Retinal Microvascular Abnormalities in Patients Treated With External Radiation for Graves Ophthalmopathy

Dennis M. Robertson, MD; Helmut Buettnner, MD; Culum A. Gorman, MD; James A. Garrity, MD; Vahab Fatourechi, MD; Rebecca S. Bahn, MD; Ivy A. Petersen, MD; Scott L. Stafford, MD; John D. Earle, MD; Glenn S. Forbes, MD; Robert W. Kline, PhD; Erik J. Bergstralh, MS; Kenneth P. Offord, MS; Diana M. Rademacher, BS; Nancy M. Stanley, BS; George B. Bartley, MD

Background: A prospective study was conducted to determine if external ionizing radiation could favorably influence the orbital manifestations of Graves ophthalmopathy. Diabetes and untreated systemic hypertension were exclusion criteria. Radiation was directed to the orbits of 42 affected patients using 0.2 rad (20 Gy) delivered in 10 doses of 0.02 rad (2 Gy). Patients were periodically examined during a 3-year interval.

Objective: To report retinal microvascular abnormalities observed in our study cohort.

Methods: Fundus findings documented with ophthalmoscopy, stereoscopic color photography, and stereoscopic fluorescein angiography prior to radiation were compared with similarly documented findings approximately 3 years following radiation.

Results: Prior to orbital radiation, retinal microvascular abnormalities were identified in 2 patients. The abnormalities were present bilaterally in one patient and unilaterally in the other. During the course of the study, microvascular abnormalities developed de novo in the unaffected retina of the latter patient while the retinopathy in the fellow eye progressed. Retinal microvascular abnormalities and their sequelae developed de novo in both eyes in 2 more patients. In addition to the radiation, other confounding factors known to be associated with microvascular retinopathy (uveitis, inadequately controlled systemic hypertension, and borderline blood glucose levels) were identified among the 3 patients whose eyes developed new retinal microvascular abnormalities.

Conclusions: Whether the retinal microvascular abnormalities observed in these patients were caused or aggravated by external beam irradiation cannot be precisely ascertained. However, the observed progression and de novo development of retinal microvascular abnormalities within 3 years of orbital radiation raise concern that 0.2 rad (20 Gy) delivered to the orbit in 10 doses of 0.02 rad (2 Gy) may aggravate existing retinal microvascular abnormalities or cause radiation retinopathy in some patients with Graves disease. These findings and the failure of external beam radiation with 0.2 rad (2000 cGy) to favorably affect Graves ophthalmopathy, as demonstrated in a previous study, have led us to discourage further treatment of Graves ophthalmopathy with radiation.

Arch Ophthalmol. 2003;121:652-657

In a recent prospective, randomized, double-masked placebo-controlled study called the Orbital Radiotherapy for Graves Ophthalmopathy (ORGO) study, Gorman et al. were unable to demonstrate any beneficial therapeutic effect with 0.2 rad (20 Gy) of external beam radiation given in doses of 0.02 rad (2 Gy) to randomly selected orbits among a cohort of 42 patients. In addition to collating general or systemic clinical parameters of Graves ophthalmopathy, the study included a fundus evaluation with ophthalmoscopy, fundus photography, and fluorescein angiography before and approximately 3 years after radiation. The purpose of this study was to report retinal microvascular abnormalities identified among these 42 patients.

STUDY DESIGN

Patients included in this study had defined orbital disease associated with Graves ophthalmopathy. Patients with diabetes mellitus and untreated systemic hypertension were excluded from participating. Eligible patients participated in a prospective, randomized, double-masked placebo-controlled clinical trial of radiotherapy for Graves ophthalmopathy using an external beam technique that permitted radiation to be delivered to a single randomly selected orbit and sham-treated the other orbit, which was used as a control. Six months after the initial treatment, the sham-treated orbit also received radiation. In addition to the standard clinical ophthalmic examination that included best-corrected

From the Department of Ophthalmology (Drs Robertson, Buettnner, Garrity, and Bartley), Division of Endocrinology (Drs Gorman, Fatourechi, and Bahn and Ms Stanley), Division of Radiation Oncology (Drs Peterson, Stafford, and Kline), Department of Diagnostic Radiology (Dr Forbes), and Division of Biostatistics (Messrs Bergstralh and Offord and Ms Rademacher), Mayo Clinic, Rochester, Minn; and the Department of Radiation Oncology, Mayo Clinic, Jacksonville, Fla (Dr Earle). No authors have any relevant financial interest in this article.
visual acuity measurements, visual field testing, D-15 color vision testing, and exophthalmometry, all patients had a careful ophthalmoscopic evaluation of the fundus, stereoscopic color fundus photography, and stereoscopic fluorescein angiography prior to receiving and within 3 years of radiation. The color fundus photographs and fluorescein angiograms were studied stereoscopically with +10.0 spherical lenses by 2 of us (H.B. and D.M.R.). The findings were recorded and assimilated for this article.

All patients gave informed consent to participate in the ORGO study and this study. The study was approved by the institutional review board and Radiation Safety Committee.

RADIOTHERAPY

In the design of our study, we wished to accomplish the goal of radiating the orbit while respecting the sensitivities of normal tissues such as the lens, the contralateral orbit and retina, and the brain. The premise to choose a dose of 0.2 rad (2000 cGy) was based on the use of this dose in other studies of Graves ophthalmopathy as well as the knowledge that damage to the retina and central nervous system is minimal at a dose lower than 0.25 rad (2500 cGy) in 0.02-rad (200-cGy) fractions, that a dose of 0.02 rad is much lower than that ordinarily required to cause radiation retinopathy, and that central nervous system damage is correlated with dose rates in excess of 0.02 rad per day.2

Radiation therapy was given using 6-megavolt photons delivering 0.2 rad (20 Gy) to the randomly assigned orbit in 10 doses for 12 days. A pair of wedged 6-megavolt ipsilateral photon fields were employed, ± 45° from direct lateral using dual asymmetric jaws and custom blocking to minimize divergence into the other structures. The patients were immobilized using a thermoplastic mask; a computed tomographic scan was obtained to ensure that the anterior orbit was encompassed in the 95% isodose volume. The dose distribution was verified using an ion chamber, thermoluminescence, and film dosimetry in an anthropomorphic phantom. Verification portal imaging of the photon fields and isocenter was obtained weekly.

The extended-source axis distance was required for patient and couch clearance and was obtained by longitudinal and lateral shifts of the treatment couch. The setup was confirmed daily. Jaw settings were determined from the pretreatment computed tomographic scan to provide a 0.5-cm margin posterior to the bony orbit.

Patients were treated once daily Monday through Friday for a total of 10 doses and 0.2 rad (20 Gy). For the sham treatment of the fellow eye, identical setup routines were used and the jaws of the linear accelerator were closed.

RESULTS

RADIATION MEASUREMENTS

Based on various measurements of 0.2 rad (20 Gy) delivered to the treated orbit, the center of the fellow orbit received approximately 0.004 rad (0.4 Gy). The maximum dose in the fellow orbit was approximately 0.02 rad (2 Gy). The ipsilateral lens received less than 0.016 rad (1.6 Gy), and the contralateral lens received less than 0.004 rad. The ipsilateral retina received approximately 0.2 rad, whereas the fellow retina received approximately 0.004 rad. The sham treatment delivered less than 0.0001 rad (0.01 Gy) to the orbits.

Figure 1. Case 1. A, Mid-phase fluorescein angiogram shows retinal microaneurysmal changes superior to the right fovea (white arrows). B, Mid-phase fluorescein angiogram shows microaneurysm inferior to left fovea (black arrow).

RETINAL MICROVASCULAR STUDIES

Of the 42 patients with Graves ophthalmopathy, retinal microvascular abnormalities were identified in 7 eyes of 4 patients. Details of these abnormalities are summarized as follows. The ages of the 4 identified patients at the time of study enrollment ranged from 41 to 50 years (mean, 46 years).

Case 1

A 45-year-old woman with Graves ophthalmopathy was enrolled in the study in April 1997. Color photographs of the fundi taken at the time of enrollment showed no recognizable microvascular abnormalities. However, the fluorescein angiogram on that same date demonstrates microvascular abnormalities in the posterior pole of each eye (Figure 1A and B). Four small microaneurysms and a focal area of capillary nonperfusion (approximately 100-200 µm in size) are located superior to the right fovea. The microaneurysms did not leak dye. In the left eye, several microaneurysms are located both inferonasal to and nasal to the capillary-free zone; another microaneurysm is located approximately 1 disc diameter inferior to the fovea along the 7-o’clock meridian. None of these reti-
Color fundus photographs taken at a follow-up visit in August 2000 were similar to the earlier fundus photographs: they did not demonstrate microvascular abnormalities. In addition, ophthalmoscopy did not reveal any retinal microvascular abnormalities. A repeated fluorescein angiogram was not done because the patient experienced an allergic reaction (urticaria) to the fluorescein at the time of the initial study. The clinical records of this patient revealed no systemic abnormalities such as diabetes or hypertension that might account for these microvascular changes. The patient underwent bilateral transantral orbital decompression, which included bilateral ethmoidectomy and sphenoidectomy, in April 1998.

Bilateral microvascular retinopathy was recognized with fluorescein angiography but not using ophthalmoscopy or color fundus photography. The retinopathy was present prior to the patient’s entrance into the ORGO study and did not appear to progress, judging by ophthalmoscopy, during the study course.

**Case 2**

A 41-year-old woman with Graves ophthalmopathy was enrolled in the study in November 1995. The color fundus photographs taken at the time of enrollment showed a single microaneurysm superotemporal to the right optic disc, which was not recognized by the examining ophthalmologist. The fluorescein angiogram on the same date showed this aneurysm and several additional microaneurysms inferior to the fovea of the right eye; no microvascular abnormalities were seen in the left eye. Color fundus photographs taken in 1999 showed 2 small microaneurysms in the inferior macula of the right eye (1000 and 2000 µm from the fovea). The fluorescein angiogram from 1999 showed several small microaneurysms within 1000 µm of the capillary-free zone in the right eye. Color photographs of the left fundus taken in January 1999 show microaneurysms in the posterior pole that are also visible in the fluorescein angiogram, along with several additional small microaneurysms located within 750 µm of the capillary-free zone (Figure 2). None of these microvascular abnormalities showed dye leakage in the late frames of the angiogram.

This patient was noted to have labile systemic hypertension (December 1997), hyperlipidemia, and borderline plasma glucose levels (98 mg/dL [5.4 mmol/L] and 115 mg/dL [6.4 mmol/L] in November 1997 and April 1998, respectively). The patient also underwent bilateral upper eyelid retraction repair (April 1998) and electroconvulsive therapy for depression (November 1998 and October 1999).

Small microaneurysms were demonstrated with fluorescein angiography in the right eye at the beginning of the study prior to radiation; at the follow-up examination, new microaneurysms were visible in the right eye, and microvascular retinopathy had developed de novo in the left eye.

**Case 3**

A 49-year-old woman with Graves ophthalmopathy was enrolled in the study in June 1998. The color fundus photographs and the fluorescein angiogram showed no recognizable microvascular abnormalities at the time of entry into the study (Figure 3B). In 1998, prior to returning for a follow-up visit, the patient was diagnosed as having uveitis and received short-term treatment with systemic corticosteroids. The uveitis resolved. Episcleritis was observed in January 1999.

In December 2000, the patient returned for a follow-up examination. Although white blood cells were not seen in the vitreous cavity by the ophthalmologist who conducted the ocular examination, posterior synechiae at the 6-o’clock position supported the history of previous uveitis. The color fundus photographs of the right eye show a focal abnormality in the inner layer of the retina approximately 750 µm superior to the fovea (Figure 3A). This has an appearance suggestive of a microaneurysm, but because it does not fill with fluorescein during angiography, it seems to represent a punctate hemorrhage. Color fundus photographs and magnified views of the fluorescein angiogram of the left eye showed multiple small dilated vessels superotemporal, temporal, and inferior to the capillary-free zone. Many of these small retinal capillaries leaked dye, contributing to a pattern of segmental cystoid macular edema confined primarily to the upper portion of the macula (Figure 3C). There were also some sites in the papillo-macular bundle where dye leakage and retinal staining appeared to arise from these incompetent capillaries.

Bilateral microvascular retinopathy developed de novo during the interval between entry and the 3-year follow-up visit in the ORGO study. An episode of uveitis could have been responsible for some of our findings.

**Case 4**

A 50-year-old woman with Graves ophthalmopathy was enrolled in the ORGO study in September 1996. Neither the color fundus photographs nor the fluorescein angiogram obtained at her entry into the study showed...
abnormalities of the retinal microvasculature. Both the color fundus photographs and fluorescein angiogram 3 years later show retinal microaneurysms in each eye. There is a prominent microaneurysm superior to the capillary-free zone in the right eye that did not leak dye (Figure 4A). Several smaller microaneurysms and capillary dilatations are visible near the inferior boundary of the capillary-free zone. Four microaneurysms located superior to the capillary-free zone of the left eye (Figure 4B) show dye leakage and patchy (fluorescein) staining in the late frames of the angiogram. The microvascular abnormalities were visible ophthalmoscopically.

This patient was receiving treatment for systemic hypertension and at 1 study visit had a blood pressure reading of 170/110 mm Hg. Plasma glucose levels during the course of the study were borderline high (99, 98, 84, 107, and 106 mg/dL [5.5, 5.4, 4.7, 5.9, and 5.9 mmol/L]; normal range, 70-100 mg/dL [3.9-5.6 mmol/L]). The glycosylated hemoglobin level was normal.

Bilateral microvascular retinopathy developed de novo between entry and the 3-year follow-up visit in the ORGO study. The findings include microaneurysms and capillary decompensation with intraretinal fluorescein staining.

**COMMENT**

Our study reports retinal microvascular abnormalities identified in a cohort of 42 patients with Graves ophthalmopathy who received external beam radiation to each orbit within the context of a prospective study designed
to test the efficacy of radiation in the treatment of orbital complications associated with Graves disease. Ocular findings documented for each patient included those found using ophthalmoscopy and those obtained with color fundus photography and fluorescein angiography of the posterior pole of each eye in advance and within 3 years of radiating the orbits with 0.2 rad (20 Gy) in doses of 0.02 rad (2 Gy) using a linear accelerator.

The color photographs and fluorescein angiograms provided an opportunity to stereoscopically study the retinal vasculature and other details of the posterior pole. We identified microvascular abnormalities in 3 eyes at the baseline evaluation and in 5 additional eyes during the follow-up visit after orbital radiation.

In exceptional instances, patients with Graves ophthalmopathy have developed retinal microvascular abnormalities following orbital radiation, but these abnormalities appear to be uncommon in patients with Graves ophthalmopathy. For example, in a review detailing the clinical features of 120 patients with Graves ophthalmopathy, retinal microvascular abnormalities were not reported in any of the eyes. Similarly, in a 5-year follow-up study of 96 patients with Graves ophthalmopathy, no patients were reported to have retinal microvascular abnormalities. In 3 separate reviews of patients with Graves ophthalmopathy in childhood and adolescence, there was no mention of abnormal retinal microvasculature. However, none of those studies included evaluations of the fundi with fluorescein angiography, as in this study. In the 3 eyes in which we recognized subtle microvascular abnormalities at the beginning of our study (prior to radiation), these abnormalities were recognized only by stereoscopic study of the fluorescein angiograms (cases 1 and 2). In 2 of the 3 eyes, retinal microvascular abnormalities were not seen clinically or with magnified study of the color fundus photographs. How can we explain the retinal microvascular abnormalities identified in these 3 eyes prior to radiation?

Although common causes of retinal microvascular abnormalities include diabetes mellitus and untreated systemic hypertension, all of our patients were evaluated for both of these conditions before, during, and after completion of the study. Neither of these diagnoses were confirmed in our patients at the time of enrollment, although during the course of the study, 2 patients had labile hypertension (1 while receiving treatment for systemic hypertension). The same 2 patients had borderline high plasma glucose levels: 107 and 115 mg/dL (5.9 and 6.4 mmol/L), respectively. In some instances, retinal microvascular abnormalities might develop as a consequence of Graves ophthalmopathy without other contributing factors. For example, a serious complication of Graves ophthalmopathy is optic neuropathy with papilledema. Congestion of the retinal vessels associated with papilledema can lead to capillary dilatation and microaneurysmal abnormalities. None of our patients had papilledema during the course of the study, however.

Duke-Elder suggested another possible cause of retinal microvascular abnormalities arising from Graves disease. He implied that central retinal vein occlusion could occur with Graves ophthalmopathy as a consequence of venous congestion of the orbit. This was also the opinion of Boniuk. In a discussion of ophthalmic vein and aseptic cavernous sinus thrombosis, Boniuk reviewed 3 cases of Graves ophthalmopathy in which there was an obstruction of the superior ophthalmic veins. Although the fundi in each case were apparently normal (described as normal in 2 cases; not described in the third), in his summary he stated that the clinical manifestations of ophthalmic vein occlusion include dilatation of the retinal veins and multiple small hemorrhages in the retina, consistent with central retinal vein occlusion. Ophthalmic vein obstruction in Graves ophthalmopathy has been reported by others in studies with computed tomography. In a report of an experimental animal model of orbital venous stasis simulating Graves orbitopathy, Safer et al referenced from a personal communication a case in which slow flow retinopathy was seen in a patient with Graves disease. Although none of our patients appeared to have congestion of the central retinal veins at any time during the study, it is possible that the retinal microvascular abnormalities could have arisen from chronic obstruction of the central retinal vein secondary to congestion of the orbital venous circulation. Sur- gical transanal orbital decompression might also be a putative factor in compromising the orbital circulation. Only case 1 of our 4 patients had a surgical decompression, and that patient had retinal microvascular abnormalities at the time of study enrollment, well before the surgical decompression.

Other fundus abnormalities seen with Graves ophthalmopathy include the presence of chorioid folds, which may occur unilaterally or bilaterally, and none of the eyes in this study had clinically recognized chorioid folds, nor were any folds recognized with the fluorescein angiograms. One would not expect chorioid folds to be associated with abnormal retinal vessels.

The retinas in this study each received approximately 0.2 rad (20 Gy) in 10 doses. Although this dose is generally considered to be lower than the threshold necessary to cause radiation retinopathy, eyes receiving this amount of radiation for Graves ophthalmopathy and reasons other than Graves ophthalmopathy have been observed to develop microvascular retinopathy. In only 4 (9.5%) of 42 patients were any retinal microvascular abnormalities detected by a detailed review of color fundus photographs and fluorescein angiograms. Although the microvascular abnormalities did not affect the vision of any of these patients at the last follow-up examination, they have been advised of the findings and the need for continued surveillance.

The de novo development of clinically recognizable retinal microvascular abnormalities in 3 eyes within 3 years of radiation (cases 2, 3, and 4) and the progression of retinal microvascular abnormalities in 1 of the 3 eyes that had microvascular abnormalities before the radiation (case 2) suggests a cause-and-effect relationship. Certainly the appearance of microvascular abnormalities was consistent with the early radiation retinopathy that we and others have observed in human eyes. The findings were also consistent with the radiation retinopathy we have observed in subhuman primate eyes treated with iodine 125 brachytherapy. However, confounding factors in each of these cases may have contributed to the observed abnormalities. These factors include bor-
derline high blood glucose levels (cases 2 and 4), a history of uveitis (case 3), and intermittent blood pressure elevations (cases 2 and 3).

Our observations are similar to those of other investigators who noted retinal microvascular abnormalities after orbital radiation for Graves ophthalmopathy.18,21-23 Whereas the others concluded that radiation was the cause of these observed abnormalities, the role played by radiation in our cases is less certain. Our observations of microvascular abnormalities that were documented using stereofluorescein angiography in advance of radiation suggest that Graves ophthalmopathy alone may be sufficient to cause these abnormalities. Graves ophthalmopathy may also act as a predisposing condition that allows the retinal vasculature to be more susceptible to other potential causes of vascular damage, such as borderline diabetes mellitus or radiation. Some chemotherapeutic agents and certain systemic conditions such as diabetes mellitus can lower the threshold for developing radiation retinopathy.17 Graves ophthalmopathy may be a condition that should be added to this list. We remain concerned that 0.2 rad (20 Gy) of external beam radiation delivered to the orbit in 10 doses of 0.02 rad (2 Gy) may be sufficient to aggravate existing retinal microvascular abnormalities or cause de novo damage to the retinal microvasculature in some patients with Graves disease. The findings in this study documenting a temporal relationship between radiation and the development of retinal microvascular abnormalities, as well as the demonstration in a previous study that external beam radiation with a dose of 0.2 rad (2000 cGy) is ineffective for Graves ophthalmopathy,1 have led us to discourage further treatment of Graves ophthalmopathy with radiation.

Submitted for publication July 22, 2002; final revision received December 5, 2002; accepted December 19, 2002.

Supported in part by a grant from Research to Prevent Blindness, Inc., New York, NY, and the Mayo Foundation, Rochester, Minn.

We thank Ms Bonnie Ronken for her secretarial assistance.

Corresponding author and reprints: Dennis M. Robertson, MD, Department of Ophthalmology, Mayo Clinic, Rochester, MN 55905 (e-mail: robertson.dennis@mayo.edu).

REFERENCES

of Mary. The author and printer are not known. Figure 3 is a detail from a 1498 print by Johann Schönsperger. This is a pirated copy of the Ship of Fools by Sebastian Brant (figure 7 in the original article).

I appreciate Mr Timm’s willingness to share these additional examples with me.

Charles E. Letocha, MD
York, Pa


Error in Conversions. In the article titled “Retinal Microvascular Abnormalities in Patients Treated With External Radiation for Graves Ophthalmopathy,” published in the May issue of the ARCHIVES (2003;121:652-657), the conversions from rad to gray and centigray were incorrect. The correct conversions are as follows: 2500 rad (or 2500 cGy) = 25 Gy; 2000 rad (or 2000 cGy) = 20 Gy; 200 rad (or 200 cGy) = 2 Gy; 160 rad = 1.6 Gy; 40 rad = 0.4 Gy; 1 rad = 0.01 Gy. The ARCHIVES regrets the error.