Three Cases of Large Retinal Capillary Hemangiomas Treated With Verteporfin and Photodynamic Therapy

Thomas M. Aaberg, Jr, MD; Thomas M. Aaberg, Sr, MD; Daniel F. Martin, MD; James P. Gilman, CRA; Robert Myles, CRA

Objective: To investigate the efficacy of verteporfin and photodynamic therapy in the treatment of large retinal capillary hemangiomas.

Methods: Case reports of 3 patients with large retinal capillary hemangiomas treated with photodynamic therapy using verteporfin. Standard verteporfin dosages (6 mg/m² of body surface area) were given. Both standard and modified photodynamic protocols were followed. Modified protocols included shorter verteporfin infusion times and longer light exposure times.

Results: Pretreatment best-corrected Snellen visual acuity of the 3 affected eyes were 20/100, 20/50, and 2/200, respectively. All cases had associated exudative retinal detachments involving the macula. Cases 1 and 2 were classic endophytic retinal capillary hemangiomas. Case 3 was a reactive retinal capillary hemangioma. Case 1 had 2 photodynamic therapy treatments, and after 8 months, visual acuity improved to 20/40. Two years after initiating photodynamic therapy, the visual acuity was 20/30 and there was no reperfusion of the hemangioma. Case 2 had 3 photodynamic therapy treatments. The hemangioma was fibrotic, and 20 months after initiating photodynamic therapy visual acuity improved to 20/30. Case 3 had 1 treatment, 11 weeks later and visual acuity improved to 20/400. Four months after treatment, visual acuity returned to counting fingers because of tractional elevation of the macula as the capillary hemangioma fibrosed. Vitrectomy surgery was performed, and choroidal and retinal neovascularization was discovered. Three months after vitrectomy visual acuity was 20/400. In cases 1 and 2, the capillary hemangioma ultimately regressed, and the exudative detachment resolved.

Conclusions: Verteporfin and photodynamic therapy were effective in achieving closure of large retinal capillary hemangiomas. In all cases, the hemangioma underwent fibrosis with consequent macular puckering due to retinal traction. In all cases, the visual acuity improved.

Arch Ophthalmol. 2005;123:328-332

REPORT OF CASES

CASE 1

A 10-year-old white girl complained of decreased vision in her left eye for approximately 1 month. Her medical history and family medical history were not contribu-
tory to her findings. Examination revealed best-corrected Snellen visual acuities of 20/15 OD and 20/70 OS. The anterior segments were normal. Indirect ophthalmoscopy and biomicroscopy revealed a normal right vitreous cavity, retina, and optic disc. In the left eye, an RCH was seen in the superonasal quadrant anterior to the equator. Clinically, the RCH measured 7 × 8 mm in basal dimension and 4 mm in thickness. There were a dilated feeding arteriole and a draining vein. No fibrosis of the tumor was seen. An associated exudative retinal detachment extended from the tumor through the macula. Diagnostic A- and B-scan ultrasonography revealed a solid, highly reflective retinal tumor measuring 7.3 × 8.4 mm in basal dimension and 4.1 mm in thickness. Magnetic resonance imaging of the brain showed no abnormalities. The patient was felt to have a solitary RCH of the left eye.

Three weeks after the initial examination, the patient's Snellen visual acuity declined to 20/100 OS. While the tumor remained clinically unchanged, the exudative detachment had enlarged (Figure 1A). Treatment options discussed with the family included cryotherapy, vitrectomy with direct diathermy to the feeding arteriole and hemangioma, brachytherapy, transpupillary thermal therapy, and PDT. Given the size of the tumor and extent of the exudative detachment, cryotherapy was not advised. Transpupillary thermal therapy in our experience was relatively ineffective for RCHs. Photodynamic therapy, although investigational, was more attractive to the parents when weighed against the more invasive nature of brachytherapy or vitrectomy.

Photodynamic therapy with verteporfin was delivered to the tumor on October 11, 2001. The patient received 6 mg of verteporfin per square meter of body surface area infused over 10 minutes. Fifteen minutes after the initiation of infusion, a diode laser (689-nm wavelength) was used to apply a 6400-µm spot (using a 160° contact lens) to the tumor for 166 seconds and to the feeding and draining vessels for an additional 166 seconds. One month after treatment, the exudative detachment appeared to have improved and the macula was reattached. Her visual acuity remained 20/100. Vitreous condensation and traction were forming at the apex of the tumor, and venous beading of the draining vein was noted. However, the RCH still appeared perfused. By December 21, 2001, no further improvement was noted, and a second regimen of PDT was performed. The patient again received 6 mg of verteporfin per square meter of body surface area. In this session, it was delivered over 5 minutes and laser was applied 6 minutes after initiation of infusion. Again, a 6400-µm spot was delivered to the tumor for 166 seconds and to the feeding and draining vessels for an additional 164 seconds. One month later, her best-corrected Snellen visual acuity was 20/100. The exudative detachment had completely resolved and the RCH appeared fibrotic. Vitreoretinal traction had resulted in a falciform fold extending from the tumor to the disc (Figure 1B). Eight months after her last PDT, visual acuity had improved to 20/40. Two years after initiating PDT, the hemangioma remained fibrotic, the tractional fold was unchanged, there was mild macular distortion with rotation toward the RCH, and visual acuity was 20/30.

CASE 2

A 29-year-old white man with a known 1-year history of a nasal RCH in the left eye was examined on December 19, 2001. His medical history had been normal. His best-corrected Snellen visual acuity was 20/20 OD and 20/50 OS. Indirect ophthalmoscopy and biomicroscopy revealed a normal right vitreous cavity, retina, and optic disc. In the left eye, an RCH was seen in the nasal midperipheral retina. A coexistent exudative retinal detachment extended from the RCH around the disc and into the macula (Figure 2A). Ultrasonography confirmed the vascular lesion measuring 2.9 mm in height and 6.7 × 7.8 mm in basal diameter. As with case 1, a thorough dis-

Figure 1. A, Left eye of case 1 prior to treatment. Arrow indicates the endophytic retinal capillary hemangioma. Arrowhead indicates a feeding retinal arterial. B, Left eye of case 1, 8 months after first photodynamic therapy treatment. Arrow indicates the fibrotic retinal capillary hemangioma. Arrowhead indicates the tractional fold.
cussion of treatment options was conducted, and the patient elected to proceed with PDT, which was performed on January 23, 2002. The patient received 6 mg of verteporfin per square meter of body surface area infused over 10 minutes. Fifteen minutes after the initiation of infusion, a diode laser (689-nm wavelength) was used to apply a 6400-µm spot (using a 160° contact lens) to the tumor for 166 seconds. He returned on April 24, 2002, with best-corrected Snellen visual acuity of 20/40+, a decrease in subretinal fluid, and clinically reduced tumor size. As the RCH was still perfused, PDT was repeated using similar parameters. On July 24, 2002, his visual acuity was 20/30. Subretinal fluid was gone and hard exudate had precipitated along the retinal vessels. The tumor was approximately 50% of its original size. However, the feeding and draining vessels remained somewhat dilated. A third PDT treatment was delivered with 166 seconds of laser exposure begun 5 minutes after a 10-minute infusion of verteporfin. When the patient was examined on February 5, 2003, the RCH was 25% of the original size and appeared fibrotic with a decrease in the caliber of the feeding and draining vessels (Figure 2B). The macula, however, was dragged toward the disc, an epimacular membrane had formed, and visual acuity dropped to 20/60 despite further decrease in exudate around the RCH. Twenty months after initiating PDT, a spontaneous posterior vitreous separation had occurred. The epimacular membrane had also separated from the retinal surface. The RCH was fibrotic. Visual acuity improved to 20/30.

CASE 3

A 16-year-old white adolescent girl was found to have a temporal RCH on April 10, 2002. Her medical history was unremarkable except for being 5 months pregnant. Her best-corrected Snellen visual acuity was 20/20 OD and 20/80 OS. Indirect ophthalmoscopy revealed a large RCH extending from the posterior equator to the ora serrata with a terraced angiomatous ridge surrounded by exudate that extended posteriorly into the fovea. A minimally dilated tortuous feeder artery and draining vein were noted. Clinically this appeared to be consistent with a large reactive capillary hemangioma (Figure 3A). The fellow eye (right) was normal. Ultrasonography measurements were 3.8 mm in height and 6.3 × 7.0 mm in basal diameter. It had irregular, predominantly high internal reflectivity. No treatment was performed because of her pregnancy. Her visual acuity dropped to 2/200 by the time she was delivered of her infant in September 2002.

Photodynamic therapy using 6 mg of verteporfin per square meter of body surface area was performed on November 13, 2002. Verteporfin was delivered over 10 minutes and laser therapy was begun 5 minutes after completion of dye infusion. Treatment utilized a 6400-µm spot with a 166-second duration delivered to the tumor. Another 6400-µm, 166-second duration spot was delivered to the feeding and draining vessels. Eleven weeks later, her visual acuity was 20/400. Fifty percent of the exudate was absorbed, and there was approximately a 40% reduction in the size of the hemangioma. Retreatment was deferred to see if continued regression would occur from the single treatment. The capillary hemangioma continued to fibrose; however, the retinal traction concurrently worsened. Four months after treatment, visual acuity dropped to counting fingers because of tractional elevation of the macula (Figure 3B). Vitrectomy was performed. Intraoperative findings included choroidal neovascularization extending through the fovea into the epiretinal membranes and posterior hyaloid. Multiple epicenters of retinal neovascularization were noted elsewhere along the temporal retinal arcades. Two weeks after vitrectomy, PDT of the tumor was performed using standard verteporfin dosing, a bolus infusion (over 5 minutes) and 166-second spot duration. Fifteen months after initiating PDT, visual acuity was 20/400.

COMMENT

Singh et al12 reported on 174 retinal capillary hemangiomas in 68 patients. The initial treatment of 169 RCHs included either laser photocoagulation, cryotherapy, transpupillary thermal therapy, brachytherapy, or vitrectomy. Laser photocoagulation effectively controlled 100% of extrapapillary RCHs less than 1.5 mm in thickness.6 However, laser controlled only 47% of larger RCHs. Cryotherapy was used with greater frequency in larger tumors when compared with smaller ones. Overall, cryotherapy controlled 72% of the selected RCHs. Transpupillary thermal therapy was applied to 3 juxta-papillary tumors. One completely fibrose; however, the remaining 2 appeared unaffected. Four larger tumors (3-6 mm) were initially or secondarily treated with brachy-

Figure 2. A, Left eye of case 2 prior to treatment. Arrow indicates the endophytic retinal capillary hemangioma. Arrowheads indicate a feeding retinal arterial vessel. B, Left eye of case 2, 3 months after second photodynamic therapy treatment.
therapy. All 4 cases were effectively controlled. The authors stated that vitreoretinal surgery was usually required for larger RCHs complicated by rheumatogenous or traction retinal detachment. Brachytherapy, vitrectomy, and transscleral diathermy, while shown to be effective in the treatment of these vascular tumors, have the inherent risks of surgery and anesthesia.

Verteporfin is a lipid-based preparation that partitions into the lipoprotein phase (particularly the low-density lipoprotein fraction) and has enhanced selectivity for tissues with up-regulated low-density lipoprotein receptors. Choroidal neovascular membranes up-regulate low-density lipoprotein receptors, and consequently PDT with verteporfin is effective in choroidal neovascularization related to age-related macular degeneration, presumed ocular histoplasmosis syndrome, and angiod streaks. Retinal capillary hemangiomas are vascular hamartomas of the retina. Findings from histologic examination of RCHs demonstrate normal endothelial cells, basement membranes, and pericytes, but new vessels can develop on the anterior surface of the tumor. Murine hemangoendothelioma-derived cell lines and tumorigenic murine vascular endothelial cell lines have active uptake of acetylated low-density lipoprotein, much like choroidal neovascular membranes. It is reasonable to believe PDT should therefore also be effective in stimulating a thrombotic effect in these vascular tumors. Several articles have shown this to be the case in the treatment of choroidal hemangiomas. Schmidt-Erfurth et al demonstrated efficacy in reducing the tumor size and exudative activity of peripapillary capillary hemangiomas in 5 patients. All tumors were located within the central and temporal portion of the optic nerve. Tumor size ranged from 1.6 to 3.5 mm in thickness. The typical PDT protocol was used (6 mg/m² of body surface area infusion over 10 minutes and 83-second spot duration). Lesions showed short-term thrombosis followed by partial regression of the tumor. Unfortunately, 3 patients had a decline in visual acuity due to occlusion of retinal vessels or ischemia of the optic nerve. Atebara has reported successful involution of a large peripheral RCH with PDT and verteporfin. Verteporfin was delivered using the typical protocol (6 mg/m² of body surface area infusion over 10 minutes). The patient required 3 treatments over 9 months to achieve decreased tumor leakage. The initial treatment used an 83-second laser spot. The following 2 treatments used a 166-second laser spot. Follow-up was 10 months from the initial treatment and 3 weeks from the last treatment. No comment was made whether complete regression was achieved.

The 3 cases we currently described demonstrate the possible efficacy of verteporfin and PDT in the treatment of RCHs. This is particularly attractive for large RCHs, which are active and at risk for subsequent exuberant exudative detachments after cryotherapy. We used 2 different treatment protocols. Potentially, case 1 required only the initial treatment. However, while the exudative detachment improved, it continued to persist, and the tumor continued to appear perfused. For these reasons, repeat PDT was performed until no significant vascular perfusion was present and the feeding vessels returned to a more normal caliber. During the second treatment of case 1, verteporfin was given as a bolus and laser therapy was initiated within a minute of completing the infusion. We rationalized that a bolus of drug ac-
tivated early would increase drug concentration and minimize time for drug clearance in the relatively high-flow vascular tumor. In contrast, case 2 used a standard PDT protocol for the first and second treatments. The third treatment used a bolus delivery of verteporfin, which ultimately resulted in complete fibrosis of the hemangioma.

During the cicatricial process, the retina was tractionally displaced toward the capillary hemangioma in all cases. This resulted in macular distortion and, in 2 cases, decreased acuity. While this may be an inevitable consequence of achieving complete fibrosis of the capillary hemangioma, perhaps a partial or slower response would be preferable. Modifying the rate of regression might be achieved through modification of the treatment protocol. Case 3 had an exaggerated cicatricial reaction, which resulted in tractional elevation of the macula and choroidal and retinal neovascularization. Such a reaction was not seen in cases 1 and 2. This response may be particular to a reactive hemangioma. One can speculate that there is already a presence of angiogenic factors resulting in the growth of the reactive retinal hemangioma. Perhaps PDT exacerbated local ischemia and promoted production of angiogenic factors.

In summary, while the optimal protocol for PDT in the treatment of RCHs is unknown, the parameters we used did appear to be effective in the treatment of these 3 patients. Furthermore, none of the cases was complicated by a posttreatment exudative response. Intrinsic retinal contraction from the fibrosing RCH may limit the degree of visual recovery.

Submitted for Publication: August 4, 2003; final revision received August 12, 2004; accepted August 12, 2004. Correspondence: Thomas M. Aaberg, Jr, MD, Associated Retinal Consultants, 1000 E Paris St, Suite 246, Grand Rapids, MI 49546 (aaberg3@comcast.net).

Funding/Support: This study was supported by core grant 5P30EY006360 from Research to Prevent Blindness, New York, NY.

REFERENCES