindness, Inc.

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thy.[4,31] Increased dosage, however, whether given locally or with external beam, does not necessarily cause the radiation retinopathy to develop sooner.[4,8,12,19]

Several studies have shown that increased fraction size correlates with an increased incidence of retinal complications.[4,6,21,22,27] The concomitant administration of chemotherapy also increases the risk of visual complications,[4,6,12,18,25,27] potentiates the development of radiation retinopathy at lower radiation doses,[25] and may shorten the latent period between exposure and retinal changes.[4,12,18,25] The total elapsed time in the course of irradiation also may be a risk factor for the development of radiation retinopathy.[27] Patients with a concomitant systemic disease—such as hypertension, diabetes mellitus, and autoimmune disorders—probably also are more susceptible to the retinal complications of radiation treatment.[4,6,27,32]

Histopathology

The retinopathic effects of irradiation may be classified as acute or chronic. Histologic studies of monkey eyes by Cibis and Brown suggest that acute changes (within six hours) include nuclear pyknosis, predominantly among rods, and edema restricted to outer retinal layers.[33] The chronic changes of radiation retinopathy in humans have been described extensively. The fundamental abnormality of chronic radiation damage is endothelial cell injury,[8,34-36] primarily in capillaries, followed by capillary closure (demonstrable with fluorescein angiography),[5,37,38] subsequent retinal ischemia, necrosis of nerve tissue, and fibrovascular proliferation.[4,6,8,9,36]

Histologic studies of human eyes by Egbert and associates have shown pronounced thickening of retinal arteriolar and capillary walls due to an accumulation of a fine, fibrillary "material."[34] Irvine and Archer and colleagues have described an apparent preferential loss of endothelial cells early in the pathologic process.[8,35,36] This differs from diabetic retinopathy in which pericytes reportedly disappear first.[8,35,39] Also, in contrast to diabetic retinopathy, microaneurysms and capillary hypercellularity were relatively less common among specimens showing radiation retinopathy,[8,36] and neovascularization has experimentally remained confined to the retina and choroid, without intravitreal extension.[36] In severely affected capillaries, both pericytes and capillary endothelial cells showed pyknosis, striking vacuolization, and loss of organelles as demonstrated with electron microscopy.[8,36] In advanced retinopathy, degeneration of the choriocapillaris lamina becomes evident,[8] and choroidal neovascular growth may ensue.[36]

Clinical Manifestations

The ophthalmoscopic manifestations of radiation retinopathy are frequently likened to the retinal vascular abnormalities of diabetic retinopathy.[4,8,11] Microaneurysms appear first, followed by retinal hemorrhages, capillary nonperfusion, and infarcts of the nerve fiber layer (Figure 1).[2-4,6,8,9] Retinal edema, hard exudates, telangiectasia, and vascular sheathing may follow in variable sequence and latency.[2-6,9-12] Neovascularization may develop later (Figure 2),[4-7,9,10] with subsequent vitreous hemorrhage and traction retinal detachment,[5,9,10,15] clinically similar to the fibrovascular proliferation seen in diabetic retinopathy. A feature of radiation retinopathy that distinguishes it from diabetic retinopathy is the atrophy of the retinal pigment epithelium seen sometimes after radiation treatment (Figure 3).* Vascular obliteration also gives rise to radiation optic neuropathy, which may manifest as papillitis and optic atrophy (Figure 4).[2,5,12,19,40,41] The latency period between radiation exposure and the clinical manifestation of vascular changes varies, ranging from three weeks to seven years,[6] but most typically is six months to three years.[4,6,9,11,12,31]

The retinopathic changes following radiation exposure are more severe in the posterior than in the anterior retina, and this difference is purportedly due to the increased number of capillaries and higher blood flow of the macular region.[4,12,19] Macular changes may include hard exudates,[11,14] cystoid and noncystoid macular edema (Figure 5),[4,5,9,14] and serous detachment.[11] As would be expected, macular abnormalities frequently lead to a significant loss of vision.

Treatment

Although considerable attention has been focused on the pathogenesis, clinical presentation, and prevention of radiation retinopathy, few articles address treatment. Chaudhuri and co-workers detail therapeutic success using argon laser panretinal photocoagulation in patients with proliferative retinopathy and vitreous hemorrhage.[10] Fluorescein angiography two weeks after treatment showed complete regression of peripheral and optic disc neovascularization. In 1984 Kinyoun and colleagues reported the use of argon laser panretinal photocoagulation in both eyes of a man with neovascularization and vitreous hemorrhage[9]; active fibrovascular proliferation became inactive following treatment. Subsequently, Kinyoun and associates reported the successful treatment of radiation-induced macular edema[38]; leaking microaneurysms were treated with focal photocoagulation and areas of capillary nonperfusion with limited-scatter argon laser photocoagulation. Three of six patients treated with panretinal photocoagulation for proliferative radiation retinopathy showed the regression of new vessels. Similarly, Amoaku and Archer reported a favorable treatment response after focal argon laser photocoagulation in two patients with radiation-induced macular edema.[37] These initial uncontrolled studies indicate that some cases of proliferative radiation retinopathy and macular edema respond favorably to photocoagulation treatment, the goal of which is to decrease vision loss. With respect to the treatment of radiation optic neuropathy, the use of hyperbaric oxygen within two weeks of the loss of vision has proved efficacious in some patients.[42]

Research Issues

Experimentally induced radiation retinopathy is an interesting model for the study of retinal ischemia and proliferative retinopathy. Further research of the biochemical and histologic changes of radiation retinopathy may provide useful information regarding pathophysiology and the rationale for the treatment of ischemic and proliferative retinopathies, regardless of the cause. Irvine and co-workers, using a 4 Mev linear accelerator to irradiate the eyes of capuchin monkeys (*Cebus capucinus*), have proposed that vaso-occlusive retinopathy occurs after a latency period of 12 to 24 months.[8,36] The early retinal vascular abnormalities may progress to intraretinal proliferative retinopathy,[36] with apparent release of a vasoproliferative factor leading to rubeosis iridis. Consequently, vitreous assays may be feasible to monitor biochemical changes after lensectomy and vitrectomy and the

*References 4, 8, 11, 12, 15, 18, 19, 27, 28, 30, 31.

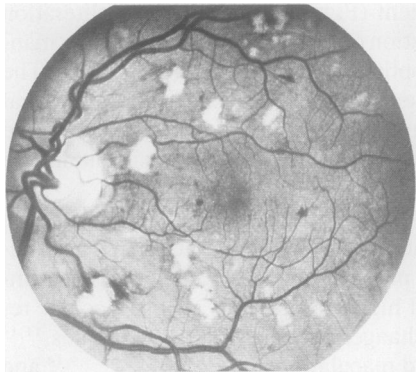

Figure 1.—Fundus photographs of left eye show extensive infarcts of the nerve fiber layer, retinal hemorrhages, and microaneurysms.

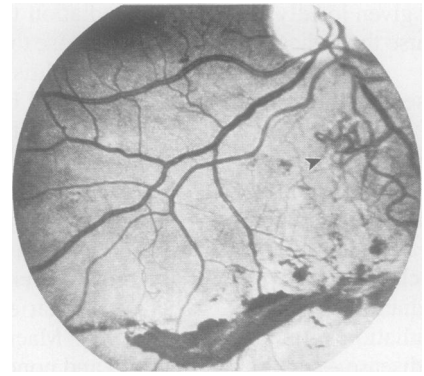

Figure 2.—Retinal neovascular proliferation is shown **(arrowhead)**, with associated hemorrhage.

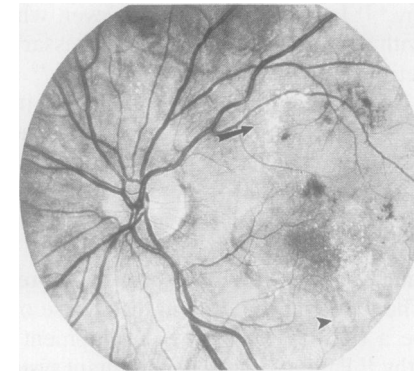

Figure 3.—In radiation retinopathy, atrophy of the macular retinal pigment epithelium occurs **(arrowhead)** in addition to retinal hemorrhages and hard exudates **(arrow).**

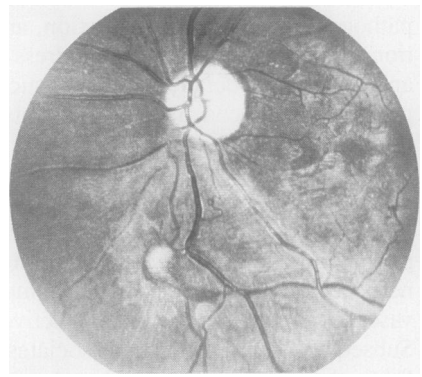

Figure 4.—The eye shows optic atrophy, vascular sheathing, and fibrovascular proliferation.

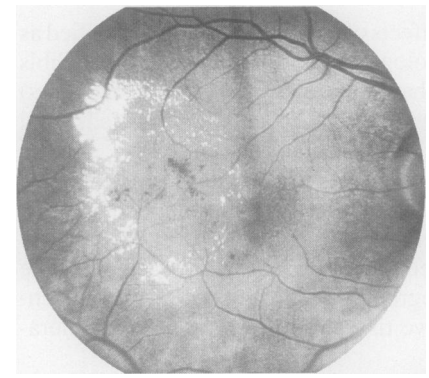

Figure 5.—The macula retinae shows edema with an incomplete ring of hard exudates.

relationship of those changes to the development of rubeosis iridis. An important goal of such research is the development and use of vasoproliferative inhibitors in human disease, such as diabetes mellitus. This model also allows repeated, long-term ophthalmoscopic observations of retinal ischemia as well as easily retrievable pathologic specimens for correlating fluorescein angiography with light and electron microscopy.

Conclusion

Because radiation is being used with increasing frequency for the treatment of ocular and periorbital diseases, it is reasonable to expect that radiation retinopathy may become a more frequently encountered treatment complication despite refinements of dosage calculation and the delivery of the radiation. Consequently, vision loss from radiation retinopathy also may become more common, highlighting the need for new treatments to retard or prevent sight-threatening radiation retinopathy. Photocoagulation is only an initial step in this effort. Although it may be impossible to eliminate the risk of radiation retinopathy, the vision-threatening sequelae can be reduced by good management of these patients. Health care professionals should know the factors that may potentiate the retinopathic effects of radiation, including increased radiation dosage, increased fraction size, concomitant systemic vascular disease, and the concurrent administration of chemotherapeutic agents. These potentiating factors should be minimized. Furthermore, physicians should inform patients about risks and assure ophthalmologic follow-up as indicated.

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THE OLD ONE AND THE FISH

Laced to her wheelchair,
she watches a fish in a tank
drift through bands of light.
A nurse with tea and cakes
points to a cracker she can have.
With hooded eyes, the old one glares
at the nurse, lifts an elbow
stiff as a shield, and takes a brownie
rich in butter, chocolate chips and nuts.
The eye of the fish, black as death,
tilts to her, diamonds on veined hands,
silk knotted at her throat. In a froth
of gauzy fins the fish rips up
a blade of grass, spits a burst
of salt and pepper sand,
and rams the glass.
"Do it!" the old one says. "Do it again!"

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